JORNADA de DEBAT / JORNADA de DEBATE

L'ACCÉS A NOUS FÀRMACS ONCOLÒGICS I EL SEU FINANÇAMENT: REPTES I FUTUR A EUROPA

EL ACCESO A NUEVOS FÁRMACOS ONCOLÓGICOS Y SU FINANCIACIÓN: RETOS Y FUTUROS EN EUROPA

Barcelona, 23 d'Octubre de 2006

Barcelona, 23 de Octubre de 2006

Institut d'Estudis Catalans

Sala Prat de la Riba

C/ Carme, 47 - Barcelona

Jornada organizada conjuntamente por:

Fundación SALUD INNOVACIÓN SOCIEDAD

IECentanys 1907 2007

ICO Institut Català d'Oncologia Hospital Duran i Reynals

Pla Director d'Oncologia

Patrocinada por:

NOVARTIS ONCOLOGY

NOVARTIS 1996-2006 10 AÑOS

CONTINGUT / CONTENIDO

1. New drugs and survival: does the Karolinska report make sense?. Michel Coleman. Cancer World. September-October 2006

New drugs and survival: does the Karolinska report make sense?

Michel Coleman

Is it possible to demonstrate that access to new drugs impacts on a country's survival rates? Last September, the Karolinska report claimed to have done just that. Here, **Michel Coleman** argues that its conclusions were misleading and unsupported by the data and analysis. In the Debate that follows, the authors respond and health economists and policy advisors offer their views.

IN a recent cancer debate in the British House of Commons, the opening statement by John Baron MP included the following: "The Opposition recognise that there have been improvements in outcomes, but they have not outstripped comparable improvements in continental survival rates. **According to last year's report from the Karolinska Institute, the UK still lags behind other European countries** when it comes to survival rates over periods of one year and five years. In fact, Britain has one of the worst survival rates in all of western Europe: whereas 81 per cent of cancer patients in France survive for one year, the equivalent UK figure is only 67 per cent. Even Albania and Lithuania have better one-year and five-year survival rates than we do." (Bold text throughout indicates emphasis added.)

These remarks are seriously misleading, but Mr Baron is not to blame. The report from the Karolinska Institute has gained wide currency since its publication in September 2005. But the report is seriously flawed: the cancer survival data in the report, the statistical models of survival as a function of the availability of chemotherapy drugs, the authors' conclusions from those models – they are all wrong. It seems important to set the record straight, since the faulty data and conclusions may lead to inappropriate decisions by politicians, or undue frustration among cancer patients.

The efficacy of many cancer drugs in improving survival and reducing mortality is supported by solid evidence from high-quality randomised trials, and it is no part of my intention here to challenge that evidence.

But I do challenge the nature and scope of the cancer survival data presented in the Karolinska report, and the way in which those data have been modelled with data on the national availability of cancer drugs. If my critique of the Karolinska report is correct, those analyses cannot be used to support its policy-related conclusions about the impact of the availability of cancer drugs in a given country on cancer survival rates in that country.

*Michel Coleman is Professor of Epidemiology and Vital Statistics in the Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine. He was one of the authors of the EUROCARE-3 report into the survival of cancer patients in Europe, which was the original source of the survival data used in the Karolinska report

"It is important to set the record straight, as faulty data and conclusions may lead to faulty decisions"

What the report says

The executive summary and the conclusion show that the potential policy i mpact of linking cancer survival with the availability of drugs in Europe is clearly understood. The report says: "These results [on the speed of uptake of drugs throughout Europe] underscore the reality that cancer patients in Europe do not have equal or rapid access to cancer drug therapies, but what is the real-life impact of this imbalance? Dr Frank Lichtenberg of Columbia University highlights that **access to more cancer drugs means improved survival rates for patients.** His analysis of the situation in the US demonstrated that the increase in the stock of cancer drugs accounted for 50–60% of the increase in survival rates in the first 6 years post diagnosis.

"In addition, his examination of the USA and selected European countries indicates that an increase in the number of available drugs is associated with an increase in both the one-year and five-year survival rates. Therefore, with the importance of new drug therapies in the battle against cancer, it is clearly in the best interest of cancer patients that new, innovative drug therapies are made available to them as soon as possible. **Reduced or delayed access to cancer drugs has a very real impact on patient survival."**

The evidence for this assertion is based on chapter 7 of the report, "Pharmaceutical innovation and cancer survival", which is described as a 'commentary' prepared by Frank Lichtenberg at Columbia in August 2005. He examines cancer survival trends in the US in relation to drug availability, and carries out a similar exercise with European data. This is described as an investigation of "the effect of availability of new drugs on survival from 17 types of cancer in more than 35 countries." The data sources and the description of the methods are reprinted here in the box on p 28. No other detail is provided on either data sources or methods. No reference for the method is given.

Results are shown for 38 European countries (Table 7.2, p89 of the report) in the form of one-year and five-year survival rates (%), for all cancers combined in both sexes, along with the annual number of cases and the number of new drugs launched since 1982. No survival data are shown for 17 different cancers. No results are given from the modelling of cancer survival as a function of the availability of drugs. Instead, these results are summarised as follows:

"The estimates indicated that an increase in the number of available drugs is associated with an increase in both the 1-year and the 5-year survival rates. The sample includes both European and non-European countries. Two additional analyses related to this distinction have been performed:

1. We estimated survival models using the full sample of countries but allowed the ln(N_DRUG) coefficient to be different in the European and non-European sectors. We saw no evidence of a difference. Availability of drugs seems to have the same effect on cancer survival within Europe as it does in the rest of the world.
2. We tried estimating survival models using data for European countries only. This reduces the sample size by

THE KAROLINSKA REPORT

A pan-European Comparison Regarding Patient Access to Cancer Drugs, generally known as 'the Karolinska report', was written by Nils Wilking of the Karolinska Institute in Stockholm, Sweden, and Bengt Jönsson of the Stockholm School of Economics. The data modelling and analysis was carried out by Frank Lichtenberg of Columbia University in the US. The report was funded by Roche and was published by the Karolinska Institute in collaboration with the Stockholm School of Economics in September 2005. It can be accessed at http://ki.se/content/1/c4/33/52/Cancer_Report.pdf.

60%. We did not obtain statistically significant results. However, one might well obtain statistically significant results based on European data only using time-series incidence, mortality and drug utilisation data."

Interpretation

Several serious problems complicate the interpretation of this material.

First, the report says of the GLOBOCAN data (used for survival, see box below): "These incidence data are collated from national cancer registries". This is not so. The GLOBOCAN website (http://www-dep.iarc.fr/globocan/database.htm) makes it clear that "Incidence data are available from cancer registries. They cover entire national populations, **or samples of such populations from selected regions.**" This leads the authors into modelling what are often regional cancer survival rates with national drug marketing data.

Second, the International Agency for Research on Cancer (IARC), which compiles the GLOBOCAN database, does not itself collect or produce cancer survival data. As the website clearly states, survival data in GLOBOCAN 2002 were taken directly from the EU-sponsored EUROCARE study into cancer survival in Europe, in this case EUROCARE-3 (Berrino et al. *Ann Oncol* 14:v1–v155). They relate to patients who were diagnosed during 1990–94 and followed up to 1999. Yet those survival data have been deployed in the model in the Karolinska report in relation to the number of drugs available in 2000, as if they were for patients who had been diagnosed in the year 2000 or later.

Third, five-year survival data for cancer patients diagnosed in 2000 could not have been published at the time of these analyses (August 2005). Only so-called 'period estimates' (Brenner et al. *Int J Epidemiol* 31:456–462) could have been used to 'predict' such survival rates, but period survival estimates were not included in the GLOBOCAN database that was the source of the data.

Fourth, in 12 of the 38 countries (Albania, Bosnia-Herzegovina, Bulgaria, Cyprus, Greece, Hungary, Luxembourg, Macedonia, Moldova,

KAROLINSKA REPORT: DATA SOURCES AND METHODS

The data used to model drug availability against survival in the Karolinska report came from three different sources.

- The *survival* data were taken from the GLOBOCAN 2002 database (though in the Karolinska report this was given as GLOBOCAN 2000)
- Data on drugs approved by tumour type were taken from the Cancer Care Ontario (CCO) Formulary
- Data on *drug availability* were taken from the IMS Lifecycle New Product Focus

The model to which these data were applied is described in the report as follows:

"These data are used for estimating a model that included both fixed cancer-type effects and fixed country effects, which control for all determinants of cancer survival that are invariant across cancer types within a given country and that are invariant across countries for a given cancer type.

$$SURVij = , \ln(N\_DRUGij) + \bullet i + \%_{o}j + \hat{A}ij\ 1$$

Where:

SURVij = the (1-year or 5-year) survival rate for cancer type i in country j

N_DRUGij = the number of drugs for cancer type i available in country j

ai = a fixed effect for cancer type i

dj = a fixed effect for country j

eij = a disturbance

"Due to inclusion of fixed cancer-type and country effects in the model, , [sic: i.e. the comma ","] represents the effect of relative drug availability within a country on relative survival rates within the country. Suppose that, on average (across all countries), the survival rate of cancer type A is 25% higher than the survival rate of cancer type B, and the number of drugs for cancer type A is 35% higher than the number of drugs for cancer type B.

"Then one would expect that if, in a particular country, the number of drugs for cancer type A is only 20% higher than the number of drugs for cancer type B, the survival rate of cancer type A is less than 25% higher than the survival rate of cancer type B. Indeed, estimation of the model requires that the relative availability of drugs for different cancer types varies across countries."

"It treats the number of drugs on the market as the sole explanation for differences in cancer survival"

Romania, Serbia-Montenegro, Ukraine) for which the authors purport to give national survival rates for patients diagnosed in 2000, no cancer registry was in operation in those countries in that year, and in most cases there is still no such registry. In fact, the 'survival rates' for those countries, reproduced in the Karolinska report, were taken in GLOBOCAN to be a weighted average of survival rates in other countries in the same region of Europe for which national or pooled multi-registry estimates of survival *were* available from EUROCARE-3. For example, for Albania, in Southern Europe, survival rates in GLOBOCAN were taken to be a weighted average of the cancer-specific survival rates reported from EUROCARE-3 for Italy, Malta, Portugal, Slovenia and Spain, weighted by the cancer-specific mortality rates in Albania. Equivalent procedures were adopted for other countries from which no survival data were available. This was done in order to estimate cancer prevalence[1], *not* as the basis for an international comparison of survival, and *certainly not* as the basis for modelling international variation in survival as a function of the availability of cancer drugs.

Fifth, almost no information is given on the methods or the results of the modelling. The results are simply summarised in the form of the conclusion "that an **increase** in the number of available drugs is associated with an **increase** in both the 1-year and the 1-year survival rates. The sample includes both European and non-European countries."

Sixth, the survival data from Europe that are used in the model represent a single time point (supposedly in the year 2000). No data on survival trends are presented that could support a conclusion of any *increase* in survival over time as a function of drug availability.

Lastly, the model is extremely simplistic. It treats the number of drugs available on the market, regardless of their availability to patients, or their actual use in individual patients included in the survival analyses, as the sole explanatory factor for international differences in cancer survival. Most of the Karolinska report deals in detail with the marketing of cancer drugs in Europe over the last 20 years. I have no comment on the analysis of the availability of cancer drugs per se, except that the report seems to be pervaded by an assumption that the market availability of a licensed cancer drug is the chief factor influencing the national survival rate for that cancer, whereas surgery and radiotherapy remain the mainstay of treatment for most of the common malignancies.

Conclusion

The analysis of cancer survival in relation to the availability of cancer drugs in the Karolinska report is very misleading. It purports to show cancer survival data from several countries for which no such data are available: those incorrect data have already been cited in a parliamentary debate in the UK, and quite possibly elsewhere. The report provides no data on cancer survival beyond those published in 2003 for EUROCARE-3. Real survival data from some countries are then used alongside imaginary data for other countries in a crude statistical model designed to estimate the 'effect' of the number of cancer drugs on the market in 2000 on cancer survival (all cancers, both sexes combined). Worse, the survival data used to model the impact of cancer drugs available in 2000 are for patients who were diagnosed in 1990–1994 – some *six to ten years before the currency of the drug data*. For 12 of the 38 countries, the 'survival data' are actually the average survival rates from four or five completely different countries from the same broad geographic region of Europe. The conclusion that an *increase* in the availability of cancer drugs is associated with an *increase* in cancer survival rates is also completely unsupported by the data presented in the report.

Neither the cancer survival data nor the analyses of them can support the policy conclusions in the Karolinska report.

1. Methods of estimating prevalence: "Partial prevalence (1-, 3- and 5-year prevalent cases) were obtained by combining the annual number of new cases and the corresponding probability of survival by time. ... Several sources of site-specific survival were used. ... Europe: The EUROCARE-3 project provid[ed] figures from several European cancer registries for [patients diagnosed during] the period 1990–1994. Where possible, country-specific survival estimates were used, based on regional cancer registries, and **four regional estimates were prepared for countries where no local survival data were available.**" (Ferlay J et al. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. IARC 1 May 2006; http://www-dep.iarc.fr).

THE DEBATE

CancerWorld asked the authors of the Karolinska report to respond to the points raised in Coleman's critique, and European health economists and policy advisors were asked to comment on the report, and more generally on whether it is possible to draw out the impact one particular aspect of cancer therapy has on survival rates, and if so, how this can be done in the most meaningful way.

In their response, the authors said that the report's findings show significant differences in access to new drugs and the implications of these differences merit discussion. "The Karolinska report provides for the first time comprehensive information on the use of new cancer drugs in different countries, and it documents substantial variation in the uptake of new drugs, and systematic differences between countries. The UK, for example, is slower than other European countries in the uptake and use of new cancer drugs." The report goes further, they said, and investigated different reasons for the observed differences. While it concluded that economic factors play a role, "countries with lower GDP and health-care expenditures per capita, such as Poland, the Czech Republic and Hungary, tend to have slower uptake of new cancer drugs," most of the variation, said the authors, "seems to be explained by factors related to how cancer care is funded and paid for, and by attitudes towards innovation."

"We think that it is important to point out these differences and to discuss the factors behind them, and to consider what can be done to achieve a more rational allocation of resources to cancer care in Europe. This is of interest not only for oncologists and other health-care professionals, but for patients and the general public as well."

Coleman's criticisms related both to the quality of the data and to the methodology used to model survival data against access to new drugs. On the question of the data, the authors agreed that Coleman's criticisms regarding the use of drug availability rather than actual use in the models was fair comment. "The point is well taken, and in the follow-up report to be published later this year, we will have a new set of estimates based on the vintage of drugs actually used. This may strengthen the relation, but probably not lead to a different conclusion since availability and use are correlated."

However, they rejected the other charges relating to the quality of data, arguing that, though "the data available for assessing the relation across countries between actual use of new cancer drugs and improvements in survival over time are far from perfect", the limitations are by no means sufficiently serious to invalidate the findings of the report.

Taking Coleman's points in turn, they stated, "First, we do not see any problem modelling regional cancer survival rates with national data on drug availability. If a drug has not been launched in a given country, then it is not available for use in any region of the country. So regional drug availability = national drug availability.

"Second, the estimated survival rates were obtained by dividing one-year or five-year prevalence by incidence. The results of this procedure appear to be consistent with other estimates of survival rates. For example, the method used implies that the five-year survival rate for all sites other than non-melanoma skin for males in the US is 63.8% [=2431746/ (5*762399)]. According to the US National Cancer Institute, the five-year survival rate for all sites for males in the US during 1995–2000 was 64.0%.

"Third, the fact that the incidence and prevalence data may refer to different time periods would, of course, introduce errors of measurement in the estimates of survival rates. However, these errors are likely to be random, i.e., uncorrelated with the drug availability measure. Random errors of measurement in the dependent variable do not cause any statistical bias."

Regarding Coleman's point about

the GLOBOCAN/EUROCARE 3 data having been compiled to estimate cancer prevalence and not as a basis for modelling survival as a function of the availability of cancer drugs, the authors said "The argument that [these data] can only be used for the specific purpose for which they were collected is absurd."

As for the criticism that changes in survival as a function of access to new drugs cannot be explored using survival data from a single time point, the authors commented, "We did not use international data on survival trends since such data are not available. The analysis on changes in survival over time is done for the US survival alone."

CancerWorld asked European experts from a variety of fields to what extent they felt that Coleman's criticisms of the quality of the data were valid.

Renée Otter is a director and medical oncologist at the Comprehensive Cancer Centre North-Netherlands, who sits on the board of the Netherlands' National Comprehensive Cancer Plan and is involved in many European projects relating to registries, benchmarking of cancer care and guidelines.

She agreed with Coleman's analysis and said the flaws he pointed to effectively invalidated the claim of the Karolinksa report to demonstrate an impact of drug availability on survival.

"If you don't have other data, the only report you can make is about two different things. One part is the survival analysis, the other one is the availability of drugs." These results, she said, could be used as the basis to propose a project that could use both data but in a different way. "You should try to get these data over the same period, and only use data that are not an expectation, but are actually observed in the different countries."

Isabelle Durant-Zaleski is a health economist based at the Hôpital Henri Mondor in Paris, and has a long history of working with epidemiological data to investigate disparities in health outcomes. She says that international comparisons in healthcare are difficult, but can be useful. "What these very large macro-economic comparisons do is draw your attention to something strange. And to me that is exactly what the Karolinska report does.

"It is very good academic practice to challenge the methods and challenge the results, and this is what Michel Coleman is doing, but it is also useful to do some perhaps imperfect comparisons and difficult comparisons, as the authors of the Karolinska report do, because it puts access to cancer care on the political agenda."

Her views are echoed to an extent by Mattias Neyt, a pharmaco-economist who works for the Belgian health technology assessment agency, the KCE, and has recently been involved in assessing the cost-benefits of Herceptin [trastuzumab] in an adjuvant setting. He argues that you have to work with the data you have. "What is best? To do no research or to research with the best available data? I would choose the second. You can find interesting results. How robust they are is another question, but if they don't have more recent figures, that doesn't mean they shouldn't do research at all."

Mike Richards, the UK's National Cancer Director, in contrast, thinks that modeling survival rates from one period against the number of drugs available in another is very likely to come up with misleading results. "The only accurate measure we have of survival rates between countries come from EUROCARE 3, and they relate to patients diagnosed between 1990 and 1994. None of the new drugs we are now talking about, except for Taxol [paclitaxel], had even been licensed at that point. Everything people are talking about now, like Herceptin or Glivec [imatinib] or Rituximab [mabthera], weren't even available so they could not possibly have affected survival rates for people diagnosed in 1990–1994."

The authors counter that they could have chosen to use drug availability for 1995 or 1997 instead of 2000. "But since availability (and vintage) in different years is strongly correlated that will not make the results misleading."

Methodology

In addition to the issues relating to the data used, Coleman also criticised the methodology of the Karolinska report. He argued that the methods used to analyse access to drugs as a function of survival did not provide any basis for the assertion made in the executive summary that "Reduced or delayed access to cancer drugs has a very real impact on patient survival." Firstly, says Coleman, no information was given on the methods or results of the modelling, and secondly, the number of drugs available on the market was treated as the sole explanatory factor for differences in survival.

The authors say they were surprised by these criticisms, particularly as Coleman himself acknowledges that "The efficacy of many cancer drugs in improving survival and reducing mortality is supported by solid evidence from high-quality randomised trials." Information from clinical trials needs to be supplemented with studies based on drug availability and use in actual clinical

"How can our results be misleading if they support the results from clinical studies?"

practice, said the authors, particularly given the fact that of the 57 cancer drugs approved by the US Food and Drug Administration through the regular process since 1994, only 18 were approved on the basis of a survival endpoint, and in none of the 14 granted accelerated approval was a survival endpoint used (see *J Clin Oncol* 21:1404–11).

"Observational studies enable investigation of the impact of innovation in cancer management on costs as well as outcomes… How can our conclusions be misleading if they support the results from the clinical studies?"

While welcoming serious discussion and comments on the methods and data used for these sorts of observational studies, the authors argued that it would have been better if Coleman had read the original research papers before concluding that the models were all wrong. "A number of misunderstandings could have been avoided." The full paper to the similar study conducted by Lichtenberg in the US can be accessed at www.nber.org/papers/w10328, and a revised version taking into account the European data will be posted there soon, say the authors.

They also point out that Coleman fails to provide any alternative explanation or interpretation of the results, and merely implies that the results obtained should not have been obtained.

On the question of the methodology, Zaleski said, "In my view the method is not appropriate for the causal relationship, but it is appropriate to attract attention to discrepancies. It showed there might be a correlation, but establishing causal relationships between a treatment and an outcome – in this case new drugs and survival – is very difficult outside of randomised controlled trials."

She mentions, however, a similar piece of research carried out by the OECD health policy unit, which looked at the use of mammography and survival of breast cancer. "It is not quite the same exercise, but it is not very different. In the case of the OECD report, they identified the fact that, for example, France has 10 times as many mammographs as Canada, standardised by women over the age of 40, yet the survival in Canada from breast cancer is exactly the same as in France. So this means that for people who are interested in public health, you have to look more in-depth."

The Karolinska report, she says, "is a good attempt to have comparisons that would enable you to go further. It is very much what the OECD is doing, but it is more far-fetched in the case of the Karolinska report. The OECD is extremely prudent."

Zaleski suggests one possible explanation for the correlation found between survival and access to new drugs could be that the latter is a "surrogate marker" for something else. "Countries which have speedy access to new drugs may also have better coordination of care and better access to specialised oncologists. It also means access to research protocols, possibly access to multidisciplinary teams, or even access to other innovative or state-of-the-art cancer treatments." This, she stresses, can only be conjecture, which can only be validated by more detailed research, "which is what the Karolinska report and Michel Coleman's piece urge us to do."

Otter also questions whether the methodology used could ever demonstrate a causal relationship between new drugs and survival. "I don't think that in the way they have put their project together you can make any relationship – even if it was in the same time period. It sounds like the story I was told in my first course on epidemiology about there being an increasing number of births because we have an increasing number of storks."

The issue, she suggests, should be whether patients are getting the drugs recommended in evidence-based guidelines. "The drugs you give are dependent on the stage of the tumour. So in some countries you routinely give adjuvant chemotherapy, and in others you will rarely give adjuvant chemotherapy, because there are no stage I patients in these countries. They come too late to the doctor."

She also argues that the role of drugs in cancer management makes it unlikely that they are a big factor in explaining differences in survival. "Very good surgery and very good radiotherapy are more relevant for survival than drugs. The exceptions are all haematological diseases, children's cancer and testicular cancer. For all the others we know that the

additional drugs influence your survival chances less than surgery with or without radiotherapy. Drugs have more influence on survival in the palliative phase of the tumour than in the curative setting."

More fundamental still, says Otter, is getting the diagnosis right so you can plan the most appropriate treatment. "Everything starts with a very accurate diagnosis and staging. Then you need people who are very specialised for the surgery, people who are very specialised for the radiotherapy with access to state-of-the-art radiotherapy equipment. Third comes the medical oncology."

Back in 2000, Richards called in a team of international experts to look at exactly the same survival data as was used in the Karolinska report, with the brief that they were to establish whether the data that showed the UK bumping along the bottom of the European cancer survival league table were an actual reflection of reality, and if so, what could explain the poor results.

"The overwhelming view from that meeting was that we did have to accept the UK had worse survival rates than comparable Western countries. But we also found that the main reason for that was due to patients presenting with more advanced disease in the UK than in those other countries. What that tells me is that it matters as much what goes on before diagnosis as what goes on after diagnosis, if not more."

This finding was reached by looking at the patient data on stage of diagnosis that was available from a number of high-resolution studies that were included in EUROCARE-3. "But that's all the registry studies can tell us – they can't tell us more because they have insufficient data on treatment."

Richards speculates that drug expenditure may be a proxy for overall cancer expenditure.

Future studies

As a policy maker whose job is to use the resources available in the most effective way to improve Britain's cancer services, Richards warmly welcomes studies that throw light on the relative contribution of different aspects of cancer care to the overall outcome. He says, however, that to be of practical value they need to look at a range of input variables. He points to the growing body of evidence that in certain cancers, such as colorectal cancer, the quality of surgery is decisive in reducing local recurrence rates, and is therefore likely to be important in explaining differential survival rates.

"You would need data on stage at presentation, then compare that with a whole load of different things like what treatments are actually being given, what training is being given, what is the quality of surgery and the radiotherapy."

He accepts that such studies are not easy, because it is difficult to get comparable measurements across countries. The best way, he suggests, would be to get countries that are prepared to do this well to work together. "I think you need to engage with people from the individual countries who know what is going on and can advise as to what the data might mean and what is a realistic and reasonable comparison to make."

Zaleski points to a study recently carried out by Stanford University, which posed the question: Has the introduction of new technologies for heart treatment changed the outcome in heart attack? It also looked at how variations in the speed at which these new technologies were introduced into routine practice impacted on survival. "Heart attacks is a much easier topic, because people die quickly, so survival data are easy to get. They have been able to show correlations between the introduction of new technology, the use of health care, and survival. But that is a multicountry endeavour with a very large database and a lot of work to have comparable data."

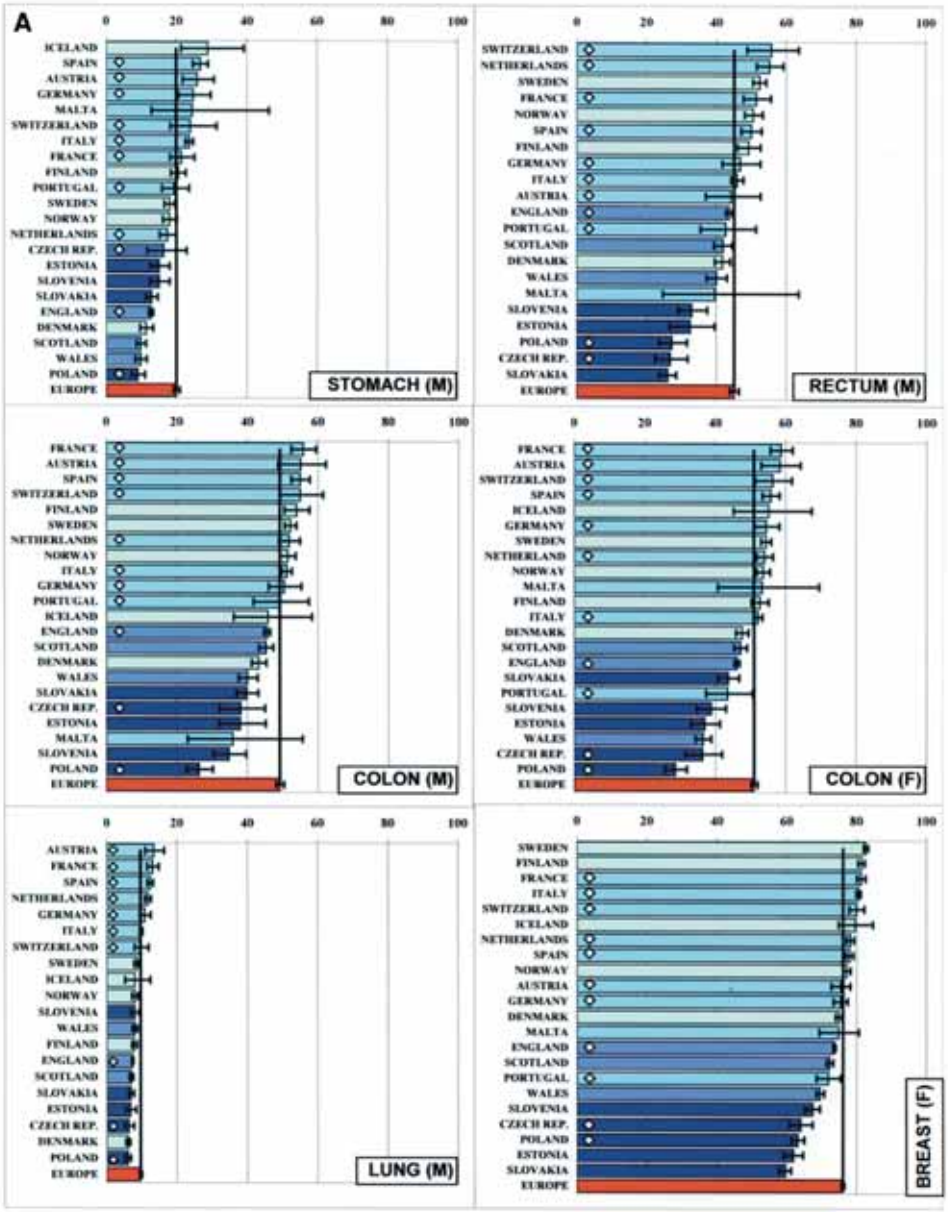
It should in principle be feasible to apply a similar methodology to cancer, says Zaleski. "The idea there would probably be to look at one type of cancer and begin with a case study. This would have to be done with multicountry comparisons. You would need to have a large number of countries, because there are so many treatment variables. You want to have more countries than variables, and you need longitudinal data of good quality."

Longitudinal data are needed to track the treatments a single patient has throughout their cancer journey. Getting hold of this data, says Zaleski,

"It is very much what the OECD is doing, but it is more far-fetched in the case of the Karolinska report"

Why the disparity? The EUROCARE results showed that in some countries cancer patients stand a better chance of survival than in others. The reasons will vary from cancer to cancer. In colorectal cancers, good quality surgery is known to be critical in avoiding recurrences. In breast cancer, expert surgery, radiotherapy and appropriate drugs all play a role. Catching the cancer early and getting the diagnostic work-up right are enormously important. Evidence showing the relative contribution made by each factor on survival rates would be very helpful for policy makers deciding where to concentrate their resources

CANCER SURVIVAL ACROSS EUROPE



Source: MP Coleman et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol* 14 (Suppl 5):v137. Reprinted with permission from Oxford University Press

"It would be worth looking in detail at what accounts for survival differences"

Access to drugs may be a proxy for general expenditure on cancer or state-of-the-art innovations

could prove a problem. "In many countries, like France, you do not have linkage of discharge data. When a patient has had several treatments, there is no national database where those treatments can be linked to the same patient. That is why they looked at heart attacks, because most of the treatments are done on the first admission."

She also mentions the need to look at how reimbursement systems determine which patients actually have access to drugs that are on the market – something also highlighted in the Karolinska report.

Otter suggests that it would be worthwhile comparing some regions in Eastern Europe with some in Western Europe and looking in detail at what accounts for survival differences. Incidence and survival data would have to come from well-documented regional-based cancer registries, but the study would have to be hospital-based, using 'cancer centres of excellence', to get good data on diagnosis and treatment. It should look at one cancer at a time, focusing on high-incidence cancers in order to have enough patients to be able to identify small differences. The variables she would like examined include the use of good diagnostic procedures and good staging procedures, the education of surgeons, the volume of surgeons, multidisciplinary discussions, radiotherapy equipment and the availability of drugs.

"First we should identify some countries which are able to get drugs or not able to get drugs, able to give adequate radiotherapy or not, and high-quality surgery or not. And this is what we should try to compare between countries."

She feels there is potential for making better use of existing networks and data. She mentions in particular the EUROCHIP project – a Europe-wide study to compare different indicators of diagnostics and treatment in different countries.

"I think by combining high-resolution studies, EUROCHIP and some additional data, at least we can try a pilot study. It won't be easy, but I think it should be possible, and it is a much better approach than the Karolinska one.

Otter believes that working to coordinate European guidelines and find ways to ensure that guidelines are followed is the way forward, not just for drugs, but also for diagnostics, radiotherapy, surgical procedures and so on. The availability of a given therapy is not the issue, she says, because if that therapy is not in the guidelines, it won't be paid for and it won't be used.

She mentions the European project CoCanCPG, which is bringing together all the bodies responsible for drawing up guidelines in countries and institutions. It aims firstly to identify the level of evidence in relevant publications to reach conclusions for international guidelines, and, secondly, to gain insight into the problems and processes of translating the evidence into national guidelines that are regularly revised and applied in practice.

Better research needed

The Karolinska report flagged up some significant differences in the rate at which cancer drugs hit the market across Europe. There seems to be general agreement that the suggested correlation with survival merits further examination. Though the experts *CancerWorld* spoke to do not believe the evidence in the report substantiates the claim that "Reduced or delayed access to cancer drugs has a very real impact on patient survival," they do believe access to drugs may be a proxy for general expenditure on cancer, or access to research protocols or state-of-the-art innovations in general – a point also made in the report.

The authors themselves are committed to further refining the findings of the report, "We are well aware of limitations of methods and data, and will continue to work to improve on both, because questions about the relation between innovation, costs and outcome in cancer deserve answers."

The contributors to this discussion, however, clearly believe that modelling drug availability alone against survival cannot guide policy makers in deciding where to concentrate resources and efforts to get the best impact on survival.

This can only be done through more in-depth studies that can look at the contribution of a variety of aspects of stage of detection, diagnostics and treatments.

The Debate was compiled by Anna Wagstaff

2. NICE welcomes new initiative to help NHS reduce spending on treatments that do not improve patient care. NICE 2006/042. 5th September 2006.

NICE 2006/ 042

Issued: 5th September 2006

National Institute for Health and Clinical Excellence

Mid City Place
71 High Holborn
London
WC1V 6NA

Tel: 020 7067 5800
Fax: 020 7067 5801
nice@nice.org.uk

www.nice.org.uk

PRESS RELEASE

NICE welcomes new initiative to help NHS reduce spending on treatments that do not improve patient care

The National Institute for Health and Clinical Excellence (NICE) welcomes today's announcement by Health Minister Andy Burnham asking NICE to launch a new programme of work to help the NHS identify interventions that are not effective.

NICE will develop a new set of products to help the NHS make better use of its resources by reducing spending on ineffective treatments, that is, treatments that do not improve patient care or do not represent good value for money. Moving away from ineffective practice will save money that the NHS can invest in drugs and approaches to care that make a positive difference to patients' lives. NICE will work in partnership with healthcare professionals working in the NHS to identify topics that it would be useful to develop guidance on.

NICE will develop three new types of product:

- **Technology appraisals and clinical guidelines aimed at reducing ineffective practice.** NICE will use its existing methods to give advice on the use of technologies or approaches to care currently used by the NHS where evidence suggests that current practice is no longer appropriate or effective and does not improve patient care. For example, a clinical guideline could be developed on how to manage sore throats in children. Antibiotics are known to be largely ineffective, for example they will not work if it is a viral infection. Antibiotics also encourage antibiotic resistance (the more bacteria are exposed to antibiotics, the greater the chance that they will build up resistance to the drugs). Guidance from

NICE would make clear when it is appropriate to use antibiotics, and when alternative treatments are more effective.

- **Recommendation reminders.** NICE will highlight recommendations from its existing guidance that advise the NHS to stop an intervention that is ineffective or poor value for money. For example, NICE will issue a reminder that suitable patients with end stage renal failure should be offered the choice between home haemodialysis or haemodialysis in a hospital or satellite unit. Approximately 2% of the NHS budget is absorbed by treatment of patients with end stage renal failure. Home haemodialysis is at least as clinically effective as hospital haemodialysis. In 2002, only 2% of patients received haemodialysis at home while around 10-15% of patients, given the choice, would opt for home haemodialysis. The annual cost to the NHS of home dialysis is less than that of hospital and satellite dialysis. If the number of patients receiving home dialysis increased to 15% then the potential saving will be £9.7 million.

- **Commissioning guides.** NICE will offer practical advice for NHS commissioners on how to commission routine services in line with NICE recommendations. The guides will set benchmarks for commissioning and provide data for local comparison with those benchmarks. An interactive spreadsheet will help decision makers calculate the associated costs and savings involved in any service changes. For example, NICE will develop a commissioning guide on upper gastrointestinal endoscopy that advises commissioners on the standard clinical specification for the services they routinely commission and is underpinned by recommendations already published in the Institute's clinical guidelines on dyspepsia and referral for suspected cancer.

Commenting on today's announcement, **NICE Chief Executive Andrew Dillon** stated: "NICE already advises the NHS on when it should invest in new drugs and treatments that work well for patients. It's common sense for us to also advise the NHS on when it is appropriate to stop using treatments that don't benefit patients or do not represent good value for money where there are better alternatives available. I would like to encourage anyone who has suggestions for topics that NICE should consider to let us know."

The new programme is supported by the Chief Medical Officer, Sir Liam Donaldson, who suggested in his 2005 Annual Report that NICE should be asked to issue guidance to the NHS on moving away from established interventions that are no longer appropriate or effective, or do not represent good value for money. In his report he stated that: “Although not easily quantifiable in financial terms, these problems lead to the waste of time and limited resources, poor outcomes of care, harm to patients and lost opportunities.”

Ends

For more information call Fraser Woodward on 020 7067 5905 and 07879 846787.

Notes to Editors

1. NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

3. Effectiveness, efficiency, and NICE. A NICE start but evidence costs money. M.Sculpher, M. Drummond and B. O'Brien. BMJ 2001;322,943-944.

membrane disease might affect the COL4A3 and COL4A4 genes too.[6 7] While carriers of X linked Alport's syndrome may also have thinned membranes, these have distinctive regions of lamellation, and there is usually a family history of X linked Alport's syndrome, renal failure, or inherited deafness.

We have confirmed that thin basement membrane disease is linked to the COL4A3/COL4A4 genes in six of 13 affected families (46%).[8] We suspect that more families with thin basement membrane disease also have mutations in these genes, but that we cannot show this because some family members have pathogenic mutations but no haematuria (incomplete penetrance) and because some mutations have arisen in younger family members and are absent from previous generations (de novo mutations). Our results indicate only that thin basement membrane disease is often due to COL4A3 and COL4A4 mutations and not that affected individuals are necessarily carriers of autosomal recessive Alport's syndrome.

Many studies, as well as the name benign familial haematuria, attest to the generally excellent prognosis of thin basement membrane disease. This condition does not predispose to hypertension or pre-eclampsia, and though some renal impairment is present in 7% of our hospital based patients,[9] this has often resulted from coincidental superimposed glomerulonephritis.[10] Individuals with thin basement membrane disease will nevertheless face unnecessary worry and investigations when their doctors are unfamiliar with the condition, and, of course, will pass on mutations to half their offspring, most of whom will have haematuria. We suspect, however, that thin basement membrane disease is not often a carrier state for autosomal recessive Alport's syndrome and that the offspring of two parents with haematuria due to the condition are unlikely to develop renal failure. Finally, the risk is small that a child or woman might be misdiagnosed with thin basement membrane disease when the true diagnosis is X linked Alport's syndrome.

In summary, thin basement membrane disease should be suspected when there is lifelong glomerular haematuria, minimal proteinuria, and normal renal function in the absence of a family history of renal failure or deafness that suggests X linked Alport's syndrome. The diagnosis is confirmed when another family member also has persistent glomerular haematuria. A renal biopsy is warranted only if the diagnosis is unclear, especially if X linked Alport syndrome cannot be excluded or a superimposed glomerulonephritis is suspected. The major differential diagnosis is IgA glomerulonephritis, which is characterised by episodic macroscopic haematuria with intercurrent infections (synpharyngitic haematuria), proteinuria, hypertension, and progressive renal impairment in one third of individuals and no family history of haematuria. In practice, differentiating between thin basement membrane disease and IgA glomerulonephritis is usually not difficult using these clinical features alone.

Judy Savige *renal physician*
Mark Buzza *scientist*
Hayat Dagher *scientist*

University Department of Medicine, Austin and Repatriation Medical centre, Heidleberg, VIC 3084, Australia
(jsavige@austin.unimelb.edu.au)

1 Del Mar C. Asymptomatic haematuria … in the doctor. *BMJ* 2000;320:165-6.
2 Reynard J, Finlayson JAD, Andrews PA, Ledingham JGG, Warrell DA, Weatherall D, et al. Asymptomatic haematuria. *BMJ* 2000;320:1598-2000.
3 Fairley KF, Birch DF. Haematuria: A simple method for identifying glomerular bleeding. *Kidney Int* 1982;21:105-8.
4 Kincaid-Smith P. Thin basement membrane disease. In: Massry SG, Glassock RJ, eds. *Textbook of nephrology*. Philadelphia: Lippincott, Williams, and Wilkins, 1995;pt 13:760-4.
5 Blumenthal SS, Fritsche C, Lemann J. Establishing the diagnosis of benign familial hematuria. *JAMA* 1968;259:2263-6.
6 Lemmink HH, Nillesen WN, Mochizuki T, Schroder CH, Brunner HG, van Oost BA, et al. Benign familial haematuria due to mutation of the type IV collagen α4 gene. *J Clin Invest* 1996;98:1114-8.
7 Boye E, Mollet G, Forestier L, Cohen-Solal L, Heidet L, Cochat P, et al. Determination of the genomic structure of the COL4A4 gene and of novel mutations causing autosomal recessive Alport syndrome. *Am J Hum Genet* 1998;63:1329-40.
8 Buzza M, Wilson D, Savige J. Linkage of thin basement membrane disease (TBMD) to the loci for X-linked and autosomal recessive Alport syndrome. *J Am Soc Nephrol* 1998;9:387A.
9 Auwardt R, Savige JA, Wilson D. A comparison of the clinical and laboratory features of thin basement membrane disease and IgA glomerulonephritis. *Clin Nephrol* 1999;52:1-4.
10 Cosio FG, Flakenhain ME, Sedmark DD. Association of thin glomerular basement membrane with other glomerulopathies. *Kidney Int* 1996;46: 471-4.

Effectiveness, efficiency, and NICE

A NICE start but evidence costs money

The National Institute for Clinical Excellence (NICE) was established in England and Wales in 1999 to "provide guidance to the NHS on the use of selected new and established technologies."[1] NICE synthesises evidence on the effectiveness and cost of treatments and reaches "a judgment as to whether, on balance, the intervention can be recommended as a cost-effective use of NHS resources."[1] How has the institute measured up to these ambitious goals, and what has been learnt about the demands of an explicit process for assessing health technology?

The institute attracted attention from the international media with its first judgment that "health professionals should not prescribe zanamivir (Relenza) during the 1999/2000 influenza season."[2] The additional cost to the NHS would have been about £10m ($15m) for the benefit of reducing episodes of flu from six days to five. Although subsequently revised,[3] the decision showed that the institute has teeth and is prepared to bite even home grown drug companies like GlaxoWellcome (now GlaxoSmithKline). In some places, such as Australia[4] and Ontario, Canada,[5] pharmaceutical companies must prove that their products are cost effective before they can be reimbursed by the government. Although NICE operates differently in that it does not automatically assess new products and provides guidance rather than mandates, it is clear

BMJ 2001;322:943–4

that products will need to be both effective and provide good value for money to be recommended for use in the NHS. Unusually, NICE's remit also includes medical devices and other healthcare programmes, and its activities are surely being scrutinised by other healthcare systems.

But the evidence on which the analyses of costs and benefits are based is often incomplete or inappropriate. The appraisal of hip prostheses, for example, suffered from the dearth of long term data on revision rates. Similarly, the continuing deliberations about interferon beta are likely to be constrained by data from short term trials with outcome measures that are of limited relevance to decisions about the allocation of resources. The institute, however, is pragmatic about any shortfalls in evidence: give the best advice possible using the data available today, but be prepared to revisit judgments when better data arrive. For many technologies—particularly those without a sponsoring company—the onus for generating adequate data will lie with the NHS health technology assessment programme; its budget may need to be increased, but using NHS resources to generate evidence may be money well spent.

The institute's appraisals are likely to have major implications for the drug and medical device industries because these industries supply much of the information for appraisal. The need to submit dossiers in support of their products is making companies think carefully about their research and development programmes. When products have been marketed for some time it is possible for companies routinely to accumulate data, although the data are not typically gathered within the framework of experimental studies. NICE will, however, increasingly have to consider products which have yet to reach the market, so such "real life" data will be lacking. Before launching a new product, drug companies have in the past focused on generating evidence for the drug licensing authorities. Such data are generally of limited value to NICE, so companies are likely to invest in more pragmatic clinical trials with broader population bases to collect the data on cost and health outcomes which are relevant to NICE's decision making.

The institute's interest in finding value for money puts the methods of economic evaluation under the microscope. Although analytical economic methods have developed rapidly, they have yet to make a major impact on applied economic evaluations and on the data submitted to NICE. The institute's recent publication of more detailed guidance for economic evaluation provides greater clarity about the institute's view of best practice.[6] The international evidence on the quality of drug companies' economic evaluations to support reimbursement is not encouraging. Between 1994 and 1997 a total of 326 evaluations were submitted to the Australian Department of Health and Aged Care, and 218 of these had major problems detected by critical review.[7] However, 62% of these problems were caused by the absence or poor quality of clinical data used in the studies. The quality of data on effectiveness will probably also be a problem for NICE.

What impact will the institute's guidance have on practice in the NHS? There will be particular interest in how the NHS reacts to appraisals that find that a technology benefits patients but introduces extra costs to the health service, such as coronary stents and taxanes. The rationale for NICE is, in part, based on the desire to end the uneven geographical distribution of particular forms of health care. However, unless funding is earmarked and made available to health authorities for these interventions, they can only be offered to patients if the provision of other services elsewhere in the system is curtailed. Hence, local variations in the availability of particular services will remain; the appraisal process will simply shift the unevenness between services. The institute's role in developing clinical practice guidelines, taken together with national service frameworks, promises to ameliorate this problem. It will be necessary to expand the appraisal process, particularly to identify widely used technologies that are not cost effective, to release resources for new interventions. In principle, NICE's role in looking at a wide range of both new and old technologies is important, although the focus of the latest group of interventions to be appraised is narrow and concentrates largely on new cancer drugs.[8]

The NHS and other healthcare systems that are collectively funded need transparent decision making about which types of health care offer value for money and thus can justifiably be funded; this decision making needs to use appropriate and explicit methods. There is much to commend in the early stages of the institute's appraisal process, not least the openness and transparency it has achieved through its website (www.nice.org.uk). Part of the challenge for NICE and the assessment of health technology in England and Wales is economic: gathering, synthesising, and scrutinising data is a valuable exercise but it is costly. The amount and allocation of research funds should also pass the test of cost effectiveness. This will depend on whether clinicians and managers in the NHS take notice of NICE's guidance.

Mark Sculpher *senior research fellow*
Michael Drummond *professor*

Centre for Health Economics, University of York, York YO10 5DD

Bernie O'Brien *professor*

Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada L8N 3Z5

1 National Institute for Clinical Excellence. *Appraisal of new and existing technologies: interim guidance for manufacturers and sponsors*. London: NICE, 1999. www.nice.org.uk/nice-web/Embcat.asp?page=oldsite/appraisals/apr_gide.htm (accessed 19 March 2001).
2 National Institute for Clinical Excellence. *Zanamivir (Relenza) guidance from NICE*. 12 October 1999. www.nice.org.uk/nice-web/Article.asp?a=427&c=153 (accessed 19 March 2001).
3 National Institute for Clinical Excellence. *Use of Zanamivir (Relenza) in the treatment of influenza*. http://www.nice.org.uk/pdf/NiceZANAMIVAR15guidance.pdf (accessed 19 March 2001).
4 Commonwealth of Australia. *Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee: including major submissions involving economic analyses*. Canberra: Australian Government Publishing Service, 1995.
5 Ministry of Health. *Ontario guidelines for economic analysis of pharmaceutical products*. Ontario: Ministry of Health, 1994.
6 National Institute for Clinical Excellence. *Technology appraisal programme: new guidance documents*. http://www.nice.org.uk/pdf/brdfeb01item6.pdf (accessed 19 March 2001).
7 Hill SR, Mitchell AS, Henry D. Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme. *JAMA* 2000;283:2116-21.
8 National Institute for Clinical Excellence. *Technology appraisals work programme*. http://www.nice.org.uk/pdf/Technology_Appraisals_timetable_Jan_2001.pdf (accessed 19 March 2001).

We ask all editorial writers to sign a declaration of competing interests (bmj.com/guides/confli.shtml#aut). *We print the interests only when there are some. When none are shown, the authors have ticked the "None declared" box.*

4. NICE plans faster guidance on drugs for the NHS.

S. Mayor. BMJ 2005;331;716-.

bmj.com news roundup

Full versions of these stories are available at: **bmj.com/content/vol331/issue7519/#NEWS_ROUNDUP**

NICE plans faster guidance on drugs for the NHS

The National Institute for Health and Clinical Excellence (NICE), the body that develops guidance on the use of treatments for the NHS in England and Wales, said last week that it is discussing proposals with the Department of Health to appraise new drugs and health technologies more rapidly.

The process that NICE uses now for technology appraisals of new or existing drugs has been criticised by patients' organisations as being too slow, typically taking 14-16 months (*BMJ* 2005; 331:652, 24 Sep).

The process starts with commissioning an independent academic centre to review and report on published evidence on the technology. Patients' groups, carers, healthcare professionals, and manufacturers of the drugs or devices are then invited to comment on the report.

The assessment report and the comments are combined in an evaluation report, which is used by an independent appraisal committee to develop a consultation document that is circulated for comments to inform the final appraisal.

At a meeting last week NICE's board considered proposals on how to develop advice more rapidly on what it termed "important" new drugs and health technologies. It submitted the proposals to the health department.

Susan Mayor *London*

European Commission aims to reduce deaths from air pollution

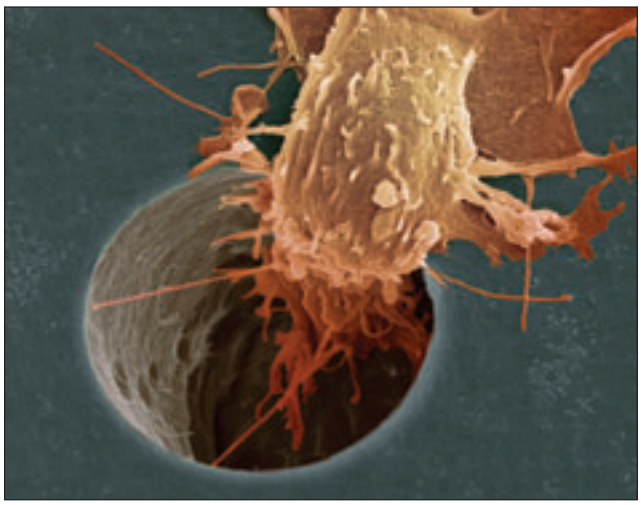
The European Commission has proposed a wide ranging, 15 year strategy to reduce the number of people who die prematurely because of air pollution. But it has had to water down its original proposals because of complaints from industry groups, and pressure groups say the present proposals do not go far enough.

The commission is looking to regulate, for the first time, people's exposure to fine airborne particulates which can penetrate deep into lungs, and ozone pollution at ground level. It aims to achieve this by introducing new standards on car emissions, setting ceilings on allowable concentrations of smog in Europe's cities, and by updating existing environmental legislation to increase its effectiveness.

The commission estimates that air pollution kills 370 000 people in Europe every year, reduces average life expectancy by up to nine months, and costs the EU economy between €427bn (£290bn; $514bn) and €790 a year.

Reductions for fine dust and ground level ozone pollution had initially been to set at 80% over the next 15 years. But protests from industry led to targets of 75% for fine dust and 60% for ground level ozone.

Rory Watson *Brussels*



Cancer cells on the move

The ability of cancer cells to move about is vividly illustrated in the photograph that won first place in the medicine and life category of the 2005 Visions of Science awards this week.

The photograph shows a skin cancer cell migrating across a matrix, with the cell caught moving through a pore in the material used for its culture. It was taken by Anne Weston, scientific officer in the electron microscopy department at the charity Cancer Research UK. She explained: "This cell was part of a sample in an ongoing project investigating tumour biology. We were fortunate enough to find the cell in the process of passing through a pore and thought that it nicely illustrated a cell in motion."

Susan Mayor *London*

More photographs from the competition can be found at www.visions-of-science.co.uk.

UK charity did not break law in giving information about late abortions

A leading British provider of abortions did not break the law when it told women who wanted late terminations about a clinic in Spain that would perform them, a report by Liam Donaldson, the chief medical officer for England, concluded last week.

Professor Donaldson investigated the charity the British Pregnancy Advisory Service (BPAS) after a newspaper reported that it was illegally referring women to Spain for abortions after 24 weeks' gestation, the limit in Britain for abortions for "social" reasons.

Professor Donaldson has decided that BPAS did not break the law by telling women about the Spanish clinic. But he criticised it for giving out the clinic's telephone number too readily.

A few days after Professor Donaldson's report was published an unnamed GP from the West Midlands was said to be under police investigation for taking her daughter to the same clinic for an abortion at 31 weeks. According to the story in the *Daily Mail* (Sep 24: 11) the mother and daughter were to learn this week whether they would face criminal charges, after being arrested last February on suspicion of conspiracy to commit child destruction.

Clare Dyer *legal correspondent, BMJ*

NHS trusts urge caution over BMA finance survey

The NHS Confederation, which represents NHS trusts and health authorities, has urged caution over the results of a BMA survey on NHS funding, which found that three quarters of trusts were in financial difficulty.

The survey claimed that most trusts faced funding shortfalls—but the confederation's policy director, Nigel Edwards, said the survey covered only a minority of trusts and, although not inaccurate, does not give a complete picture.

The BMA survey was sent to 530 medical directors, of whom only 120 responded. Half of those responding were from acute trusts and a quarter were from primary care trusts.

Of those who responded 73% said their trust was facing a funding shortfall in the current financial year. They predicted shortfalls ranging from £0.2m ($0.4m; €0.3m) to £25m, and the average predicted shortfall was £6.2m.

A third of respondents reported that their trust was intending to reduce services as a result of a shortfall. This included staff redundancies, bed closures, and a freeze on recruitment.

One in seven respondents said medical staff posts would be included in recruitment freezes. Mr Edwards said the NHS Confederation was confident that any cost cutting measures would be done in a way that safeguarded the quality of frontline care.

Lynn Eaton *London*

5. England lags behind Scotland in assessing cancer drugs. R. Dobson. BMJ 2005;331;652-.

In brief

CJD study gets the go ahead: A study by the Medical Research Council to monitor pentosan polysulphate as a treatment for Creutzfeldt-Jakob disease (CJD) and variant CJD has received ethical approval from an NHS monitoring body. It follows two High Court cases in the UK, in which relatives sought use of this experimental treatment that has showed signs of slowing progress of the disease (*BMJ* 2003;327:765).

Older men less likely to receive statins: Men aged 74-85 were 60% less likely to be prescribed statins compared with men aged 62-73. This was the finding of a study of secondary prevention of coronary heart disease in British men and inequalities before and after implementation of the National Service Framework (*Journal of Public Health*, http://jpubhealth.oxfordjournals.org, doi:10.1093/pubmed/fdi053).

Children's rights to be aired: The General Medical Council is to set up a citizens' jury to examine what rights children should be entitled to when receiving medical care. The 16 member jury will hear evidence for four days in November before delivering its verdict.

Hostel dwellers have brain damage: One in five of Glasgow's homeless hostel dwellers have alcohol related brain damage, says a study in the *European Journal of Public Health* (http://eurpub.oxfordjournals.org, doi:10.1093/eurpub/cki036).

US to help Vietnam with flu surveillance: The United States has pledged $2.5m to help Vietnam build up its H5N1 avian influenza surveillance network over the next five years. The virus has killed 63 people in Asia, 44 of them in Vietnam.

Australian women are getting heavier: Australian women in their 20s have put on an average 5 kg in weight in seven years, a 40 000 strong longitudinal study of women's health has found. More than half of the middle aged subjects were found to be overweight (www.health.gov.au).

Charity says NICE takes too long to assess cancer drugs

Lynn Eaton *London*

A cancer charity is calling for reform of the way in which cancer drugs are made available on the NHS, claiming that there are sometimes delays of up to three years between a drug being licensed and it becoming widely available.

CancerBACUP, an information service for people with cancer, says that approval for a total of 23 cancer treatments is being held up because of delays in the system.

After drugs are granted a licence, they still have to be approved by the National Institute for Health and Clinical Excellence (NICE) before being prescribed routinely throughout the NHS.

"Cancer treatments should be examined within three months of a licence being granted," said the charity's chief executive, Joanne Rule.

Delays can begin with the initial referral from the Department of Health to NICE for approval. Some drugs have been waiting a year for referral, says the charity. NICE's approval process can take at least 14 months on top of that, it says.

CancerBACUP chief executive Joanne Rule: Treatments should be examined within three months of being licensed

During this period, it says, most patients find that newly licensed drugs are unavailable in large areas of the country. Treatment becomes a postcode lottery.

One treatment, rituximab for non-Hodgkin's lymphoma, is subject to a three year delay and another, cetuximab for advanced colorectal cancer, has been delayed for two and a half years, says CancerBACUP.

Instead of the current procedure, the charity says that there should be a group of experts, including oncologists, who monitor forthcoming treatments, look at outcomes from the drug within three months of it being licensed, and recommend which should be fast tracked by NICE.

NICE's chief executive, Andrew Dillon, said that NICE was trying to improve the situation. He added that there was no ban on prescribing licensed drugs that had not been appraised by NICE. The Department of Health issued instructions to the NHS in 1999 that, in the absence of NICE guidance or while guidance was being developed, local organisations should make their own assessment of available evidence before deciding how, and whether, to fund the drug locally (*Health Service Circular* 1999; (176)). □

See www.cancerbacup.org.uk.

England lags behind Scotland in assessing cancer drug

Roger Dobson *Abergavenny*

The National Institute for Health and Clinical Evidence (NICE) is looking at ways to speed up the delivery of its guidance on the use of new drugs following complaints from charities, such as CancerBACUP (see above), and the achievement of faster approval times by a comparable body elsewhere in the UK.

The Scottish Medicines Consortium, which fulfils the role of NICE in Scotland, appears able to assess drugs more quickly than its English counterpart. It has given its decision on the breast cancer drug anastrozole (Arimidex), for example, while NICE's appraisal of the drug for England and Wales is not due out until November next year.

Studies show that the drug, an aromatase inhibitor, is significantly more effective in prolonging disease-free survival and has important tolerability benefits compared with tamoxifen, when given as an adjuvant treatment in postmenopausal women with early breast cancer (*Lancet* 2005; 365:60-2).

In its advice, issued earlier this month, the Scottish Medicines Consortium advised NHS boards and area drug and therapeutic committees that anastrozole is accepted for restricted use for the supporting treatment of postmenopausal women with early invasive breast cancer which is hormone sensitive.

"Patients should be very encouraged by the news of the [Scottish Medicines Consortium] decision for Arimidex," said Jennifer Whelan, head of CancerBACUP Scotland. "But with this new choice now available to Scottish women, it is more important than ever that patients enter into a discussion with their specialist to become fully informed about the treatment options open to them."

Professor Jeffrey Tobias, a consultant in clinical oncology at University College Hospitals, London, who helped design one of the key studies of the drug, says that the gap between drug licensing and formal appraisal weakens NICE's authority.

"It is a good illustration of the gap between de facto and de jure. Things are clearly happening in England which are strictly beyond the brief, but no one is going to be able to stop it or would wish to. But the fact that the difference exists does weaken the credibility and authority of NICE because it increasingly becomes a rubber stamp. The later it publishes its appraisal the more out of step it is likely to be."

NICE's chief executive, Andrew Dillon, says that the NHS needs to have timely advice. "The institute knows that sometimes its guidance is published after drugs are licensed. It wants to minimise the time gap between licensing and publication and is actively considering solutions that may make this possible in the future." □

6. A pan-European comparison regarding patient access to cancer drugs. N. Wilking and B Jönsson. Karolinska Institutet in collaboration with Stockholm School of Economics, Stockholm, Sweden.

A pan-European comparison regarding patient access to cancer drugs

Nils Wilking
Bengt Jönsson

Karolinska Institutet in collaboration
with Stockholm School of Economics
Stockholm, Sweden

Karolinska Institutet

Foreword

One of the great triumphs of scientific research has been to advance our knowledge of the causes and pathophysiology of malignancy. This has resulted in the development of new ways to treat the many diseases included under the term 'cancer'. Over the past 30-40 years, an ever-increasing number of patients have received treatments that can either cure them or significantly improve their survival and quality of life. Nowhere is this more apparent than in the development of medicines for the systemic treatment of cancer. These advances have, however, outstripped the resources necessary to provide optimal care for the large cancer patient population around the world.

It may come as a surprise to readers to find that it is difficult to obtain reliable data on the true total costs of caring for patients with cancer. Where data are available in some countries in Europe (eg Germany and France), they show that cancer care accounts for a similar proportion of overall healthcare expenditure to that in the USA (approximately 5%). Although drug costs account for less than 10% of the total healthcare expenditure for cancer, it can be argued that because drug acquisition costs can be easier to identify and calculate, they become a greater focus for cost control than some of the more general (and more difficult to calculate) costs of cancer healthcare. The issue of having accurate and timely data on all cancer costs merits further consideration, as the current reality has been that decisions are being made in the absence of such information.

There is little surprise that the management of cancer is a particular challenge in the developing world. However, it is not always appreciated how resource intensive the requirements are for the modern management of cancer in the developed countries. Currently, no society can afford all of the potential treatments for all the patients that could benefit from them. How the necessary resources should be provided is one of the great contemporary debates and different countries approach this problem in different ways. It is therefore not surprising that availability of modern treatments varies widely from country to country.

In order to inform the debate on to how to prioritise healthcare, it is essential to have as accurate as possible a knowledge base of the current distribution of resources and their uptake by the medical profession and patients. In this fascinating report, Wilking and Jönsson have surveyed access to and uptake of new anticancer drugs across the European states. They have reviewed data from 19 countries accounting for 447 million people, or 76% of the total population in Europe (excluding Russia and Turkey); after excluding Norway and Switzerland, this constitutes 96% of the total population of the 25 EU member states. Their report focuses on the treatment of common cancers such as breast, lung and colorectal cancer and non-Hodgkin's lymphoma, and aspects of palliative medicine using the example of malignant metastatic bone disease.

The data show, on average, the introduction of two new cancer drugs per year, with considerable variation in both the availability and the uptake of these new drugs across Europe. The authors discuss these differences in the context of the state of cancer research funding, the drug approval process, the role of health economics and health technology assessments, as well as healthcare budgets and funding allocation for drugs.

Ever-increasing interest from the public in the management of cancer, together with vastly improved access to information, leads to an inevitable pressure on the medical profession and healthcare providers to make the latest advances available as rapidly as possible. >>

Foreword *(continued)*

One area of importance is the licensing procedure for new medicines now centralised by the Committee for Medicinal Products for Human Use (CHMP) for the EU (formerly known as the Committee for Proprietary Medicinal Products [CPMP]). The most recent data suggest that the median time for approval of a European licence for a new anticancer drug is 418 days.

There are considerable variations in the time from a licence being granted to the actual availability of new medicines in different member states and the speed at which patients are able to gain access to new cancer drugs. Although there is little excuse for lack of knowledge of these new advances amongst the medical profession, the health-economic issues that influence whether or not new medical approaches can actually be delivered to the individual patient are often poorly appreciated. Austria, Spain and Switzerland are good in terms of the uptake of new drugs and this is reflected in sales.

Although France has a quick uptake when the drug is introduced, there is lower usage 4 years on compared with that initial rate. The UK has a poor uptake, which is lower than the average throughout Europe, and a slow rate even after the drugs have been available for 4 years.

A significant influence on the uptake of new drugs is the role of the health technology assessment processes used throughout Europe. In this report, particular focus is given to the UK's National Institute for Health and Clinical Excellence (NICE), which, since its establishment in 1999, has identified cancer as a priority area. As the UK's National Health Service provides free care to all patients at the point of delivery, it is not surprising that the NICE studies have a significant impact on resource allocation for new medicines in the UK. However, delays in health technology assessments (such those undertaken by NICE) and their advice on the use or uptake of an EU-licensed drug have a significant negative impact by further delaying the availability of licensed new medicines.

The authors of this excellent report offer some key conclusions but the complexity of this issue raises many more questions than can be answered in a review of this nature. The essential facts are: cancer is a significant cause of morbidity and mortality in Europe, and scientific advances have given us the potential for more treatment approaches than are currently provided. New medicines have no benefits unless they are used by the patients who need them, and the need to balance benefits, costs and available resources should not prevent patients from gaining access to novel drug therapies.

As with many medical conditions, cancer is becoming a chronic condition - treatable though incurable. How society determines its priorities for cancer care in relation to other major health issues and for healthcare versus other public expenditure is a fascinating and highly complex issue that is likely to become more complicated in the years ahead.

I congratulate the authors of this interesting report for their contribution to this very contemporary debate. ■

John F Smyth
President-Elect of the Federation
of European Cancer Societies

Preface

In 2004, nearly 3 million Europeans living in the 25 EU member states were diagnosed with cancer, most commonly lung, colorectal, breast, prostate and stomach cancer. Until a few decades ago, cancer was seen as fatal for all patients affected. However, the outlook for most cancer patients has changed dramatically over the last 20-30 years (for some cancers, such as testicular cancer, we have been able to find a virtual cure). Despite this, approximately 1.7 million Europeans died from the disease in 2004.

The present revolution in the basic understanding of cancer is starting to pay dividends in the forms of new treatments for patients. Both academic institutions and the pharmaceutical industry are investing in cancer research at levels previously unseen. For the most common cancers, such as breast, prostate, colorectal and now also lung cancer, the outcome for patients has significantly improved. These advancements have come as a result of improvements in diagnostic methods identifying patients earlier, the development of surgical techniques and, to a great extent, through innovations in the medical treatment in the form of drug therapies. Over time, the quality and speed of the development process for new drugs has also improved.

It is in society's interest that new innovative drug therapies with proven clinical and survival benefit are made available to patients as quickly as possible. Yet cancer patients across Europe do not have equitable access to these new drugs.

This report focuses on the access of cancer patients in countries throughout Europe to new, innovative cancer drugs. In addition to a general background on recent advances in cancer, we cover specific information on three major disease areas in solid tumour oncology: breast cancer, colorectal cancer, and non-small-cell lung cancer. We have also included non-Hodgkin's lymphoma as an example of an area in haematological malignancy where significant progress has been made during the last decade, and we have illustrated the importance of supportive care in oncology by focusing on malignant metastatic bone disease.

We believe that this report will be of particular interest to patients, physicians, health policy makers and decision makers. In exploring the uptake and access to new cancer drug therapies, we have examined the mechanisms in Europe that either support or hinder rapid uptake. It is for this purpose that we have looked into the state of research funding and the drug approval process, as well as the issue of budgetary pressures, drug reimbursement and the role of health technology assessments.

Nils Wilking, MD, PhD
Karolinska Institutet

Bengt Jönsson, PhD
Centre for Health Economics
Stockholm School of Economics

The core group members who have worked on this project include:

- *Nils Wilking, MD, PhD, Karolinska Institutet, Stockholm, who led the entire project and provided medical expertise in oncology*
- *Professor Bengt Jönsson, PhD, Stockholm School of Economics, who was the project lead for the health economics perspectives*
- *Christer Svedman, MD, PhD, Karolinska Hospital, Stockholm, who provided the medical background of the report*
- *Niklas Zethraeus, PhD, Stockholm School of Economics, who provided much of the health economics background for this project*

This project was supported by an unrestricted grant from F. Hoffmann La Roche Ltd, Basel, Switzerland. Our hope is that this report will highlight the importance of equal and rapid access to new innovative cancer treatments for cancer patients in Europe, and inspire decision makers to take action to address these inequities. ■

Stockholm, 7 September 2005

Table of contents

1. EXECUTIVE SUMMARY

1.1 Objective

This report examines whether patients across Europe have equal and early access to new innovative cancer drug therapies and highlights the existence of inequities.

1.2 Methodology

The countries included in this report are Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, Sweden and the UK. The total population of these 19 countries is 447 million, which constitutes 76% of the total population in Europe (excluding Russia and Turkey) and, after excluding Norway and Switzerland, constitutes 96% of the total population of the European Union (EU) 25.

This report addresses three of the five most common tumour types in Europe, including breast cancer, colorectal cancer and lung cancer (specifically non-small-cell lung cancer). Haematology is also covered through non-Hodgkin's lymphoma, as is supportive care (specifically bone metastasis). Incidence and mortality data for these cancers were obtained from the International Agency for Research in Cancer (IARC) database and are current to 1997 and 2002, respectively.

The current state of research spending in the EU, the timelines for the drug approval process and the roles of health technology assessments, economic evaluations and budgetary limitations were also examined in an effort to determine their contribution to the opportunity of European cancer patients to access new innovative cancer drugs.

In order to obtain an understanding of the European situation regarding the adoption and uptake of cancer drugs, a study was undertaken on 56 cancer drugs in the 19 countries (Portugal was included in the macro-analysis of general uptake of cancer drugs, but not included in the analysis regarding specific drugs due to the lack of available data). Sales data from IMS Health, IMS MIDAS/ Q4 2004 were used as evidence of the drugs' uptake. Three time periods were selected and the drugs were categorised as those introduced before 1993, from 1993-1998 and from 1999-2004 (defined as the first date of introduction in any of the included countries).

Finally, drugs recognised as important advances for a specific tumour type or therapeutic area were selected. These included: trastuzumab for breast cancer; oxaliplatin, irinotecan and capecitabine for colorectal cancer (capecitabine is also indicated for the treatment of metastatic breast cancer); gemcitabine and vinorelbine for lung cancer; rituximab for non-Hodgkin's lymphoma; imatinib for chronic myeloid leukaemia; and a group of four drugs for bone metastasis including clodronate (clodronic acid), ibandronate (ibandronic acid), pamidronate (pamidronic acid) and zoledronate (zoledronic acid). Some of the drugs included in the study (eg trastuzumab, rituximab and imatinib) are known as 'targeted therapies'. Countries were compared to each other, as well as against the European sales average.

1.3 Results

It is important to note that, overall, the incidence rate of cancer in Europe is increasing, meaning that more patients are being diagnosed with cancer. The mortality rate is stabilising however, and in some countries in on the decline, meaning that fewer patients are dying of cancer. The exception exists with lung cancer in women, for which the mortality rate is on the increase.
Our analysis indicates that there are imbalances and inequities in the ability of cancer patients to access cancer drugs in Europe, with access varying according to the country of residence. There are large differences between countries with regard to the level of uptake and the time period over which cancer drugs become available to patients.
Austria, Spain and Switzerland were the top three countries overall in terms of adoption of the newest cancer drug therapies, made available between 1999 and 2004. Italy was also identified as a leader with regard to some specific drugs examined in this report. The Czech Republic, Hungary, Norway, Poland and the UK were consistently identified as below-average adopters of new cancer drugs for the treatment of breast cancer, colorectal cancer, lung cancer, non Hodgkin's lymphoma and supportive care (Figure).

Figure 1.3.

Furthermore, there is significant variation in terms of the timelines followed by these countries for the uptake of new cancer drugs. Four years after the drugs' introductions, several countries still have a large patient population not being treated. This represents a substantial loss to patients.

In addition to inequalities in access to new cancer drugs, there are also structural barriers that prevent patient access to advances in cancer drug therapies. For example, an oral version of 5-flurouracil (5-FU), capecitabine, is available to cancer patients undergoing treatment for colorectal or breast cancer and offers an efficacious, more cost-effective and convenient way to take their treatment. Yet some healthcare systems (eg Germany and the USA) provide payment incentives for physicians to use a hospital-based intravenous administration instead. >>

1.3 Results *(continued)*

UK hospitals would lose revenue by shifting from an intravenous administration to an oral therapy, as an intravenous administration is counted as an in-patient stay and the number of in-patient stays is a factor in determining overall hospital funding. Such situations that provide economic or structural incentives to use a form of therapy that is neither the most cost-effective nor the most beneficial to patients begs further scrutiny.

The only drug analysed in this report for which drug uptake is fairly consistent across Europe is imatinib, a drug used to treat chronic myeloid leukaemia. This disease is represented by a limited patient population with a limited number of treating physicians. These factors, combined with imatinib's recognised efficacy, seem to have facilitated a uniform and rapid uptake on the European market.

These results underscore the reality that cancer patients in Europe do not have equal or rapid access to cancer drug therapies, but what is the real-life impact of this imbalance? Dr Frank Lichtenberg of Columbia University highlights that access to more cancer drugs means improved survival rates for patients. His analysis of the situation in the USA demonstrated that the increase in the stock of cancer drugs accounted for 50-60% of the increase in survival rates in the first 6 years post diagnosis.

In addition, his examination of the USA and selected European countries indicates that an increase in the number of available drugs is associated with an increase in both the one-year and five-year survival rates. Therefore, with the importance of new drug therapies in the battle against cancer, it is clearly in the best interest of cancer patients that new, innovative drug therapies are made available to them as soon as possible. Reduced or delayed access to cancer drugs has a very real impact on patient survival.

Acknowledging that these differences exist and that there is a significant negative impact of delay in access to cancer drugs for patients, the question is: why do these differences exist? In fact, the differences cannot be attributed to just one reason and are likely due to a number of factors. Some elements, however, are widely recognised as contributing factors to the availability of new cancer drugs, for instance research funding, the drug approval process, the role of health economics (including health technology assessments and economic evaluations) and budgetary issues limiting the uptake to new drugs. Therefore, the report also includes an examination of these important fundamentals.

Approximately €3.5-3.9 billion is spent on cancer research in Europe each year, through a combination of public (€1.43 billion) and private (€2.1-2.5 billion) efforts. The charitable sector accounts for 50% of all public cancer research spending. Interestingly, the USA spends as much as seven times more in public funding of cancer research than Europe.

It is interesting to note that the UK ranks as the number one country in the amount of direct cancer research funding, with the charitable sector contributing more than the government in research funding. Yet this report illustrates that the UK lags behind other EU countries in terms of the ability of cancer patients to access new cancer drugs.

Cancer drugs represent 3.5-7% of total pharmaceutical sales. From 1987-2004, 8.1% of all new drugs brought to the European market were cancer drugs. The pharmaceutical industry spends approximately 15% of all its research expenditure on cancer research.

1.3 Results *(continued)*

Recent data also show that 27% of all research projects have cancer as one of their therapy area targets (up from 13% in 1985). Therefore, the amount of investment into cancer research by the pharmaceutical industry is double the percentage of new cancer drugs coming to the European market, and is two to four times greater than the proportion of cancer drugs in terms of total pharmaceutical sales.

Discovery of a new drug therapy is, however, only the starting point on the road to making new cancer drugs available to patients in Europe. Firstly, there is a complex and time-consuming process known as the Centralized Procedure used to establish safety, efficacy and quality before a new drug can be authorised to enter the European market.

The Centralized Procedure by the Committee for Human Medicinal Products (CHMP) approves all new cancer drugs in Europe. According to the data presented in this report, 20 anticancer agents have been authorised in the EU via the Centralized Procedure for approval since its implementation in 1995. (Newly approved drugs such as bevacizumab and erlotinib are not included in this analysis). Currently, the median time for approval of new cancer drugs in Europe is over a year, at 418 days.

Following EU market authorisation and licence approval, there are additional hurdles. In countries such as Italy, Spain, France, Belgium and the Netherlands, government agencies are in place to negotiate the price of the new drug and/or to make a decision on the reimbursement of the new product. In some countries, such as the Netherlands, cancer drugs are mainly used in the hospital setting, theoretically enabling a cancer drug to be available to patients shortly after registration approval. It is worth noting that cancer drugs in the EU ultimately do receive price and reimbursement approval in countries, where required, but there can be delays.

Although there is an EU timeline of 180 days, within which new drugs are supposed to be available on national markets following CHMP EU approval (which, as stated, takes a median 418 days), this timeline is not always enforced. Therefore, delays in access to cancer drugs may also be introduced at this stage. It is also worth noting that, despite the CHMP granting one marketing authorisation for the entire EU, countries may still apply restrictions as part of their own price negotiations and reimbursement criteria thus establishing yet another level of inequity within Europe.

Health technology assessments and economic evaluations are sometimes referred to as the 'fourth hurdle' with regard to patient access to new cancer drug therapies. Health economics, and in particular economic evaluations, have emerged as a method to evaluate the trade-off between the cost and benefit of new drug therapies (commonly referred to as 'cost-effectiveness') by those making decisions on reimbursement and market access.

The review of health technology assessments in this report shows that during the 1990s there was an increase in the number of health technology assessment studies and economic evaluations related to cancer.

During the last year the number of published studies declined which may reflect a change in the number of studies undertaken and/or patterns of dissemination. Studies related to cancer account for 10-15% of all studies. While such information is increasingly published and discussed, its impact on decision-making and resource allocation in healthcare is less clear. . >>

1.3 Results *(continued)*

In some countries there are formal requirements for economic evaluations regarding reimbursement decisions while in other countries budget impact analysis and price comparisons play a larger role.

Nowhere in Europe is the decisive role played by economic evaluations more evident than in the UK, where the National Institute for Health and Clinical Excellence (NICE) issues guidance for England, and the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC) issue guidance for Wales and Scotland, respectively.

While a positive NICE review should lead to more rapid and wider access to new treatments, there is, in fact, an issue with NICE's capacity to cope with the growing workload of evaluations and undertake such reviews. The time for a product to be referred to NICE can be up to 18 months and this is prior to the beginning of any review. The actual timeline of a NICE review is 62 weeks while it is 3 months for the SMC.

In addition to the delay of these reviews, there is the impact of these delays. Budgetary resources are not allocated to new drugs during the time that the NICE review is delayed and, as a result, new drugs are not introduced into the healthcare system through hospitals and clinical practice. This leads to further delay for cancer patients in the UK getting access to new innovative drug therapies and this is clearly demonstrated by the comparison of the UK with other European countries studied in this report.

There are a number of questions regarding the use of economic evaluations by health authorities and decision makers. For example, should the threshold value for the cost-effectiveness of new innovative cancer drugs or drugs that are large biological proteins be the same as that used to evaluate traditional small molecules? Can a process be put in place that evaluates the total economic impact of a new drug therapy, as opposed to focusing only on the cost of the drug or defined healthcare budgets?

While there are a number of procedural barriers, perhaps no obstacle is more dominant on the uptake of new drugs than the structural hurdle of budgetary limitations. The ability of patients to access cancer drugs is highly dependent on the allocation of appropriate and adequate funding or financial resources within the healthcare systems to facilitate the availability of these drugs and the speed at which they may be accessed. This issue of funding for new cancer drugs has become critical as a result of the introduction of new and innovative cancer drugs such as targeted therapies.

Although cancer drugs account for less than 10% of the total healthcare expenditures for cancer and represent 3.5-7% of the total drug costs, they are an easily identified target. In efforts to manage healthcare or budgetary costs, healthcare policy and decision makers may therefore seek to delay or restrict access to these new innovative drugs. Such actions have very real impact on survival rates.

Stretched healthcare budgets trying to meet the growing needs and demands of the population, the introduction of new innovative cancer drugs and increasing costs for these drugs have implications for cancer patients in Europe. This fifth hurdle for patient access to cancer drug therapies is the issue of whether healthcare systems, hospitals and payers are allocating adequate funding and budgets in a timely and expeditious manner to accommodate these new advances.

1.3 Results *(continued)*

Therefore, this very significant and very current issue of adapting healthcare budgets in general, and hospital budgets in particular, to the introduction of new cancer drug therapies must be immediately addressed if the issue of inequitable patient access to cancer drugs is to be resolved.

This report's analysis indicates that there are opportunities for procedural and structural improvements with regard to access to cancer drug therapies to potentially address some of the current imbalance.

These include:

- *expediting the review time for the marketing authorisation of new innovative cancer drugs through the Centralized Procedure (Switzerland has been identified as a leader in terms of patient access to cancer drugs and, due to their status as a non-member of the EU, they follow their own national approval process)*

- *ensuring that once a cancer drug has obtained its EU marketing authorisation (median time 418 days) it is then available at the national level within 180 days, without further delays due to price and reimbursement negotiations and additional restrictions*

- *ensuring that any economic evaluation/health technology assessment regarding a new cancer drug is done expeditiously to facilitate, rather than delay, patient access (Austria, Spain and Switzerland have been identified as leaders in this report; three countries where there is no formal economic evaluation implemented)*

- *ensuring that appropriate and adequate funding for new innovative cancer drugs is included in healthcare system and hospital budgets, preferably on a proactive and not a retrospective basis.*

There are signs across Europe that countries are recognising the need and the challenge to provide patient access to new innovative cancer drugs. For example, in countries such as France and Denmark, national cancer plans are in place and acknowledging the contribution of cancer drugs. Also, in France and Germany there are separate lists of innovative drugs that may include special funding for the drugs to be accessed outside of the hospital systems. In France, this facilitates access to these drugs since the budget is more open and drugs on the list are fully reimbursed when prescribed according to the 'good use contract'. In Germany, hospitals may apply to get new cancer drugs placed on the list, thereby allowing them to switch to innovative drugs within the restrictions of their hospital budgets.

These are recognised as attempts to facilitate faster patient access to drug therapies and to address the inflexibility of most public budgets to accommodate new drug costs. The broader application of these approaches should be encouraged so as to expedite the uptake of new innovative cancer drug therapies across Europe and address inequalities of patient access. Industry and government/payers must collaborate on any new initiatives to ensure patients get the benefits of access to new innovative cancer drugs.

This report highlights the inequities in Europe regarding the ability of patients to access new innovative cancer drug treatments in Europe and the importance of equal and rapid access. It is hoped that this report inspires and results in action by policy and decision makers to address these inequities and imbalances..

2. CANCER AND THE SIZE OF THE PROBLEM IN EUROPE

Summary

- The incidence of cancer is increasing across Europe and the reasons for this are multifactorial.
- While there have been improvements, and some countries in Europe have seen a plateauing of mortality rates. However, cancer still currently accounts for approximately 1.7 million deaths annually in Europe.
- Cancer accounted for 16.7% of all 'healthy years' lost in 2002. However, the share of healthcare expeture allocated to cancer is significantly lower than the share of the burden of the disease.
- Cancer drugs represent 3.5-7% of total pharmaceutical sales and 9% of total healthcare expenditure for cancer.

2.1 Cancer incidence and mortality

In 2004, nearly 3 million Europeans living in the 25 EU member states were diagnosed with cancer. The most common malignancies were lung, colorectal and breast cancer, followed by prostate and stomach cancer. Mortality from cancer comes second only to cardiovascular diseases, and in 2004 approximately 1.7 million individuals died from the disease. The highest mortality from cancer was seen for lung, colorectal and stomach cancer.[1]

The European population has been stable for a number of years and is anticipated to remain so for the years to come. However, the ageing of the population means that overall cancer incidence will increase. The International Agency for Research on Cancer (IARC) provides the most current data on the incidence of, and mortality due to, cancer (with incidence data to 1997 and mortality data to 2002).[2] These data are expressed as an 'age-standardised rate'; this is a summary measure of a rate that a population would have if it had a standard age structure and, as age has such a powerful influence on the risk of cancer, is necessary when comparing several populations that differ with respect to age. The most frequently used standard incidence is called the world age-standardised rate, which is expressed per 100,000.

During the period 1963-1997, there was an approximately 50% increase in the overall incidence of all cancers (excluding non-melanoma skin cancer) in Europe, with little or no difference between the constituent countries (Figure 2.1). The increased incidence is not totally explained by an ageing population. Lifestyle factors, such as increasing prevalence of female smokers, change of sun-tanning habits and lower rates of reproduction, all contribute to an increase in the incidence of cancer.

CANCER AND THE SIZE OF THE PROBLEM IN EUROPE

Figure 2.1.

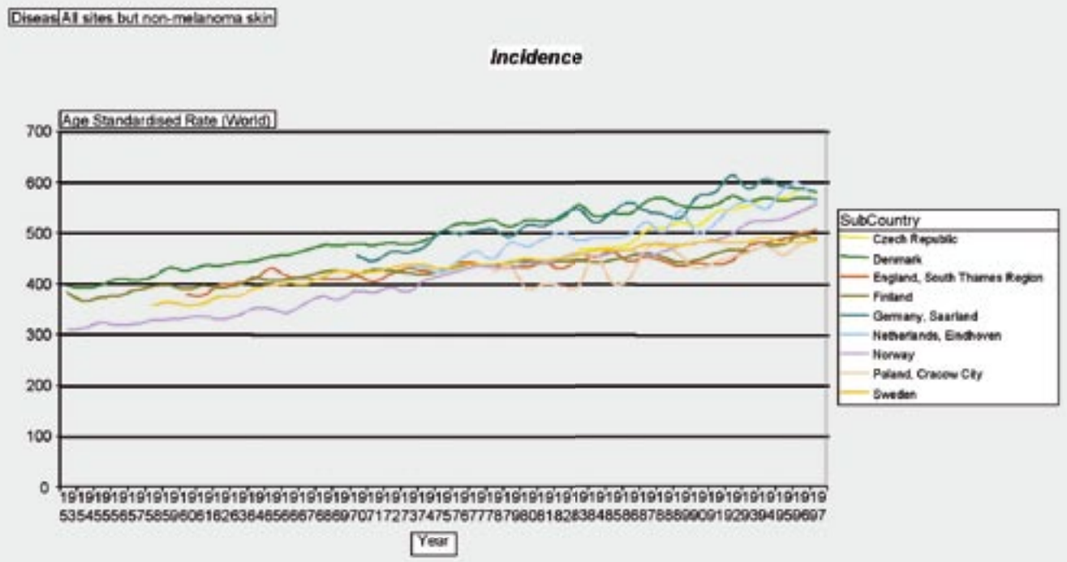


Figure 2.1. Cancer incidence expressed as the world age-standardised rate (per 100,000) in a selection of European countries (the Czech Republic, Denmark, Finland, Germany, the Netherlands, Norway, Poland, Sweden and the UK).[2]

The development of overall cancer mortality rates over time is complex and varied across Europe (Figures 2.2a-c). In some countries, such as the Nordic countries, Germany, the UK and France, mortality has decreased since the early 1990s. In other countries, such as Spain, Greece, Hungary and Poland, mortality rates have reached a plateau, but no decrease has been seen.

It is likely that a number of factors influence the difference in the registered mortality rates, particularly population-based cancer registration, mandatory reporting, the quality of cause-of-death registration, access to screening and healthcare, and differences in management between countries.

Figure 2.2a.

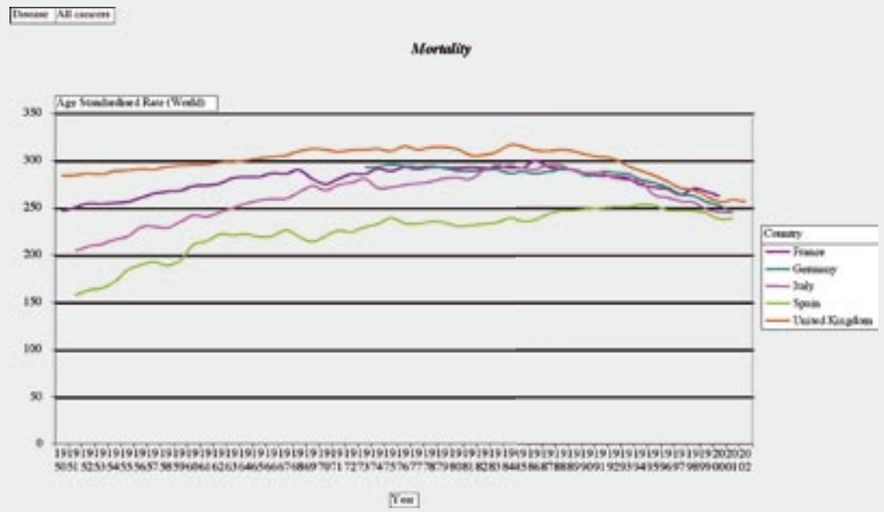


Figure 2.2a. Cancer mortality expressed as the world age-standardised rate (per 100,000) in France, Germany, Italy, Spain and the UK.[2]

Figure 2.2b.

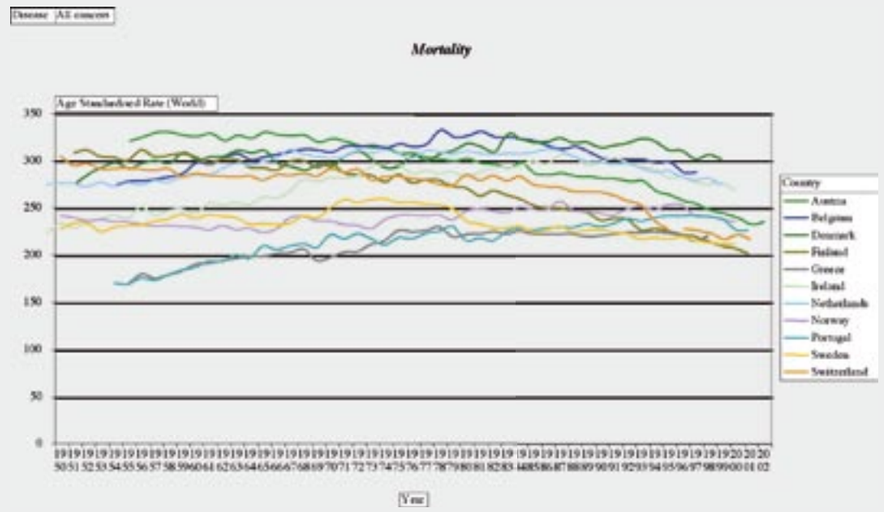


Figure 2.2b. Cancer mortality expressed as the world age-standardised rate (per 100,000) in Austria, Belgium, Denmark, Finland, Greece, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland.[2]

CANCER AND THE SIZE OF THE PROBLEM IN EUROPE

Figure 2.2c.

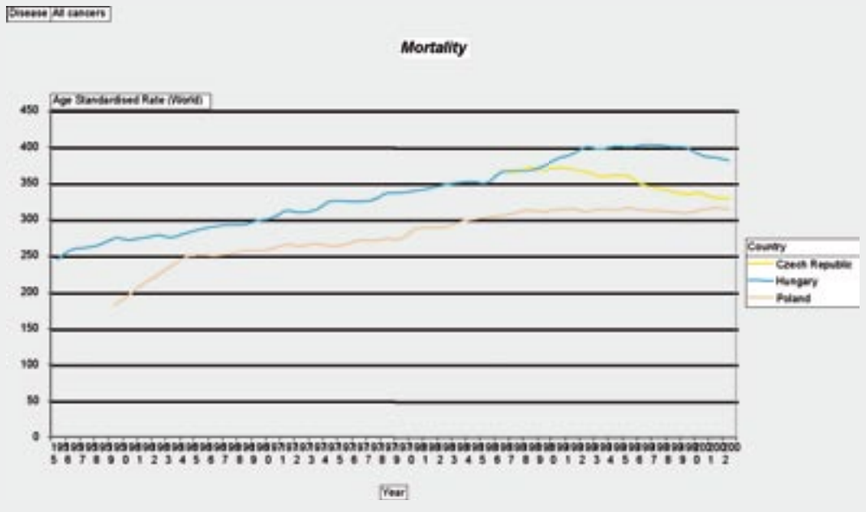


Figure 2.2c. Cancer mortality expressed as the world age-standardised rate (per 100,000) in the Czech Republic, Hungary and Poland.[2]

2.2 The burden of cancer

Measures of the burden of disease complement statistics about the incidence and prevalence of disease, and they are most often used for health policy purposes rather than for epidemiological analyses.

The most commonly used measure of the burden of cancer is 'Disability-Adjusted Life Years' (DALYs). This is an integrated measure of mortality and disability developed by the World Health Organization and the World Bank. One DALY can be thought of as one lost year of 'healthy' life and the burden of disease as a measurement of the gap between actual health status and an ideal situation where everyone lives into old age free of disease and disability.

As shown in Table 2.1, in 2002, cancer accounted for close to 10 million DALYs lost in the EU 25 (Austria, Belgium, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the UK). As a proportion of all DALYs lost in 2002 in the EU 25, cancer was third only to mental illnesses and cardiovascular disease in terms of overall disease burden, representing 16.7% of all DALYs lost.[3]

	EU 25			EU 15		
	Total DALYs	DALY /1000	%	Total DALYs	DALY /1000	%
All disease groups	58,807,846	129.7	100	47,092,868	124.2	100
Mental disease	14,857,720	32.8	25.3	12,379,282	32.7	26.3
Cardiovascular disease	10,088,093	22.2	17.1	7,637,493	20.1	16.2
Cancer	9,839,035	21.7	16.7	7,989,864	21.1	16.9
Injuries	5,099,011	11.2	8.7	3,644,620	9.6	7.7
Respiratory disease	3,523,243	7.8	5.9	3,167,675	8.4	6.7

Table 2.1. Top 5 disease groups in terms of burden of disease in the EU 25 and EU 15 in 2002.[3]

2.3 The costs of cancer

The costs to society of cancer can be divided into direct and indirect costs:
- *Direct costs are the resources used for prevention, treatment, etc.*
- *Indirect costs are resources lost due to an inability to work and are relevant for diseases that strike in the early years before normal retirement. Indirect costs include costs of lost production due to short-term absence from work, permanent disability and death before 65 years of age.*

There are few studies that measure and compare both direct and indirect costs of cancer. Available studies show that indirect costs account for 70-85% of the total costs.[4] The studies are, however, becoming rather old and the share of direct costs as a proportion of total costs could be expected to increase over time as more treatment options become available. Indirect costs are dominated by cost of mortality in persons of working age.[4] However, as the survival of cancer patients improves with earlier detection and improvements in cancer treatment, the share for indirect costs due to morbidity can be expected to increase and the share for mortality drop. This has been seen in the USA, where the share for the cost of mortality declined from 71% to 65% between 1975 and 1985.[4]

2.3.1 Direct costs of cancer

Statistics from the Organisation for Economic Co-operation and Development (OECD)[5] allow estimates of the total healthcare costs for cancer in Europe to be made (2.2). The proportion of healthcare cost associated with cancer has been estimated based on individual studies in different countries. The data for Germany and France indicate that 5.4%[6] and 5.3%[7] of total healthcare budgets, respectively, are spent on cancer. The information from these two countries is very close to the estimates from the USA, where the share for cancer costs has consistently been approximately 5% of total healthcare expenditure from 1963 to 1995.[8] A study from the Netherlands reports that cancer accounts for 4.1% of the total cost of healthcare that can be attributable to specific diseases.[9] Where no studies are available, it has been assumed that cancer accounts for 6.5% of total healthcare expenditure.

As shown in Table 2.2, total healthcare costs for cancer in the 19 European countries covered by OECD is estimated at €54 billion, or €120 per inhabitant. France, Germany, Italy, Spain and the UK combined account for three-quarters of the total spending.

	Direct costs for cancer (€ million)	Direct costs for cancer per capita (€)	Cancer costsas % of total healthcare costs	Total healthcare expenditure[5] (€ million)	Population[5] (2003)
Total	54,263	120	6.4	844,800	451,263,000
Austria	923	114	6.5	14,200	8,067,000
Belgium	1,469	142	6.5	22,600	10,372,000
Czech Republic	663	65	6.5	10,200	10,202,000
Denmark	748	139	6.5	11,500	5,387,000
Finland	587	113	6.9	8,500	5,213,000
France	7,091	119	5.3[7]	133,800	59,768,000
Germany	12,100	150	5.4[6]	224,000	82,502,000
Greece	1,112	101	6.5	17,100	11,036,000
Hungary	566	56	6.5	8,700	10,124,000
Ireland	468	118	6.5	7,200	3,953,000
Italy	6,578	114	6.5	101,200	57,478,000
The Netherlands	1,525	94	4.1[9]	37,200	16,224,000
Norway	871	191	6.5	13,400	4,564,000
Poland	1,300	34	6.5	20,000	38,195,000
Portugal	943	90	6.5	14,500	10,449,000
Spain	3,855	92	6.5	59,300	41,874,000
Sweden	1,253	140	7.0[4,10,11]	17,900	8,958,000
Switzerland	1,391	189	6.5	21,400	7,343,000
UK	10,823	182	10.6[8]	102,100	59,554,000

Table 2.2. Direct cost for cancer in study countries in 2002/2003. Total in million Euro, per capita Euro and share of total healthcare expenditures.

	Cancer costs as % of total healthcare costs	Inpatient care	Ambulatory care	Drugs	Total
Germany (2002)	5.4%	67% + 9% other	16%	8%	100%
Sweden (1996)	6%	94%	Not included in the estimate	6%	100%
Sweden (2002)	10%	75% (hospital)	15% (including home care)	10%	100%
France (1998)	5.3%	83%	7% + 6% transport costs	4%	100%
The Netherlands (1994)	4.6%	60% + 11% non-hospital institutional care	18%	11%	100%

Table 2.3. Cancer healthcare costs as a proportion of total costs and distribution of direct costs of cancer on inpatient care, ambulatory care and drugs.[6,7,10-13]

Table 2.3 shows the distribution of the costs of cancer across different types of services for a selection of EU countries, based on data from a variety of sources. These data show that inpatient hospital care dominates, accounting for approximately 70% of the total costs of cancer care. The proportion of total spend on ambulatory care costs was dependent on what was included in this category across the data sources (eg in France, transportation of patients is a major cost calculated separately). The proportion of the cancer healthcare costs attributed to drug costs was reported to be lowest in France (4%) and highest in the Netherlands (11%).

2.3.2 The costs of cancer drugs

The cost of cancer drugs can be considered (1) in absolute terms, (2) in relation to the total healthcare spending for cancer, and/or (3) in relation to the total drug spending. One of the challenges in estimating and reporting the cost of cancer drugs is that payment of drugs varies. For example, in some cases cancer drugs are used in hospital inpatients and therefore paid for through the financing of inpatient care per diem (based on day of hospital stay), through a global hospital budget or through a Diagnosis Related Groups (DRG) system. In the last case, budget is allocated for hospitalisation costs based on a classification of patients in different disease categories. In other cases, drugs are used in hospital outpatient departments and reimbursed separately.

Additionally, cancer drugs such as anti-emetics drugs (used to combat the nausea and sickness that can be brought on by cancer treatment) are prescribed by the physicians, delivered through the pharmacy and paid for through the national reimbursement system for prescription drugs.

Table 2.4 indicates the costs for cancer drugs in different EU countries in 2002/2003. It is important to acknowledge, however, that reliable data are difficult to obtain. Thus the numbers presented are estimates based on assumptions regarding the share of drug costs spent on cancer drugs in those countries where good data exist. There is a need for more work in this area to arrive at more precise figures.

We have estimated that cancer drugs account for 3.5% of the costs of all drugs, in line with how drug costs are usually reported in the OECD health statistics. This estimate is consistent with the estimate of the cost of cancer drugs from our extracted sample shown in Table 2.4. Other estimates may give a higher percentage (up to 7%) but there are a number of the explanations why different estimates for the cost of cancer drugs can be found from different sources. Higher estimates may be due to (1) the definition of 'oncology drugs', (2) inclusion of sales of some 'oncology drugs' for other indications (such as rheumatoid arthritis and hepatitis), and (3) the price level in which drug costs are reported (including or excluding distribution costs for wholesales and pharmacies). It may also depend on which definition of drug costs that is used (hospital/prescription/over the counter) and if taxes are included or not.

Total drug cost is estimated at €11 per inhabitant, which amounts to 9% of total healthcare expenditure for cancer, given that the total healthcare cost for cancer is estimated at €120 per inhabitant. The total cost of cancer drugs would be calculated at approximately €5.1 billion. However, comparing this estimate with total sales of cancer drugs (see figure 4.1), which were approximately €4.5 billion in 2002 (ex-factory prices), indicates it is probably rather accurate.

	Total drug expenditure per capita (€ [purchasing power parity])	Costs for cancer drugs (€ million)	Costs for cancer drugs (€ per capita)	Costs for cancer drugs (% of total drug costs)
Total	329	5,050	11	3.4
Austria	283	80	10	3.5
Belgium*	371	135	13	3.5
Czech Republic	219	78	8	3.5
Denmark	210	40	7	3.5
Finland	261	48	9	3.5
France	467	978	16	3.5
Germany	390	988	12	3.1
Greece	248	96	9	3.5
Hungary	238	84	8	3.5
Ireland	201	28	7	3.5
Italy	384	773	13	3.5
The Netherlands	262	149	9	3.5
Norway	263	42	9	3.5
Poland*	146	195	5	3.5
Portugal*	333	122	12	3.5
Spain	309	453	11	3.5
Sweden	351	110	12	3.5
Switzerland	307	79	11	3.5
UK*	275	574	10	3.5

Table 2.4. Costs for cancer drugs in different countries in 2002/2003.[6] *Drug expenditure for Belgium, Portugal and the UK are calculated based on the fraction of drug and total expenditure on health in the period 1995-1999. Poland is assumed to have the same fraction as Hungary in 2002.

These estimates indicate that, in Germany, cancer drugs accounted for 8.1% of the total expenditure on cancer in 2002. In Sweden in 2004, approximately SEK 1000 million (€110 million) was spent on all cancer drugs; thus, cancer drugs accounted for 10% of total cancer costs, and approximately 3.5% of the total drug costs in Sweden (SEK 28.6 billion in 2004, €3.13 billion).

2.3.3 Indirect costs of cancer

Data from Germany[5] show that, in 2002, 431,000 working life-years were lost due to cancer in the working population, representing 8% of the all life-years lost in the general German population (Table 2.5). There are great differences in the distribution of the indirect costs between different types of cancer, with breast and lung cancer being the most important in terms of working years lost. >>>

Type of cancer	Lost working years (000)			Total years lost (000)		
	Total	Men	Women	Total	Men	Women
All cancers	431	238	193	3,099	1,564	1,535
Stomach cancer	19	12	7	155	87	69
Colorectal cancer	20	13	8	221	110	111
Lung cancer	59	43	15	557	390	167
Melanoma etc	10	5	4	47	24	23
Breast cancer	65	0	65	389	3	386
Cervix cancer	6	0	6	32	0	32
Prostate cancer	8	8	0	100	100	0
Leukaemia	22	14	8	108	57	51

Table 2.5. Life-years lost due to cancer for different types of cancer in Germany 2002.[5]

Multiplying the gross average 2002 German wage of €34,000 (including social insurance contributions) by the number of the working years lost, the total amount lost is €14.7 billion. However, costs due to morbidity should be added to this total to gain a better understanding of the indirect costs of cancer.

Similar data from other European countries are not available. However, it is important to ensure the indirect costs are not forgotten when considering the overall picture of the costs of cancer to society. Despite the fact that most cancers occur in older persons, indirect costs of cancer are still 2-3 times greater than the direct costs and constitute a major part of total costs for all diseases.

2.4 Conclusions

This section of the report highlights the importance of cancer as a common and major healthcare issue in terms of mortality, morbidity, and indirect and direct costs, yet the share of healthcare expenditure allocated to cancer (5-7%) is significantly lower than the share of the burden of the disease (accounting for 17% of all DALYs). Healthcare costs for cancer are dominated by costs for inpatient care, with drug costs accounting for less than 10% of total healthcare expenditure for cancer.

Of concern is that the introduction of new innovative cancer drugs will result in an increase in the costs of cancer drugs, both in absolute terms and as a share of total healthcare costs. ■

References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005; 16: 481-488.
2. CANCERMondial. International Agency for Research on Cancer. 2005. Available at: http://www-dep.iarc.fr/.
3. World Health Organization. Priority medicines for Europe and the world. WHO/EDM/PAR/2004.7. 2004. Available at: http://whqlibdoc.who.int/hq/2004/WHO_EDM_PAR_2004.7.pdf.
4. Jönsson B, Karlsson G. Economic evaluation of cancer treatments. In Domellöf L (ed). Drug Delivery in Cancer Treatment III. Springer-Verlag, Berlin-Heidelberg; 1990: pp.63-84.
5. Organisation for Economic Co-operation and Development. OECD Health Data 2005: statistics and indicators for 30 countries. 2005. Available at: http://www.oecd.org/document/30,02340,en_2469_201185_12968734_1_1_1_1,00.html.
6. Gesundheit – Krankenheitskosten 2002, Statistisches Bundesamt, Wiesbaden 2004..
7. Santé-Solidarités. Publications de la DREES. 2002. Available at: http://www.sante.gouv.fr/htm/publication/.
8. Bosanquet N, Sikora K. The economics of cancer care in the UK. Lancet Oncol 2004; 5: 568-574.
9. National Institute for Public Health and the Environment. RIVM. Cost of illness in the Netherlands. 2004. Available at: http://www.rivm.nl/kostenvanziekten/site_en/index.htm.
10. Ragnarson Tennvall G, Karlsson G. Cancer treatment in Sweden--costs of drugs, inpatient and outpatient care from 1985 to 1996 and cost effectiveness of new drugs. Acta Oncol 1998; 37: 447-453.
11. Center for Medical Technology Assessment. Cost of illness in the county of Östergötland in 2002. CMT report.
12. Koopmanschap MA, van Roijen L, Bonneux L, Barendregt JJ. Current and future costs of cancer. Eur J Cancer 1994; 30A: 60-65.
13. Swedish Council on Technology Assessment in Health Care. SBU Yellow Report. Chemotherapy for cancer. Report no. 155/2. 2001. Available at: http://www.sbu.se/www/index.asp.

3. ADVANCES IN CANCER MANAGEMENT

Summary

- Cancer treatment today is characterised by multimodal treatment using surgery, radiotherapy and a rapidly increasing number of available antitumour agents. This approach requires the cooperative efforts of multidisciplinary teams including surgeons, radiotherapists, medical oncologists, diagnostic radiologists, pathologists, specialised nurses and psychosocial support.
- Antitumour agents are used in conjunction with surgery and/or radiotherapy in an increasing number of situations, improving cure rates significantly.
- Antitumour agents are used in metastatic disease in an expanding number of tumour types, increasing life expectancy significantly.
- Traditional antitumour agents have been generally cell toxic with often severe side effects. Progress in molecular medicine have enabled the development of new agents with milder side effects that target disease specific mechanisms.
- Most antitumour agents are introduced in patients with late stage (metastatic) disease. In many cases, efficacy in metastatic disease translates to increased cure rates when the agent is introduced in earlier stages of the disease in conjunction with surgery.
- Improved diagnostic methods and screening programmes have assisted in the early detection of tumours, improving cure rates and prognosis.
- Increased survival in almost all tumour forms has led to the development and introduction an increasing number of compounds to improve the quality of life for patients – supportive drugs. The decreased toxicity of new agents, a trend towards oral agents and the use of supportive drugs have enabled patients to spend fewer days in hospital and led to an increased number of day-care treatments.
- It is already possible to predict if a tumour is likely to respond to treatments in some instances. Gene/protein expression analyses of tumours are likely to improve accuracy in the treatment offered to individual patients and improved imaging techniques may enable visualisation of tumour response at an early stage of treatment.
- More detailed information on the tumour types considered in this report (breast and colorectal cancer, non small-cell lung cancer, non-Hodgkin's lymphoma and bone metastases) can be found in Appendix A.

Historically, surgery was the only available treatment against cancer but it wasn't until the introduction of general anaesthesia and antiseptic procedures that surgical oncology developed in a way that enabled significantly advances (for instance, extensive breast and colorectal surgery). Radiation was discovered at the end of the 19th century and used to successfully treat the first tumours only a few years later. During the 20th century considerable progress has been made in radiotherapy, resulting in improved local control and fewer side effects.

Agents that inhibit cancer growth (chemotherapy) were first discovered in the 1940s. These agents were generally cell toxic with severe side effects. Further classes of cell toxic agents were discovered during the 1950-70s. Gradually, chemotherapy has been introduced in various tumour forms, as palliative treatment to relieve symptoms and increase the quality of life in late stages of the disease, or in conjunction with surgery and/or radiotherapy, in order to increase cure rates.

In general, there has been a trend towards using combinations of chemotherapy agents with different mechanisms of action in order to achieve maximal effect. Major obstacles for maximal efficacy using conventional chemotherapeutic agents have been severe side effects and the development of drug resistance in tumours.

This section reviews some of the most significant advances seen in the management of cancer patients from improvements in diagnostics to advances in treatment and towards cure.

3.1 Advances in the diagnosis of cancer

Diagnostic radiology and pathology help to determine whether a tumour has spread locally or to distant organs and provide detailed information about the tumour cells. This is essential in order to optimise the patient's treatment. Improvements in diagnostic and screening methods also contribute to early diagnosis, when the prognosis is improved and chance for cure is increased.

3.1.1 Radiology

Radiology plays a key role in oncology, not only as a diagnostic tool, but also as a method of evaluating the efficacy of treatment by measuring progression or regression of tumours and metastatic lesions. The introduction of new radiological methods in the 1980s and 1990s such as computed tomography (CT) and magnetic resonance imaging (MRI) have greatly improved the diagnostic accuracy and evaluations relating to the effects of treatment. Other methods such as ultrasound and bone scintigraphy also play an important role as diagnostic tools and can help in directing local therapy such as radiotherapy. Currently, a new radiological method, positron emission tomography (PET) (alone and in combination with CT) is being introduced in clinical practice. PET has the advantage of being more sensitive than earlier alternatives in differentiating between viable and non-viable tumour tissue.

3.1.2 Pathology

Traditional pathology examines tissue and tumour samples on a macroscopic and microscopic basis. Using characteristics such as cell structure, appearance, differentiation and growth patterns it has been possible to classify tumours and make fairly accurate predictions relating to the aggressiveness of the tumour and the potential for the tumour to spread. The last twenty years have seen the birth of new powerful techniques using gene and protein analysis offering the potential to change the classification of tumours. These techniques are gradually becoming more important diagnostic and prognostic tools.

3.1.2.1 Gene analyses

Different sets of genes are expressed in different cell populations and at different stages of life. It is estimated that, of the 30,000 genes in our genome, only one-tenth are expressed in each cell. >>>

Cancer tumour cells are characterised by genetic instability and altered gene expression. By analysing the gene expression of a wide range of tumours, it has been possible to identify genes that are responsible for tumour-specific characteristics. In some cases it is also possible to predict if an individual tumour will respond to certain treatments.1 Pharmacogenomics (the study of the way genes determine how the body responds to a drug both positively [efficacy] and negatively [side effects]) has become an important field in cancer research and drug development. Soon, pharmacogenomics, together with analyses performed on sampled tumour material to determine the potential for a response to treatment (chemosensitivity tests), will be available on a larger scale in the clinical setting and promise a much more individualised approach to treatment, with better chances for improved outcomes.

3.1.2.2 Protein analysis

The uncovering of the entire human genome less than 50 years after the description of the DNA helix has been an immense achievement. Less than 2% of human diseases are caused by one gene (monogenic). However, the rest are caused by multiple genes in combination or by changes in the proteins they encode.
The deciphering of the entire human proteome (the complete set of proteins that can be expressed by genetic material) is underway and will undoubtedly shed new light on disease mechanisms and possible points of intervention. Already, the individual protein patterns of different types of tumours are being mapped and it has been demonstrated that patients with a specific type of cancer have certain protein patterns in the blood. Such methods have the potential to be used in the future for diagnostic purposes.[2]

3.2 Advances in cancer surgery

Cancer surgery has made important progress during the last 20 years with the introduction of less invasive surgical techniques such as laparoscopy in colorectal cancer3 and robot-assisted surgery in prostate cancer.4 Improved surgical techniques such as total mesorectal excision in rectal cancer have also resulted in a reduced risk of local recurrence of the disease (5-10% vs 20-30% for earlier techniques).[5]
Progress has also been made in determining the requirement for extensive lymph gland resection during surgery using the sentinel node technique. The sentinel node is the closest lymph node to the tumour and is the node through which any cancer cells would first pass during metastasis to other areas of the body. It is identified by injecting a marker into the tumour area and then, through the removal and pathological examination of the node during surgery, it is possible to determine if the lymph gland is also affected by cancer. If the sentinel node is not affected there is not further need for lymph gland resection.

3.3 Advances in radiotherapy

Radiotherapy plays an important role in local control of tumour growth, both in curative situations and in the palliative setting (when there is metastatic disease). During the latter half of the 20th century, the administration of radiation was refined, with more specific targeting of tumour tissue (3D conformal radiotherapy), the application of higher energy levels and improved dose-planning leading to fewer side effects to the surrounding normal tissue and better antitumour effects within the malignant tissue.

Other advances such as brachytherapy, a technique based on the insertion of a radioactive source ('needles' or 'seeds') in or very close to the tumour, has enabled treatment of certain cancers, such as localised prostate cancer, without surgery.[6]
Stereotactic radiation therapy, where radiation is given from a large number of directions resulting in high doses where the radiation fields converge on the tumour tissue but comparatively low doses reach surrounding tissue, have enabled treatment of inoperable tumours, for instance, in the brain.[7]
Radionuclides such as strontium, samarium and radium have gained ground in the treatment of bone metastases and radionuclides have recently been combined with antibodies against tumour markers, allowing direct targeting of the radioactive particles to the cancerous cells.[8] In addition, the value of new types of radiation sources, such as protons and light ions, is being evaluated and new data indicate advantages to using these new modalities.

3.4 Advances in the medical treatment of cancer

3.4.1 Targeting different aspects of cancer evolution

Progress in molecular medicine has led to increased understanding of how cancer evolves and how cancer cells are characterised by defects in their DNA repair mechanisms, leading to an increased accumulation of genetic defects and fuelling tumour development. Some individuals are genetically predisposed to developing cancer due to the existence of altered genes that normally act as gatekeepers against cancer (tumour suppressor genes). The development of invasive cancer (Figure 3.1) is a process with many steps and an accumulation of genetic changes thought to occur over a prolonged time period (as much as 5-20 years).[9]

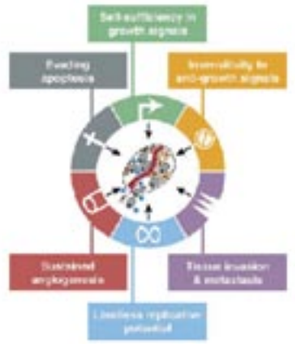


Figure 3.1. Processes in the development of invasive cancer. Adapted from Hanahan & Weinberger 2000.[9]

In the 21st century, medical oncology has entered a new phase in which increased knowledge of cancer biology has led to a move away from highly cell-toxic treatments towards more disease-specific agents targeting particular weaknesses in tumour development and progression. >>>

The main areas where new agents have been developed and now are used in clinical practice:

- *Targeting of the cell cycle and apoptosis (also known as 'programmed cell death' since normal cells are programmed to die at a determined point in time and in response to certain stimuli), DNA replication/transcription and repair*
- *Inhibition of hormones, growth factors and cell signalling pathways*
- *Inhibition of the formation of new blood vessels (angiogenesis).*

3.4.1.1 Targeting the cell cycle & DNA translation/replicatio & repair

One of the characteristics of cancer is uncontrolled growth and proliferation of cancer cells. In healthy cells, cell growth is normally a highly controlled process whereby the cell goes through different phases, leading to duplication of genetic material and cell division. These stages involve several regulatory pathways, and there are a number of critical checkpoints at which normal cells trigger programmed cell death (apoptosis) if signs indicate that something has gone wrong. In contrast, cancerous tumour cells often have defects in these checkpoint mechanisms, enabling unhindered cell growth. Several potential ways of interfering with the cell cycle and cell division in tumour cells have been identified, and most conventional chemotherapeutic agents act via mechanisms interfering with cancerous cell growth.

3.4.1.1.1 Microtubules

Microtubules play an important role, enabling cell division and proliferation as well as a range of other cell activities including chemotaxis (the phenomenon in which cells direct their movements according to certain chemicals in their environment), intracellular transport, cell secretion, anchorage of organelles and receptors, cell adhesion and locomotion. Microtubules are continually broken down and reconstructed according to the shifting needs of the cell; blocking the dynamic instability of microtubules blocks the ability of the cell to divide.

Two types of agents derived from plant toxins are vinca alkaloids (including vinblastine, vincristine, and vinorelbine) and taxanes (including paclitaxel and docetaxel): vinca alkaloids bind to the end of growing microtubules, allowing them to breakdown but preventing them from reconstructing; taxanes stabilise microtubules, blocking the disassembly process. Since their introduction in the 1990s, these agents have had an important impact on the treatment of cancer, with impressive responses in a wide variety of tumour forms. There are several new agents in clinical trials with similar antitumour mechanisms, for instance a group of compounds called epothilones.[10]

3.4.1.1.2 DNA replication

Doubling of DNA, transcription (the process that occurs when gene sequences on chromosomes are converted from DNA to messenger RNA in the nucleus) and cell division require constant packing and unpacking of these structures. This is achieved through enzymes known as topoisomerases, which help in untangling large strands of intertwined DNA. Inhibiting topoisomerase activity results in the inhibition of cell growth. It has been demonstrated that most classical chemotherapeutic agents (platinum compounds [eg cisplatin], alkylating agents [eg cyclophosphamide] and bleomycin) act by inhibiting DNA replication in some way.

In 1984, it was shown that anthracyclines, one of the most efficient class of compounds in conventional chemotherapy at that time (including agents such as daunorubicin, doxorubicin, epirubicin and idarubicin), worked by affecting topoisomerase activity.[11] In the 1990s, the topoisomerase inhibitors irinotecan and topotecan were introduced. Although these agents have demonstrated antitumour effects in many cancers, the side effects are often quite severe. Several new agents inhibiting topoisomerase are undergoing clinical trials.

3.4.1.1.3 Antimetabolites

Antimetabolites are a group of compounds similar to normal substances within the cell. When the cells incorporate these substances into the cellular metabolism they become unable to divide. Methotrexate and 5-fluorouracil (5-FU), which are frequently used classical chemotherapeutic agents, are examples of antimetabolites. Newer antimetabolites include gemcitabine, one of few agents to show efficacy in pancreatic cancer,[12] and pemetrexed,[13] which has demonstrated efficacy in lung cancer. The development of capecitabine, a drug similar to 5-FU but in an oral form as opposed to iv formulation, has been an important step forward reducing the number of necessary hospital visits, giving patients increased convenience and quality of life, and resulting in improved cost-effectiveness.

3.4.1.2 Targeting hormones, growth factors & cell signalling pathways

Cells are not static, independent units but are interacting components that must be able to respond to a wealth of stimuli, ranging from nerve signals and hormones to signals of local tissue damage. The intracellular communication systems (known as signal transduction pathways) have evolved to respond to proteins, amino acids, lipids, gases and even light. Most signals from outside the cell, such as factors that regulate cell growth, bind to receptors on the cell surface. In other cases, the molecules diffuse into the cell and bind to receptors within it. Binding to the receptors activates various enzyme systems, ultimately resulting in changes in cellular behaviour or growth. Some signalling pathways that are critical and deregulate in cancer have been investigated as therapeutic targets.

3.4.1.2.1 Endocrine therapy

Some organs and tissues (eg prostate, breast and endometrium) are particularly sensitive to hormones, which play a critical role in regulating the activity and proliferation of cells in the body. Cancers arising in these tissues are, in many cases, caused by prolonged exposure to hormones, resulting in increased proliferation and thereby an increased risk of DNA copy errors. The same hormones that cause cancers in these organs/tissues also often stimulate further growth of the cancer. Interfering with the production of hormones or blocking their action through drug therapies have become cornerstones in the treatment of breast and prostate cancer. In many ways, the introduction of these endocrine agents represents the first steps from highly toxic agents to treatments focused on well-defined molecular targets.

The importance of hormones in breast cancer has been known since the late 19th century, when it was noted that the removal of the ovaries in patients with inoperable breast cancer had a striking effect on the breast cancer.14 Tamoxifen, which acts by blocking oestrogen stimulation, was the first hormonal agent to be used widely in breast cancer. Since its introduction in the 1970s, tamoxifen has proved valuable in the treatment of metastatic breast cancer as an adjuvant treatment after surgery, decreasing the risk of relapse. The efficacy and relatively low toxicity of tamoxifen has led to the development of a large number of similar drugs, and increased knowledge of hormone synthesis and metabolism has led to the development of several new classes of hormonal agents.

>>>

ADVANCES IN CANCER MANAGEMENT

In breast cancer, a number of agents such as aromatase inhibitors (drugs that block the production of oestrogen; eg anastrozole, letrozole and exemestane) and agents with similar mechanisms of action (eg fulvestrant, megestrol and others) have shown efficacy and constitute valuable therapeutic options in metastatic breast cancer. Aromatase inhibitors are also gaining acceptance as adjuvant treatment in postmenopausal women. In prostate cancer, anti-androgens (eg flutamide, bicalutamide and nilutamide) have been developed as an alternative to testicular ablation (removal of the testes). Additionally, gonodotrophin releasing hormone analogues (eg goserelin, leuprolide), which block the production of testosterone, have been developed to achieve chemical castration.

Recent research has focused on the potential for hormonal agents to prevent cancer (section 3.7). In breast cancer, tamoxifen has been identified as a potential preventative agents and in the USA, the Food and Drug Administration (FDA) has approved its use in prevention of breast cancer in high-risk patients. However, no such licence exists in the Europe. Ongoing studies are evaluating the potential of aromatase inhibitors and raloxifene, an agent similar to tamoxifen, as preventive agents for breast cancer. In prostate cancer, finasteride, which affects the conversion of testosterone to dihydrotestosterone (the biologically active form of testosterone), has been studied and has shown potential as a preventive agent against prostate cancer.[15]

3.4.1.2.2 Inhibiting growth factors and signal transduction systems

Growth factors play an important role in stimulating cell growth during development and in cell populations where constant proliferation and tissue renewal is required (eg the skin, bone marrow and intestines). Growth factors stimulate cell growth by binding to cell surface receptors and starting a cascade of activity of specific enzymes in the cell. Signal transduction is simply an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter, growth factor)m mediated via the coupling of a receptor/enzyme to a second messenger system or an ion channel. Many cancers have mutations that lead to defective growth signal transduction, resulting in abnormal growth as well as invasion of normal tissue.

There are several potential targets for drug treatment. Primarily, monoclonal antibodies can block growth factors and/or their receptors. Small molecular drugs that enter the cell can block tyrosine kinases, activating enzymes through which most growth factors exert their effects. Most research efforts have focused on families of growth factors overexpressed in various tumour types, such as the epidermal growth factor receptor (EGFR; also known as HER1/erbB), vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor and insulin-like growth factor (IGF-1) receptor.

Cetuximab is a monoclonal antibody developed against EGFR that has shown positive results in metastatic colorectal cancer in slowing time to disease progression.[16] In combination with radiotherapy, cetuximab also increased overall survival from 28 to 54 months in patients with advanced head and neck tumours.[17] However, these clinical trials results are difficult to translate into the clinical setting, since most patients with head and neck cancer receive combinations of chemotherapy and radiotherapy. Tyrosine kinase inhibitors against the EGFR pathway have also been introduced. Erlotinib[18] has demonstrated efficacy and positive survival data as monotherapy in non-small-cell lung cancer, and gefitinib[19] has demonstrated efficacy in a subset of patients with the same disease. Several clinical trials are ongoing in other tumour types.

Increased secretion of VEGF by tumour cells (and the resultant activation of the VEGF receptor pathway) produces an increase in the formation of blood vessels.

Both monoclonal antibodies against VEGF and tyrosine kinase inhibitors targeting the VEGF receptor pathway have been developed. Further details of these agents are included in the next section (3.5.3; Inhibiting angiogenesis).

There is another growth factor that is particularly important in breast cancer. Approximately 20-30% of all breast cancer tumours overexpress the HER2 receptor, and treatment against the receptor with the monoclonal antibody trastuzumab has led to markedly prolonged survival in metastatic disease.[20] Patients HER2 status is determined through a diagnostic test thereby making testing of patients an important step in determining eligibility for trastuzumab treatment. Recently, adjuvant treatment with trastuzumab has been reported to result in an approximately 50% reduction in recurrence of the disease after a median follow-up of 1-2.4 years' treatment in patients with HER2-positive disease.[21]

These agents that inhibit growth factors and their signal transduction systems represent a new class of antitumour agents and their place in the clinical setting continues to evolve. In some cases (eg tumour types such as gastrointestinal stromal tumours, for which there are no active chemotherapy alternatives) they are first-line options. In other tumour forms it remains to be seen if these agents will replace conventional chemotherapy as first-line treatment. Present data seem to support the concept of combining these agents with radiotherapy and chemotherapy and combining agents inhibiting different pathways (eg bevacizumab [targeting VEGF] in combination with erlotinib [targeting EGFR] in both renal and non-small-cell lung cancer).[22,23] The additive value of combining drug therapies that target the same pathway or sequential use of these drug therapies does, however, need to be determined.

Another key issue with these agents, as with conventional chemotherapy, is the ability to predict responders. The clinical trials and initial introduction of gefitinib (outside the EU) may serve to illustrate the complexity of clinical trials in different patient populations, the value of post-marketing surveillance and the potential of today's biological research. The first studies of gefitinib indicated high response rates in the Japanese population that subsequently were not consistently seen in other patient populations. Further analysis indicated that certain subgroups (non-smokers, women and patients whose tumours had particular histological characteristics) were more likely to respond to treatment.[24] Genetic analysis has also led to the identification of mutations in the EGFR that correlate to response to gefitinib.[25]

3.4.1.3 Inhibiting angiogenesis

The development of new blood vessels (angiogenesis) is an important function in daily life, especially during pregnancy, normal growth, inflammation and wound healing. The regulation of angiogenesis is complex, with many stimulating and blocking factors that, under normal conditions, strike a fine balance.

It has long been recognised that some tumours are highly vascularised. However, it was not until the 1970s that Judah Folkman hypothesised that tumours need angiogenesis for their continued growth.[26] We now know that tumours will not grow beyond 1-2 mm3 if they are unable to develop blood vessels of their own. In addition, autopsies have shown that patients who die from cancer may also have small early-stage cancers (such as of the thyroid gland, breast and prostate) that were never detected.[27] The point at which the tumour starts producing pro-angiogenic factors is one of the most important steps in transforming these 'dormant' tumours into rapidly growing tumours with metastatic potential.[28]

>>>

Several growth factors are involved in angiogenesis, of which VEGF has been identified as the most important in many tumours. Both monoclonal antibodies against VEGF and tyrosine kinase inhibitors targeting the VEGF receptor pathway have been developed.

Bevacizumab, a monoclonal antibody against VEGF, has demonstrated increased survival in patients with metastatic colon, breast and lung cancer.[29-31] In renal cancer that does not respond to conventional chemotherapy, bevacizumab has extended the period of time over which the cancer is stable.[32] Bevacizumab represents an important breakthrough in cancer therapy because it is the first agent in this new class of drugs that show impressive response and efficacy over a range of tumours. Several studies are ongoing to investigate the effects of bevacizumab on other tumour forms, in earlier stages of disease, and both as monotherapy and in combination with other agents.

Several agents inhibiting tyrosine kinase inhibitors targeting the VEGF receptor pathway have been developed, many of which are in late-phase clinical trials. SU 11248, AG013736 and sorafenib are examples of agents that have demonstrated efficacy in a variety of tumour forms, such as renal cancer.[33,34] It has also recently been shown that continuous low-dose chemotherapy (rather than the conventional high-dose intermittent dosing) has an effect on tumour angiogenesis, thereby inhibiting tumour growth.[35]
As with other new classes of agents, the final place for anti-angiogenesis treatment in the management of cancer remains to be seen. The ability to predict which patients will benefit from this type of treatment is an interesting question. Initial studies using anti-angiogenesis treatment combined with conventional chemotherapy have led to varied results, but mostly indicate the additive value of such a combination. Trials are also ongoing to determine the role of angiogenesis inhibition in disease prevention and in early disease stages.

3.4.2 Biological therapies as a new approach

The body has many defence mechanisms against intrusion/infection. One cornerstone in this defence system is antibodies, large molecules with the ability to bind to foreign proteins. As early as the beginning of the 20th century, scientists suggested the potential for using the body's own defence systems treating cancer. In the 1950s, the regression of tumours was described after treatment with animal serum immunised with tumour cell extracts, which contained a large number of antibodies; however, the majority of the antibodies were not directed against tumour antigens and the results could not be reliably reproduced.
In the 1970s, the hybridoma technique[36] enabled mass production of antibodies with the same binding sites, known as monoclonal antibodies. The first clinical trials were conducted using murine antibodies (from mice) targeting tumour cell surface structures (antigens). Unfortunately, the results did not meet expectations, largely because of inefficiency of the antibodies and the development of human antibodies against murine antibodies, leading to increased elimination. The development of antibodies where the majority of the molecule is of human origin and only the binding fraction is murine (humanised antibody) has overcome these problems. The high specificity and, in general, low toxicity of antibodies makes them attractive therapeutic options, with a number on the market (Table 3.1) and more than a dozen in late-phase clinical trials.

Generic name	Tradename	Indication	FDA approved	EMEA approved	Year of first approval
Rituximab	Mabthera	Non-Hodgkin's lymphoma	ü	ü	1997
Trastuzumab	Herceptin	Breast cancer	ü	ü	1998
Gemtuzumab	Mylotarg	Acute myeloid leukaemia	ü		2000
Alemtuzumab	Campath / MabCampath	Chronic lymphocytic leukaemia	ü	ü	2001
Ibritumomab tiuxetan	Zevalin	Non-Hodgkin's lymphoma	ü	ü	2002
Tositumomab	Bexxar	Non-Hodgkin's lymphoma	ü		2003
Bevacizumab	Avastin	Colorectal cancer	ü	ü	2004
Cetuximab	Erbitux	Colorectal cancer	ü	ü	2004

Table 3.1. Monoclonal antibodies approved for use in oncology.

In the 1990s, the first monoclonal antibody (rituximab) was introduced in oncology-haematology and approved for the treatment of non-Hodgkin's lymphoma, fuelling renewed belief in antibodies as a treatment option in oncology. It was not long before the first antibody for solid tumours, trastuzumab, was approved. Trastuzumab is an antibody against the HER2 receptor, which is overexpressed in cancer cells in 15-25% of patients with breast cancer, and has demonstrated impressive results in metastatic breast cancer and as adjuvant treatment in non-metastatic disease.[20,21]
One of the challenges in developing efficient antibody therapies is finding parts of the tumour cell that can be targeted that differ from normal cells. Targets other than tumour cell surface structures have, however, proven successful. Bevacizumab is an antibody against a growth factor important for blood vessel development in tumours (essential for tumour growth) and has demonstrated efficacy in several solid tumour forms (colon, breast, lung and renal cancer).[29-32] The binding of radionuclides, immunotoxins or chemotherapeutic agents to the antibody may also enhance the effect of antibodies. Ibritumomab tiuxetan, an antibody targeting CD20 with an attached radionuclide is one example.
The large size of antibodies is, however, regarded as suboptimal, since it affects drug penetration in poorly vascularised tissues and tumours. It remains to be determined whether it will be possible to design smaller molecular drugs with the same binding sites and maintained efficacy.

3.5 Advances in supportive drug treatment

As survival rates of cancer patients have increased, the development of new classes of 'supportive drugs' has been essential in increasing quality of life for patients suffering from adverse symptoms of cancer or its treatment.
Patients with metastatic disease and those treated with chemotherapy often develop fatigue, low levels of red blood cells (anaemia), decreased white blood cell counts (neutropenia) and nausea, all of which can be successfully managed by supportive drug treatment. >>>

The fatigue of cancer patients is often multifactorial. It may be related to side effects of treatment and psychological stress, and many tumours secrete substances (cytokines) that may cause fatigue. However, in many cases fatigue is primarily caused by anaemia. Traditionally, anaemia has been treated with blood transfusions, but new drugs (eg epoetin alpha, epoetin beta, erythropoietin) that increase the production of red blood cells have now been developed.
During the last 10 years, several new agents have been developed to prevent nausea (eg ondansetron, granisetron) and to stimulate the production of white blood cells (filgrastim, pegfilgrastim), decreasing patients' risk of infection. Bone metastasis is another field where new drugs have been introduced. Known as bisphosphonates, these drugs delay the risk of skeletal events (fractures) as well as providing relief from the pain caused by skeletal metastases.

3.6 Advances towards curing cancer

Although cancer is a common disease affecting roughly every third person during their lifetime, approximately 50-60% of patients diagnosed with cancer will either be 'cured' or will die from other causes. Progress in the medical community's ability to 'cure' cancer has been made in almost every area of oncology. In the future, we expect see the impact on mortality of further improvements in therapeutic and diagnostic strategies that have been implemented more recently.
In most tumours, stepwise and relatively modest improvements in oncology management have, over time, resulted in impressive increases in the proportion of patients considered 'cured' of their cancer. For instance, breast cancer mortality in the USA and UK has been reduced by 25% from the 1980s to 2000.37 In some areas, such as testicular cancer and Hodgkin's disease, the changes in 'cure' rates have been sudden and dramatic. However, since breast cancer is a more common disease, the number of patients cured of breast cancer far exceeds that of those cured of testicular cancer or Hodgkin's disease, in absolute terms.

3.6.1 Hodgkin's disease

Hodgkin's disease was one of the first cancers in which the combination of several chemotherapy agents with different mechanisms of action demonstrated increased efficacy. This aggressive form of lymphoma (cancer of the lymph nodes or tissue) mainly affects younger adults, who usually present with enlarged lymph glands, weight loss, fever and profuse night sweating. With the introduction of the MOPP regimen (nitrogen mustard, vincristine, procarbazine and prednisone) in 1967, cure rates of over 50% were obtained in patients with advanced disease.[38] This was a milestone in medical oncology, proving the ability of chemotherapy to cure even in advanced stages of disease. Since then, even higher cure rates (90%) have been obtained using new combinations of chemotherapy.[39]

3.6.2 Testicular cancer

Testicular cancer was the first solid tumour for which chemotherapy resulted in cure for patients with widespread metastatic disease. The prognosis has turned from one of the worst to one of the best among oncological diagnoses. Testicular cancer is the most common tumour form in males aged 15-35 years. Until the early 1970s, the disease was incurable unless patients were diagnosed before the tumour had spread to other parts of the body (metastasised).

The introduction of a chemotherapy drug known as cisplatin in the 1970s was an immediate breakthrough in the treatment of testicular cancer.[40] The addition of further chemotherapy agents to surgery and local radiotherapy has further increased curative rates in patients with metastatic testicular cancer disease to approximately 90-95%. Even after disease relapse, the chances of cure using a cisplatin-based chemotherapy combination are high.

3.6.3 Aggressive non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma is not one disease but a group of at least 15-20 different diseases with varied characteristics and prognoses that have traditionally been classified as either indolent or aggressive. Until the introduction of new chemotherapy combinations in the 1970s, aggressive non-Hodgkin's lymphoma was an incurable disease. In the past 20 years, doxorubicin-based chemotherapy combinations have been the standard first-line treatment for most types of aggressive lymphomas and have resulted in cure rates of approximately 40% in aggressive non-Hodgkin's lymphoma. Survival rates have increased further, especially in older patients, with the introduction of the monoclonal antibody rituximab.

3.6.4 Chronic myeloid leukaemia and gastrointestinal stromal tumour

Chronic myeloid leukaemia occurs mainly in middle-aged and elderly people. It has distinct phases, with a relatively stable initial phase (usually lasting several years), followed by a more aggressive phase. Chronic myeloid leukaemia was the first malignant disease for which a characteristic genetic abnormality, the Philadelphia chromosome (1960), was described.[41] In the 1980s, this genetic alteration led to the identification of the BCR-ABL fusion gene and its corresponding protein, which was established as the cause of the initial phase of chronic myeloid leukaemia. In the late 1990s, imatinib, an agent inhibiting BCR-ABL activity, was developed.[42] Treatment with imatinib results in complete responses in 80% of patients.[43]
Unfortunately, resistance to imatinib can occur, but the mechanisms of resistance have been clarified and an agent that restores sensitivity to imatinib in 14 of the 15 resistance mechanisms described is already in clinical trials.[44]
Imatinib also inhibits another cell enzyme, C-KIT, which is mutated in 95% of patients with a very rare type of cancer known as gastrointestinal stromal tumour. Treatment with imatinib results in long-lasting tumour regression[45] and has been an enormous step forward, since the disease does not respond to conventional chemotherapy.

3.7 Advances towards the prevention of cancer

A number of agents that cause cancer have been brought to light. Epidemiological research has shown that cancer risk is associated with various external and lifestyle factors such as smoking, alcohol consumption, obesity, exercise habits and exposure to certain viruses. Cancer can be prevented. For example, it has been known for more than 50 years that smoking increases the risk of developing many cancers, especially lung cancer. Very little has been done in order to change smoking habits, which has resulted in the global epidemic of lung cancer we now see.
The strong relationship between hormone exposure and breast cancer was the rationale for the first chemoprevention trials in women with an increased genetic risk of breast cancer who were found to benefit from treatment with tamoxifen (50% risk reduction).[51]

>>>

Ongoing studies are evaluating the potential of raloxifene (an agent similar to tamoxifen) and the aromatase inhibitors, which block the production of oestrogen, as preventive agents for breast cancer. Other agents that have indicated their effect as preventive agents are non-steroidal anti-inflammatory drugs in colon cancer,[46] finasteride in prostate cancer,[15] and recently statins in breast cancer.[47] The fact that there are agents that can be used for prevention of cancer is in itself an important milestone in oncology.
The area of cancer prevention is complex and involves political as well as medical measures. From a medical perspective, the main challenge is finding preventative agents/measures that are non-toxic and well tolerated.

3.8 A summary of breast and colorectal cancer, NSCLC, NHL and bone metastases

3.8.1 Breast cancer

Breast cancer is the most common cancer in women. Advances in the treatment of breast cancer since the 1970s have resulted in a decline in mortality that can be attributed to extensive screening programmes (leading to early detection of the disease) and early surgical intervention combined with medical treatment such as radiotherapy, chemotherapy and endocrine treatment. Improved treatment methods have resulted in increased life expectancy in metastatic disease, improved quality of life during chemotherapy and enabled many women to have breast-sparing surgery.
Recent advances in the knowledge of the biology of the disease and its risk factors have resulted in new, less toxic targeted treatments, such as the monoclonal antibody trastuzumab (targeting HER2-overexpressing cells), and new screening/preventive strategies. Women identified as being at high risk for breast cancer can already take advantage of risk-reducing interventions that are potentially life saving.

3.8.2 Colorectal cancer

Colorectal cancer is the third most common malignancy after cancers of the breast and prostate. The past decade has seen the introduction of screening programmes in many countries in order to find the tumours at an early stage, aiming at improving survival.
Colorectal cancer was treated with surgery alone up until the 1980s. Since then, 5-fluorouracil (5-FU) plus leucovorin combination regimens have been standard treatment. During the past 10 years, new agents have been introduced and life expectancy has increased from 5 to 20 months in patients with metastatic disease. Post-operative (adjuvant) chemotherapy treatment in select groups of patients has substantially increased survival. The addition of biological agents, like the monoclonal antibodies bevacizumab and cetuximab, to chemotherapy has further improved response rates in metastatic disease.
Progress in molecular medicine has led to the identification of several disease-specific targets, resulting in optimism on future treatments with even higher response rates and less toxicity.

3.8.3 NSCLC

The incidence of NSCLC is increasing rapidly in women but is unchanged or slightly decreasing in men. Only about 15% are cured from the disease and lung cancer mortality represents one-fifth of all cancer-related deaths in the European Union. In most cases, NSCLC is diagnosed at a late stage when curative treatment is not an option.

In 2003, the first positive results concerning survival benefit from giving post-operative chemotherapy in earlier stage tumours were presented. Advances in molecular medicine have led to the identification of disease-specific mechanisms and cell surface structures that may be targets for future therapy, leading to increased response rates and less toxic treatments.

3.8.4 NHL

On a global level, incidence rates for NHL, a group of at least 15-20 separate diseases, especially aggressive lymphomas, have increased in the past four decades, although reasons for this are not entirely clear.
Forty years ago, NHL was a disease where cure was obtained in a very limited number of cases. The introduction of different chemotherapy combinations has improved cure rates in aggressive lymphomas as well as improving quality of life and increasing duration of response in indolent lymphomas. Within the past decade, advances in molecular medicine have provided insights into the biology of NHL. This has led to new treatments like the monoclonal antibody rituximab, which has improved survival rates in patients with aggressive NHL and become an important therapeutic option in the treatment of indolent lymphomas.

3.8.5 Bone metastases

Bone is, after the lungs and liver, the third most common location for metastases. Breast and prostate cancer are the most common cancers in which bone metastasis are seen. Increased survival in many cancers has led to an increased prevalence of patients with bone metastases.
Until 20 years ago, bone metastases were treated with analgesics, external radiation therapy or surgery. Increased knowledge in osteoporosis and bone metabolism has led to the development of new drugs such as bisphosphonates, which have proved to be valuable in preventing and treating bone pain and hypercalcaemia and postponing skeletal complications in cancer patients. Radionuclides that target radiation to metastatic lesions in the bone have been also been developed. Improved surgical techniques, bone replacement materials and the development of multidisciplinary teams focused on treating patients with bone metastasis have also contributed to improved quality of life and reduced morbidity in this group of patients.
The treatment of bone metastases is an example of a rapidly expanding field in oncology that aims to give patients best possible supportive care.

3.9 Conclusions

Oncology has entered an exciting phase in which extensive research is paying dividends in the form of new treatments designed to target disease-specific mechanisms. The number of new agents with antitumour effects has accelerated during the last 10 years and, judging from the number of ongoing trials and pipelines of pharmaceutical companies, there is every reason to believe that this trend will continue in years to come. Intense research in molecular medicine and tumour biology will also lead to the identification of more potential targets for intervention.
The dividends mentioned above are, however, only realised once drugs are adopted into routine clinical practice; only then can patients benefit from the huge investment in cancer research. The following section looks at the speed of uptake of a number of new agents that have recently become licensed in the EU across selected countries. Within the report, we then go on to look at factors that impact the availability of innovative treatments to patients. ■

References

1. Hofmann WK, de Vos S, Elashoff D, et al. Relation between resistance of Philadelphia-chromosome-positive acute lymphoblastic leukaemia to the tyrosine kinase inhibitor STI571 and gene-expression profiles: a gene-expression study. Lancet 2002; 359: 481-486.
2. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002; 359: 572-577.
3. The Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004; 350: 2050-2059.
4. Abbou CC, Hoznek A, Salomon L, et al. Laparoscopic radical prostatectomy with a remote controlled robot. J Urol 2001; 165: 1964-1966.
5. McNamara DA, Parc R. Methods and results of sphincter-preserving surgery for rectal cancer. Cancer Control 2003; 10: 212-218.
6. Ragde H, Blasko JC, Grimm PD, et al. Interstitial iodine-125 radiation without adjuvant therapy in the treatment of clinically localized prostate carcinoma. Cancer 1997; 80: 442-1553.
7. Loeffler JS, Alexander E 3rd, Shea WM, et al.: Radiosurgery as part of the initial management of patients with malignant gliomas. J Clin Oncol 1992; 10: 1379-85.
8. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 2453-2463.
9. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57-70.
10. Wartmann M, Altmann KH. The biology and medicinal chemistry of epothilones. Curr Med Chem Anti-Canc Agents 2002; 2: 123-148.
11. Tewey KM, Rowe TC, Yang L, Halligan BD, Liu LF. Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II. Science 1984; 226: 466-468.
12. Rothenberg ML, Moore MJ, Cripps MC, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol 1996; 7: 347-353.
13. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589-1597.
14. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. Lancet 1896; 2: 104-110.
15. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003; 349: 215-224.
16. Lenz HJ, Mayer RJ, Gold PJ et al. Activity of cetuximab in patients with colorectal cancer refractory to both irinotecan and oxaliplatin. J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition): 22, 14S (July 15 Supplement), abs 3510.
17. Bonner JA, Giralt J, Harari PM, et al. Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: A phase III study of high dose radiation therapy with or without cetuximab. J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition): 22, 14S (July 15 Supplement), abs 5507
18. Shepherd FA, Pereira J, Ciuleanu TE, et al. A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial. Proc Am Soc Clin Oncol Late-Breaking Abstracts Booklet 2004; 23: 18, abs 7022.
19. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer. A randomized trial. JAMA 2003; 290: 2149-2158.
20. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783-792.
21. Piccart M. First results from the HERA trial. Presented at the annual meeting of the American Society of Clinical Oncology 2005. www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005816-00_21-001,00.asp
22. Hainsworth JD, Sosman JA, Spigel DR, et al. Bevacizumab, erlotinib, and imatinib in the treatment of patients (pts) with advanced renal cell carcinoma (RCC): A Minnie Pearl Cancer Research Network phase I/II trial. J Clin Oncol (Meeting Abstracts) 2005; 23: 388s, abs 4542.
23. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. J Clin Oncol 2005; 23: 2544-2555.
24. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. J Clin Oncol 2004; 22: 1103-1109.
25. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 2004; 350: 2129-2139.
26. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285: 1182-1186.
27. Black WC, Welch HG. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. N Engl J Med 1993; 328: 1237-1243.
28. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996; 86: 353-364.
29. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-2342.
30. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005; 23: 792-799.
31. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III Trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial - E4599. Proc Am Soc Clin Oncol 2005; 23: abs 4.
32. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003; 349: 427-434.
33. Motzer RJ, Rini BI, Michaelson MD, et al. Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC). J Clin Oncol (Meeting Abstracts) 2005; 23: 380s, abs 4508.
34. Escudier B, Szczylik C, Eisen T, et al. Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma (RCC). J Clin Oncol (Meeting Abstracts) Late Breaking Abstracts 2005; 23: 1093s, abs 4510.
35. Wang J, Lou P, Lesniewski R et al. Paclitaxel at ultra low concentrations inhibits antiangiogenesis without affecting cellular microtubule assembly. Anticancer Drugs 2003; 14: 13-19.
36. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 1975; 256: 495-497.
37. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. Lancet 2000; 355: 1822.
38. Devita Jr VT, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann Intern Med 1970; 73: 881-895.
39. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003; 348: 2386-2395.
40. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977; 87: 293-298.
41. Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. Science 1960; 132: 1497-1501.
42. Druker BJ, Lydon NB. Lessons learned from the development of an Abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J Clin Invest 2000; 105: 3-7.
43. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003; 348: 994-1004.
44. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004; 305: 399-401.
45. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347: 472-480.
46. Thun MJ, Namboodiri MM, Heath Jr CW. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991; 325: 1593-1596.
47. Kochhar R, Khurana V, Bejjanki H, et al. Statins reduce breast cancer risk: a case control study in US female veterans. Proc Am Soc Clin Oncol 2005; 23: abs 514.

ADVANCES IN CANCER MANAGEMENT

4. MARKET UPTAKE OF NEW ONCOLOGY DRUGS IN EUROPE

Summary

- For the drugs analysed in this report there are great variations and inequities between European countries, in terms of the level of uptake of new drugs following introduction. Imatinib is an identified exception to this rule.
- Austria, Spain and Switzerland are seen as leaders in the uptake of trastuzumab in breast cancer and are above the European average. The Czech Republic, Hungary, the Netherlands, Norway, Poland and the UK are well below the European average.
- Belgium, Italy and Switzerland are leaders in the uptake of oxaliplatin and irinotecan in colorectal cancer. The Czech Republic, Hungary, Poland and the UK are below the European average.
- Austria, Finland and Switzerland are leaders in the uptake of capecitabine (indicated for both colorectal cancer and breast cancer). Belgium, the Czech Republic, France, Germany, Hungary and Poland are below the European average.
- In non-small-cell lung cancer, Austria and Switzerland are leaders in the uptake of gemcitabine and vinorelbine. The Czech Republic, Greece, Hungary, Norway, Poland and the UK are well below the European average.
- Austria, Spain and Switzerland are leaders in the uptake of rituximab in non-Hodgkin's lymphoma. Most other countries tend to be just below or close to the European average.
- Austria, Belgium, Italy and Switzerland are leaders in the overall uptake of bisphosphonates.

This chapter describes the market introduction and total sales of 56 oncology products in 19 countries in Europe. The total sales in the period 1993-2004 are divided into three periods: drugs available before 1993, drugs introduced from 1993-1998 and drugs introduced from 1999-2004. Table 4.1 lists these drugs along with their year and month of first introduction in Europe.

Drugs first introduced before 1993	Date of launch	Drugs first introduced 1993-1998	Date of launch	Drugs first introduced 1999-2004	Date of launch
Methotrexate	Jan 1955	Paclitaxel	Apr 1993	Trastuzumab	Aug 1999
Cyclophosphamide	Jan 1958	Cladribine	Oct 1993	Tasonermin	Sep 1999
Fluorouracil	Jan 1962	Fludarabine	Jan 1994	Exemestane	Nov 1999
Megestrol	Jan 1963	Gemcitabine	Apr 1995	Zoledronic acid	Nov 2000
Vincristine	Jun 1965	Bicalutamide	May 1995	Imatinib	Jul 2001
Daunorubicin	Jan 1967	Anastrozole	Sep 1995	Alemtuzumab	Aug 2001
Cytarabine	Dec 1969	Irinotecan	Sep 1995	Gefitinib	Jan 2002
Bleomycin	Aug 1970	Docetaxel	Nov 1995	Fulvestrant	Aug 2002
Doxorubicin	Jan 1971	Oxaliplatin	Jul 1996	Ibritumomab tiuxetan	Jan 2004
Tamoxifen	Dec 1973	Ibandronic acid	Oct 1996	Cetuximab	Feb 2004
Ifosfamide	Feb 1976	Letrozole	Nov 1996	Bortezomib	Feb 2004
Tegafur	Feb 1978	Topotecan	Dec 1996	Pemetrexed	Apr 2004
Cisplatin	Oct 1979	Rituximab	Dec 1997	Bevacizumab	Oct 2004
Etoposide	Aug 1980	Capecitabine	Jun 1998		
Flutamide	Mar 1984	Temozolomide	Jul 1998		
Epirubicin	May 1984				
Mitoxantrone	Jun 1984				
Buserelin	Sep 1984				
Clodronic acid	Mar 1985				
Interferon alfa-2a	Jun 1986				
Triptorelin	Jun 1986				
Carboplatin	Sep 1986				
Goserelin	Mar 1987				
Nilutamide	Dec 1987				
Toremifene	Jan 1989				
Vinorelbine	Jun 1989				
Idarubicin	Feb 1990				
Pamidronic acid	Oct 1990				

Table 4.1. Drug and first date of introduction in Europe.

Twenty-nine of the 56 cancer drugs (52%) in the 19 European countries were introduced before 1993 (defined as the first date for introduction in any of the included countries), 15 (27%) were introduced in the period from 1993-1998, while 12 (21%) were introduced in the period from 1999-2004. During the past 12 years, we have thus seen on average the introduction of just over 2 new cancer drugs per year.

Quarterly and annual sale statistics for the drugs launched from 1993-2004 were obtained from IMS Health, IMS MIDAS/Q4 2004 (via Roche, Basle) for the following 13 European countries: Austria, the Czech Republic, France, Germany, Greece, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, Switzerland and the UK. IMS data for Portugal include only a limited number of oncology drugs, thus data from this country have only been used for the macro-evaluation and not for uptake of individual drugs. The same data were available for Belgium, Denmark, Finland, Hungary and Ireland for the time period 1994-2004 and for Norway for 1997-2004. >>>

The total population in these 19 countries is 447 million, which constitutes 76% of the total population in Europe (excluding Russia and Turkey) and, after excluding Norway and Switzerland, constitutes 96% of the total population in the EU [25]. The sales taken from IMS Health, IMS MIDAS/Q4 2004 were based on manufacturers' prices in most countries, except in Denmark, Finland, Greece, Norway, Sweden and the UK, where the sales were based on trade prices. The sales are presented in nominal prices and have been converted to Euros where necessary, using the 2004/2005 exchange rate. IMS audits in the Czech Republic, the Netherlands, Poland, Sweden and Switzerland measure sales to hospitals from wholesalers and directly from manufacturers. In Austria, Belgium, France, Italy, Germany, Spain and the UK, hospital usage is established by receiving data from a panel of hospitals reporting the product issues from pharmacy; these data are projected to a national level. In certain markets with fewer hospital panels, eg Spain, highly specialised products may not completely represent the true market. No data for the hospital markets in Ireland or Portugal were available for this analysis, so the data in this report represents retail sales only. Total sales by country and period of introduction are shown in Appendix B.

4.1 Sales of new oncology drugs in Europe

The data show that total sales of oncology drugs have increased substantially over the period 1993-2004 from €840 million to €6 170 million (Figure 4.1). The increase in sales for oncology products over this period can be explained by the introduction of new innovative drugs.

Figure 4.1.

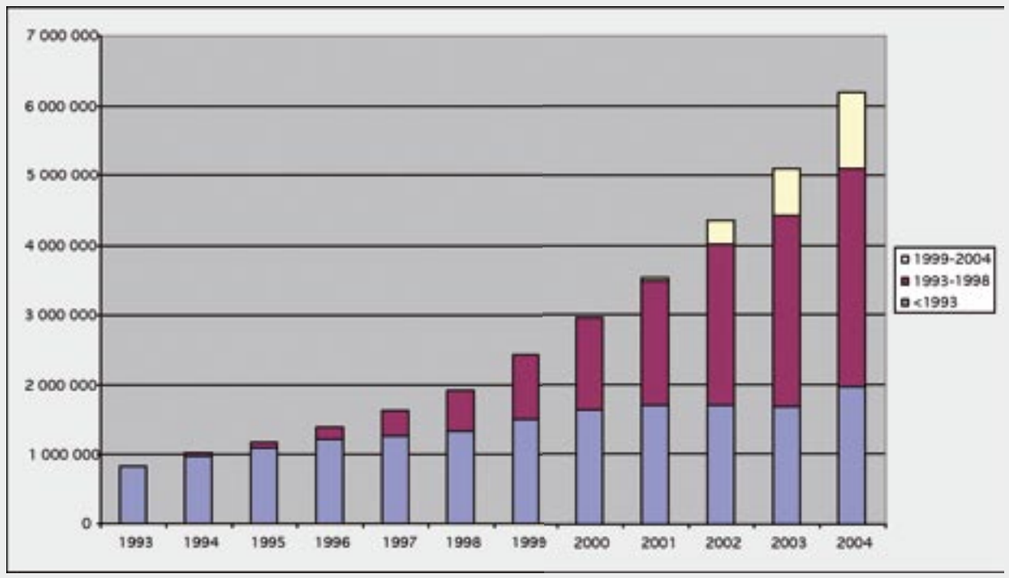


Figure 4.1. Total cancer drug sales (€000s) in all 19 countries. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.2 shows the market uptake of new drugs in Europe (defined by the first introduction date in any of the 19 countries). In 2004, new drugs introduced over the period 1993-1998 constitute 51% of total sales, while the corresponding figure for drugs introduced over the period 1999-2004 is 17%.

Figure 4.2.

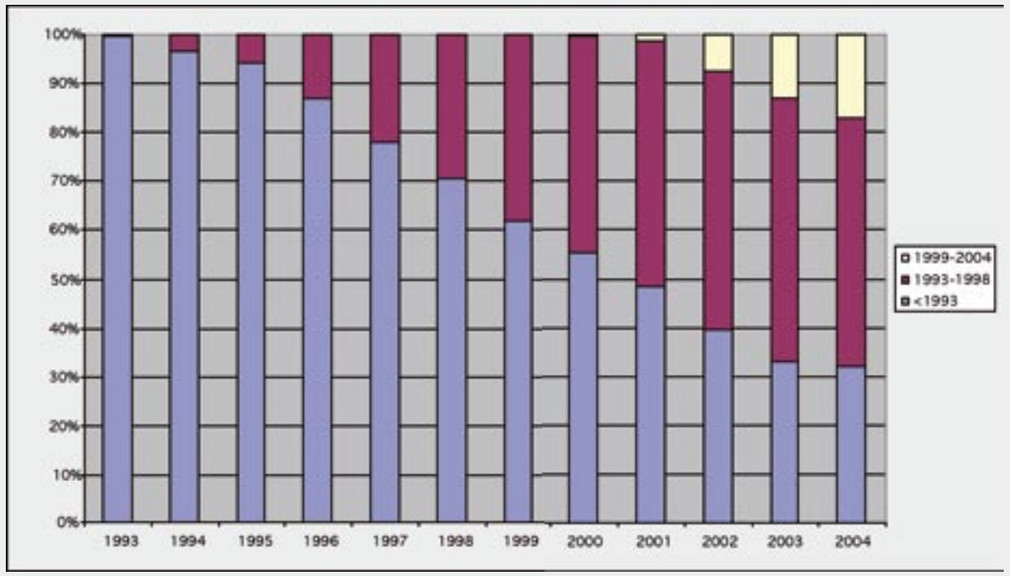


Figure 4.2. The portion of total sales of cancer drugs by time period of introduction. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

4.2 Uptake of selected oncology drugs

In this section of the report, we describe the uptake of a number of specific oncology drugs in the 18 countries from which we have consistent IMS data (Portugal is not included in this analysis). For each drug we present, uptake is presented as sales (€) from the time of local introduction or first period of sales (a drug could have been sold under special licence prior to national authorisation). Data are given for sales per patient dying of a specific cancer for which there is a dominating or single indication for the drug described.

We have grouped the diagrams as follows: the five major markets of France, Germany, Italy, Spain and the UK; the Nordic region; remaining Western European countries; and Eastern European countries who joined the EU in 2004.

We have selected the drugs in order to have representation of the tumour areas discussed in detail (Appendix A). These are breast cancer (represented by trastuzumab sales), colorectal cancer (irinotecan, oxaliplatin and capecitabine sales), non-small-cell lung cancer (NSCLC; gemcitabine and vinorelbine sales), non-Hodgkin's lymphoma (NHL; rituximab sales), chronic myeloid leukaemia (CML; imatinib sales) and an illustration of the supportive care market (sales of four bisphosphonates). Table 4.2 lists these agents and the launch dates in the individual countries.

	Capecitabine	Gemcitabine	Imatinib	Irinotecan	Oxaliplatin	Rituximab	Trastuzumab	Vinorelbine
Europe	Jun 1998	Apr 1995	Jul 2001	Sep 1995	Jul 1996	Dec 1997	Nov 1998	Jun 1989
Austria	Sep 2000	Jun 1995	Dec 2001	Sep 1997	Jun 1998	Jul 1998	Oct 2000	Jun 1992
Belgium	Sep 2001	Jan 1997	Oct 2002	Jun 1999	Oct 2001	Jul 2000	Apr 2001	Jul 1999
Czech Republic	Feb 2001	Apr 1996	Apr 2002	Nov 1997	Feb 2001	Oct 1999	Mar 2001	Oct 1993
Denmark	Sep 2001	Mar 1997	Dec 2001	Dec 1998	NA	Dec 1998	Dec 2000	Jun 1998
Finland	Mar 2001	Sep 1995	Nov 2001	Apr 1997	NA	Jul 1998	Oct 2000	Nov 1996
France	Nov 1998	Jul 1996	Apr 2003	Sep 1995	Jul 1996	Jun 1998	Sep 2000	Jun 1989
Germany	Mar 2001	May 1996	Nov 2001	Sep 1998	Sep 1999	Jul 1998	Oct 2000	Feb 1996
Greece	Dec 1999	Jan 1997	May 2002	Feb 1998	NA	May 1999	May 2000	May 1997
Hungary	Jan 2002	Jan 1997	Dec 2001	Jul 1999	NA	Apr 2000	Jul 2001	Jan 1998
Ireland	Mar 2001	Apr 1998	Jan 2002	Sep 1998	NA	Aug 1998	Dec 2000	NA
Italy	Oct 2001	Jul 1996	Jan 2002	Nov 1997	Jun 2000	Mar 1999	Feb 2001	Mar 1992
Netherlands	Jun 2001	Jun 1995	Nov 2001	Sep 1998	Aug 1999	Jul 1998	Sep 2000	NA
Norway	Oct 1998	Mar 1997	Aug 2001	Aug 1998	NA	Feb 1998	Nov 1998	Oct 1998
Poland	Dec 2000	Mar 1997	Jan 2002	Jan 1999	Sep 2003	Dec 2000	Mar 2002	Oct 1994
Spain	Feb 2001	Nov 1995	Apr 2002	Jun 1997	Apr 2000	Sep 1998	Nov 2000	Apr 1993
Sweden	Feb 2001	Apr 1995	Nov 2001	Jun 1998	Sep 1999	Jun 1998	Oct 2000	Oct 1996
Switzerland	Jun 1998	Jun 1997	Jul 2001	Sep 1998	Sep 1999	Dec 1997	Aug 1999	Mar 1996
UK	Feb 2001	Dec 1995	Nov 2001	Mar 1997	Sep 1999	Jun 1998	Sep 2000	Jun 1997

Table 4.2. National launch dates for and capecitabine, gemcitabine, imatinib, irinotecan, oxaliplatin, rituximab, trastuzumab and vinorelbine; NA = not launched or not available.

4.2.1 Breast cancer

Breast cancer represents the most drug-intensive area when it comes to treatment of solid tumours. Tamoxifen, launched in 1975 and once also considered a costly treatment with limited effects, has established itself as the most cost-effective cancer treatment to date. Its broad indication for the treatment of advanced disease and adjuvant treatment (and prevention in the USA) represents a major breakthrough in the treatment of breast cancer. Newer, innovative drugs (aromatase inhibitors) are now gradually replacing some of the previous roles of tamoxifen. In addition, anthracyclines and taxanes have established themselves as very valuable palliative and adjuvant treatments.

Trastuzumab, a HER2 receptor antibody, has now become a cornerstone of treatment for patients with advanced breast cancer overexpressing HER2, and data now also support a role in the adjuvant setting. Diagnostic testing of women diagnosed with breast cancer determines whether a patient is an eligible candidate for trastuzumab. We have, therefore, illustrated the adoption of new drugs in breast cancer with the uptake of trastuzumab in different countries (Figures 4.3-4.6).

4.2.1.1 Trastuzumab uptake across Europe

Figure 4.3.

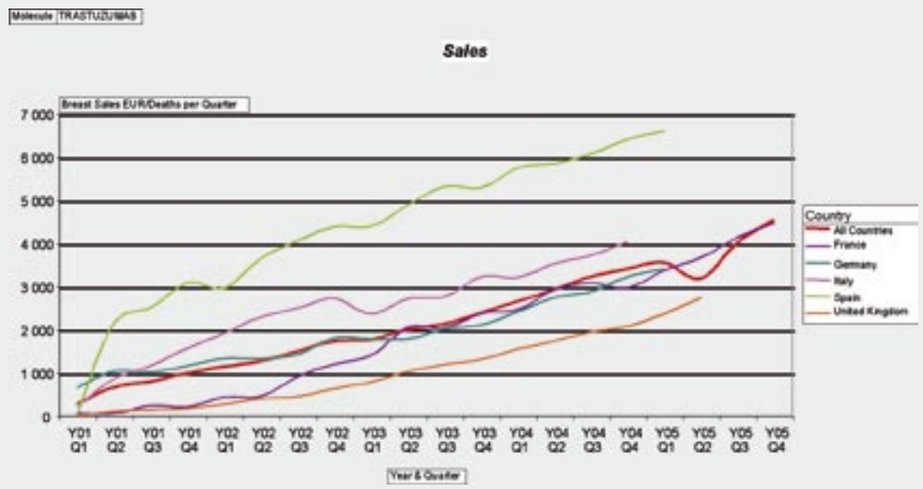


Figure 4.3. Trastuzumab sales per individual dying of breast cancer in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.4.

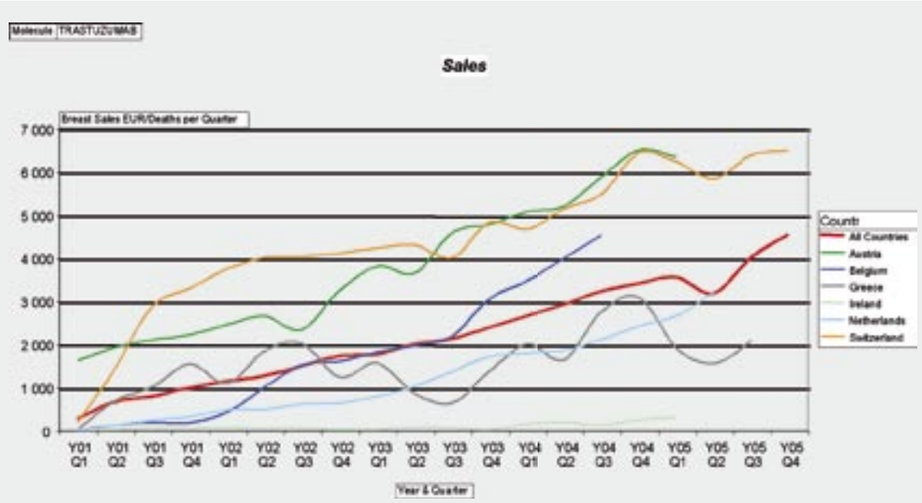


Figure 4.4. Trastuzumab sales per individual dying of breast cancer in Austria, Belgium, Greece, Ireland, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.5.

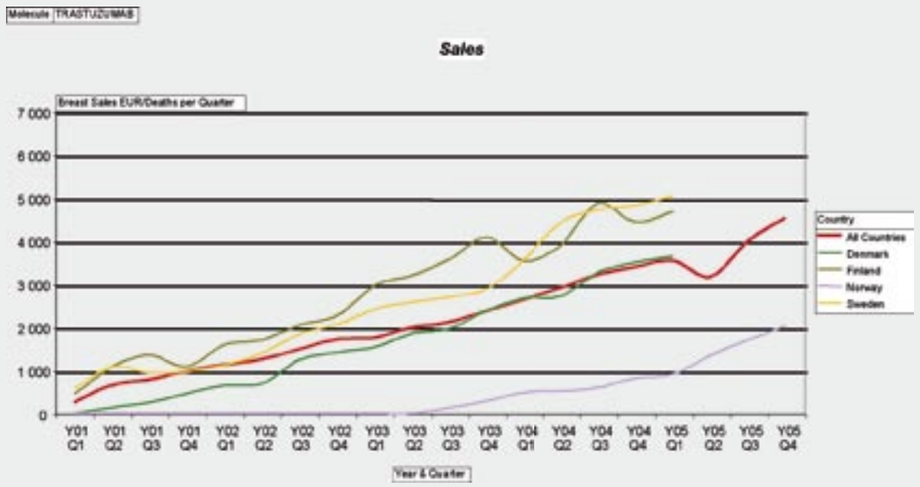


Figure 4.5. Trastuzumab sales per individual dying of breast cancer in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.6.

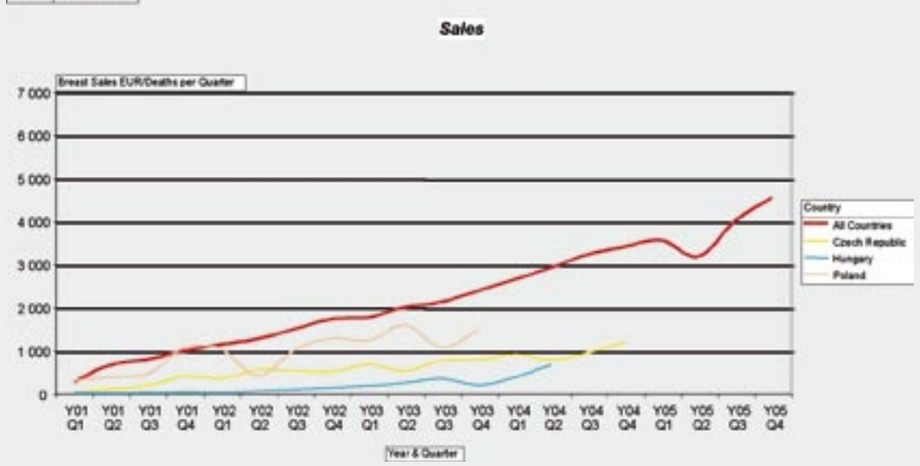


Figure 4.6. Trastuzumab sales per individual dying of breast cancer in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

As can be seen, there are large differences in both the time and level of uptake across Europe. Four years after introduction, several countries still have a large patient population not being treated. This represents a substantial loss of patient benefit. Austria, Spain and Switzerland are seen as leaders in uptake of trastuzumab and above the European average. The Czech Republic, Hungary, the Netherlands, Norway, Poland and the UK are well below the European average.

4.2.2 Colorectal cancer

Until the end of the 1980s, colorectal cancer remained a therapeutic area in which medical treatment had little or no effect. Developments in diagnostic and surgical techniques were major contributors to outcome improvement. With the publication of the adjuvant data on modulated 5-fluorouracil (5-FU)-based therapy in the late 1980s and mid 1990s, colorectal cancer rapidly became an area of focus for further drug development. In the mid 1990s, both irinotecan and oxaliplatin became established additive agents to modulated 5-FU, which was still the cornerstone of treatment for both early and advanced colorectal cancer.
Recently, two new innovative drugs, bevacizumab and cetuximab, have also been approved for the treatment of advanced colorectal cancer, representing a new breakthrough in the treatment of the disease.

Here we illustrate drug uptake in colorectal cancer through the sales of oxaliplatin and irinotecan in the different markets (Figures 4.7-4.14).

4.2.2.1 Oxaliplatin uptake across Europe

Figure 4.7.

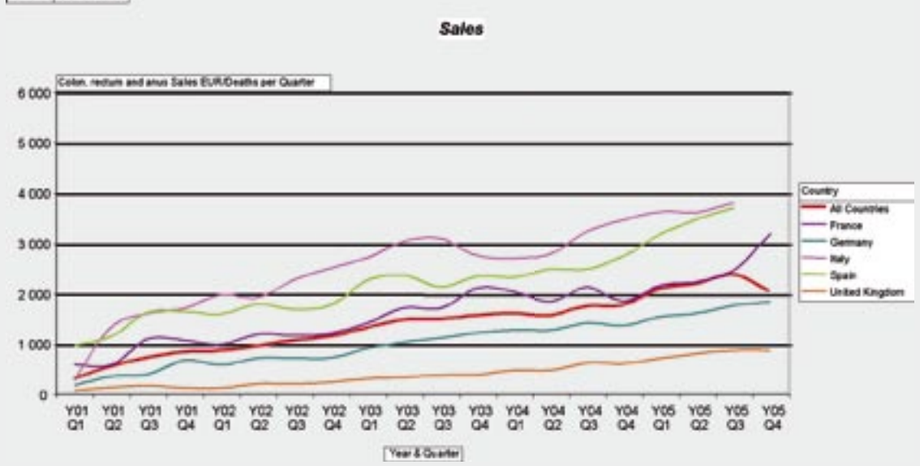


Figure 4.7. Oxaliplatin sales per individual dying of colorectal cancer in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.8.

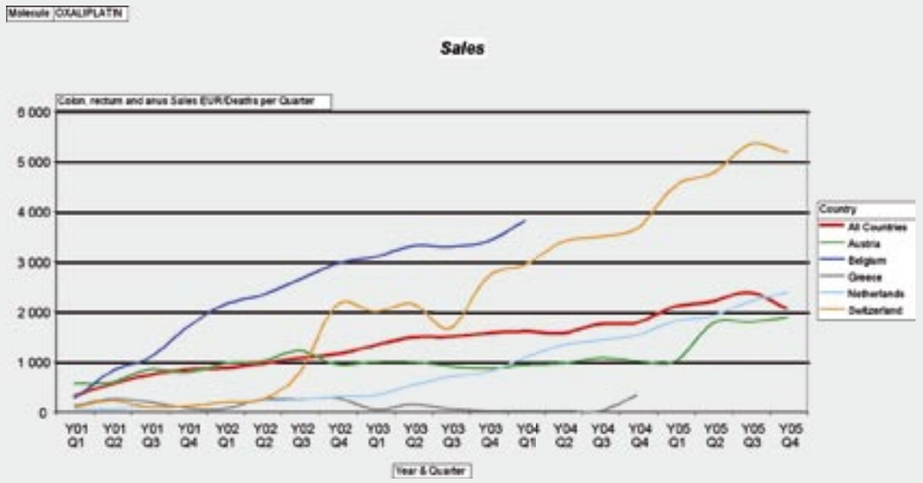


Figure 4.8. Oxaliplatin sales per individual dying of colorectal cancer in Austria, Belgium, Greece, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.9.

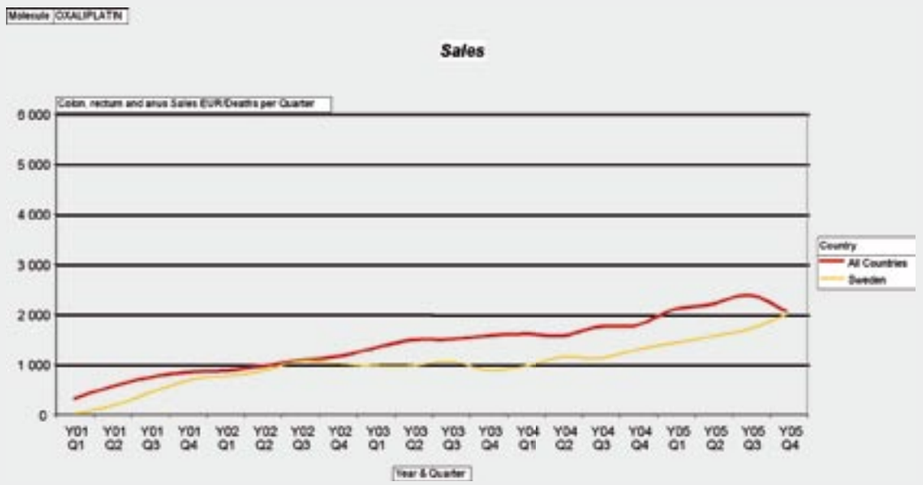


Figure 4.9. Oxaliplatin sales per individual dying of colorectal cancer in Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.10.

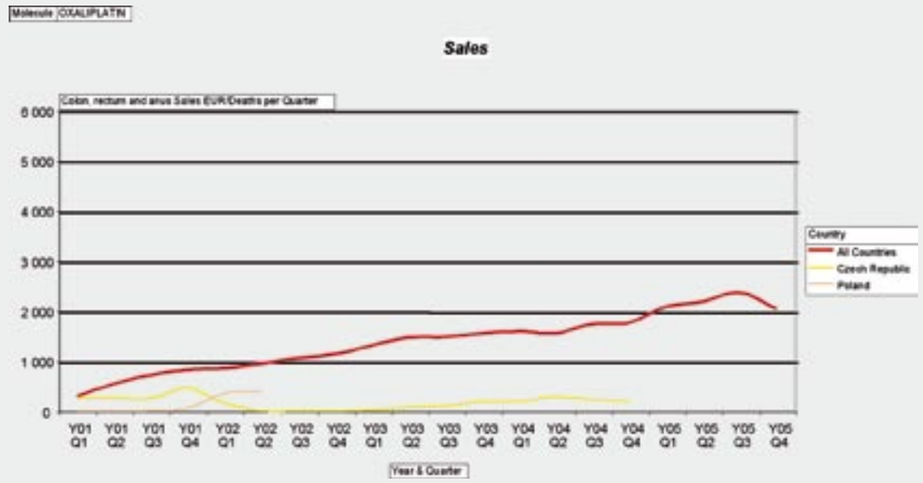


Figure 4.10. Oxaliplatin sales per individual dying of colorectal cancer in the Czech Republic and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

4.2.2.2 Irinotecan uptake across Europe

Figure 4.11.

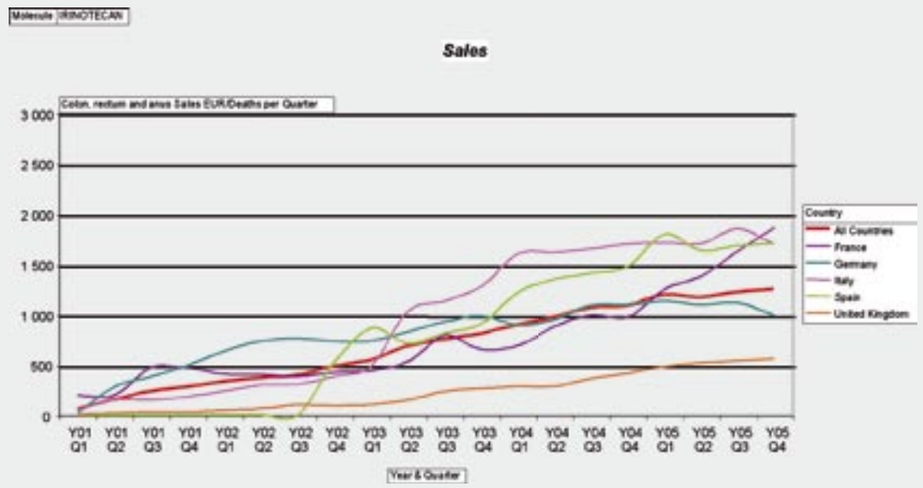


Figure 4.11. Irinotecan sales per individual dying of colorectal cancer in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.12.

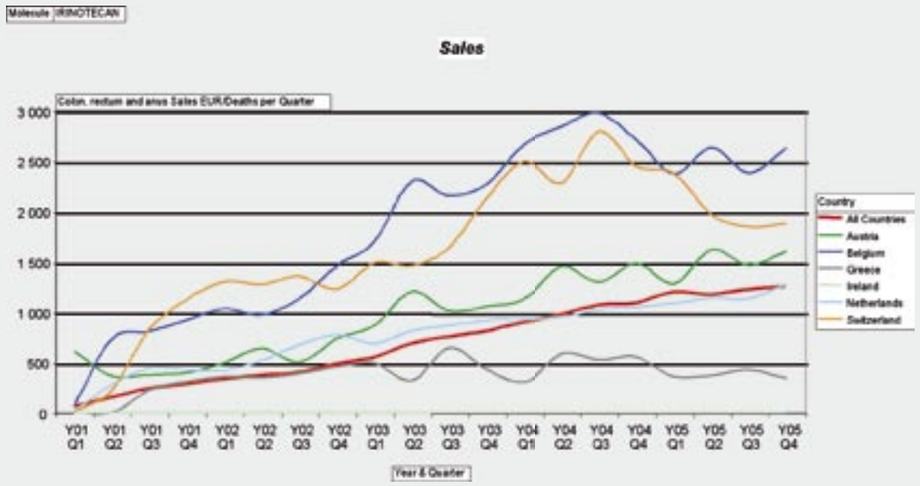


Figure 4.12. Irinotecan sales per individual dying of colorectal cancer in Austria, Belgium, Greece, Ireland, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.13.

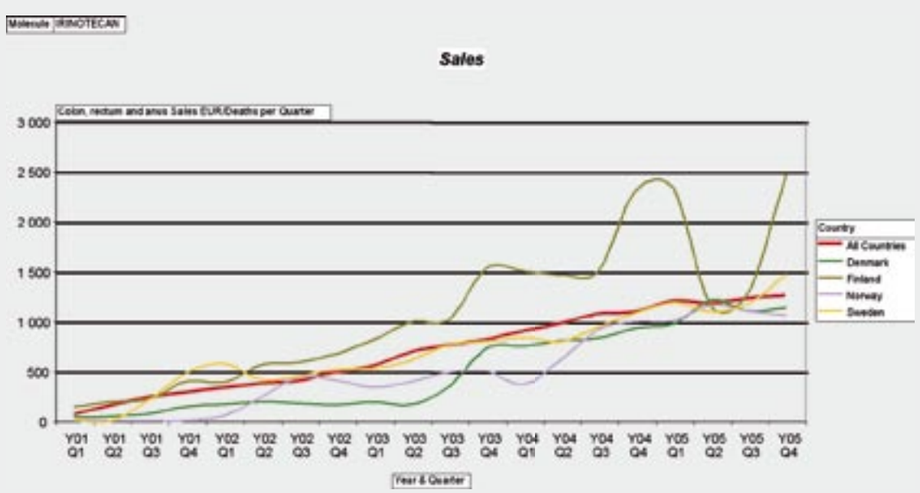


Figure 4.13. Irinotecan sales per individual dying of colorectal cancer in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.14.

Figure 4.14. Irinotecan sales per individual dying of colorectal cancer in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

The data illustrate uptake in the advanced colorectal cancer market, as the adjuvant indication of oxaliplatin was not approved until 2004. As illustrated with trastuzumab uptake, large differences between European countries are seen with respect to uptake (time as well as level) of both oxaliplatin and irinotecan. Belgium, Italy and Switzerland are leaders in the uptake of both drugs in colorectal cancer. The Czech Republic, Hungary, Poland and the UK are below the European average.

4.2.2.3 Capecitabine uptake across Europe

Modulated 5-FU has remained a corner stone of treatment for gastrointestinal malignancies. All new drugs introduced to this market have been used in combination with or in relation to this agent. A major downside of intravenous 5-FU treatments has been the schedules that have been proven to be effective, which often require either frequent visits to an outpatient clinic or use of complicated devices for continuous infusion.
Oral 5-FU (capecitabine) has now been introduced into the market, giving patients a cost-effective, home-based, convenient method of administration with full efficacy retained and a similar or better toxicity profile compared with hospital-based intravenous administration schedules. It is indicated for both breast and colorectal cancer. The uptake of capecitabine is presented below in Figure 4.15-4.18.s.

Figure 4.15.

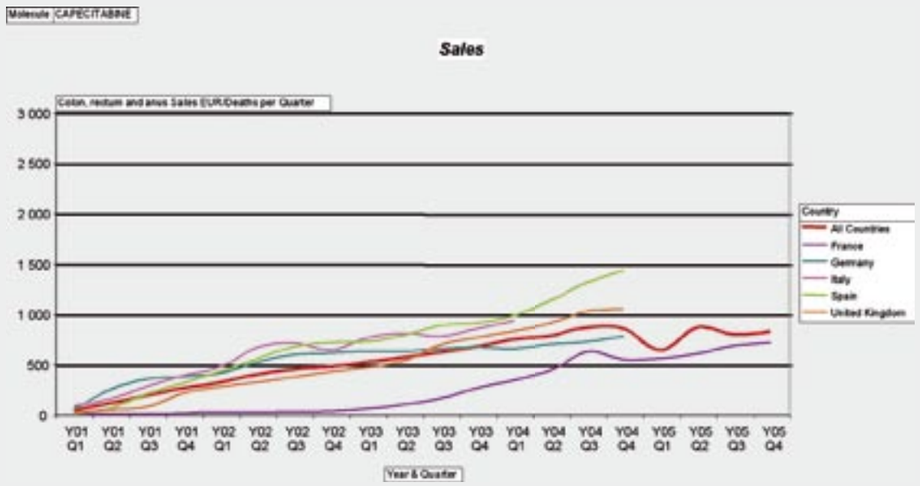


Figure 4.15. Capecitabine sales per individual dying of colorectal and breast cancer in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.16.

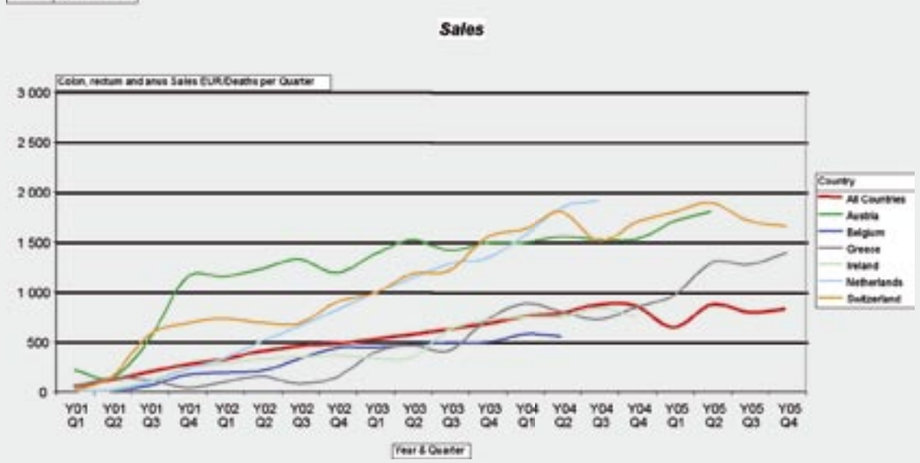


Figure 4.16. Capecitabine sales per individual dying of colorectal and breast cancer in Austria, Belgium, Greece, Ireland, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.17.

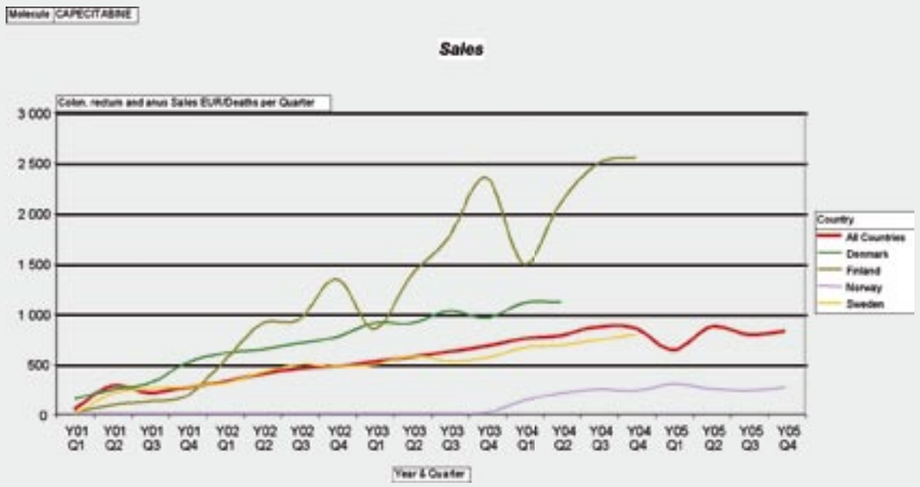


Figure 4.17. Capecitabine sales per individual dying of colorectal and breast cancer in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.18.

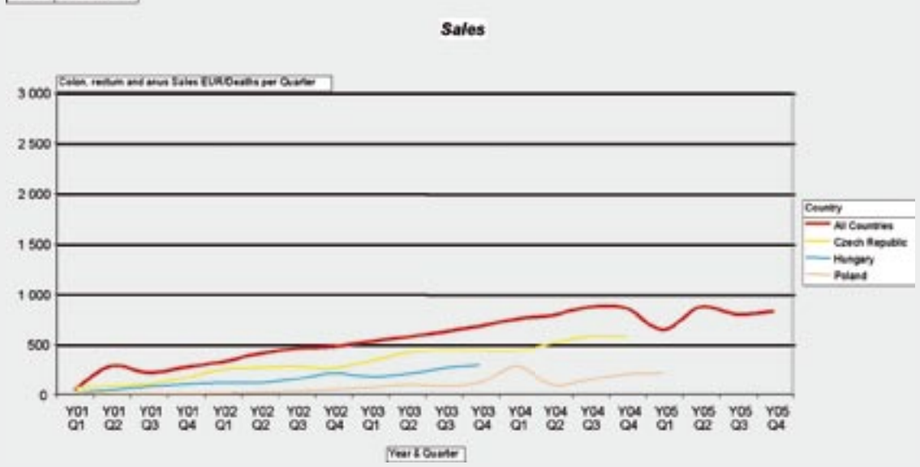


Figure 4.18. Capecitabine sales per individual dying of colorectal and breast cancer in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

As can be seen once again, there are major differences in the rate of uptake between different European countries. As capecitabine is also indicated in breast cancer, differences in uptake can relate to use in both colorectal and breast cancer. Austria, Finland and Switzerland are leaders in the uptake of capecitabine. Belgium, the Czech Republic, France, Germany, Hungary and Poland are below the European average.

4.2.3 Non-small-cell lung cancer

NSCLC has long been an area of therapeutic nihilism in many countries. It was not until a decade ago, when platinum-based chemotherapy was shown to provide a clear benefit for patients with advanced disease, that the development of modern chemotherapy in this area of oncology escalated. We now also have solid clinical evidence that adjuvant chemotherapy will also give substantial benefit in selected patients. Gemcitabine's initial indication was in pancreatic cancer. Within 3 years it was also indicated in NSCLC and then became a cornerstone of combined chemotherapy (with either cisplatin or carboplatin) for NSCLC in Europe. In some parts of Europe, the combination of platinum salts with vinorelbine has become standard. In order to illustrate this development, we show the uptake in NSCLC of gemcitabine and vinorelbine.
There are also new therapeutic options in NSCLC, including EGFR-targeting agents such as gefitinib and erlotinib and chemotherapy with pemetrexed. At present it is too early to comment on the uptake of the most recently approved drugs in NSCLC.

Figure 4.19.

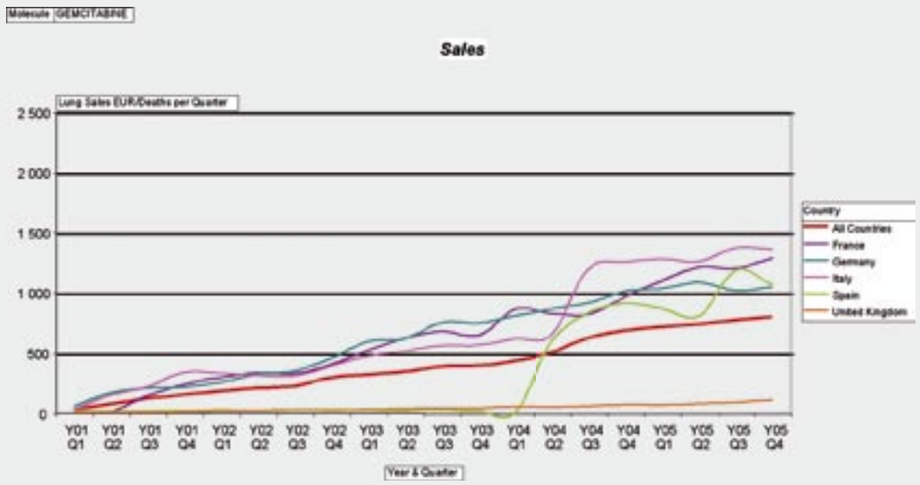


Figure 4.19. Gemcitabine sales per individual dying of lung cancer in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.20.

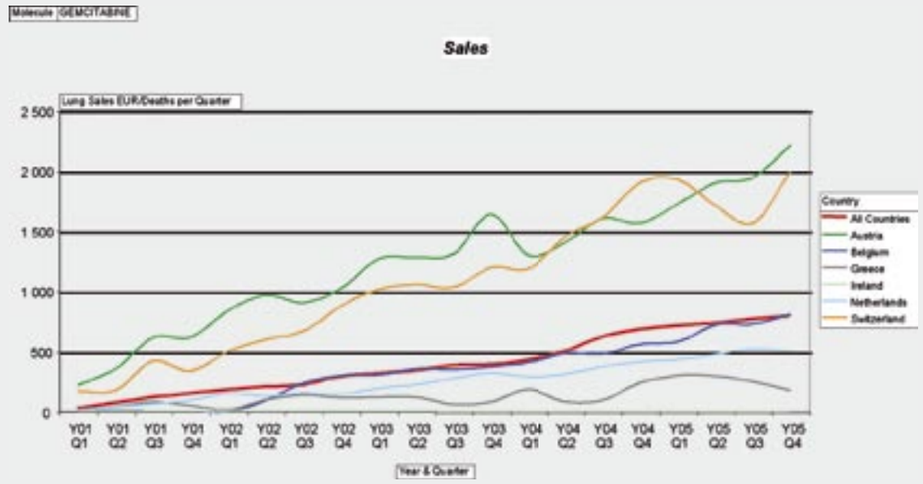


Figure 4.20. Gemcitabine sales per individual dying of lung cancer in Austria, Belgium, Greece, Ireland, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.21.

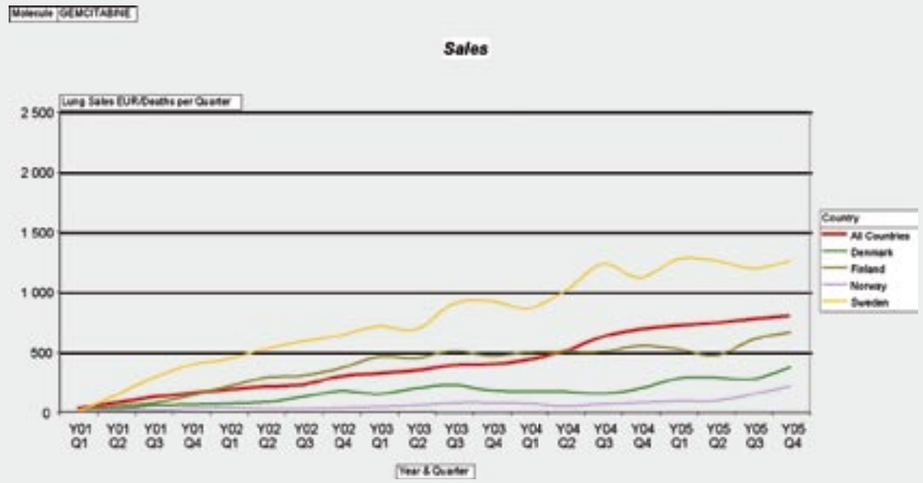


Figure 4.21. Gemcitabine sales per individual dying of lung cancer in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.22.

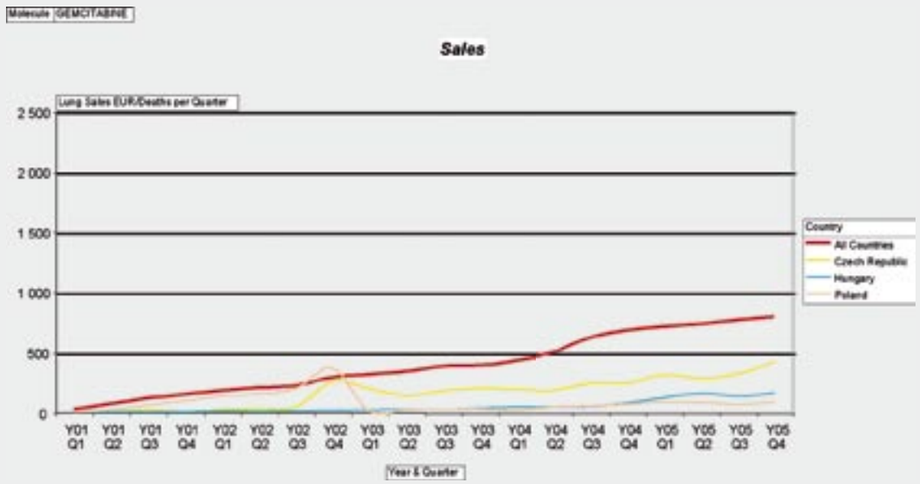


Figure 4.22. Gemcitabine sales per individual dying of lung cancer in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.23.

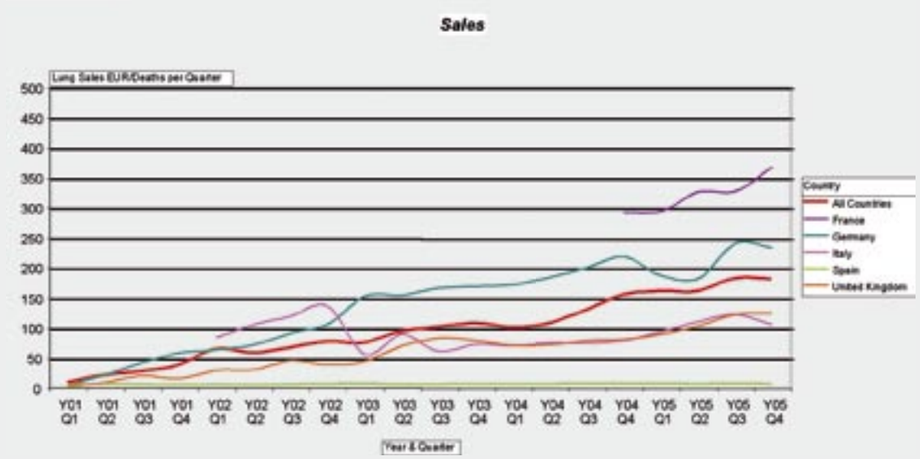


Figure 4.23. Vinorelbine sales per individual dying of lung cancer in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.24.

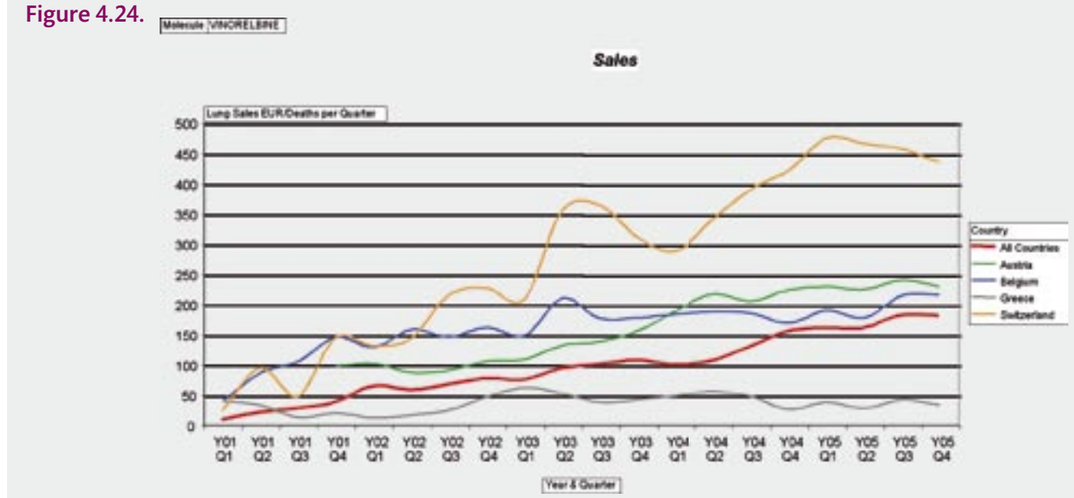


Figure 4.24. Vinorelbine sales per individual dying of lung cancer in Austria, Belgium, Greece, and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.25.

Figure 4.25. Vinorelbine sales per individual dying of lung cancer in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.26.

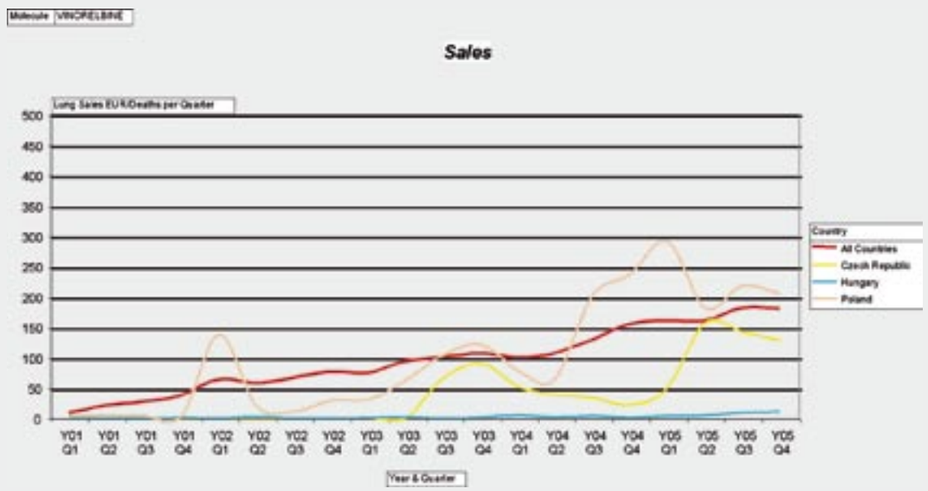


Figure 4.26. Gemcitabine sales per individual dying of lung cancer in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

The data show that Austria and Switzerland are leaders in the uptake of gemcitabine and vinorelbine. The Czech Republic, Greece, Hungary, Norway, Poland and the UK are well below the European average.

4.2.4 Non-Hodgkin's lymphoma

NHL represents another malignant disease in which major breakthroughs have been seen. Rituximab has become an important treatment option and has, with expanding indications, become a standard component in the treatment of NHL. Figures 4.27-4.30 show rituximab sales throughout Europe.

Figure 4.27.

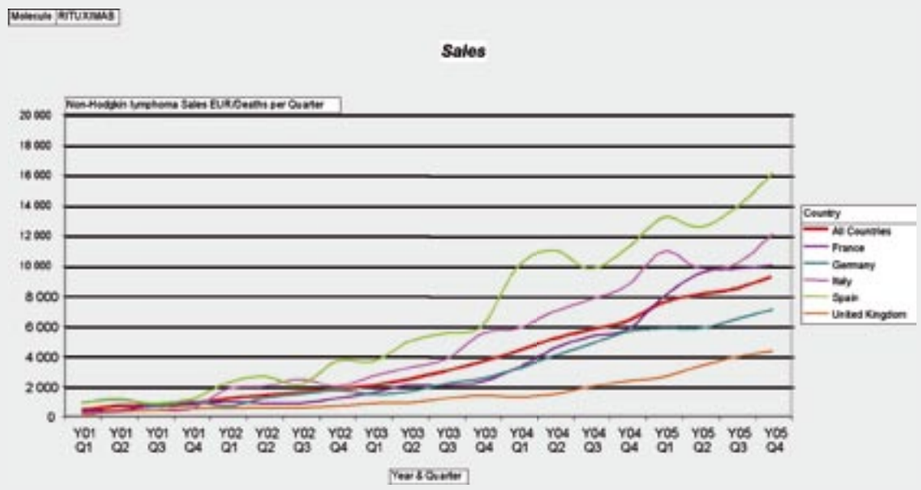


Figure 4.27. Rituximab sales per individual dying of NHL in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.28.

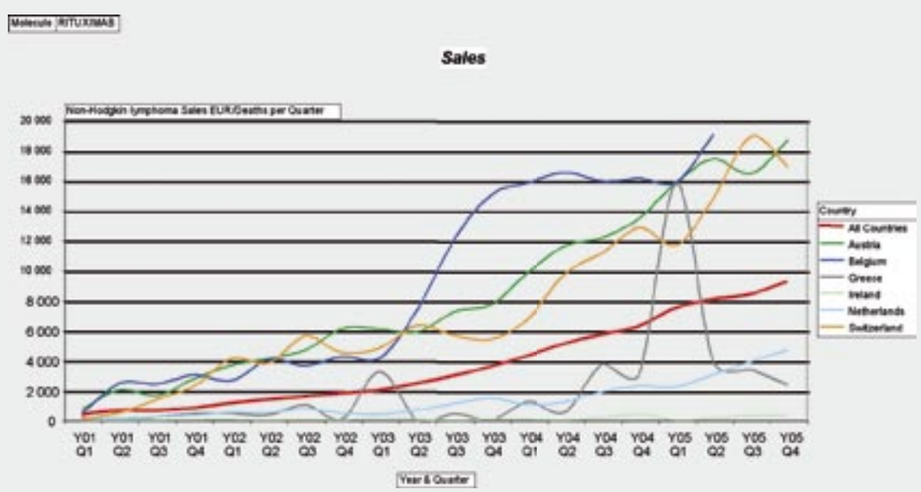


Figure 4.28. Rituximab sales per individual dying of NHL in Austria, Belgium, Greece, Ireland, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.29.

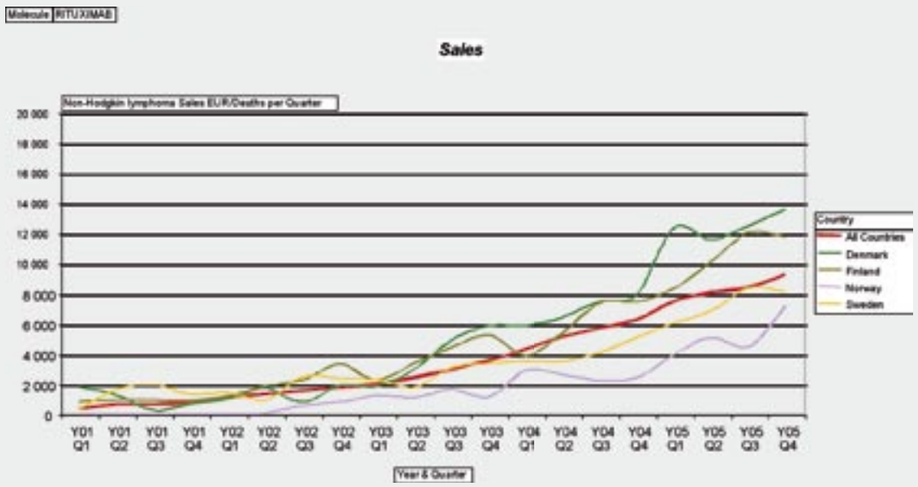


Figure 4.29. Rituximab sales per individual dying of NHL in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.30.

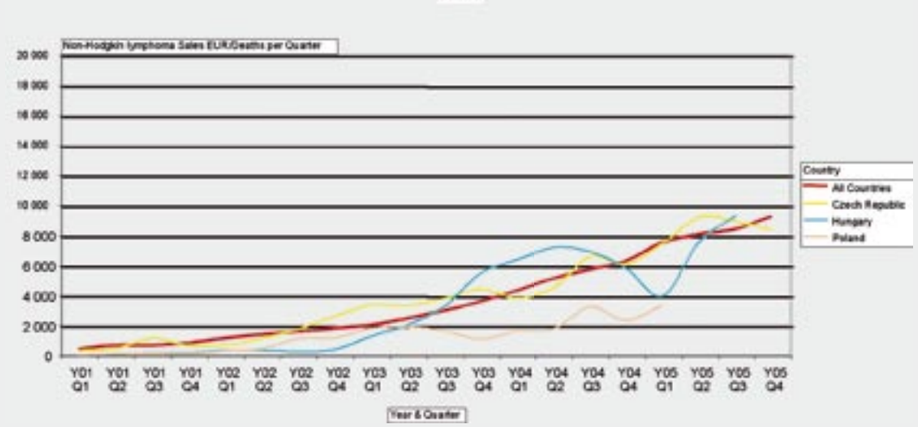


Figure 4.30. Rituximab sales per individual dying of NHL in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

As shown in Figure 4.28, Austria, Spain and Switzerland are leaders in the uptake of rituximab. Most other countries tend to be just below or close to the European average.

4.2.5 Bone pain/management of bone metastases

Figure 4.31 shows the sales of four bisphosphonates (clodronate, ibandronate, pamidronate and zoledronate) in 2004 as an illustration of the supportive care market. The sales are presented per individual dying of cancer according to the respective bisphosphonate.

Figure 4.31.

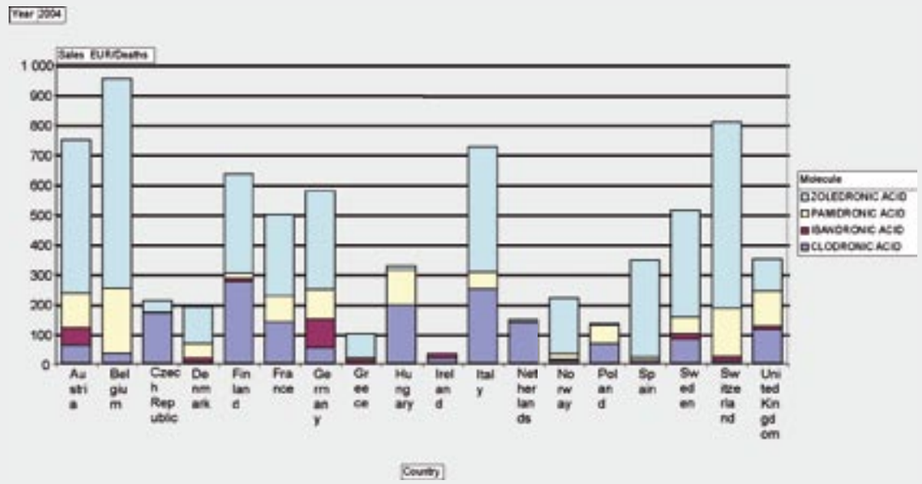


Figure 4.31. 2004 sales of clodronate, ibandronate, pamidronate and zoledronate per patient dying of cancer (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Source IMS Health, IMS MIDAS Quantum / Q4 2004.

As can been seen from this figure, the use of bisphosphonates indicated for metastatic bone disease varies across Europe. The uptake of newer drugs (such as zoledronic acid) also varies across the countries studied. Austria, Belgium, Italy and Switzerland are leaders in the overall uptake of bisphosphonates.

4.2.6 Imatinib

As a comparison to the main tumour types under consideration, we have included imatinib sales for leukaemia in order to illustrate a drug that is considered to have had a rapid uptake in most markets. This drug is an example of a case where the therapeutic agent was specifically developed to target preclinical theories relating to the aetiology of CML. This very specific rationale for treatment efficacy and the fact that CML represents a limited patient population with a limited number of treating physicians seem to have facilitated a uniform and rapid uptake on the European market in all European countries, as illustrated in Figures 4.32-4.35.

Figure 4.32.

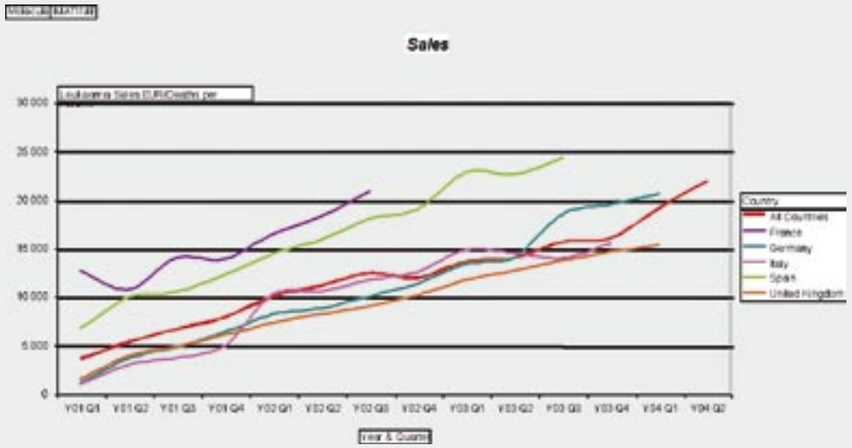


Figure 4.32. Imatinib sales per individual dying of CML in France, Germany, Italy, Spain and the UK (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.33.

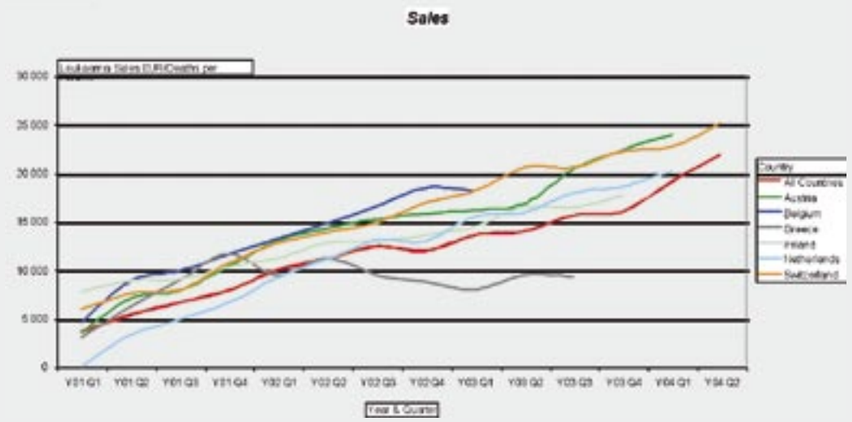


Figure 4.33. Imatinib sales per individual dying of CML in Austria, Belgium, Greece, Ireland, the Netherlands and Switzerland (number of deaths by year to 2000, except for Belgium [1997] and Greece [1999]). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.34.

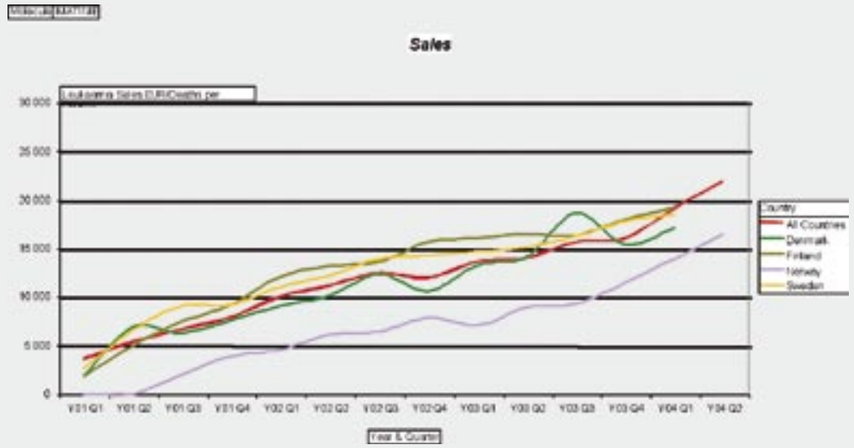


Figure 4.34. Imatinib sales per individual dying of CML in Denmark, Finland, Norway and Sweden (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

Figure 4.35.

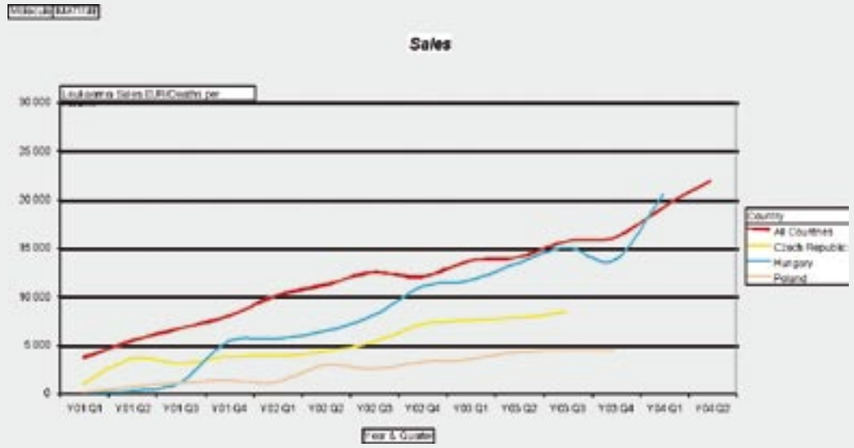


Figure 4.35. Imatinib sales per individual dying of CML in the Czech Republic, Hungary and Poland (number of deaths by year 2000). Year 01 Q1 represents the time of introduction and/or first sales in each respective country. Source IMS Health, IMS MIDAS Quantum / Q4 2004.

4.3 Summary of uptake in Europe

NSCLC has long been an area of therapeutic nihilism in many countries. It was not until a decade ago, when platinum-based chemotherapy was shown to provide a clear benefit for patients with advanced disease, that the development of modern chemotherapy in this area of oncology escalated. We now also have solid clinical evidence that adjuvant chemotherapy will also give substantial benefit in selected patients. Gemcitabine's initial indication was in pancreatic cancer. Within 3 years it was also indicated in NSCLC and then became a cornerstone of combined chemotherapy (with either cisplatin or carboplatin) for NSCLC in Europe. In some parts of Europe, the combination of platinum salts with vinorelbine has become standard. In order to illustrate this development, we show the uptake in NSCLC of gemcitabine and vinorelbine.
There are also new therapeutic options in NSCLC, including EGFR-targeting agents such as gefitinib and erlotinib and chemotherapy with pemetrexed. At present it is too early to comment on the uptake of the most recently approved drugs in NSCLC.

Figure 4.36.

Figure 4.36. Summary of innovative oncology drug uptake in Europe.

4.4 Conclusions

There are great variations both in the level of uptake 3-5 years after introduction and in the speed of uptake for all drugs included in these analyses except imatinib. This highlights the inequality in access and how the ability of cancer patients across Europe to access new cancer drugs depends on where they live.
There could be many factors influencing why uptake and speed of uptake varies between these countries. The next section of this report overviews the investment by public and private sectors in researching new drugs and the process of gaining marketing approval, before we look in more detail at some of the reasons for the variability across Europe and inequality for patients. ■

5. CANCER RESEARCH AND DRUG DEVELOPMENT AND APPROVAL IN EUROPE

Summary

- The development of new innovative drug therapies for cancer depends on a combined effort by public and private investment into cancer research. This includes (1) the discovery of new targets within cancer cells, and in cells interacting with tumours, against which new innovative cancer therapies can be developed, (2) the clinical 'proof of concept' of these new cancer drugs, essentially proving the theory that these drugs are effective and do provide benefit, and (3) the clinical development and clinical trials process to prove efficacy and effectiveness and provide comparisons with established treatments.
- This section highlights the research and development funding for cancer in Europe, examining the role of both public and private sectors.
- €1.43 billion is spent on cancer research per year in Europe by public funding organisations, including charities and governments (50:50). The USA outspends Europe with regard to public funding of cancer research by as much as sevenfold.
- It is estimated that the European pharmaceutical industry spends between €2.1 and €2.5 billion on cancer research per year.
- Today approximately 15% of research expenditure by the pharmaceutical industry is spent on cancer research. This is 2-4 times more than the proportion of cancer drug sales (3.5-7% of total drug sales) vis-à-vis total pharmaceutical sales.
- From 1987 to 2004, 8.1% of all new drugs brought to the European market were cancer drugs (45 oncology drugs out of a total of 555 new chemical entities). Currently the median time for approval of new cancer drugs in Europe is 418 days.

5.1 Public funding for cancer research

The European Cancer Research Managers Forum has recently published the findings of the first survey on cancer research funding across Europe (Figure 5.1).1 Supported by the European Commission (EC), the report provides details of direct funding by non-commercial groups (ie charities), government bodies and other European organisations.
This 'direct' spend includes salaries of researchers, laboratory equipment and any consumables and/or other costs of research.

Figure 5.1.

For the purposes of the survey, research funded by charities (organisations for public benefit that rely on donations for financial support, eg Cancer Research UK) was combined with that of private and not-for-profit organisations (those whose securities are not offered to the public, eg Wellcome Trust). Funding by a government agency was defined as an administrative unit of government, supported in whole or part by public funds, charged by another official body or agency to make reports, investigations or recommendations (eg Medical Research Council or National Institutes of Health).

The survey found that, in total, absolute spending on cancer research in the fiscal year 2002/2003 by public funding organisations across Europe was €1.43 billion, with the EC contributing approximately €90 million over this period. EU Member States accounted for 93% of total funding for cancer research. The EU 15 countries (France, Germany, Italy, Spain, the UK, Sweden, Finland, Denmark, Austria, Belgium, the Netherlands, Luxembourg, Ireland, Portugal and Greece [not including those countries that joined the EU on May 1, 2004]) accounted for just over 50% of this spending.

The National Cancer Institute's Common Scientific Outline is the only validated tool that categorises expenditure according to the research domain. According to those organisations that report their annual research spend according to these research domains, the EU spends proportionally more on basic research and less on clinical research than the USA.

The average spending per country was €44.3 million with a median of €3.9 million; however, this varied greatly across Europe (Figure 5.2):

- *3 countries (UK, Germany and France) spent more than €100 million per year on cancer research*
- *9 countries (Italy, the Netherlands, Sweden, Belgium, Denmark, Norway, Spain, Finland and Ireland) spent more than €10 million*
- *10 countries spent less than €1 million*
- *of all the countries involved in this survey, only Bulgaria failed to report any financial information and only Malta reported a zero spend.*

Figure 5.2.

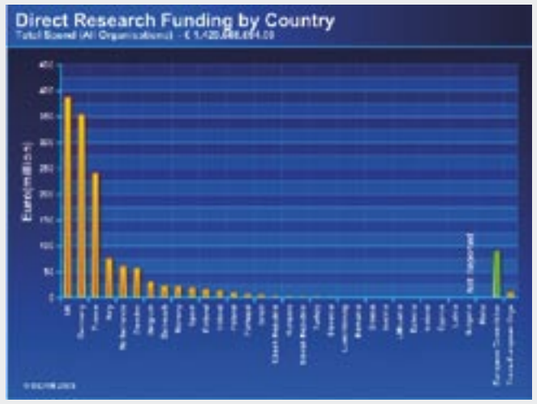


Figure 5.2. Direct cancer research spend by country, including the EC and Trans-European Organisations (2002/2003).[1]

The highest per capita spending was found in Sweden and the UK with just over €7 per capita, followed by approximately €5 per capita in Norway and Germany (Figure 5.3). The average per capita spending on cancer research across the entire EU (including the EC and Trans-European Organisations) was €2.56. However, the spend of the EU 15 countries is €3.67 per capita compared with spend in the USA of €17.63 per capita.

Figure 5.3.

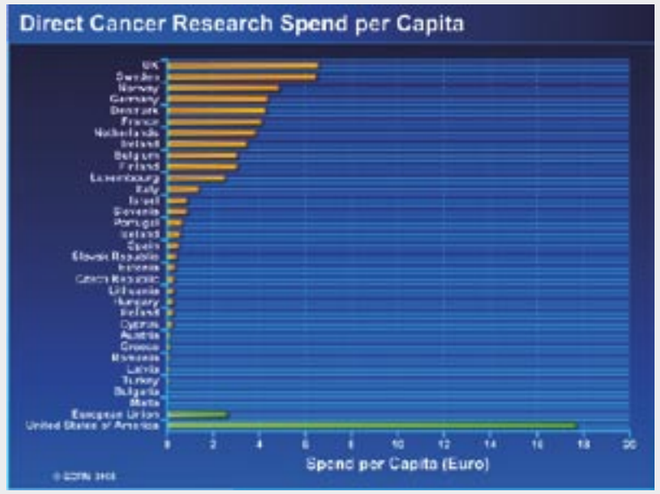


Figure 5.3. . Direct cancer research spend per capita for all Member States in the 2002/2003 survey, as well as the EU and the USA for comparison.[1]

5.1.1 Distribution of cancer research funding between government and the charitable sector

The survey identified 139 different sources of European cancer research funding contributing to the total spend of €1.43 billion for the fiscal year 2002/2003.

Of these sources, 25 accounted for 80% of the total spend on research. Approximately half of public funding for cancer research in the EU (including the European Free Trade Association and Associate States) was provided by the charitable sector.

- 65 major charities across 23 countries contributed around €667.3 million to cancer research; average spending for charities was €21.5 million (median spend of €400,000; ranging between €0 and €232 million)
- 74 governmental sources of cancer research funding across 28 countries reported a spend of €662.3 million in 2002/2003; average spending for government agencies was €21.4 million (median spend of €1.9 million; ranging between €0 and €226 million)
- 8 countries had no charitable organisational spend (Bulgaria, Estonia, Greece, Latvia, Lithuania, Malta, Romania and Slovenia) and 3 countries had no governmental spend (Bulgaria, Cyprus and Malta)
- 11 countries (Cyprus, Denmark, Hungary, Iceland, Israel, Italy, the Netherlands, Norway, Poland, Sweden and the UK) had a charitable spend on cancer research greater than the government spend and 18 countries (Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Ireland, Latvia, Lithuania, Luxembourg, Portugal, Romania, Slovak Republic, Slovenia, Spain and Turkey) had a governmental spend on cancer research greater than the charitable spend (Figure 5.4).

Figure 5.4.

Figure 5.4. Direct cancer research spend by organisation type and country 2002/2003.[1]

5.2 Private/commercial funding for cancer research

The pharmaceutical industry accounts for the overwhelming majority of all private commercial research funding. However, due to the lack of available data, the exact contribution of commercial organisations other than the pharmaceutical industry to cancer research funding cannot be determined. From 1987 to 2004, 45 oncology drugs out of a total of 555 new chemical entities (NCEs) [8.1%] entered the European market. In this report, three different approaches have been used to assess the spending in Europe on cancer research by private commercial organisations.

- *Considering the cost of developing a new drug (NCE) and the number of NCEs entered into the European market. This gives an estimate of the private/for-profit spending supporting the new drugs coming to the European market regardless of where this money is spent.*
- *Estimating the total research and development (R&D) expenditure by pharmaceutical companies in Europe on cancer research as a proportion of the total research expenditure. This approach highlights research spending by the European pharmaceutical industry regardless of whether this spending results in products marketed beyond the EU.*
- *Utilising a worldwide survey of pharmaceutical expenditure according to the disease area (assuming that the share spent on cancer research is the same in Europe as in the rest of the world).*

5.2.1 Cost of an NCE

In 2002, the European Federation of Pharmaceutical Industries and Associations highlighted the increasing costs of developing an NCE over time (Table 5.1).

Year	Reference	Cost of NCE (€ million)
1993	Office of Technology Assessment	307
1997	Myers and Howe	378
2001	DiMasi J., Tufts University – Centre for the Study of Drug Development	895

Table 5.1. Three estimates of the capitalised costs (in € million) of an NCE2.

In this approach to determining pharmaceutical industry funding for cancer research, the total spending for each year was obtained by multiplying the number of oncology NCEs by the cost of a single NCE that same year (Table 5.2).

Years	Number of NCEs	Cost per NCE (€)	Total spending (€)	Spending per year (€)
1990-1994	8	307,000,000	2,456,000,000	491,200,000
1995-1999	19	378,000,000	7,182,000,000	1,436,400,000
2000-2004	12	895,000,000	10,740,000,000	2,148,000,000

Table 5.2. Total spending of oncology NCEs in € between 1990 and 2004, with an interval of 5 years.

This results in an estimate of approximately €24 billion as the total spending over 18 years (1987-2004) to develop new oncology drugs. This represents an average of €1.3 billion per year. Over the past 5 years, the estimated average annual spending on cancer research by the pharmaceutical industry would be in the magnitude of €2.1 billion.

5.2.2 Total R&D expenditure in the European pharmaceutical industry

R&D investment by pharmaceutical companies in Europe has risen more than sevenfold2,3 over the past 20 years and doubled over the past 10 years (to reach €18,800 million in 2001 from €7800 million in 1990). Between 1987 and 2004, 8.1% of all the NCEs that entered the market have been oncology drugs. The second method used to calculate pharmaceutical funding of cancer assumes that this proportion of oncology NCEs to total NCEs is equivalent to that for cancer research as a percentage of total R&D expenditure.

Years	Total R&D expenditure	R&D expenditure in cancer (8.1%)	Total expenditure in cancer per year
1990-1994	45,316,400,000	3,670,628,400	734,125,680
1995-1999	67,863,800,000	5,496,967,800	1,099,393,560
2000-2004	99,860,667,000	8,088,714,027	1,617,742,805

Table 5.3. R&D expenditure for cancer in Europe in €, 1990-2004.

This calculation estimates total R&D expenditure for cancer in 2002 at €1.6 billion (Table 5.3).

5.2.3 Pharmaceutical expenditure according to disease area

The 2004 Centre for Medicines Research International Ltd (CMR) International R&D Factbook provides a comprehensive, up-to-date overview of emerging trends in worldwide pharmaceutical R&D. Source data are derived exclusively from primary sources that include all major pharmaceutical companies and which account for some 80% of the industry's global R&D spend.
In 2003, global pharmaceutical R&D expenditure reached US$50 billion worldwide4 and oncology accounted for 15% of total R&D expenditure, or US$7.5 billion. Europe accounted for about 38% of total R&D expenditure in 2003. Thus, approximately US$3 billion was spent on oncology research in Europe in 2003, or €2.4 billion (an exchange rate of 1.2439 US$/€ has been used).[4] This estimate of private funding into cancer research in Europe - €2.4 billion - is higher than the two previous estimates.

5.2.4 Comparison of different methods of calculating private/commercial funding for cancer research

Thus there are different estimates for private R&D spending:

- *Based on cost of an NCE (2000-2004)* *€2.1 billion*
- *Based on total R&D expenditure in Europe weighted by share of marketed oncology drugs (2003)* *€1.6 billion*
- *Total expenditure in cancer (2003) according to CMR* *€2.4 billion*

CANCER RESEARCH AND DRUG DEVELOPMENT AND APPROVAL IN EUROPE

The estimates give a range of €1.6 to €2.4 billion being invested by the private/for-profit pharmaceutical sector in cancer research. The estimate is probably rather low since the share of research going into oncology has increased over time (it has been noted that the share of cancer publications out of all health economic publications has increased).

Estimating R&D expenditure based on the share for introduced oncology drugs is also inaccurate since this reflects spending in previous periods. It is also important to realise the amount of time and cost needed to develop drugs in different therapeutic areas is not the same. Cancer drugs are more expensive to develop and have higher attrition rates than other drugs, such as anti-infectives. A share of 10-12% for cancer research is more accurate based on this trend of increased investment in cancer research. This would then result in an estimate of €2.1 to €2.5 billion being spent by the European pharmaceutical industry (based on total R&D investment by the European pharmaceutical industry).

5.2.5 Comparison of pharmaceutical industry R&D expenditure to sales

Global pharmaceutical sales reached US$466 billion in 2003.5 Based on data from the CMR, oncology accounts for 7% of total global sales; ie US$33 billion in 2003. The same report states that Europe accounts for about 33% of total global sales. This results in total European sales of oncology drugs of approximately US$11 billion, or €8.8 billion. This estimate is higher than our previous (Table 2.4) estimates of sales of cancer drugs (€5050 million). There are several possible reasons for this. It can occur when the definition of Europe is not the same. Our estimate is also based on drug sales at public prices, which may explain lower cancer drug sales as a proportion of all drug sales. Also, the definition of 'an oncology drug' may differ from our definition, including drugs that have significant sales for other indications as well.

In 2003, companies indicated that they reinvest approximately 15% of their total global sales in R&D (using the R&D expenditure to sales ratio and calculated as a median of data supplied).[5] This is almost double the percentage of new cancer drugs vis-à-vis the total of NCEs introduced (8.1%) in the past 15 years, and is 2-4 times more than the proportion of cancer drug sales (5-8%) vis-à-vis total pharmaceutical sales. This assessment would result in approximately €1 billion being reinvested by the pharmaceutical industry into cancer drug research.
It is therefore possible to conclude that approximately 25% of total cancer drug sales are being reinvested into cancer drug research. This is greater than indicated by traditional measures of sales to R&D investment. Present cancer drug sales represent investment of years past while today's investments will generate new drugs for the future. It can be expected that the share of cancer drugs of total pharmaceutical sales will increase from 5-8% to 12-15%, thus reflecting the share of cancer research in total private/for-profit pharmaceutical company research.

5.3 The process of approval of new cancer drugs in Europe

The introduction of new cancer drugs is dependent on public and private investment in R&D. The public arena is focused on basic research, while the major investment in clinical R&D is made in the private pharmaceutical industry. But investment in R&D is not enough to get new drugs to patients. There is a complicated and time-consuming regulatory process to establish safety, efficacy and quality before a new drug can get a market authorisation or licence. >>>

Forty-five new cancer drugs were introduced between 1987 and 2004, and 39 of these were introduced between 1990 and 2004.

Currently, oncology drugs can be authorised in the EU via two different routes. The Mutual Recognition Procedure can be used for all oncology drugs except biotech products. The Centralised Procedure (CP) can be used for all innovative oncology drugs and has to be used for products manufactured by certain biotechnological processes. Beginning in November 2005, all new oncology drugs will have to be authorised via the CP and thus will be reviewed by the CHMP (Committee for Medicinal Products for Human Use), formerly known as the CPMP (Committee of Proprietary Medicinal Products).

5.3.1 Regulatory approval time lines

In the EU, 20 anticancer agents have been authorised via the CP since its implementation in 1995. The time for regulatory approval of these 20 cancer drugs is shown in Table 5.4.

In this table:

• 'Active time' is the time needed for scientific evaluation by the CPMP and 'clock-stop time' is the time needed by the applicant to answer the objections raised by the authorities as given in the annual reports of the European Agency for the Evaluation of Medicinal Products (EMEA).

• 'Scientific time' is the time needed for scientific evaluation by the CPMP plus the time needed by the applicant for answering the authorities' objections (calculated as the interval between the start of the procedure and the CPMP opinion; theoretically, the sum of the active time and clock-stop time. Yet these times do not always add up exactly to the total review times due to apparently different approximations used in the different sources. Where discrepancies across reports were noted, the time intervals were manually recalculated).

• 'Administrative time' is the time needed for translation, approval of the national product information and publication of the EC decision. According to current EU legislation, the administrative time is foreseen to be 90 days. The administrative time was calculated as the interval between the CPMP opinion and the date of decision of the EC as given in the annual reports of the EMEA.

• 'Total time' is the time needed for the overall duration of the marketing authorisation procedure and was calculated as the interval between the start of the procedure and the date of decision of the EC as given in the annual reports of the EMEA, ie the sum of the scientific time and the administrative time.

CANCER RESEARCH AND DRUG DEVELOPMENT AND APPROVAL IN EUROPE

Trade name	Generic name	EU CP approval	Active time (days)	Clock-stop time (days)	Administrative time (days)	Scientific time (days)	Total time (days)	Administrative time of total time (%)
Fareston	Toremifene	Oct 1995	240	50	138	192	330	42
Taxotere	Docetaxel	Nov 1995	100	93	120	289	409	29
Caelyx	Doxorubicin	Feb 1996	222	150	129	408	537	24
Hycamtin	Topotecan	Nov 1996	154	28	116	185	301	39
Mabthera	Rituximab	Jun 1998	179	132	125	313	438	29
Temodal	Temozolomide	Jan 1999	203	60	96	265	361	27
Beromun	Tasonermin	Apr 1999	188	204	145	391	536	27
Paxene	Paclitaxel	Jul 1999	179	251	173	432	605	29
Myocet	Doxorubicin	Jul 2000	167	91	92	257	349	26
Herceptin	Trastuzumab	Aug 2000	147	305	95	454	549	17
Xeloda	Capecitabine	Feb 2001	201	159	106	364	470	23
Targretin	Bexarotene	Mar 2001	197	159	133	335	468	28
MabCampath	Alemtuzumab	Jul 2001	203	142	99	349	448	22
Foscan	Temoporfin	Oct 2001	215	238	119	615[2]	734	16
Glivec[3]	Imatinib Mesilate	Nov 2001	119	0	104	121	225	46
Trisenox	Arsenic trioxide	Mar 2002	180	51	138	233	371	37
Zevalin	Ibritumomab tiuxetan	Jan 2004	153	28	113	185	298	38
Faslodex[4]	Fulvestrant	Mar 2004	212	57	111	269	380	29
Velcade[4]	Bortezomib	Jan 2004	175	155	96	331	427	22
Erbitux[4]	Cetuximab	Jun 2004	214	33	97	247	344	28
Mean			182	119	117	312	429	29
Median			184	113	115	301	418	28

Table 5.4. Timelines for regulatory approval of cancer drugs. Adapted from[6]

The median time for regulatory approval of cancer drugs is 418 days. The mean time is 429 days, with a variation from 225 to 734 days. Regulatory time approval has been reduced during the past decade. However, there seem to be opportunities to further reduce the administrative time, which according to the EU legislation is foreseen to be 90 days but is, on average, 117 days (range 92-173).

5.3.1.1 Exceptional circumstances

The current EU drug law (Commission Directive 2003/63/EC) enables marketing authorisation to be granted based on a reduced development programme (eg only based on Phase II studies) under so-called 'exceptional circumstances'. These exceptional circumstances include development for use in a rare condition (eg orphan drug status) or where comprehensive information cannot be provided in the knowledge base currently available or when it would be unethical to collect further data.

In 2000, the EU implemented Orphan Drug legislation, the purpose of which is to facilitate development of drugs for treatment of less frequent cancers such as gliomas, renal-cell cancer or certain haematological tumours. Two out of the 20 investigated oncology drugs have been granted orphan drug status before the initiation of their marketing authorisation procedure (imatinib and arsenic trioxide).

The CPMP Note for Guidance on Anticancer Medicinal Products further explains how to use these provisions in order to facilitate the development of oncology drugs. According to this guideline, a marketing authorisation application can be based on data from uncontrolled clinical trials when there is no approved treatment available and an investigational drug shows outstanding anticancer activity. Additionally, this guideline endorses the use of tumour response as a surrogate end point, if it is justified to predict clinical benefit. Although this anticancer guideline provides no information for development of non-cytotoxic agents, it has been used for the assessment of a number of these agents.

Of the 10 oncology drugs authorised since the beginning of 2001, 6 (60%) were authorised under exceptional circumstances (only 1 had been authorised in this manner by the CP since its inception in 1995 prior to this date). Based on additional clinical data submitted by the applicant, docetaxel has meanwhile received full approval. As the other drugs have only been authorised during the past 3 years they are still regarded to be authorised under exceptional circumstances and have to fulfil post-marketing obligations in order to achieve full approval status. These include alemtuzumab, temoporfin, imatinib, arsenic trioxide, ibritumomab and bortezomib.

5.3.1.2 Accelerated evaluation

Overall, it turns out that the exceptional circumstances provision has been frequently used over the past 3 years to facilitate the marketing authorisation of innovative oncology drugs in the EU. However, only one of the investigated oncology drugs has been authorised using an accelerated evaluation procedure - imatinib.

In 1996, the EMEA provided the first guidance on an accelerated evaluation of products. This guidance gives a scientific review time of 120 days instead of the standard 210 days for drugs that meet the following three cumulative criteria:

- *indicated for treatment of a heavily disabling or life-threatening disease*
- *absence of an appropriate alternative therapeutic approach*
- *anticipation of exceptionally high therapeutic benefit.*

As a consequence of the accelerated evaluation, imatinib has the shortest total time for the EU marketing authorisation procedure (225 days) among all investigated oncology drugs.

CANCER RESEARCH AND DRUG DEVELOPMENT AND APPROVAL IN EUROPE

5.4 Conclusions

Significant investment is being made in cancer research. From a public-funding perspective, the EU lags behind the USA. The pharmaceutical industry prioritises approximately 15% of its research expenditure towards this particular area. Between 1987 and 2004, 45 new oncology drugs were brought to the market. Regulatory time approval has been reduced over the past decade, although the administrative time (for translation and approval of the national product information and publication of the approval decision) remains longer than the target 90 days.

Following market authorisation there is also a time delay for the drugs to be available to patients due to time needed to obtain price approval and public reimbursement in some countries. These time delays vary from country to country. The following section of this report looks at the influence of economic factors, the role of economic evaluations, health technology assessments and budgetary limitations on patient access to new innovative cancer drugs. ■

References

1. European Cancer Research Managers Forum. First survey of cancer research funding in Europe. 2005. Available at: http://www.ecrmforum.org/report/index.cfm.

2. European Federation of Pharmaceutical Industries and Associations. 2001-2002. The year in review. 2002. Available at: http://www.efpia.org/6_publ/annual/Report2002.pdf.

3. European Federation of Pharmaceutical Industries and Associations. The pharmaceutical industry: a key asset to the European economy. Available via: http://www.efpia.org/6_publ/default.htm.

4. Centre for Medicines Research International Ltd, The 2004 CMR R&D Factbook. Chapter 2.

5. Centre for Medicines Research International Ltd, The 2004 CMR R&D Factbook. Chapter 7.

6. Netzer T. The EU Centralized Procedure for marketing authorization of oncology drugs: An in-depth review of its efficiency. Eur J Cancer. In press.

6. MARKET ACCESS FOR CANCER DRUGS AND THE ROLE OF HEALTH ECONOMICS

Summary

- If the issue of inequitable patient access to cancer drugs is to be resolved, the very significant and current issue of how to adapt healthcare, and especially hospital, budgets to accommodate the introduction of new cancer drug therapies must be addressed.

- Following the granting of EU marketing authorisation, price negotiations approval and the granting of reimbursement should be completed within the 180-day time line identified by the EU for when drugs must be available on national markets following authorisation. National price negotiations and reimbursement approval have been identified as other areas that delay patient access.

- Cost-effectiveness is one factor used for decisions on reimbursement in some countries. However, only a few countries require a full economic evaluation to support the decision for reimbursement.

- Cost-effectiveness information is an important part of health technology assessment (HTA) reports published by HTA agencies.

- A significant number of health economic evaluations related to cancer have been published, in particular in the mid and later part of the period from 1990 to 2004. This must be seen as a sign of the growing importance of economic evaluation and cost-effectiveness as considerations regarding market access.

- Europe plays a major role in the production of HTAs and economic evaluations. In particular, the UK is the leader in terms of the number of HTA reports produced, driven by the National Institute for Health and Clinical Excellence.

- Those countries that lead HTA development (the Netherlands, Sweden and the UK) are not the leading countries with regards to patient access to cancer drugs (Austria, Spain and Switzerland).

It can be argued that no obstacle poses more of threat to the optimal uptake of new drugs than the issue of budgetary limitations. Though cancer drugs account for less than 10% of the total healthcare expenditure for cancer (and approximately 3.5-7% all drug costs), they are easily identified. In efforts to manage healthcare or hospital and drug costs, healthcare policy-makers and decision-makers may seek to delay or restrict access to these new innovative drugs. Such actions have very real impact on survival rates of patients.

6.1 The challenge of funding new drugs in a hospital setting

With most cancer drugs being used in hospitals, the problem of adapting healthcare budgets in general, and hospital budgets in particular, for the introduction of new drug therapies is a very real and much-discussed issue. Hospital budgets are more rigid than financing of ambulatory care and it is necessary to plan several years in advance in order to make budgetary space for new treatment alternatives. Therefore, the ability of patients to access cancer drugs is highly dependent on the allocation of appropriate and adequate funding or financial resources within the healthcare systems. >>>

In some cases, hospital-administered drugs are paid for through the financing of inpatient care on a per diem basis through the hospital budget (based on per day of hospital stay), or through a Diagnosis Related Groups (DRG) system, where budget is allocated for hospitalisation costs based on a classification of patients in different disease categories. Payments based on fixed per diem or DRG systems are problematic unless there is budget flexibility to increase the amount of budget available when new drug therapies come to market.

Another issue for hospital budgets is the persistence of what has been called 'budget silos', which prevent the allocation of money from one budget to another (at least in the short term).[1] The introduction of a new drug therapy into the hospital may increase hospital costs but produce tangible benefits to patients, as well as resulting in savings in ambulatory care or social insurance payments. If payments to hospitals from governments, health authorities or healthcare trusts are not flexible, the introduction of new drug therapies can be delayed, as there is no budget to pay for new treatments even if they are cost-effective.

In addition to the challenges in funding new cancer therapies in a hospital setting, certain systemic barriers also exist, further inhibiting patient access. For example, capecitabine, an oral version of 5-fluorouracil, is available to cancer patients undergoing treatment for colorectal or breast cancer and offers an efficacious, more cost-effective and convenient way to take their treatment. Yet some healthcare systems such as Germany (and the USA) provide payment incentives for physicians to use an intravenous administration instead. In the UK, hospitals would lose revenue by shifting from intravenous administration (which is counted as an 'inpatient stay', a factor in determining overall hospital funding) to an oral therapy. Such situations, which provide economic or structural incentives to use a form of therapy that is neither the most cost-effective nor the most beneficial to patients, beg further scrutiny.

Therefore, this very significant and current issue of adapting healthcare, and especially hospital, budgets to the introduction of new cancer drug therapies must be immediately addressed if the issue of inequitable patient access to cancer drugs is to be resolved.

6.1.1 How can new drug therapies be funded?

There are a number of ways in which different countries have attempted to address some of the issues of drug funding.

In some countries (such as France and Germany), separate lists of innovative drugs exist. These may include special funding for the drugs to be accessed outside of the hospital systems or enables hospitals to apply for new cancer drugs placed on the list, allowing them to switch to innovative drugs within the restrictions of their hospital budgets.

In other countries (such as Denmark), there are special initiatives to make budgets available for new medicines, such as the recent decision to allocate 200 million DKK for new cancer drugs.

In addition, in some countries (such as France, Denmark and the UK) national cancer plans that emphasise the need for access to new cancer drug therapies have been put in place.

However, in order to facilitate faster patient access to new cancer medicines, we may need to think more broadly.
Can a policy of separate funding for new cancer drugs be introduced on a wider scale?

Can access to separate funding be combined with the collection of relevant data in the market place to help further define the optimal number of patients who could benefit from the treatment?

As indications for use of new cancer drugs change over time as more evidence is gathered, can a separate funding mechanism be established to cover the cost for new cancer drugs during their first 3 years on the market while data on 'real life' use is gathered?

It is important to distinguish between regulatory decisions regarding (1) the availability of the drug in the national market, (2) the reimbursement of a new drug therapy and (3) health technology assessments (HTAs) by government agencies. As previously highlighted, EU guidance indicates that a new drug therapy should be available in the Member States within 180 days of approval. Following the granting of the EU licence, it should not be necessary to undertake another safety and efficacy appraisal of the new drug in order to make reimbursement decisions. The national decision is whether the drug should or should not be reimbursed and available through the national healthcare system. As we explain later in this section, the requirement for HTAs within this reimbursement process differs from one country to another.

6.1.2 Reimbursement at a national level

Some countries (for example Belgium, the Netherlands and Sweden) have formal mechanisms for making national reimbursement decisions, while in others (mainly the UK and Germany) no specific decisions have to be made before a doctor can prescribe the drug under the reimbursement system. For countries with formal decision processes, part of the reimbursement decision includes a discussion of the price and often the expected sales.

The only two countries in Europe that lack overt restrictions on pricing are Germany and the UK. This does not, however, mean that the authorities in these two countries do not intervene in issues of drug costs. In the UK, the Pharmaceutical Price Regulation Scheme of the Department of Health controls company profits and can ask for price cuts and paybacks from companies. In Germany, there are also reimbursement restrictions in place as physicians bear a greater responsibility for the use of drugs and accountability for how a specific drug will be used against their own office budget.

In some countries, it is not necessary to apply for reimbursement if the drug is used only for hospital inpatients. The rationale for this is that drug costs are part of the overall hospital costs and the hospital pays for the drug costs from its budget that takes into consideration the number and type of patients treated. In these situations it is the hospital that makes decisions regarding availability of new cancer drugs. If drugs used in hospitals are financed outside the regular hospital budget system, administrative rules and regulations for price and volume may apply. Since new cancer drugs may be used in the hospital setting initially but later transferred to ambulatory use, it is sometimes unclear how they should be handled in the reimbursement process. >>>

In France, Italy and Spain, health economic evidence is used for the assessment of new drugs for price and reimbursement decisions. However, budget impact is probably a more relevant factor when hospitals are making decisions regarding availability of new cancer drugs in their own facilities.

In Belgium, Finland, the Netherlands, Norway, Portugal and Sweden there is a formalised decision-making process where economic evaluation and the issue of cost-effectiveness play an important (though not mandatory) role. For Denmark and Switzerland the role of economic evaluation and cost-effectiveness is less evident.

6.1.3 Impact of reimbursement decisions on speed of drug availability

In the 1980s and 1990s, discussions regarding access to new drugs focused on the time lag between application and granting of marketing authorisation. This delay was identified as the first barrier for patient access to new medicines. Additional barriers have since been identified in the form of country-specific negotiations for price approval and the granting of reimbursement.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) approached IMS to prepare a database to be used to analyse delays in market access for pharmaceutical drugs in Europe. The database measures total time delays from marketing authorisation of a new drug to its availability to a patient in Europe and is updated every 6 months. It records the average delay between marketing authorisation and availability of all new active substances (not just cancer drugs) for each country, as well as the rate of availability (measured by the numbers of approved products available to patients under normal reimbursement conditions). Delays due to launch delays are not included. As previously noted, within the EU there is a timeline of 180 days in which new drugs are supposed to be available on the national markets following EU approval.

For each country, all products with an identified first marketing authorisation date during the study period of June 2000-2004 have been included. Products included in the calculation are those for which the appropriate pricing, reimbursement and/or publication dates have been identified. If pricing, reimbursement and/or publication dates are not available, products have been excluded. This includes products awaiting a pricing or reimbursement decision and those for which data have not been found.

The database covers 23 countries and the results for the latest update are shown in Table 6.1.

Combined	No. of products	Average time delay between approval and market access	Maximum time delay between approval and market access	Minimum time delay between approval and market access
Austria	69	82	994	0
Belgium	69	435	1094	28
Cyprus	6	130	250	0
Czech Republic	62	389	1461	31
Denmark	61	54	1084	0
Estonia	41	131	958	0
Finland	76	226	1293	0
France	55	431	1393	58
Germany	82	0	0	0
Greece	73	427	1039	39
Hungary	20	214	548	76
Ireland	69	170	1372	0
Italy	66	345	1049	26
Netherlands	58	259	1201	56
Norway	31	302	1071	20
Poland	106	2190	2190	2190
Portugal	64	361	1524	0
Slovakia	40	453	914	31
Spain	64	327	1382	0
Sweden	68	122	1173	0
Switzerland	42	159	676	26
UK	86	0	0	0
USA	100	0	0	0

Table 6.1. Average time delay between marketing authorisation and effective market access – all products (marketing authorisation 30 June 2000 to 30 June 2004). Status 31 December 2004.[2]

We can see that in Germany (and the USA) there is no reimbursement delay. The figure given for the UK is misleading, as we know that there are significant delays in reimbursement and availability of new drugs due to the impact of National Institute for Health and Clinical Excellence (NICE) reviews. France, Italy and Spain have a delay of approximately 1 year due to the time it takes for the formal reimbursement decision. This is significantly longer than the 180 days stipulated by EU regulation. For Poland, the true delay could not be calculated as no new innovative products have been reimbursed for almost 7 years.

It should also be noted that this measure of patient delay, while applicable to cancer drugs, is not exactly the same. The formal reimbursement process for cancer drugs is not applicable to all countries in the report. In Germany and the Netherlands, for example, cancer drugs used in hospitals are immediately available once the marketing authorisation is granted. Still, the decisive factor for the ability of patients to access new innovative cancer drugs is the availability and allocation of budget within the hospital sector.

Therefore, there are clear opportunities for procedural improvements with regards to access to cancer drug therapies to potentially address some of the current imbalance. These include:

- *expediting the review time for the marketing authorisation of new innovative cancer drugs through the Centralised Procedure (Switzerland has been identified as a leader in terms of patient access to cancer drugs and given their status as a non-member of the EU, they follow their own national approval process).* >>>

- *ensuring that, once a cancer drug has obtained its EU marketing authorisation, it is then available at the national level within 180 days without further delays due to price and reimbursement negotiations and additional restrictions*
- *ensuring that any economic evaluation/HTA regarding a new cancer drug is done expeditiously to facilitate (as opposed to delay) patient access (Austria, Spain and Switzerland have all been identified as leaders in this report: three countries where there is no formal economic evaluation implemented)*
- *ensuring that appropriate and adequate funding for new innovative cancer drugs is included in healthcare system and hospital budgets preferably on a proactive and not retrospective basis.*

6.2 Some policy issues in the allocation of resources for new drugs

The inequities in access to cancer drugs should be debated and efforts must be made to eliminate, or at the very least reduce, these imbalances. The EFPIA survey was recently quoted in relation to the decision by the Greek authorities to extend reimbursement to another 1000 drug therapies in Greece.

When considering whether or not to grant reimbursement or allocate budgetary resources for a new drug or other treatment, one issue that is arising is the uncertainty regarding long-term consequences of the use of new drug therapies. Currently, clinical trial data are used to evaluate the use of the new drug therapy and extrapolate its use in the long term. Payers do express uncertainty, however, regarding the 'real life' use and the future potential of these new drugs before they have been introduced in the market.

One option being explored with regards to uptake of new drugs (there is no specific example to date regarding cancer drugs) has been the concept of 'risk sharing' between the company and the payer. This concept could perhaps be extended to new cancer drugs by the establishment of joint responsibility between the manufacturer and the payer. Here the provision of additional effectiveness documentation in different indications would be done by the manufacturer (when additional indications are granted by the European Agency for the Evaluation of Medicinal Products) in exchange for appropriate budgetary allocation by the payer to make the drug available to patients in the new indications.

While HTA and economic evaluations are helpful to assess the value of new drug therapies in relation to their costs, the allocation of appropriate budgetary resources is a real issue. Costs of new drugs are concentrated in the budgets for medicines in hospitals and ambulatory care settings. Patients will not have access to new medicines and experience the benefits of these new innovative cancer medicines unless budgets are made available, as very few patients can pay for new cancer medicines by themselves.

Cost-effectiveness is one factor used for decisions on reimbursement in some countries. However, only a few countries require a full economic evaluation to support the decision for reimbursement. Table 6.2 indicates how economic evaluations influence reimbursement decisions in different countries. Clearly economic evaluations are country specific due to country-specific costs.[3] It is also clear that different government agencies can use economic evaluations for different policy decisions.

In Sweden, for example, the pharmaceutical benefits board uses economic evaluations as one piece of information for reimbursement.

decisions, the HTA agency uses them as part of technology assessments and the National Board of Health and Welfare (Socialstyrelsen) uses them for treatment guidelines.
The table shows that it is not easy to quantify the influence of economic evaluations. The main conclusion is that economic evaluations are used differently in different healthcare systems. There is no clear and consistent pattern of development, though many countries have introduced them into health policy.

	France	Germany	UK	Italy	Norway	Spain	Sweden	The Netherlands
Institutional requirements of economic evaluation studies (eg NICE, commissions and other expert groups)	[+]	[-]	[+]	[+]	[+]	[+]	[+]	[+]
The existence and design of positive/negative lists	[+]	[+]	[+]	[+]	[+]	[/]	[/]	[-]
Influence of economic evaluation studies on health policy process	[+] Not so many, in face of existence of GEM	[/]	[+]	[/]	[/]	[+] Extent of influence not explicitly mentioned	[/]	[+] More indirectly
Use of economic evaluation studies for old products/patent products and innovative products	[/]	[+]	[+] Stress is on innovative products	[/]	[/]	Not at all - less	[/]	[/]
Influence of economic evaluation studies on pricing and reimbursement of drugs/ medical devices	[+] Studies part of contract with industry	[/]	[-] Influence is through NICE guidance	[+] Studies are supporting	[+] Studies are supporting	[+] Little	[+] Studies are supporting	[+] Studies are supporting
Influence of economic evaluation studies on prescription patterns and treatment guidelines	[/]	[/]	[+] Impact of guidance is uncertain	[+]		[+]	[+]	[+]
Key players in decision making	[+]	[+]	[+]	[+]	[+]	[+]	[+]	[+]
Distribution of knowledge studies of economic evaluation studies at different levels of decision making	[/]	[+]	[+] Less knowledge at lower levels	[/]	[+]	[+]	[+]	[/]
Existence of governmental HTA	[+]	[+]	[+]	[-]	[+]	[+]	[+]	[+]
Influence of economic evaluations for health programmes (eg disease management programmes)	[/]	[-]	[/]	[/]	[/]	[-]	[/]	[/]
Informal and formal requirements and guidelines for economic evaluation studies at present and in future	[/]	[+]	[+] Formal NICE guidelines	[+]	[-]	[+] Informal	[/]	[+]

Table 6.2. Influence and use of economic evaluation studies in decision making in different European countries. Adapted from [3]

6.3 The role of health technology assessments

Cost-effectiveness information is an important part of HTA reports published by HTA agencies. The evaluation involves the study of the medical, social, ethical and economic implications of the development, distribution and use of health technology, classified as prevention, rehabilitation, vaccines, pharmaceutical drugs and devices, medical and surgical procedures.

Reports produced by HTA agencies supporting decision-making in healthcare aim at improving the quality and cost-effectiveness of the use of health technologies. They are intended for those who make choices regarding healthcare options (including professional caregivers, healthcare administrators, planners and health policy-makers). Therefore, HTA assessments can be expected to have a strong influence on market access.

In many cases there is also a direct link between the assessment by the HTA agency and funding for the technology appraised. For example, in the UK there is a direct link between the issuance of a positive guidance on a new drug therapy by NICE and budget allocated for the reimbursement of this new drug therapy by the National Health Service (NHS).

We have performed a review of three databases containing HTA information to answer a number of questions.

- *What is the role of HTAs regarding assessments of new cancer drugs?*
- *What has been the level of development of HTAs by HTA agencies in different countries?*
- *How many economic evaluations related to cancer has been published between 1990 and 2004, and has the number of these reports increased over time?*
- *Which countries prepare these reports?*
- *How many of these reports focus on breast cancer, colorectal cancer, non-Hodgkin's lymphoma (NHL) and non-small-cell lung cancer (NSCLC)?*

To address these questions, we undertook a search of three databases containing HTA information: the HTA database and the Health Economic Evaluation Database (HEED) [both from 1990 to 2004] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) database (from 1998 to 2004)).

6.3.1 The health technology assessment database

The HTA database, created in 1998, is produced in collaboration with the International Network of Agencies for Health Technology Assessment (INAHTA) Secretariat, based at the Swedish Council on Technology Assessment in Health Care (SBU) in Sweden. The INAHTA was established in 1993 to promote cooperation and information sharing between the many organisations throughout the world assessing healthcare technology. The database, which is updated every 6 months, contains records of ongoing projects being conducted by members of the INAHTA as well as publications reporting completed technology assessments carried out by INAHTA members and other HTA organisations. The abstracts in the database are descriptive and give information about publication year, HTA organisation, country and, sometimes, study purpose and type of intervention.

All records in the HTA database consist of publications and projects from nationally funded HTA organisations (Appendix C). In the period 1990-2004, the HTA database covered 58 HTA agencies in 21 countries (Australia, Austria, Belgium, Canada, Chile, Cuba, Denmark, Finland, France, Germany, Hungary, Israel, Malaysia, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, the UK and the USA). Canada, the USA and the UK account for almost half (47%) of all agencies included in the HTA database. Overall, 31 (53%) of the agencies are situated in Europe. The Netherlands, Spain and the UK account for 55% of all the agencies in Europe and the UK alone accounts for seven (26%) of the European HTA organisations.

A total of 3933 HTA reports were published in the period 1990-2004, of which 71% were published from 2000-2004. A peak was reached in 2002, where 661 HTA reports were identified but the number of reports in 2003 and 2004 is somewhat lower. The factors behind the decline in the number of reports published after 2002 are difficult to assess but may reflect a change in the number and type of studies undertaken by the agencies (ie fewer but more comprehensive studies). Figure 6.1 and Table 6.3 show the number of HTA reports (1990-2004) specifically on cancer. A total of 496 HTA reports on cancer were identified, of which 77% were published in the period 2000-2004, again with a peak (of 99 reports) in 2002.

It should be remembered that the published HTA reports do not represent all HTA studies undertaken in the healthcare systems in different countries. Providers and drug formulary committees undertake more or less ambitious studies or ask the companies providing technologies or drugs to do such studies for them as a basis for a decision.

Figure 6.1.

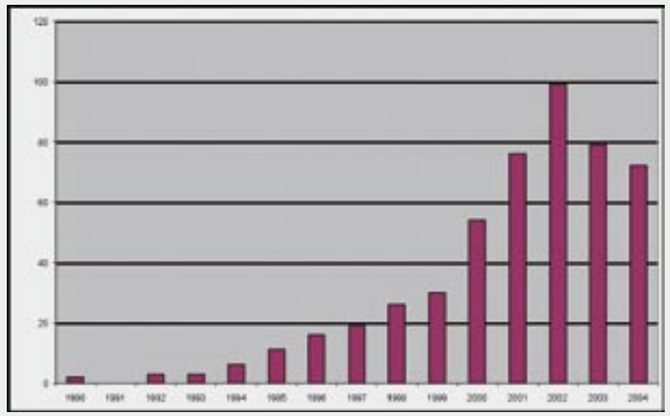


Figure 6.1. Number of HTA reports regarding cancer between 1990 and 2004.

The proportion of all HTA reports focusing on cancer has increased slightly over the past 15 years, from 8% (14/181) in 1990-1994 to 11% (102/956) in 1995-1999 and 14% (380/2796) in 2000-2004.

	1. Colorectal	2. Breast	3. NSCLC	4. NHL	Cancer 1-4	All cancer	All studies
1990						2	9
1991						0	27
1992		1	1		2	3	36
1993		1			1	3	55
1994		1			1	6	54
1995		2			2	11	87
1996	2	5	1		8	16	162
1997	1	2			3	19	187
1998	2	3	1		6	26	207
1999	5	2	2	1	10	30	313
2000	4	11	2	2	19	54	479
2001	9	10	4	3	26	76	560
2002	11	22	6	6	45	99	661
2003	7	9	3	1	20	79	569
2004	4	18	3	2	27	72	527
1990-2004	**45**	**88**	**23**	**15**	**171**	**496**	**3933**

Table 6.3. HTA reports in the HTA database on specific cancers and year of publication.

There were 171 HTA reports on the 4 selected cancers (breast cancer, colorectal cancer, NSCLC and NHL) representing 34% of all cancer HTAs in the period 1990-2004. Of the 496 cancer HTAs found, 18% focused on breast cancer, 9% on colorectal cancer, 5% on NSCLC and 3% on NHL.Table 6.4 illustrates the distribution of reports by the country in which the HTA was located. Fifty-four percent of all the HTA reports were produced in Europe. The UK accounted for 36% of all the reports.

	1. Colorectal	2. Breast	3. NSCLC	4. NHL	Cancer 1-4
Europe	26	41	16	10	93
Austria					
Belgium					
Czech Republic					
Denmark	1				1
Finland	1	1			2
France		2	1		3
Germany		1			1
Greece					
Hungary					
Ireland					
Italy					
Netherlands	1	1	1	2	5
Norway	2	1	2		5
Poland					
Portugal					
Spain	1	6	1		8
Sweden	2	5			7
Switzerland					
UK	18	24	11	8	61
Rest of the world	19	47	7	5	78
Australia	3	2		1	6
Canada	6	10	3	1	20
USA	10	33	4	3	50
New Zealand		2			2
All countries	45	88	23	15	171

Table 6.4. HTA reports in the HTA database on specific cancer diseases and country where the HTA report originates.

Interestingly, despite the amount of HTA activity in the UK, the ability of cancer patients to access new innovative cancer drugs in the UK lags behind other countries, as shown in this report.

6.3.2 The Health Economic Evaluation Database

The HEED has been developed as a joint initiative between the Office of Health Economics and the International Federation of Pharmaceutical Manufacturers' Associations. It contains information on cost-effectiveness studies and economic evaluations of medicines and other treatments and medical interventions.`

Figure 6.2 presents the number of studies in the HEED related to cancer. In total, 2873 cancer studies were identified in the period (11% of all the studies), with a peak in 1997. The decline in the number of published studies started in 1997, several years before the decline in the number of published HTA reports. It is difficult to say if the decline in the number of studies in recent years reflects a decline in the number of studies undertaken or just a decline in the number of studies published. One problem with publication is the long time lag from completion of a study until publication. It may, therefore, be that sponsors of studies have found other ways of making the results available (such as the ISPOR conference meetings discussed in Section 6.3.3).

Figure 6.2.

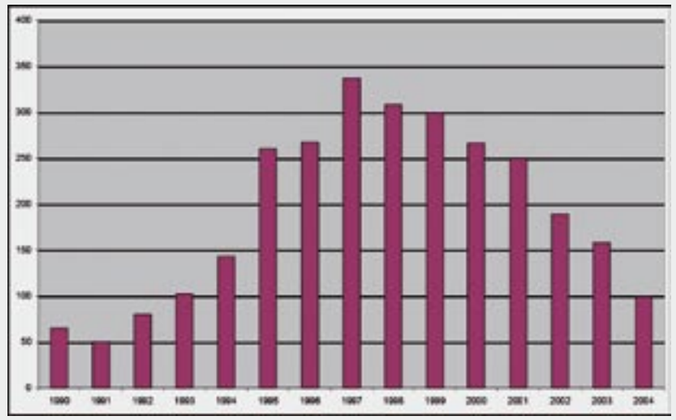


Figure 6.2. Studies included in the HEED related to cancer published between 1990 and 2004.

The percentage of all studies in the HEED focusing on cancer has increased over the past 15 years from 9% in 1990-1994 to 12% in 1995-1999 and 2000-2004.

Table 6.5 demonstrates that studies relating to breast cancer, colorectal cancer, NSCLC and NHL account for approximately 35% of all studies on cancer. Of the specific cancer studies, the largest number were related to breast cancer (17%).

	1. Colorectal	2. Breast	3. NSCLC	4. NHL	5. Leukaemia	6. Prostate	1-6	All cancers
1990	3	0	2	0	1	2	8	65
1991	3	4	0	0	1	3	11	50
1992	0	12	5	0	8	1	26	80
1993	5	12	3	0	5	3	28	102
1994	10	26	15	4	11	12	78	143
1995	22	57	22	4	18	32	155	260
1996	18	52	34	2	19	21	146	267
1997	19	56	34	6	28	32	175	337
1998	26	74	49	9	34	30	222	308
1999	20	57	20	5	24	22	148	299
2000	29	40	20	3	11	16	119	266
2001	13	36	12	4	13	15	93	250
2002	14	26	25	4	16	12	97	189
2003	12	21	12	6	12	10	73	158
2004	11	8	6	4	2	7	38	99
1990-2004	**205**	**481**	**259**	**51**	**203**	**218**	**1417**	**2873**

Table 6.5. Economic evaluations in the HEED on specific cancers by year of publication.

Table 6.6 shows the distribution of economic evaluations in the HEED among different countries (as one study can be applicable to more than one country, there is a difference in total number of studies between Table 6.5 and Table 6.6).

	Colorectal	Breast	NSCLC	NHL	Leukaemia	Prostate	All cancers
Europe	71	193	110	19	89	64	546
Austria	1	0	0	0	0	0	1
Belgium	1	2	3	0	1	0	7
Czech Republic	0	0	0	0	1	0	1
Denmark	2	2	1	0	0	2	7
Finland	0	5	1	1	2	0	9
France	3	18	9	2	13	4	49
Germany	9	10	12	4	9	1	45
Greece	1	1	2	1	1	1	7
Hungary	0	0	0	0	0	0	0
Ireland	0	0	0	0	0	0	0
Italy	8	23	17	2	13	8	71
Luxembourg	0	0	0	0	0	0	0
Netherlands	7	28	15	3	8	8	69
Norway	4	9	3	1	2	4	23
Poland	1	0	1	0	0	0	2
Portugal	0	0	0	0	0	0	0
Spain	3	9	8	0	5	3	28
Sweden	6	16	5	2	9	18	56
Switzerland	1	0	4	0	5	0	10
UK	24	70	29	3	20	15	161
Outside Europe	127	331	172	26	113	138	907
Australia	6	24	5	0	4	3	42
Canada	14	45	39	5	16	16	135
Japan	5	7	10	1	5	7	35
USA	100	246	117	19	86	112	680
New Zealand	2	9	1	1	2	0	15
International	17	32	11	5	16	15	96
All countries	**215**	**556**	**293**	**50**	**218**	**217**	**1549**

Table 6.6. Economic evaluations in the HEED on specific cancers by country.

Within Europe, 29% of the studies are applicable to the UK. However, this does not imply that these studies are used as a basis for decision-making in the UK, only that studies are using UK costs in their own studies. The high number of studies for the USA and UK may correlate more with the high number of health economists in these countries than the actual use of such studies for regulatory and management decisions. This is because health economists prefer to include their own country as at least one of the countries in the study where the technology is applied.

6.3.3 The International Society for Pharmacoeconomics and Outcomes Research

ISPOR represents healthcare researchers and practitioners (including pharmacists, physicians, economists, nurses and researchers from academia, the pharmaceutical industry, government, managed care, health research organisations and purchasers of healthcare). ISPOR promotes the science of pharmacoeconomics and health-outcomes research.

The mission of ISPOR is to translate pharmacoeconomics and outcomes research into practice to ensure that society allocates healthcare resources wisely, fairly and efficiently. ISPOR meetings began in 1998 and take place twice a year split between Europe and the USA. The first Asia-Pacific conference was held in Japan in 2003. The research papers presented at these meetings (covering 1998-2004) are collated in the ISPOR Research Digest electronic database.

From 1998-2004, 4684 abstracts are available. Figure 6.3 illustrates that the number of ISPOR abstracts related to cancer has increased in the period 1998-2004 from 14 in 1998 to 93 presented in 2004.

Figure 6.2.

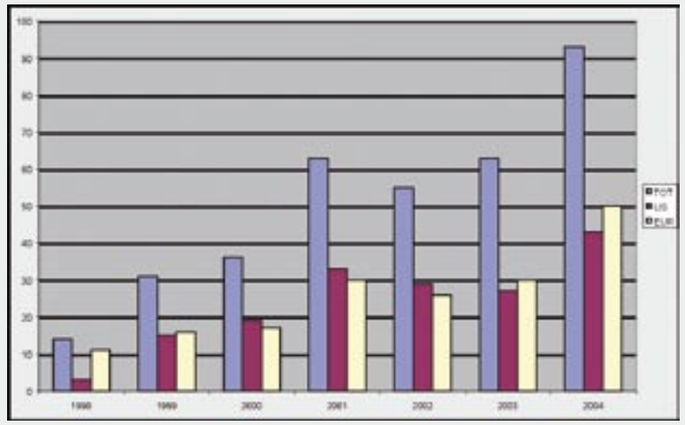


Figure 6.2. Studies included in the HEED related to cancer published between 1990 and 2004.

The studies in the ISPOR database cover the following topics: clinical outcome studies (n=256), cost studies (n=2031), healthcare use and policy studies (n=888), method and concept studies (n=854) and patient-reported outcome (n=656). Therefore, cost and healthcare use and policy studies represent 62% of all the abstracts contained in the ISPOR database.

Between 1998 and 2004, 8% of all abstracts related to cancer: 21 clinical outcomes studies, 187 cost studies, 34 healthcare use and policy studies, 60 method and concept studies and 53 patient-reported outcome studies. Therefore, cost and healthcare use and policy studies represent 62% of all the ISPOR cancer-related abstracts.

Colorectal cancer, breast cancer, NSCLC and NHL constitute 46% of all cancer studies. Table 6.7 shows the distribution of policy and cost studies within the different cancer types.

	Colorectal	Breast	NSCLC	NHL	Leukaemia	Prostate	All cancer
1998	1	1	1	0	0	0	9
1999	2	4	0	0	0	5	22
2000	5	7	0	1	1	1	24
2001	4	7	5	0	0	2	34
2002	7	3	7	3	1	4	41
2003	4	7	3	0	2	3	40
2004	2	13	13	1	3	3	51
1998-2004	25	42	29	5	7	18	221

Table 6.7. Cost and health policy abstracts in the ISPOR database according to cancer type and year of presentation.

Fifty-seven percent of all abstracts were presented at European meetings. For colorectal and prostate cancer, 44% and 28% of the presentations, respectively, originate from Europe. For breast cancer and NSCLC, 57% and 79% of the presentations, respectively, originate from Europe.

6.3.4 Main European HTA developers

This review has shown that a significant number of health economic evaluations related to cancer have been published, in particular in the mid and later part of the period 1990-2004. These evaluations have been undertaken by publicly funded agencies established to evaluate and provide information on new medical technologies, by health economists employed in the pharmaceutical industry and by independent researchers often funded by government and/or industry. This activity must be seen as a sign of the growing importance of economic evaluation and cost-effectiveness as considerations regarding market access.

Europe plays a major role in the production of HTA reports and economic evaluations. In particular, the UK is the leader in terms of the number of HTA reports produced and in terms of being the country for which a majority of economic evaluation studies are undertaken. This reflects the leading role the UK has had in development of health economics in Europe and, in particular, the methodology of economic evaluation.

One other explanation of the UK's leading role in the HTA area is NICE, the driving force behind the majority of the HTA reports being produced. Although NICE was only established in 1999, it has rapidly gained a strong position in producing guidance to the NHS on the use of new and existing drug therapies in England based on clinical and economic evidence.[4]

NICE issues guidance for England; the Scottish Medicines Consortium (SMC) issues guidance for Scotland and the All Wales Medicines Strategy Group issues guidance for Wales. Currently NICE produces guidance in four areas:

1. *Technology appraisals - guidance on the use of new and existing medicines and treatments within the NHS in England*
2. *Clinical guidelines - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England*
3. *Interventional procedures - guidance on whether interventional procedures used for diagnosis or treatment are safe enough and work well enough for routine use in England*
4. *Public health.*

Referral of a drug therapy to NICE for appraisal can take up to 18 months. Once a product is referred for NICE review and guidance, the actual time line is a minimum of 62 weeks. In contrast, the actual time line for a review by the SMC is 3 months.

NICE has been approached to share its process and guidance internationally. All information on NICE decisions is available on the internet and there is an obvious (though difficult to measure) impact on the decisions made by NICE on other countries.

The impact of a review and issuance of NICE guidance regarding a product or class of products is significant. For example, there are indications that the taxanes achieved more rapid use in the UK due to the positive NICE assessment and guidance provided to the NHS. While a positive NICE review may lead to a more rapid uptake and faster patient access to treatments, there is an issue with the capacity of NICE to undertake such reviews in a timely fashion. Also, during the period that no NICE review exists, no resources are allocated by the NHS. This leads to a delay before the new drug therapy is introduced and available to patients and physicians, and is commonly referred to as 'NICE blight'.

In addition to the UK, the Netherlands, Spain and Sweden are also active producers of HTA reports. In Sweden, the SBU was established in 1987 and has played an important role in creating the international network of HTA agencies.

6.3.4.1 Unanswered questions

While most of these agencies agree that the benefits should be measured in terms of improvements in quality-adjusted life years (QALYs), there is a lack of general agreement on which costs to include: Sweden uses a social cost perspective, the UK uses a restrictive NHS cost perspective and the Netherlands is somewhere in between. Furthermore, it is critical that economic evaluations do not delay patient access to new drug therapies.

Another potential issue to consider with QALYs is the threshold value used to determine whether a drug is cost-effective. Different countries may use different QALY values, which are either published or recognised unofficially. For example, the Netherlands has an unofficial cost per QALY of €18,000, while NICE's cost is acknowledged to be £30,000 per QALY.

However, it is important to consider whether these thresholds are still applicable to the evaluation of new cancer drugs where they are used in combination with other drug therapies such as chemotherapy. Other questions are whether the same threshold should be used for cancer drugs as for other interventions such cardiovascular drugs and whether adherence to these QALYs in the area of cancer treatment restricts, delays or prevents access to new drug therapies. >>>

Perhaps more controversially we could ask whether economic evaluations and cost-effectiveness have a role with regards to cancer drugs and whether there is another way to evaluate the cost benefit of these drugs.
Activities are now underway in Europe to establish a more formal European network of HTA agencies. Since technology assessment is based on a common pool of scientific studies, there are possible economies of scale of collaboration over national borders, at least in the collection and assessment of available scientific information. It can be expected that different countries may draw different conclusions from the results. However, it is a safe prediction that there will be more international cooperation in this field in the future.

6.3.5 Conclusions

Increasingly stretched healthcare budgets are faced with growing needs and demands of the population, increasing costs for new cancer drugs. Variations in the use of new drugs in different countries have increased the focus on the development of policies to guide the use of new medical technologies and, in particular, new drug therapies. This is reflected in the number of health economic evaluations and HTAs in general, and in cancer in particular.
Of the 19 countries included in this study, only 4 are actively involved in HTA. This does raise a question regarding the role of economic evaluation with regards to the availability of new innovative cancer drugs. For example, of the countries identified in this report as leading with regards to patient access to cancer drugs (Austria, Spain and Switzerland), only Spain designates a role for HTAs in their decisions regarding adoption of new cancer drugs.
Cancer patients are dependent on reimbursement and publicly funded healthcare systems that function well and allocate appropriate budgetary resources to new drug therapies. In the next section, Dr Frank Lichtenberg from Columbia University highlights how better access to more and new innovative cancer drugs brings survival benefits to patients. ■

References

1. Garrison L, Towse A. The drug budget silo mentality in Europe: an overview. Value Health 2003; 6 (Suppl 1): S1-S9.

2. Phase 3 Report 26 May 2005. PATIENTS W.A.I.T. Indicator Commissioned by EFPIA. IMS Global Consulting.

3. EUROMET 2004. The Influence of Economic Evaluation Studies on Health Care Decision-Making. A European Study. Eberhardt S, Stoklossa C, Graf von der Schulenburg JM (eds). Amsterdam, The Netherlands: 2005.

4. Bosanquet N, Sikora K. The economics of cancer care in the UK. Lancet Oncol 2004: 5: 568-574.

7. PHARMACEUTICAL INNOVATION AND CANCER SURVIVAL: US AND INTERNATIONAL EVIDENCE

Summary

- **This is a comment by Frank R Lichtenberg, Columbia University and National Bureau of Economic Research, 3 August 2005.**

- **This comment is based on two econometric studies of the impact of access to new cancer drugs on cancer survival rates. The first study1 examines the contribution of the introduction of new cancer drugs to increases in cancer survival rates in a single country (the USA) over many years (1975-1995). The second study2 examines the effect of access to new cancer drugs on cancer survival rates in a number of countries in a single year (2000).**

- **The increase in the number of drugs available accounted for about 50-60% of the increase in age-adjusted survival rates in the first 6 years after diagnosis.**

- **The 1975-1995 increase in the overall number of cancer drugs increased the life expectancy of the entire US population by 0.4 years, and new cancer drugs accounted for 10.7% of the overall increase in US life expectancy at birth.**

- **The estimates indicated that an increase in the number of available drugs is associated with an increase in both the 1-year and the 5-year survival rate.**

7.1 The US longitudinal study

The age-adjusted US mortality rate from all malignant cancers was essentially the same in 2000 as it was in 1969. During the same period, the age-adjusted mortality rate from all other causes of death declined by 38%. This may give the impression that the US war on cancer has been a failure. However, the relative stability of the cancer mortality rate is the result of two offsetting trends: an increase in the cancer incidence rate, and an increase in the relative survival rate. The increase in 5-year relative survival from all malignant cancers from 1975-1979 to 1995 (50.0% to 62.7%) is not due to a favourable shift in the distribution of cancers. A variety of factors, including technological advances in diagnostic procedures that led to earlier detection and diagnosis, have probably contributed to this increase.

The main objective of the first study has been to assess the contribution of pharmaceutical innovation to the increase in cancer survival rates. Only about one-third of the approximately 80 drugs currently used to treat cancer had been approved back in 1971, when the war on cancer was declared. In other words, there has been a three-fold increase in the size of the cancer drug armamentarium in the last three decades.
The percentage increase in the survival rate varied considerably across tumour types. For example, the survival rate for colon cancer increased from 41% to 63%, while the survival rate from prostate cancer increased from 43% to 98%.[3] We hypothesised that these differential rates of progress were partly attributable to different rates of pharmaceutical innovation for different types of cancer.

7.2 The International cross-section study

In the second study we investigated the effect of availability of new drugs on survival from 17 types of cancer in more than 35 countries. The data come from three different sources:

- *The GLOBOCAN 2000 database.*[5] *This database provides data on incidence and survival, by country, by tumour type. It has been built up using the huge amount of data available in the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer (IARC), part of the World Health Organization. These incidence data are collated from national cancer registries*
- *The Cancer Care Ontario (CCO) Formulary.*[6] *This is a standardised reference and operational compilation of cancer drug monographs, chemotherapy regimens, and supportive care and symptom control regimens. It provides data on drugs, by tumour type, and includes uses approved by the Therapeutic Products Programme of Health Canada as well as 'other uses' that have been reported in the literature.*
- *IMS Lifecycle New Product Focus.*[7] *This database monitors initial launches of new branded and generic pharmaceuticals, enabling identification of manufacturer, date and country of launch, composition, indication, dosage, and packaging and price at first launch for over 225,000 product launches in 69 countries since 1982.*

These data are used for estimating a model that included both fixed cancer-type effects and fixed country effects, which control for all determinants of cancer survival that are invariant across cancer types within a given country and that are invariant across countries for a given cancer type.

SURVij = , ln(N_DRUGij) + ·i + ‰j + Âij 1
Where:
SURVij = the (1-year or 5-year) survival rate for cancer type i in country j
N_DRUGij = the number of drugs for cancer type i available in country j
ai = a fixed effect for cancer type i
dj = a fixed effect for country j
eij = a disturbance

Due to inclusion of fixed cancer-type and country effects in the model, , represents the effect of relative drug availability within a country on relative survival rates within the country. Suppose that, on average (across all countries), the survival rate of cancer type A is 25% higher than the survival rate of cancer type B, and the number of drugs for cancer type A is 35% higher than the number of drugs for cancer type B.

Then one would expect that if, in a particular country, the number of drugs for cancer type A is only 20% higher than the number of drugs for cancer type B, the survival rate of cancer type A is less than 25% higher than the survival rate of cancer type B. Indeed, estimation of the model requires that the relative availability of drugs for different cancer types varies across countries.

The number of post-1982 new chemical entities by country and tumour type is shown in Table 7.1. The European countries included in the study generally show a higher number, with the mean varying between 4.2 in Finland and 1.1 in Portugal.

	Mean, all sites	Bladder	Brain, nervous system	Breast	Cervix uteri	Colon/rectum	Kidney etc.	Leukaemia	Lung	Melanoma of skin	Multiple myeloma	Non-Hodgkin's lymphoma	Oesophagus	Ovary etc.	Pancreas	Prostate	Stomach	Testis
Mean, all countries	3.0	4.5	2.2	9.6	0.9	1.6	1.4	5.8	6.8	1.0	0.3	3.7	0.8	3.7	0.8	4.6	3.2	0.9
Canada	4.2	6	3	14	1	3	2	8	9	1	1	5	1	5	2	6	4	1
Finland	4.2	6	3	14	1	3	2	9	9	1	1	5	1	5	1	6	4	1
Denmark	4.1	6	3	13	1	2	2	9	9	1	1	5	1	5	1	6	4	1
USA	4.1	6	3	13	1	2	2	8	9	1	1	5	1	5	2	6	4	1
Italy	3.9	6	3	13	1	3	2	7	9	1	0	5	1	5	1	5	4	1
Switzerland	3.9	6	3	12	1	3	2	9	8	1	0	5	1	5	1	5	4	1
Netherlands	3.9	6	2	10	1	2	2	9	8	1	1	5	1	5	2	6	4	1
Argentina	3.8	6	3	11	1	2	2	8	9	1	0	4	1	5	1	6	4	1
Sweden	3.8	6	3	11	1	1	1	9	8	1	1	5	1	5	1	6	4	1
Mexico	3.8	6	3	11	1	2	2	7	9	1	0	5	1	4	1	6	4	1
UK	3.8	5	3	13	1	3	2	8	8	1	1	4	0	5	1	5	3	1
Australia	3.7	6	3	10	1	3	1	8	8	1	0	5	1	5	1	5	4	1
Brazil	3.7	6	2	13	1	2	2	5	9	1	0	4	1	5	1	6	4	1
Thailand	3.7	6	3	12	1	1	1	8	9	1	0	5	1	5	1	4	4	1
Philippines	3.6	6	2	12	1	3	1	5	9	1	0	5	1	4	1	5	4	1
Austria	3.5	4	3	13	1	2	2	6	7	1	1	4	1	4	1	4	4	1
Belgium	3.5	5	3	13	1	1	1	6	8	1	0	5	1	4	0	5	4	1
Japan	3.5	6	2	9	1	1	1	7	9	1	0	5	1	5	1	5	4	1
Greece	3.4	6	2	12	0	2	2	6	8	1	0	4	1	4	1	5	3	0
Ireland	3.2	3	1	12	1	3	2	8	5	1	1	5	1	3	0	4	3	1
Turkey	3.2	5	2	9	1	1	2	6	8	1	0	3	1	5	1	5	3	1
Spain	3.1	5	3	10	1	1	1	4	7	1	0	5	1	3	1	5	4	1
Chile	3.1	5	3	8	1	1	2	5	6	1	0	5	1	4	0	5	4	1
France	3.0	4	1	11	1	1	1	5	6	1	1	4	1	4	0	6	3	1
Pakistan	2.9	6	2	9	1	0	1	4	8	1	0	4	1	4	1	3	4	1
New Zealand	2.9	4	3	8	1	2	1	6	6	1	1	3	1	3	1	4	3	1
Colombia	2.8	4	2	8	1	3	1	5	5	1	0	4	1	2	1	5	4	1
Indonesia	2.5	4	2	7	1	2	1	4	6	1	0	2	1	3	1	3	3	1
South Africa	2.5	3	2	8	1	2	1	4	6	1	0	3	1	3	1	3	2	1
Israel	2.4	2	1	9	1	1	1	6	4	1	0	3	1	3	0	5	2	1
Egypt	2.3	4	1	6	1	0	1	4	5	1	0	4	1	3	0	4	3	1
Peru	2.0	3	2	4	1	0	1	3	6	1	0	2	1	2	1	3	3	1
Malaysia	1.8	2	3	6	1	0	1	3	4	1	0	1	0	3	0	3	2	1
Ecuador	1.5	3	1	4	0	0	1	2	4	1	0	1	1	2	1	3	2	0
Saudi Arabia	1.5	4	1	4	0	0	1	2	5	1	0	1	0	2	1	2	2	0
Singapore	1.4	1	0	7	0	2	1	4	3	1	1	1	0	1	0	2	0	0
Portugal	1.1	0	1	3	1	0	1	2	1	1	0	1	0	1	0	5	1	1
Venezuela	0.4	0	0	1	0	0	1	1	0	1	0	0	0	0	0	3	0	0

Table 7.1. Number of post-1982 new chemical entities by country and tumour type.

Table 7.2 shows 1-year and 5-year survival rates for all tumour types combined (except skin) for the European countries included in the comparator report. Ireland had 8 leukaemia drugs and 5 lung cancer drugs, while Spain had 4 leukaemia drugs and 7 lung cancer drugs. One might therefore expect the ratio of the leukaemia survival rate to the lung cancer survival rate to be higher in Ireland than it is in Spain

Country	1-year survival rate (%)	5-year survival rate (%)	Annual number of cases	Number of drugs launched
Albania	74	56	6222	
Austria	80	61	36,517	27
Belarus	64	43	30,497	
Belgium	78	58	51,874	22
Bosnia Herzegovina	73	54	12,336	
Bulgaria	65	44	23,610	
Croatia	71	51	20,549	
Czech Republic	68	47	46,802	
Denmark	72	52	25,124	30
Estonia	64	43	5216	
Finland	79	59	21,078	32
France	81	61	268,742	19
Germany	76	58	407,912	
Greece	68	49	38,785	27
Hungary	64	42	49,202	
Iceland	80	63	1071	
Ireland	73	54	13,131	24
Italy	74	55	292,003	28
Latvia	69	49	7662	
Lithuania	70	50	11,694	
Luxembourg	78	59	2054	
Macedonia	74	55	5620	
Malta	73	54	1379	
Moldava	69	49	9413	
Norway	78	58	20,772	
Poland	63	42	134,569	
Portugal	74	53	37,766	
Romania	66	45	59,899	
Russian Federation	64	43	387,524	
Serbia and Montenegro	73	54	32,008	
Slovakia	67	45	18,674	
Slovenia	70	49	7785	
Spain	74	56	161,748	18
Sweden	81	62	42,670	27
Switzerland	80	61	35,444	29
The Netherlands	78	58	69,546	28
Ukraine	65	44	141,102	
UK	67	48	276,590	30

Table 7.2. Cancer survival rates (all sites except skin) and annual number of cases in different countries included in the study.

The estimates indicated that an increase in the number of available drugs is associated with an increase in both the 1-year and the 5-year survival rates. The sample includes both European and non-European countries. Two additional analyses related to this distinction have been performed:

1. *We estimated survival models using the full sample of countries but allowed the ln(N_DRUG) coefficient to be different in the European and non-European sectors. We saw no evidence of a difference. Availability of drugs seems to have the same effect on cancer survival within Europe as it does in the rest of the world.*

2. *We tried estimating survival models using data for European countries only. This reduces the sample size by 60%. We did not obtain statistically significant results. However, one might well obtain statistically significant results based on European data only using time-series incidence, mortality and drug utilisation data.*

7.3 Conclusions

The two studies indicated that variation in access to new drugs accounts for (1) some of the variation over time in the relative survival rates of North Americans with different types of cancer, and (2) some of the variation across countries in the relative survival rates of people with different types of cancer in the year 2000. Access to new drugs explains a larger fraction of the time-series variation in longevity than it does of the international variation in longevity. The evidence also supported the hypothesis that, ceteris paribus, the probability that a cancer drug has been launched in a country depends on the incidence of cancer cases eligible for treatment by that drug in that country.

In these two studies, access to new drugs was measured by the number of drugs for a particular tumour type that have previously been launched in a given country. This is not an ideal measure: launch of a drug is a necessary condition for consumption but not a sufficient condition. In future research, we hope to extend the analysis using data on utilisation of cancer agents in different European countries presented in this report for further studies of the improved outcome and cost-effectiveness for new cancer drugs. ■

8. CONCLUSIONS

This report has highlighted that patients across Europe do not have equitable access to new innovative cancer drugs. Austria, Spain and Switzerland have been shown to be leaders in terms of adoption and availability of new cancer drugs while other countries, such as the UK and Poland, lag behind. In many of these countries, the data presented in this report illustrate that it is taking too long for patients to experience the benefits of new drugs, many of which are seen as major breakthroughs in the treatment of cancer.

The data on incidence and mortality in this report demonstrate that more patients in Europe are being diagnosed with cancer yet mortality rates are declining, meaning that more patients are living longer with their disease. The exception is in women with lung cancer, where both incidence and mortality rates are on the increase.

Many countries' data on incidence and mortality are not represented in the International Association of Cancer Registries database and there is great variance in the proportion of the data captured in national cancer registries, ranging from only 4% to 100%. The issue of the completeness of incidence and mortality data needs to be addressed if we are to obtain a total and accurate understanding of the cancer situation in Europe.

For the most common cancers, like breast, prostate, colorectal and now also lung cancer, the outcome for patients has significantly improved. These advances have come as a result of improvements in diagnostic methods (meaning patients are identified earlier), the development of surgical techniques and, to a great extent, through innovations in the medical treatment of the disease in the form of drug therapies.

With recognised breakthroughs in treatment for breast cancer, colorectal cancer, non-Hodgkin's lymphoma and chronic myeloid leukaemia, we need to ask why it is that some major therapeutic breakthroughs take so long before they reach patients and why the uptake of new innovative cancer drugs varies from country to country.

As Dr Frank Lichtenberg of Columbia University has pointed out with his analysis in the USA, access to more cancer drugs means improved survival rates for patients. Therefore, with the importance of new drug therapies in the battle against cancer, it is clearly in the best interests of cancer patients that innovative drug therapies are made available as soon as possible after market authorisation. Reduced or delayed access to cancer drugs has a very real impact on patient survival. Further studies are needed to address these issues in a European context to advise policy making.

In this era of healthcare budgets being stretched to meet the needs of patients and a growing and ageing population, the debate on access to care inevitably turns to one of financial or budgetary resources. However, during the course of our work for this report, the lack of available data on the costs of cancer and cancer drugs on a national level was surprising. This is an area that merits additional study for a truly informed debate on the allocation of financial resources for new cancer treatments, including drugs.

We do know, however, that in 2002, 27% of all deaths (1.2 million) in Europe were attributed to cancer, making it the number two killer following cardiovascular disease. In 2004, 1.7 million Europeans living in the 25 EU Member States died from the disease. Yet the total healthcare cost for cancer in the countries included in this report is estimated at €54 billion, or €120 per inhabitant.

This represents only 5% of total healthcare expenditure, a proportion that has been stable for several decades. The cost of cancer drugs represents less than 10% of the total healthcare expenditure for cancer and approximately 3.5-7% of total drug costs.

The report has highlighted opportunities for procedural improvements with regards to access to cancer drug therapies to potentially address some of the current imbalances. These include:

- *expediting the review time for the marketing authorisation of new innovative cancer drugs through the Centralised Procedure*
- *ensuring that once EU authorisation is obtained the drug is available at the national level within 180 days without further delays due to price and reimbursement negotiations*
- *ensuring that any economic evaluation or health technology assessment regarding a new cancer drug, such as reviews by the National Institute for Health and Clinical Excellence (NICE) in the UK, are done quickly to facilitate, and not delay, patient access*
- *ensuring that appropriate and adequate funding for new innovative cancer drugs is available in the healthcare system and hospital budgets preferably on a proactive and not reactive basis.*

While information regarding health technology assessments or economic evaluations is increasingly published and discussed, their impact on decision-making and resource allocation in healthcare is less clear. In some countries, such as the Netherlands, Sweden, Norway and Finland, and to some extent in Italy, France and Spain, health-economic evidence is used for the assessment of new drugs for price and reimbursement decisions. The use of economic evaluations by NICE in the UK is well known.

Providing economic or structural incentives in the healthcare system to use a form of therapy that is neither the most cost-effective nor the most beneficial to patients, as is the case with an oral version of 5-fluorouracil in countries like Germany and the UK (as well as the USA), is also a situation that begs further scrutiny, as it can be a contributing factor to delayed access to a new cancer drug.
We believe that there needs to be a process in place which, most importantly, evaluates the total budget impact of a new therapy, as opposed to focusing only on the cost of the drug. What may look like increased drug cost from a budgetary perspective nonetheless also gives increased benefit to patients and long-term societal benefits.

In some countries, such as France and Germany, there are separate lists of innovative drugs that may include special funding for the drugs to be accessed by patients outside of the hospital setting. In other countries, such as Denmark, there are special initiatives to make budgets available for new medicines. Also, countries such as Denmark, France and the UK have national cancer plans where the need for new cancer drug therapies is recognised.

These different approaches to funding new cancer drugs raised questions for us, such as whether a policy of separate funding for new cancer drugs can be introduced on a wider scale, thus facilitating faster patient access to these new drug therapies. We should also ask whether this access to separate funding can be combined with the collection of relevant data in the market place to help further define the optimal number of patients who could benefit from this treatment. >>>

In most cases the introduction of new innovative drugs means a true increase in healthcare expenditure. However, this increase has to be evaluated with a long-term perspective. The nature of the drug development process and the total cost for drug development (reflecting also the costs for drugs that fail in development) have to be supported by the economic return of drugs during their period on market prior to patent expiry.

This report has shown that the amount of investment into cancer research by the pharmaceutical industry is almost double the percentage of new cancer drugs coming to the European market and is 2-3 times greater than the proportion of cancer drugs with regards to total pharmaceutical sales. These investments represent a strong commitment to developing new cancer drugs and hopes for new treatments that can improve survival and quality of life of cancer patients. But successful research in this field also means a need to reallocate resources from other healthcare sectors to take advantage of the progress. Since research is a long-term process and commitment, there is a need to plan for this today.

Different areas of oncology are also affected differently by the introduction of new drugs. For example, while drug costs in colorectal cancer have increased significantly during the past years, the drug costs for ovarian cancer (which significantly increased in the mid 1990s) have decreased significantly during the past 2-3 years due to the introduction of generic paclitaxel. Also several prostate cancer drugs introduced in the mid 1990s are coming off patent, as are drugs used to treat colorectal cancer.

It is possible that many or most of these new innovative drugs will remain as valuable cornerstones in the medical treatment of cancer for many years after their patent protection has expired. We must remember that for many of the 'new' drugs introduced just a decade or two ago (anthracyclines, taxanes, irinotecan, medical castration, etc) patents will expire in the near future or generic versions are now already available. It remains to be seen if the patent expiries of these drugs create room in the budgets for new innovative cancer drugs being brought to market.

With the introduction of new innovative cancer drugs, clear focus has to be on the following issues.

- *How we can bring new innovative drugs to the optimal patient population in as short a time as possible. This becomes particularly challenging in situations where an abundance of new data in several indications is generated.*

- *Common views on patient benefit are needed, including rapid health technology assessments and evaluations when drugs have been in clinical use for some time.*

- *There is a need for costs and budget impact to be addressed up front. Healthcare systems and the pharmaceutical industry must jointly plan for new drug introductions with a perspective of 1-2 years (as increases in costs greater than 5% are often difficult to address with ad hoc budgetary solutions)*

- *There is a need for society to take a long-term perspective on the entire life cycle of a new drug. This includes the period of the premium as well as the generic phase. For example, many new drugs have been introduced in the treatment of breast cancer and thus the cost of treatment is rapidly increasing. If we take a historical perspective, when tamoxifen was introduced it was seen as an extremely expensive option, while today it is regarded as overall the most cost-effective cancer treatment.*

The report has illustrated the inequities in access to cancer drugs in Europe. We believe that these differences in access to new innovative oncology drugs cannot persist: cancer patients in Europe will not accept that a standard of care available in one European country is not available in other countries.

It is our hope that this report will inspire policy-makers and decision-makers to take action to address these imbalances so that access to new innovative cancer drugs does not become dependent on the patient's country of residence. ■

9. ACKNOWLEDGEMENTS

Professor Jonas Bergh, Karolinska Hospital, Stockholm, Sweden

Professor Tina Dalianis, Karolinska Institutet, Stockholm, Sweden

Professor Bertrand Coiffier, Centre Hospitalier Lyon Sud, Pierre Benite, France

Professor Thierry Le Chevalier, Institut Gustave Roussy, Villejuif, France

Professor Alberto Sobrero, San Martino Hospital, Genova, Italy

Professor Ulrik Ringborg (President of Organization of the European Cancer Institutes [OECI]), Karolinska University Hospital, Stockholm, Sweden

Professor Nicholas Thatcher, Christie and Wythenshawe Hospitals, Manchester, UK

Leif Wixström, Edt AB, Enebyberg, Sweden

Dr. Stefan Manth, F. Hoffmann- La Roche Ltd., Tokyo, Japan

Judith Rogers, F. Hoffmann-La Roche Ltd., Basel, Switzerland

Catherine Steele, F. Hoffmann- La Roche Ltd., Basel, Switzerland

Dr. Willem Verhoofstad, F. Hoffmann-La Roche Ltd., Basel, Switzerland

Roche Business Analytics, Basel

Roche Oncology

APPENDIX A

A.1 BREAST CANCER

Summary

- Breast cancer is the most common cancer in women.
- Advances in the treatment of breast cancer since the 1970s have resulted in a decline in mortality that can be attributed to extensive screening programmes (leading to early detection of the disease) and early surgical intervention combined with medical treatment such as radiotherapy, chemotherapy and endocrine treatment.
- Improved treatment methods have resulted in increased life expectancy in metastatic disease, improved quality of life during chemotherapy and enabled many women to have breast-sparing surgery.
- Recent advances in the knowledge of the biology of the disease and its risk factors have resulted in new, less toxic targeted treatments, such as the monoclonal antibody trastuzumab (targeting HER2-overexpressing cells), and new screening/preventive strategies. Women identified as being at high risk for breast cancer can already take advantage of risk-reducing interventions that are potentially life saving.

A1.1 Epidemiology

Breast cancer, a disease primarily affecting women (although it may occur in men [1%]), has an estimated yearly incidence of 1 million and prevalence of 4 million, globally. The incidence of breast cancer varies widely globally with the highest rates in the USA, Europe (Figure A.1) and Australia/New Zealand. Every year over 300,000 women in Europe are diagnosed with the disease and about 25% of those will have a relapse, the majority within 5 years from diagnosis. The risk of breast cancer increases rapidly with age from 40 years and onwards and the median age at diagnosis is about 60 years. The disease may occur as early as the late twenties, especially in individuals with genetic predisposition.

In most countries, incidence is rising and, in Europe (Figures A.2a,b,c), mortality is decreasing (especially in some countries such as the UK and Germany).[1,2] This can be explained both by increased awareness of the disease and extensive screening programmes leading to early detection of the disease and better prognosis but most of all the use of multimodality treatment combining surgery, radiotherapy, chemotherapy and endocrine treatment. The use of medical treatment pre-surgery (neoadjuvant) or post-surgery (adjuvant) seems to have had a marked impact on the outcome of breast cancer.

Figure A.1.

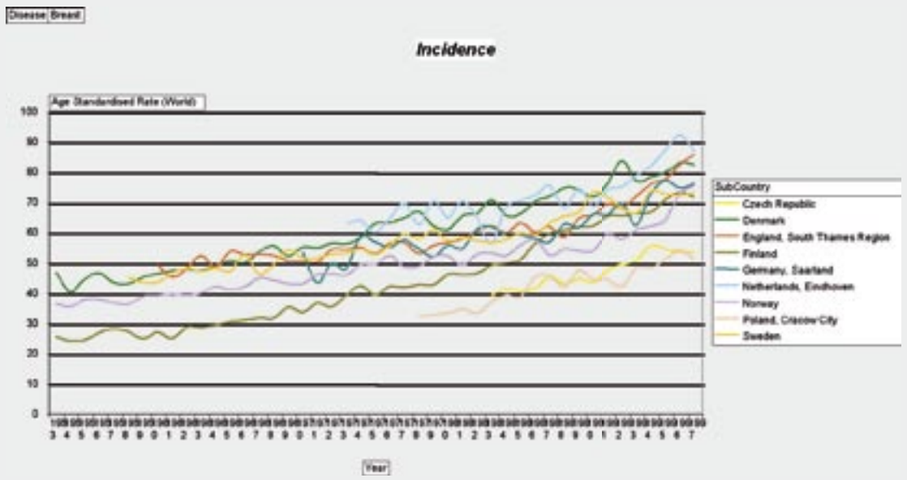


Figure A.1. Breast cancer incidence expressed as the world age-standardised rate (per 100,000) in a selection of European countries (the Czech Republic, Denmark, England, Finland, Germany, the Netherlands, Norway, Poland and Sweden).[1]

Figure A.2a.

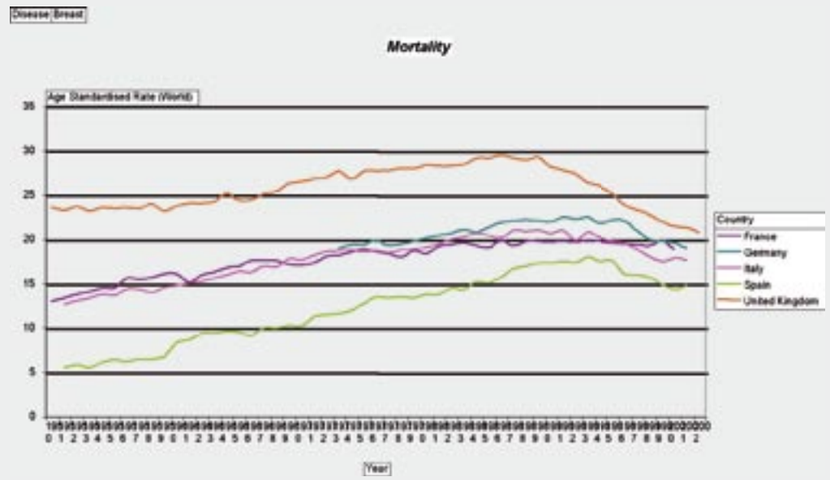


Figure A.2a. Breast cancer mortality expressed as the world age-standardised rate (per 100,000) in France, Germany, Italy, Spain and the United Kingdom.[1]

Figure A.2b.

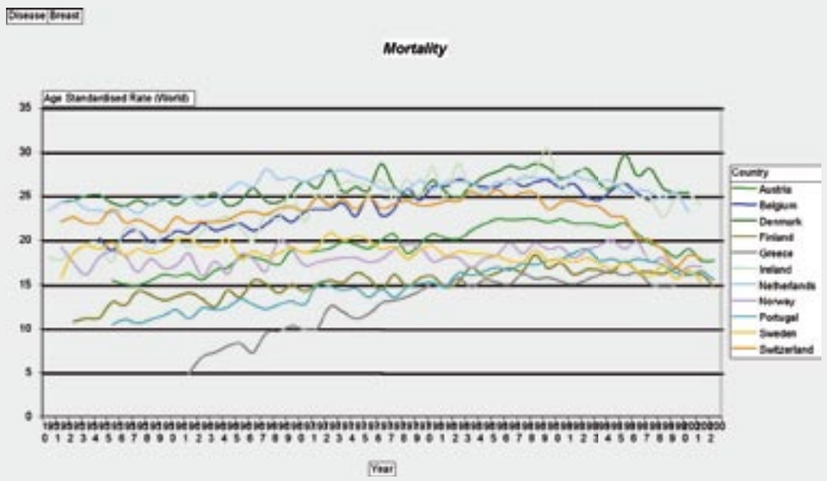


Figure A.2b. Breast cancer mortality expressed as the world age-standardised rate (per 100,000) in Austria, Belgium, Denmark, Finland, Greece, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland.[1]

Figure A.2c.

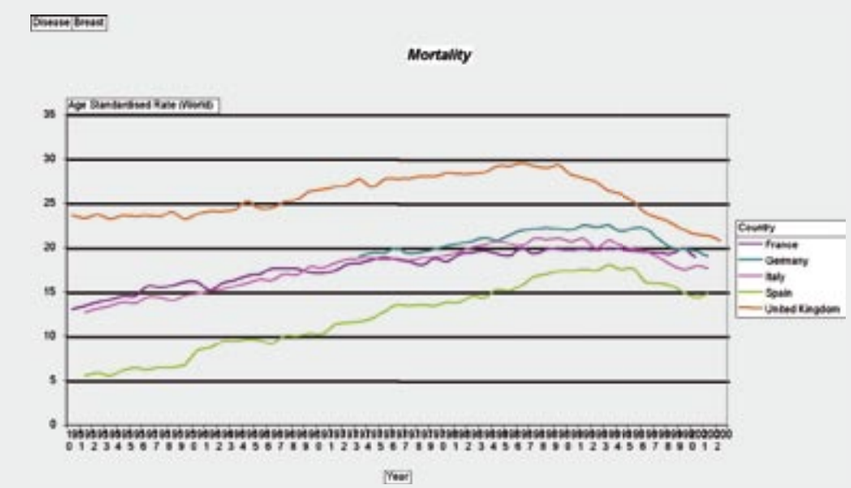


Figure A.2c. Breast cancer mortality expressed as the world age-standardised rate (per 100,000) in the Czech Republic, Hungary and Poland.[1]

A1.2 Aetiology

The causes of breast cancer involve both environmental and genetic factors. The strongest predisposing factor is oestrogen exposure.The risk of breast cancer is increased by early menarche and late menopause, as well as oral contraceptives and hormone replacement therapy at menopause (by as much as 50% for extended combined hormone replacement therapy).[3] In addition, several genes have been discovered that are associated with an increased risk in breast cancer: BRCA1 and BRCA2 are the most well known but it seems likely that more genes may be involved. It is estimated that 10-25% of breast cancers are related to familial predisposition and having BRCA1/2 mutation (approximately 5-10% of all breast cancers)4 increases the risk of developing breast cancer at an early age, bilateral breast cancer or ovarian cancer.[5,6]
A number of environmental and lifestyle factors also affect the risk of developing breast cancer including late childbirth, Western lifestyle with high-calorie diet, high saturated fat consumption and obesity.

A1.3 Screening programmes, clinical presentation and diagnostic tests

The high incidence of breast cancer, and the fact that early intervention increases the chance of cure, has led to screening programmes with repeated mammography (every 1-3 years) in most Western countries in women aged 50-69 years. The value of mammography as a screening method has been questioned. The method is expensive as interpretation can be time consuming and needs to be carried out by experienced individuals. Most countries do not screen women under the age of 50 years as the value is regarded as doubtful. More intense screening programmes with more frequent mammography examinations and sometimes genetic screening for BRCA1/2 are performed in higher risk individuals.

In most cases, the patient seeks medical advice after noticing a lump in the breast. A combination of clinical examination, biopsy and mammography or ultrasound is most commonly used in the diagnosis. In some cases ductography, ductal lavage and also magnetic resonance imaging (MRI) may be indicated, as data have suggested MRI is a superior diagnostic method compared to mammography in women with a high risk of breast cancer.[7] Biopsy material is analysed to establish hormone receptor and HER2 receptor overexpression and proliferation marker analysis is becoming increasingly used. Additionally, analysis of BRCA1/2 is indicated in women with a strong family history of breast cancer. Chest X-ray, ultrasound of the liver, bone scans and positron emission tomography (PET) may be indicated if there is a high risk of distant metastases.

A1.4 Prognosis

Prognosis depends mainly on tumour characteristics and the stage of the disease at diagnosis. The larger and less differentiated the tumour, the worse the prognosis. Spread of the tumour to local lymph glands indicates the tumour may have existed for a longer time and has the potential to metastasise resulting in a poorer prognosis.

About 85% of patients diagnosed with breast cancer are treated with curative intention and approximately 75% of them will never have a relapse. For patients whose disease relapses, recurrence is localised in approximately one-third and these patients may still potentially be cured. >>>

About 8-10% of patients present with locally biologically advanced disease, inoperable at diagnosis. In the 1970s, the 5-year survival rate for patients with locally biologically advanced disease was approximately 10% but with today's neoadjuvant chemotherapy, survival rates have increased to 44-88%.
Approximately 8% of patients with breast cancer present with metastatic disease at diagnosis and therapy is then aimed at palliation rather than cure. The median survival in this group is 2-3 years. It is estimated that, with today's treatment, the number of patients alive after 10 years will increase from 2% to 10%.

A1.5 Prevention

Tamoxifen is approved in the USA (but not in Europe) for the chemoprevention of breast cancer in high-risk populations where the level of risk may justify the side effects associated with treatment. Factors conferring high risk are BRCA1/2 positivity, family history of breast cancer among first-degree relatives or biopsy-proven lobular carcinoma in situ, or atypical hyperplasia (a pre-malignant lesion). Trials have indicated that 5 years of treatment with tamoxifen results in a risk reduction in the development of breast cancer of approximately 50%.[8] Raloxifene, a similar agent, is currently being studied in a Phase III study in postmenopausal women as an alternative chemopreventive agent. Studies also show that statin treatment results in a 51% risk reduction.[9] Other agents that are being studied as chemopreventive agents include several aromatase inhibitors.
Other preventive methods include prophylactic mastectomy and oopherectomy but they are performed only in very high-risk individuals. As the risk of ovarian cancer in also increased in BRCA1/2 carriers, prophylactic oopherectomy has the advantage of removing the additional risk of ovarian malignancy. The risk reduction is highest if performed before the age of 50 years.

A1.6 Treatment
A1.6.1 Local treatment (surgery and radiotherapy)

Of those diagnosed with breast cancer, 85% of patients are treated with surgery and radiotherapy either to the breast only or, if glandular metastasis is detected, to the breast and axilla. This combination enables most women to be operated with breast-conserving surgery with equal clinical outcome to mastectomy. Local radiotherapy decreases the risk of local recurrence in the breast and data also indicate that it reduces mortality.[10,11] The majority of patients (approximately 85%) undergoing surgery for breast cancer receive some form of additional treatment with endocrine agents (if the tumour expresses hormone receptors) and/or chemotherapy in order to eradicate micrometastatic disease.

A1.6.2 Neoadjuvant treatment

During the past 25 years, patients diagnosed with biologically or technically inoperable locally advanced tumours have been treated with pre-operative (neoadjuvant) chemotherapy. Currently, the preferred regimens are combinations of either 5-FU, cyclophosphamide and anthracylcine or taxanes and anthracyclines. Clinically complete or partial responses are seen in 60-90% of cases, enabling surgical treatment (often in the form of breast-conserving surgery).[12,13] Clinical trials are also investigating the role of trastuzumab in neoadjuvant treatment regimens. About one-third of the patients who undergo neoadjuvant treatment followed by surgery are cured of their disease. In patients with hormone receptor-positive tumours, endocrine treatment is sometimes used, especially in older patients who may not tolerate chemotherapy. Pre-operative chemotherapy has also shown beneficial effects in smaller tumours.

A1.6.3 Adjuvant treatment

Approximately 75% of breast cancer patients have tumours expressing hormone receptors and are therefore treated with endocrine agents. Five years of treatment with tamoxifen has been standard treatment since its introduction in the 1970s and reduces the annual risk of recurrence by approximately 40%. Over 15 years, there is a 12% reduction in recurrence and a 9% reduction in deaths from the disease.[14] Aromatase inhibitors have been used in post-menopausal women for several years but only when tamoxifen has been contraindicated or if the tumour was HER2 receptor positive (as a particular benefit has been shown in this sub-group).[15] Recently, evidence has shown that, in post-menopausal women, aromatase inhibitors or sequential treatment with tamoxifen and an aromatase inhibitor have better clinical outcomes than tamoxifen alone.[16-18] This has resulted in the current trend for increased use of aromatase inhibitors.

Adjuvant chemotherapy is given to patients with regional lymph gland involvement, tumours that have a high proliferation rate or that are pathologically considered at 'high risk' of being associated with micrometastatic disease. The combination of cyclophosphamide, methotrexate and 5-FU (known by the abbreviation CMF) was standard during the 1980s and early 1990s but there was a switch to 5-FU, cyclophosphamide and an anthracycline (typically epirubicin in Europe) in the late 1990s after data showed that anthracycline-based regimens resulted in 16% annual risk reduction in mortality.[10] Lately, data have indicated that the use of taxanes (such as paclitaxel and docetaxel), in combination with anthracyclines, is associated with superior clinical outcomes, such as disease-free survival.[19] Data also indicate that dose-dense treatment results improves outcome further.[20]

As with the need to determine hormone-receptor positivity and eligibility for hormone therapy, patients' tumours should also be analysed to determine HER2 status and eligibility for treatment with trastuzumab, a monoclonocal antibody. Studies are ongoing of adjuvant trastuzumab in patients with tumours over-expressing the HER2 receptor. Results of interim analyses from three large trials (HERA, NSABP and Intergroup trials) conducted in patients receiving adjuvant chemotherapy and 1 year of trastuzumab indicate a 50% decreased relapse risk.[21,22] In the combined analysis (of NSABP and Intergroup trials), a 33% reduced mortality risk was observed with a median follow-up of 2 years.[21,22]

A1.6.4 Treatment in metastatic disease

Patients with hormone receptor-positive metastatic disease are treated with endocrine therapy. Currently, patients may receive endocrine treatment first-, second- or third-line and may experience responses lasting from a few months to several years. During recent years, many new endocrine agents have been introduced in clinical trials but final data on overall survival and time to progression are still awaited.
Chemotherapy is initiated in patients with hormone receptor-negative tumours, in patients who have progressed during treatment with endocrine agents or in cases where the disease is progressing rapidly. It has been shown that chemotherapy produces higher overall response rates compared to endocrine treatment even in patients with hormone-sensitive tumours. Combination therapy results in higher response rates and prolonged time to progression.[23] However, the rate of disease progression, comorbidity and physician and patient preferences will influence the choice of therapy. Currently, combinations of 5-FU, cyclophosphamide and anthracyclines or taxanes are used as first- and second-line treatment in most patients under the age of 70 years.

>>>

Single-agent treatment with capecitabine or vinorelbine is also frequently used either as third-line treatment in elderly patients, or in patients for whom the risks of more aggressive chemotherapy outweigh the benefits. CMF is another alternative in elderly patients. In patients with HER2 over-expressing tumours, the monoclonal antibody trastuzumab (with or without chemotherapy) is the standard of care.

In patients with metastatic disease, first-line treatment with the monoclonal antibody bevacizumab, in combination with a taxane, has recently been shown to increase progression-free survival from 6 to 11 months.[24] This treatment has not yet been implemented into clinical practice and the ultimate role of this new agent in the treatment of breast cancer remains to be determined. Previously, a study combining the bevacizumab with capecitabine in patients who had received several lines of chemotherapy improved response rates but did not result in increased progression-free survival.[25]

Approximately 65-75% of breast cancer patients presenting with metastatic disease develop bone metastases (more information on the management of bone metastases is included later in this Appendix). These are associated with debilitating symptoms such as pathological fractures, severe bone pain and spinal cord compression.[26] Solitary liver, lung or brain metastases are treated with surgery or other forms of local treatment such as stereotactic radiotherapy and brachytherapy, which may also be used in skin metastases. ■

A.2 COLORECTAL CANCER

Summary

- **Colorectal cancer is the third most common malignancy after cancers of the breast and prostate. The past decade has seen the introduction of screening programmes in many countries in order to find the tumours at an early stage, aiming at improving survival.**
- **Colorectal cancer was treated with surgery alone up until the 1980s. Since then, 5-fluorouracil (5-FU) plus leucovorin combination regimens have been standard treatment. During the past 10 years, new agents have been introduced and life expectancy has increased from 5 to 20 months in patients with metastatic disease.**
- **Post-operative (adjuvant) chemotherapy treatment in select groups of patients has substantially increased survival.**
- **The addition of biological agents, like the monoclonal antibodies bevacizumab and cetuximab, to chemotherapy has further improved response rates in metastatic disease.**
- **Progress in molecular medicine has led to the identification of several disease-specific targets, resulting in optimism on future treatments with even higher response rates and less toxicity.**

A2.1 Epidemiology

Colorectal cancer accounts for approximately 10% of all cancers. In the EU, just over 200,000 new patients are diagnosed with colorectal cancer each year and about 40% die from the disease. The incidence of colorectal cancer increases dramatically over the age of 50 years. It is estimated that in unscreened persons aged 50 years or more there is a 0.5-3% risk of colorectal cancer and a 25-40% risk of an adenoma of any size.27-29 The mean age at diagnosis is 70-75 years. Colorectal cancer incidence varies widely globally. The highest incidences (50 in 100,000) are seen in the USA and Western Europe and the lowest are reported in parts of Asia (1 in 100,000). To a large extent this seems to be lifestyle related since second-generation Chinese immigrants in the USA have the same risk as the average American population.[30]

While colorectal incidence rates are still increasing in most countries (Figure A.3),1 most likely because of the ageing population, mortality is going down (Figures A.4a,b,c) in at least some countries. This is probably as a result of improvements in diagnostics and surgery and also due to an increased use of medical adjuvant treatment, as well as adjuvant radiation for rectal cancer.

Figure A.3.

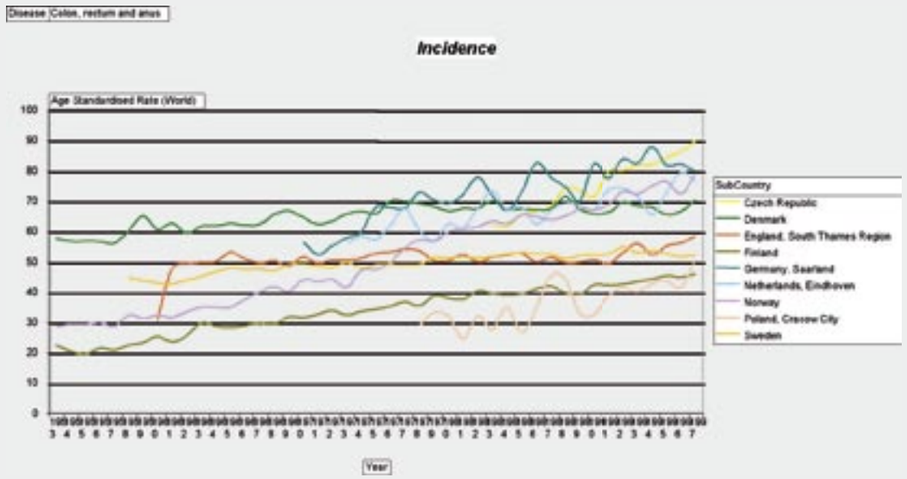


Figure A.3. Colorectal cancer incidence expressed as the world age-standardised rate (per 100,000) in a selection of European countries (the Czech Republic, Denmark, England, Finland, Germany, the Netherlands, Norway, Poland and Sweden).

Figure A.4a.

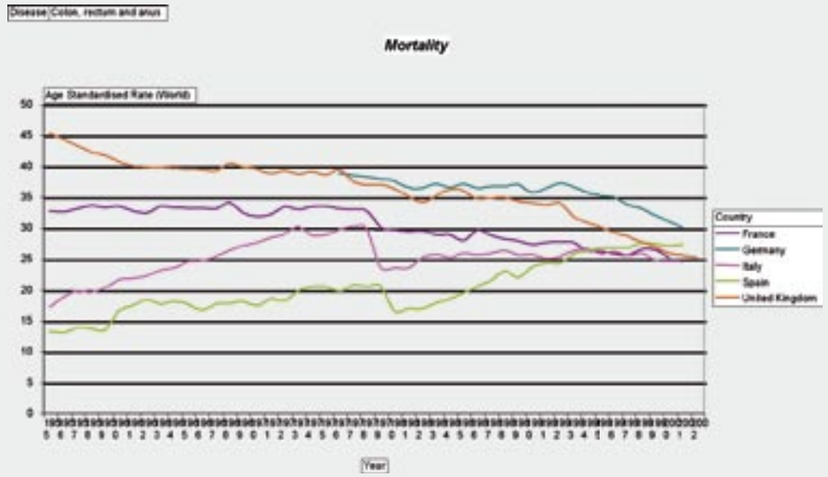


Figure A.4a. Colorectal cancer mortality expressed as the world age-standardised rate (per 100,000) in France, Germany, Italy, Spain and the United Kingdom.[1]

Figure A.4b.

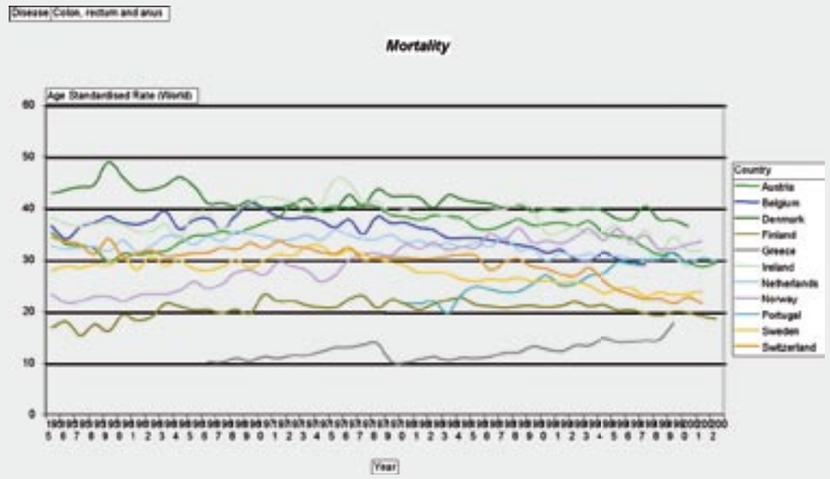


Figure A.4b. Colorectal cancer mortality expressed as the world age-standardised rate (per 100,000) in Austria, Belgium, Denmark, Finland, Greece, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland.[1]

Figure A.4c.

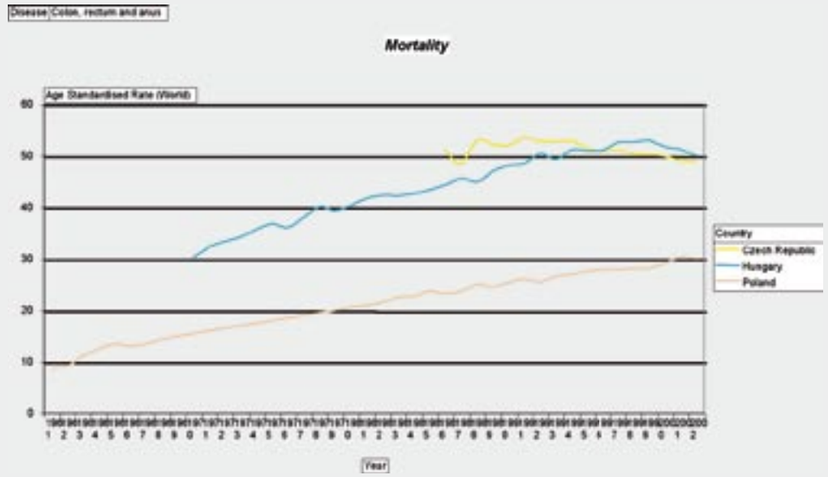


Figure A.4c. Colorectal cancer mortality expressed as the world age-standardised rate (per 100,000) in the Czech Republic, Hungary and Poland.[1]

A2.2 Aetiology

The aetiology of colorectal cancer includes both environmental and genetic factors. Colorectal cancer is believed to start out as benign polyps that over years can turn malignant. The risk of developing colorectal cancer increases with the number of polyps in the colon and there is an especially high risk in genetic diseases characterised by increased number of polyps. Inflammatory bowel diseases like Crohn's disease and ulcerative colitis increase the risk of developing colorectal cancer (10% risk after 10 years). It is estimated that as many as 20-30% of colorectal cancers are related to familial predisposition.[31]
There are also a number of environmental and lifestyle factors that affect the risk of developing colorectal cancer: high-calorie diet, high saturated fat/red meat consumption, cigarette smoking, sedentary lifestyle and obesity. Diets rich in antioxidants (incorporating fresh fruit, vegetables and exercise) reduce the risk of colon cancer and anti-inflammatory medications seem to be protective. Oestrogens also seem to have a protective effect, as women treated with estrogens at menopause have a lower risk.[32]

A2.3 Screening programmes, clinical presentation and diagnostic tests

The fact that polyps are identifiable pre-malignant stages of colorectal cancer and that early intervention increases the chance of cure has led to screening programmes in some countries (such as the USA) in people aged 50 years and above. Screening programmes usually include yearly faecal blood testing and colonoscopy every fifth year although more intense screening programmes are performed in individuals who are at higher risk. Randomised studies have indicated that regular screening reduces colon cancer mortality approximately 15% over 10 years[33] The cost:benefit ratio of screening programmes for entire populations has, however, been questioned. Patients typically present with changed bowel habits or anaemia (reduced red blood cell counts) but may also present with intestinal obstruction, perforation of the gastrointestinal wall, blood in stools or general symptoms of weight loss and fatigue. Diagnostic tests include colonoscopy with biopsy, ultrasound and/or computed tomography (CT), MRI scans to establish operability and if the tumour has spread to other organs (liver, lung) and analysis of tumour markers in blood.

A2.4 Prognosis

Prognosis depends mainly on stage at diagnosis. The more layers of the gut wall involved and the more local lymph glands involved, the worse the prognosis. If only the most superficial layer of the gastrointestinal wall is involved, the 5-year survival is 90-95%. If all layers of the wall are involved the survival decreases to approximately 60-80% (and to approximately 40-60% if lymph node involvement is detected). If the cancer has spread to other organs such as the liver and lungs the disease is considered incurable in the majority of patients. If only a single metastasis is found the possibility of cure remains if the metastasis is operable or if it can be treated with stereotactic radiotherapy or by other local treatment.

A2.5 Prevention

As colorectal cancer is associated with high costs and a large number of hospitalisations, optimal prevention strategies should be interesting from a health-economic perspective. Screening programmes exist in some countries.

Genetic analysis and screening where there is a strong family history of colon cancer is becoming increasingly common. There appears to be, however, little interest from governments in taking measures that will lead to changes in lifestyle in the general public, even if evidence clearly indicates that many colorectal cancers are lifestyle related.

Large studies investigating the effects of aspirin indicate that anti-inflammatory medication might play an important role in preventing colorectal cancer. Non-steroid anti-inflammatory drugs were considered to have too many adverse events (gastric ulcer, bleeding) to be acceptable as preventive therapy.
However, when the COX2 inhibitors that initially seemed to have a more acceptable adverse-event profile entered the market, several large prevention studies were initiated. Mid-way through the studies, however, data indicated that using COX2 inhibitors over an extended time increased the risk for cardiovascular events like acute myocardial infarction. Consequently, the studies were terminated. Therefore, the true preventive role if any of anti-inflammatory drugs in colorectal cancer is still to be determined and chemoprevention trials are also looking at other approaches. One such option that has arisen through the increased knowledge of cell surface antigens specific to tumours is the potential of vaccines (for which several studies are ongoing).

A2.6 Treatment
A2.6.1 Surgical treatment

The type of surgery required in colon cancer depends on tumour stage and location. Polyps can be removed using colonoscopy techniques but if the tumour has a broad base, or is more advanced, segmental excision of the colon with margins of at least 5 cm is necessary. In some cases hemicolectomy is performed and in rare instances complete colectomy is necessary. Local lymph gland resection is mandatory and the role of sentinel lymph node mapping is under clinical evaluation. Studies have indicated that laparoscopic techniques may be used without increasing the risk of recurrence.[34]

In rectal cancer, the extent of surgery also depends on the location and stage of the tumour. Total mesorectal excision has become the technique of choice for middle- and lower-third tumours in recent years since it results in lower risk of local recurrence (5-10% vs 20-30% for earlier techniques).[35] Wherever possible, sphincter-preserving surgery is performed.

A2.6.2 Adjuvant treatment for colon cancer

Patients with tumours involving the most superficial parts of the gastrointestinal wall are treated with surgery only. Patients are offered adjuvant chemotherapy treatment to decrease the risk of recurrence if there is local lymph node involvement or if there is tumour growth through the gastrointestinal wall with other risk factors such as perforation. Radiotherapy has no standard role as adjuvant therapy in colon cancer.
The first study that showed increased survival by adjuvant post-operative treatment with chemotherapy (semustine, vincristine and 5-FU) was published in 1988.[36] 5-FU has remained a cornerstone of treatment in the adjuvant setting and, since the early 1990s, the standard treatment is a combination of 5-FU and leucovorin (an agent that enhances the effect of 5-FU) for 6 months. This has been shown to reduce mortality between 20-30% and compared with surgery alone results in an increase in 5-year disease-free survival from 60% to approximately 70%.[37,38]

>>>

Recently, single-agent capecitabine has become accepted as an alternative adjuvant treatment39 and is increasingly used because it is a cost-effective treatment and avoids intravenous administration, being a practical and efficacious oral alternative. The preferred treatment since 2004 is a combination of 5-FU and oxaliplatin, which has shown slightly better response figures (but significantly higher toxicity) compared to 5-FU plus leucovorin.[40] The treatment is mainly given to younger patients and patients with good performance status.
Several studies using combinations of chemotherapy with monoclonal antibodies such as cetuximab and bevacizumab are ongoing.

A2.6.3 Adjuvant treatment for rectal cancer

In rectal cancer, adjuvant chemotherapy with 5-FU and leucovorin has been used since the early 1990s. Radiotherapy before or after surgery increases survival and decreases the risk of local disease relapse[41] as well as tumour volume. Many tumours initially unsuitable for surgery become operable after radiotherapy some using sphincter-preserving techniques.

A2.6.4 Treatment in metastatic disease

The combination of 5-FU plus leucovorin was also standard treatment for metastatic disease in the early 1990s, resulting in a average survival benefit of 5 months.[42] In recent years, however, standard first-line treatment in metastatic disease has switched to 5-FU/leucovorin or capecitabine in combination with either oxaliplatin or irinotecan.[43-45] These combinations provide an average survival benefit of an additional 2-3 months compared to 5-FU plus leucovorin alone. However, because the newer regimens do tend to have more side effects, they may not be offered to patients with poor performance status. Bevacizumab in combination with chemotherapy regimens (intravenous 5-FU plus folic acid or intravenous 5-FU plus folic acid plus irinotecan) is approved in Europe as first-line treatment of patients with metastatic carcinoma of the colon or rectum. Addition of bevacizumab to chemotherapy was shown to increase survival from 15 to 20 months.[46] Routine incorporation of this approach in clinical practice has been variable so far.

Second-line treatment consists of irinotecan unless the patient has received an irinotecan-based first-line regimen. The monoclonal antibody cetuximab is also being introduced in Europe for treatment of epidermal growth factor receptor (EGFR)-positive tumours. It is licensed for use in combination with irinotecan, where it improves response rates and time to progression.[47] Studies combining bevacizumab with oxaliplatin are ongoing.

Patients with solitary or a very limited number of liver or lung metastases may be treated with surgery or other forms of local treatment, such as stereotactic radiotherapy. Chemotherapy may, in some cases, enable surgical resection of previously inoperable liver metastases.[48] Successful surgical resection of a solitary liver metastasis is associated with a 5-year survival of about 10-30%.[49] ■

A.3 NON-SMALL-CELL LUNG CANCER (NSCLC)

Summary

- **The incidence of NSCLC is increasing rapidly in women but is unchanged or slightly decreasing in men. Only about 15% are cured from the disease and lung cancer mortality represents one-fifth of all cancer-related deaths in the European Union.**
- **In most cases, NSCLC is diagnosed at a late stage when curative treatment is not an option. In 2003, the first positive results concerning survival benefit from giving post-operative chemotherapy in earlier stage tumours were presented.**
- **Advances in molecular medicine have led to the identification of disease-specific mechanisms and cell surface structures that may be targets for future therapy, leading to increased response rates and less toxic treatments.**

A3.1 Epidemiology

Lung cancers are divided in two groups: small-cell lung cancer (accounting for 20% of lung cancer cases) and non-small-cell lung cancer (NSCLC) [accounting for 80% of lung cancer cases]. NSCLC represents a group of heterogeneous of tumour types, deriving from different types of cells in the lung and NSCLC incidence varies widely. The highest rates (70/100,000) are seen in parts of northern Europe (Scotland) and the USA where the levels are generally steady. Incidence rates are increasing rapidly in most other parts of the world and, in particular, Asia (China: 33/100,000). Globally, NSCLC is increasing at such an alarming rate that it is sometimes referred to as an epidemic and currently only about 15% of patients are cured from the disease.

As NSCLC is mainly caused by smoking, the incidence reflects local smoking habits. In Europe, the trends in smoking vary from country to country. On the whole, smoking is becoming less common in men whereas the number of female smokers has increased in several countries. The incidence of NSCLC is consequently increasing rapidly in women whereas it is unchanged or slightly decreasing in men (Figure A5.a).[1] The impact on cancer incidence of stricter regulation concerning smoking in public places is expected to be seen in about 20 years.
Lung cancer is the leading cause of cancer-related death globally.[50] In Europe, the disease claims over 330,000 lives annually, representing one-fifth of all cancer-related deaths in the European Union (Figure A.6a-f).[51]

Figure A.5a.

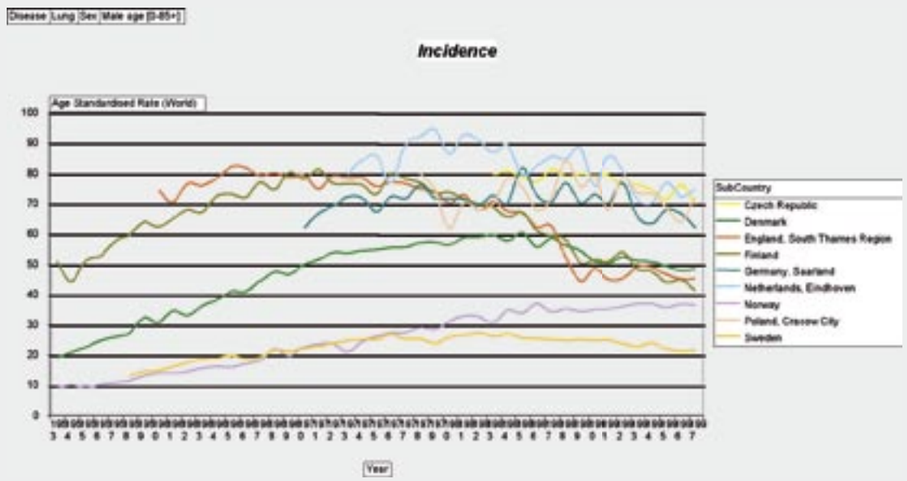


Figure A.5a. Lung cancer incidence (men) expressed as the world age-standardised rate (per 100,000) in a selection of European countries (the Czech Republic, Denmark, England, Finland, Germany, the Netherlands, Norway, Poland and Sweden). [1]

Figure A.5b.

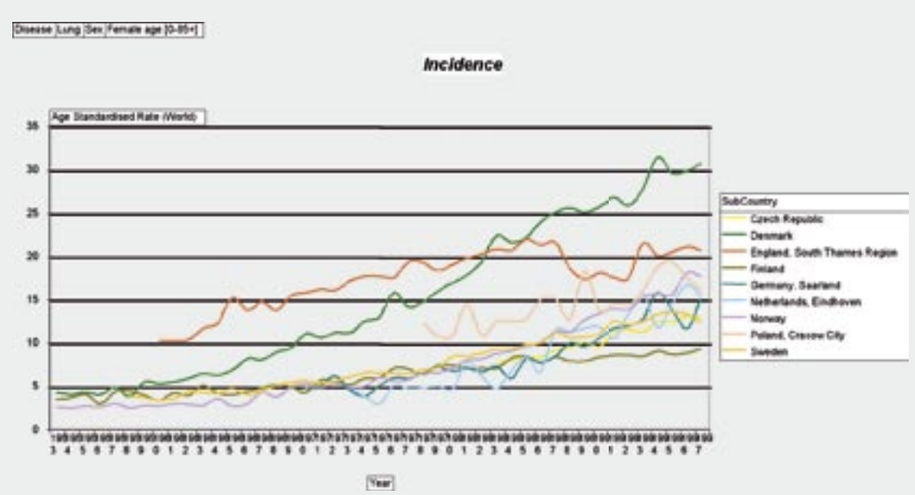


Figure A.5b. Lung cancer incidence (women) expressed as the world age-standardised rate (per 100,000) in a selection of European countries (the Czech Republic, Denmark, England, Finland, Germany, the Netherlands, Norway, Poland and Sweden).[1]

Figure A.6a.

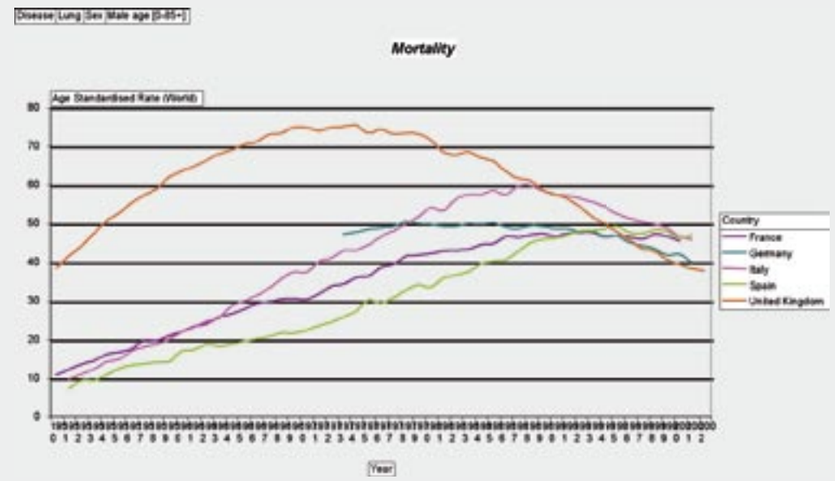


Figure A.6a. Lung cancer mortality (men) expressed as the world age-standardised rate (per 100,000) in France, Germany, Italy, Spain and the United Kingdom.[1]

Figure A.6b.

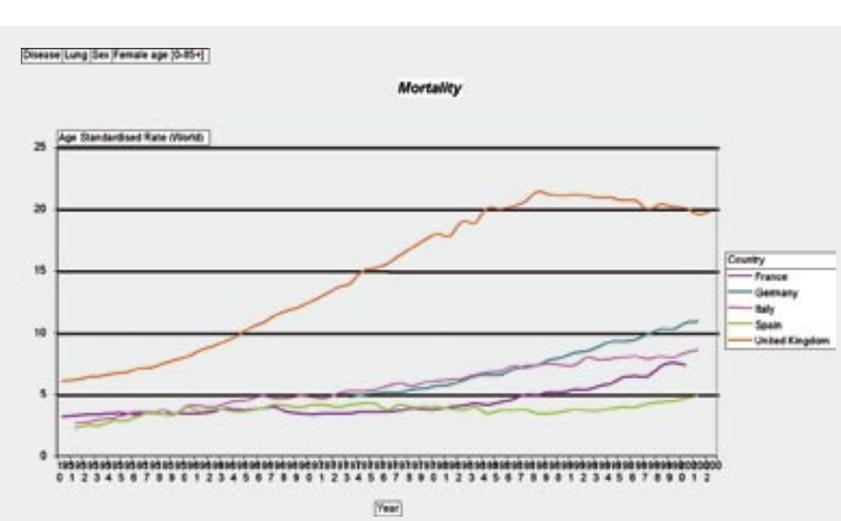


Figure A.6b. Lung cancer mortality (women) expressed as the world age-standardised rate (per 100,000) in France, Germany, Italy, Spain and the United Kingdom.[1]

Figure A.6c.

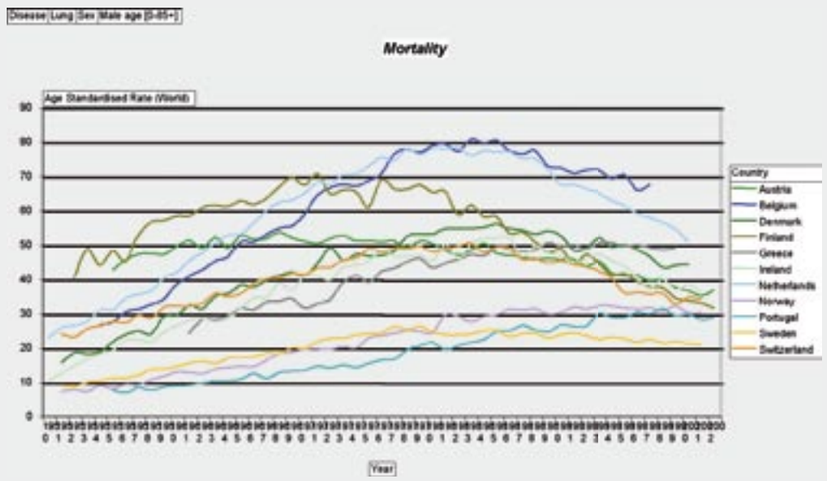


Figure A.6c. Lung cancer mortality (men) expressed as the world age-standardised rate (per 100,000) in Austria, Belgium, Denmark, Finland, Greece, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland.[1]

Figure A.6d.

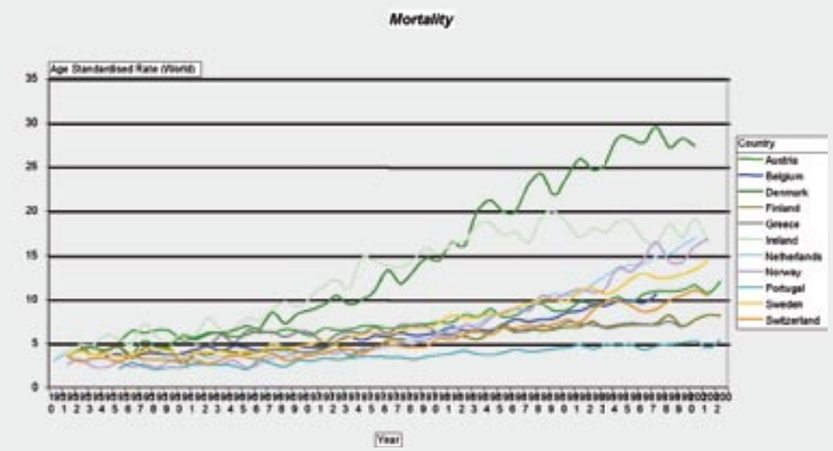


Figure A.6d. Lung cancer mortality (women) expressed as the world age-standardised rate (per 100,000) in Austria, Belgium, Denmark, Finland, Greece, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland.[1]

Figure A.6e.

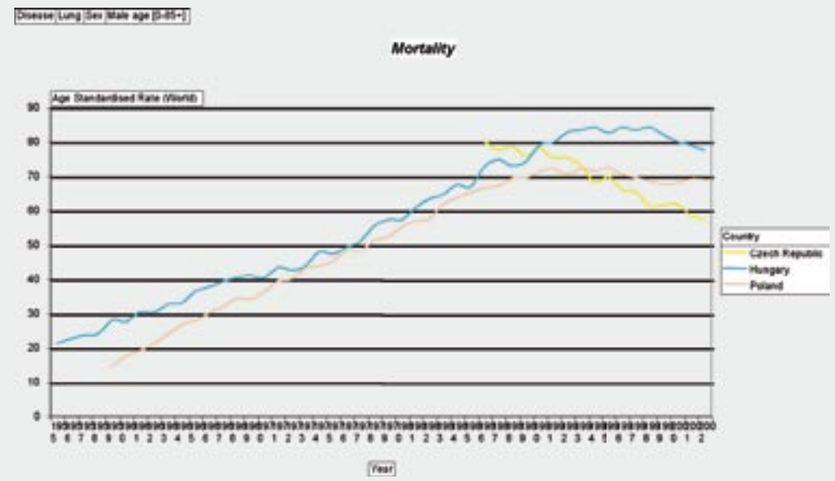


Figure A.6e. Lung cancer mortality (men) expressed as the world age-standardised rate (per 100,000) in the Czech Republic, Hungary and Poland.[1]

Figure A.6f.

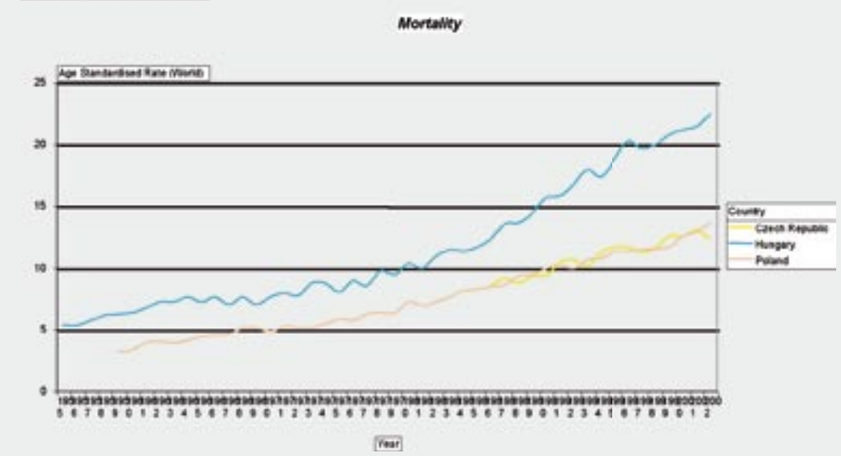


Figure A.6f. Lung cancer mortality (women) expressed expressed as the world age-standardised rate (per 100,000) in the Czech Republic, Hungary and Poland.[1]

A3.2 Aetiology

The vast majority (80-90%) of NSCLC cases are caused by smoking and about 10% of smokers develop lung cancer. There are hundreds of compounds in cigarette smoke and at least 40 of them are highly carcinogenic (cancer inducing). All forms of tobacco smoke (cigar, pipe, etc) are as dangerous as cigarette smoke. Filtered cigarettes seem to have changed mainly the pattern of where the tumours arise in the lungs, as filters let smaller particles through. Smoking filtered cigarettes is associated with more vigorous inhalation. Passive smoking is regarded as the cause for about 25% of NSCLC in individuals who do not smoke.[52]
There are also environmental factors that increase the risk of developing NSCLC. Asbestos, silica fibre and radon exposure are the best documented. In addition, there seem to be genetic factors that predispose for, as well as protect against, NSCLC.

A3.3 Screening programmes, clinical presentation & diagnostic tests

Since most patients are diagnosed with tumours in advanced, incurable stages there have been several large-scale studies evaluating screening programmes using regular chest X-ray examination that would enable earlier detection of tumours and thus result in increased survival. Unfortunately, no clear survival benefit has been shown by these studies. The utility of low-dose CT scan screening is currently being evaluated in patients at risk. Early stages of NSCLC are often asymptomatic and tumours are often therefore found when a chest X-ray is taken for other reasons. More advanced tumours present often with fatigue, cough, dyspnoea, pneumonia, pain and weight loss. Diagnostic tests usually include bronchoscopy with biopsy, or fine needle biopsy, spirometry and CT scans to establish operability and spread to local lymph glands or other organs. PET is also being increasingly used and MRI may be of value (mostly for diagnosing brain metastasis). There are presently no reliable blood tumour markers available.

A3.4 Prognosis

Prognosis depends mainly on the stage of the tumour at diagnosis (the more advanced, the worse the prognosis). With the exception of a small number of early-stage localised cancers that can be cured with surgery or sometimes loco-regional radiotherapy, cure cannot be obtained. Patients with small tumours under 3 cm in diameter without metastasis have a 5-year survival rate of 70%. Patients with larger tumours with local lymph gland involvement have a 5-year survival rate as low as 10%. Most patients with metastases to other organs die within 6 months and less than 5% of patients survive 5 years. Patients with smoking-related NSCLC also have an increased risk of developing second malignancies.

A3.5 Prevention

Addressing smoking cessation as a means of prevention is one of the few fields where governments are finally taking active measures. In Europe, regulations have been imposed to restrict smoking in public spaces. A large retrospective study indicates that statin treatment results in approximately 48% risk reduction.[53] Several trials performed using retinoid chemoprevention have all had a negative outcome. With increased knowledge related to pivotal steps in the malignant transformation and metastasis, there are several specific targets that induce optimism concerning future prevention trials. As with other tumours, knowledge of cell-surface antigens specific to tumours presents the possibility of vaccine trials.

A3.6 Treatment

Patients with NSCLC can be divided in three groups with regard to the stage of the disease at diagnosis:

1. *Patients with surgically resectable tumours have the best prognosis and a chance of cure. Surgery is, however, associated with 3-6% mortality and not all patients are suitable for surgery. Radical radiotherapy may be an alternative in these patients unfit for surgery. Adjuvant chemotherapy provides a moderate survival advantage in patients with stage IB-IIIA cancer (all tumours over 3 cm in diameter and regional lymph node involvement on the same side as the tumour but no distant metastasis).*
2. *Patients with locally or regionally advanced disease benefit from multimodality treatment. Some patients can be treated with surgical resection and either pre-operative or postoperative chemotherapy or radiation therapy. Patients with unresectable disease are treated with radiation therapy in combination with chemotherapy.*
3. *Patients with distant metastasis may benefit from chemotherapy and local radiation therapy for local control of the disease and related symptoms. Loco-regional radiation therapy does not, however, result in increased survival.[54] In advanced disease, palliative chemotherapy offers modest improvements on median survival but the overall survival is poor.[55] Chemotherapy also produces improvement in disease-related symptoms without adversely affecting the overall quality of life.*

A3.6.1 Neoadjuvant treatment

The potential value of neoadjuvant (pre-operative) chemotherapy has been indicated in two small randomised studies (total 120 patients) with patients with stage IIIA NSCLC and ipsilateral mediastinal lymph node involvement.[56,57] In both studies, patients randomised to three cycles of cisplatin-based chemotherapy before surgery had a more than three times prolonged median survival compared to patients treated with surgery alone. A large French randomised study including a total of 373 patients also showed a trend in favour of pre-operative chemotherapy but the difference did not reach a statistically significant level.[58]

A3.6.2 Adjuvant treatment

The first significant positive results giving increased survival rates using post-operative chemotherapy with cisplatin was reported in 2003.[59] Since then, similar results have been reported using taxanes and vinorelbine.[60,61] The overall survival benefit of receiving adjuvant treatment is an increased 5-year survival of about 5-10%.

Several studies in patients with unresectable stage IIIB disease have also shown that treatment with cisplatin-based chemotherapy and loco-regional radiotherapy results in improved survival compared to radiation therapy alone. An analysis of data from several randomised trials indicates that the combination of chemo/radiation therapy results in a 10% relative reduction in the risk of death compared to radiation therapy alone.[62]

A3.6.3 Treatment in metastatic disease

Chemotherapy in advanced stages of the disease has been used since the late 1980s based on results on cisplatin combinations resulting in improved survival. >>>

Currently, standard first-line treatment in most institutions is the combination of cisplatin or carboplatin with gemcitabine, or vinorelbine or a taxane, increasing survival by approximately 2-3 months. Trials have shown that using cisplatin in combination with docetaxel, gemcitabine, paclitaxel,[63] vinblastine[64] or vinorelbine[65] yield similar responses, as does carboplatin and paclitaxel.

Combining more than two chemotherapy agents has not, however, resulted in higher efficacy. As second-line treatment, docetaxel or pemetrexed offer a 2-month gain.[66,67] Single treatment with gemcitabine or vinorelbine is commonly offered to patients with poorer performance status or patients where treatment with platinum compounds is contraindicated.

The EGFR tyrosine kinase inhibitor erlotinib is being used increasingly in the clinical setting after a trial showing increased survival in previously treated with chemotherapy.68 Gefitinib, a similar agent, has mainly demonstrated efficacy in specific subsets of patients (patients with adenocarcinoma, women, the Japanese population, never-smokers). Both erlotinib and gefitinib have failed to demonstrate any benefit when given in combination with cisplatin/gemcitabine or carboplatin/paclitaxel.[69,70]

The monoclonal antibody bevacizumab, in combination with paclitaxel and carboplatin, has recently demonstrated increased median overall survival from 10 to 12 months.[71] In addition, the combination of bevacizumab plus erlotinib has also been shown recently to have additional value comparable to the available cytotoxic agents in non-squamous cell NSCLC.[72] The findings remain to be confirmed in Phase III studies.

NSCLC often metastasises to the brain and to bone. More information on the management of bone metastases is included later in this Appendix.

A.4 NON-HODGKIN'S LYMPHOMA (NHL)

Summary

- **On a global level, incidence rates for NHL, a group of at least 15-20 separate diseases, especially aggressive lymphomas, have increased in the past four decades, although reasons for this are not entirely clear.**
- **Forty years ago, NHL was a disease where cure was obtained in a very limited number of cases.**
- **The introduction of different chemotherapy combinations has improved cure rates in aggressive lymphomas as well as improving quality of life and increasing duration of response in indolent lymphomas.**
- **Within the past decade, advances in molecular medicine have provided insights into the biology of NHL. This has led to new treatments like the monoclonal antibody rituximab, which has improved survival rates in patients with aggressive NHL and become an important therapeutic option in the treatment of indolent lymphomas.**

A4.1 Epidemiology

Lymphoma, originating in cells of the immune system, has been classified into two groups since the 19th century: Hodgkin's lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell, and non-Hodgkin's lymphoma (NHL). Today, we know that NHL is not 1 disease but a group of at least 15-20 different diseases with varied biology and prognosis. Currently, these diseases are classified as originating from the immune system's B-cells or T-cells and depending on their clinical presentation, as aggressive or indolent. Aggressive NHL will lead to death relatively quickly if left untreated but is curable in many cases. Indolent NHL progresses slowly over time but is considered curable only in rare cases.

Across the world, NHL incidence rates vary as much as fivefold: the lowest incidence in seen in Asia and the highest incidence is seen in the USA, Australia and Western Europe. The number of new NHL cases in the EU every year is approximately 50,000. The average age at diagnosis is about 60 years and approximately 35% of patients diagnosed with NHL die from the disease.

Incidence rates for NHL, especially aggressive lymphomas, have increased in the past four decades (Figure A7-A8c).[1] Reasons for this are not entirely clear. This can partly be explained by improvements in diagnostics but most likely also reflects a true and dramatic increase of the disease. Some of the increase is due to AIDS-related lymphomas but an increase has also been seen in non-AIDS population. This is primarily thought to be due to an increase in the elderly population, although environmental factors and toxic exposure may also be important factors

Figure A.7.

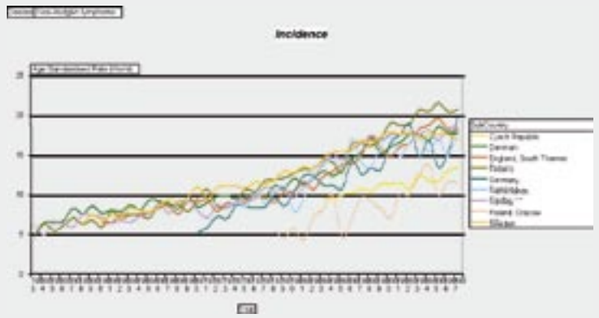


Figure A.7. NHL incidence expressed as the world age-standardised rate (per 100,000) in a selection of European countries (the Czech Republic, Denmark, England, Finland, Germany, the Netherlands, Norway, Poland and Sweden).[1]

Figure A.8a.

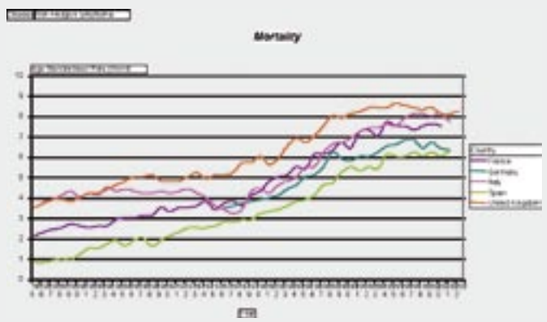


Figure A.8a. NHL mortality expressed as the world age-standardised rate (per 100,000) in France, Germany, Italy, Spain and the United Kingdom.[1]

Figure A.8b.

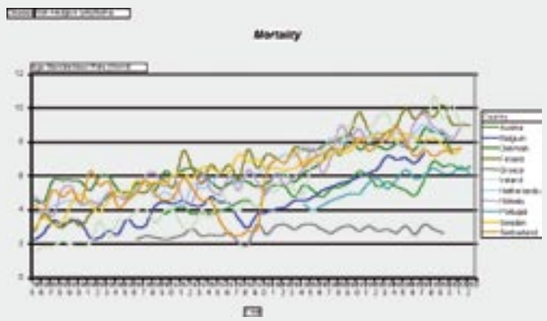


Figure A.8b. NHL mortality expressed as the world age-standardised rate (per 100,000) in Austria, Belgium, Denmark, Finland, Greece, Ireland, the Netherlands, Norway, Portugal, Sweden and Switzerland.[1]

Figure A.8c.

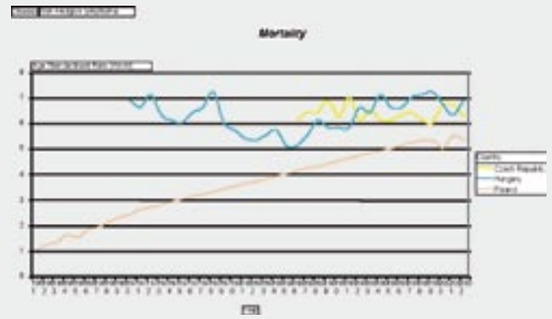


Figure A.8c. NHL mortality expressed as the world age-standardised rate (per 100,000) in the Czech Republic, Hungary and Poland.[1]

A4.2 Aetiology

In the majority of cases, the aetiology of NHL is unknown. Certain genetic and autoimmune diseases (eg, rheumatoid arthritis, coeliac disease and psoriasis), infectious agents (eg, HIV, Epstein Barr and Hepatitis C viruses and the bacteria Helicobacter pylori) and environmental substances (eg, smoking and herbicides) are known to be associated with higher risk of lymphoma. Diet also seems to play a part with studies indicating a twofold risk increase with diets rich in meat and fat.[74] Sun exposure seems to decrease the risk of NHL but the mechanisms are unclear.

A4.3 Screening programmes, clinical presentation & diagnostic tests

There are no screening programmes for NHL. In most cases patients seek medical care because of either enlarged lymphatic glands, a lump or because of general symptoms - fever, weight loss, fatigue or night sweats. Diagnostic tests commonly needed include tissue samples from tumour and bone marrow, CT or PET scans and a large set of blood tests including screening for various infectious agents.

A4.4 Prognosis

There are five parameters that have been found to have approximately an equal and independent negative impact on survival: (1) age greater than 60 years, (2) serum lactate dehydrogenase greater than upper limit of normal, (3) poor general condition (known clinically as performance status), (4) advanced-stage disease (involvement of lymph glands around the body), and (5) more than one extranodal sites (involving other organs such as the liver, brain or lung). These parameters were originally studied in patients with diffuse aggressive NHL but their prognostic value has been proven in almost all subtypes of NHL.[75]

A4.5 Prevention

So far there have been no studies aimed at preventing NHL. There are, however, several strategies that could be interesting as preventive measures, such as eradicating the infectious agents that cause some types of NHL and vaccines targeting several known tumour-specific cell surface antigens.

A4.6 Treatment

Treatment of NHL varies widely depending with specific diagnosis and stage of disease:

- ***Stage I NHL:*** *involvement of a single lymph node region or involvement of a single organ.*
- ***Stage II NHL:*** *involvement of two or more lymph node regions on the same side of the diaphragm or localised involvement of a single organ or site and its regional lymph nodes on the same side of the diaphragm.*
- ***Stage III NHL:*** *involvement of lymph node regions on both sides of the diaphragm.*
- ***Stage IV NHL:*** *disseminated (multifocal) involvement of one or more non-lymphatic sites with distant (non-regional) nodal involvement or diffuse involvement of liver or bone marrow.*

In general, aggressive lymphomas are treated with curative intent and thus more aggressive chemotherapy is used. Indolent lymphomas are treated with chemotherapy combinations or in some cases local radiotherapy and, in some cases, only when symptoms occur. The treatment overview in this section does not include the therapeutic options for rarer forms of NHL that in some cases require special treatment.

A4.6.1 Aggressive NHL
A4.6.1.1 Stage I and contiguous stage II disease

Traditionally, radiation therapy has been the primary treatment of stage I and contiguous stage II aggressive NHL (where the cancerous lymph nodes are next to each other) and can achieve local disease control within the radiation field in the vast majority of cases. However, 5-year disease-free survival using radiation therapy alone is less than 60-70%.[76] The introduction of doxorubicin-based combination chemotherapy in aggressive NHL has produced improved treatment results. There is evidence that the combination of chemotherapy and radiation therapy results in an increased overall survival at 5 years compared to chemotherapy alone[77,78] of 82% versus 72%. These results mean this combination is becoming the treatment of choice in most instances.

A4.6.1.2 Non-contiguous stage II, III and IV disease

The treatment of choice in these advanced stages of aggressive NHL is combination chemotherapy. It was with the introduction of new chemotherapy combinations in the 1970s that the first cases of advanced aggressive NHL were cured. Several chemotherapy combinations have been used that steadily improved survival rates. In the past 25-30 years a combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) became the standard first-line treatment for most types of aggressive NHL. There are, however, several doxorubicin-based combinations that show similar efficacy. The survival rates were increased further with the introduction of the monoclonal antibody rituximab in CD20-positive tumours. The combination of rituximab plus CHOP has now become standard first-line treatment increasing the 5-year overall survival from 45% to 58% in patients over 60 years[79] and increasing the 2-year overall survival from 85% to 95% in patients below 61 years.[80]

The curative rate in aggressive NHL, seen as a group, is now approximately 40-60%. Several trials have been undertaken to evaluate the role of high-dose treatment with autologous bone marrow or stem cell transplantation consolidation versus conventional chemotherapy alone in patients with one of the most common forms of NHL (diffuse large cell lymphoma) in first remission. Most of these trials have demonstrated significant increases in event-free survival by 10-20% among patients who received high-dose therapy. However, differences in overall survival have not been demonstrated.

Retrospective analyses of high-risk patients has suggested improved survival with marrow transplantation in two of the trials,[81,82] thus indicating that the treatment may be beneficial in this high-risk subgroup of patients. The definitive role of autologous bone marrow peripheral stem cell or allogeneic bone marrow transplantation in the treatment of first remission NHL awaits the results of ongoing randomised trials.

A4.6.1.3 Recurrent aggressive NHL

The treatment of choice for patients with relapsed aggressive NHL is high-dose chemotherapy with bone marrow transplantation.[83] Preliminary studies indicate that long-term disease-free status can be achieved in 20-40% of patients. The value of high-dose treatment with bone marrow transplantation has been illustrated by the PARMA trial where patients with chemosensitive relapse of aggressive NHL were assigned to either conventional chemotherapy or high-dose chemotherapy with bone marrow transplantation. Follow-up at the 5-year point indicates that those patients who received high-dose chemotherapy with transplantation achieved significantly better overall survival (53% vs 32%) and event-free survival (46% vs 12%) than those treated with conventional chemotherapy.[84]

Rituximab has been shown to induce responses in one-third of patients with relapsing aggressive CD20-positive lymphomas.[85] Several studies are ongoing exploring the additive value of new agents as well as conventional chemotherapy combinations in various administration forms and doses.

Radiolabelled anti-CD20 antibodies like ibritumomab and tositumomab have also shown to induce high response rates (60-80%) in patients with relapsed or refractory B-cell lymphoma.[86,87]

A4.6.2 Indolent NHL
A4.6.2.1 Stage I and contiguous stage II disease

Localised presentation of indolent NHL is fairly uncommon but should be treated with curative intent using loco-regional radiation therapy. Within radiation fields, long-term disease control can be achieved in a majority of patients.[88] The value of adjuvant chemotherapy has been studied using chlorambucil- and doxorubicin-based regimens but the results are not conclusive.[89,90]

In some cases, due to the slowly progressive nature of the disease, watchful waiting (or active surveillance) is a preferred alternative to active treatment,[91] especially in older asymptomatic patients.

A4.6.2.2 Non-contiguous stage II, III and IV disease

Advanced stages of indolent NHL are treated with variably aggressive treatment depending on the nature of the disease. In some cases, the disease progresses very slowly and treatment is then initiated only when symptoms arise. In other cases, more active treatment is required. Optimal treatment remains controversial in many cases since the vast majority of patients are not cured and the rate of relapses seen is fairly constant.

Rituximab, alone or in combination with traditional chemotherapeutic agents, has gained a place in the treatment of indolent lymphomas and has shown high response rates and few side effects as first-line treatment.[92] This monocloncal antibody has been shown to increase the rate of overall and complete responses in combination with cyclophosphamide, vincristine, and prednisone (CVP) compared to CVP alone in patients with follicular lymphoma (80% and 41% vs 57% and 10%, respectively).[93] The median time to treatment failure was also significantly longer in those receiving rituximab treatment in addition to CVP compared with CVP alone (27 vs 7 months). Other options include oral chlorambucil, fludarabine, 2-chlorodeoxyadenosine and cyclophosphamide. Maintenance therapy with rituximab has also been shown to prolong progression-free survival in follicular and mantle-cell lymphoma (4.2 vs 1.7 years)[94,95] but so far has been variably implemented. Rituximab has an increasing number of indications and data are indicating that rituximab treatment may lead to increased overall survival in indolent NHL. This agent's final place in the treatment of NHL is therefore not yet clear.

Recent data indicate that in some situations radionuclide agents like ibritumomab may be of value as first-line therapy in CD20-positive indolent NHL.[96] These data are still to be confirmed in larger studies with long-term follow-up. Interferon has been used in indolent NHL but its role in the treatment of indolent NHL remains controversial.

A4.6.2.3 Recurrent indolent NHL

Relapsed indolent lymphoma can be treated with chemotherapy, anti-CD20 monoclonal antibodies such as rituximab, or palliative radiation therapy. Cure is rare and long-term freedom from second relapse is uncommon. Usually, multiple relapses will occur. Adding rituximab to conventional chemotherapy regimens has been shown to increase response rates significantly.[97] High-dose chemotherapy with autologous transplantation is another therapeutic option in some patients and has been demonstrated to increase progression-free survival.[98] Mini-allogeneic transplantation is a treatment approach that is showing some promise as a way of increasing cure rates in indolent NHL but the treatment is still under experimental evaluation.

Ibritumomab, a monoclonal antibody against CD20 with an added radionuclide, has been approved for use in patients with CD20-positive rituximab-refractory follicular B-cell lymphoma. Data indicate complete response in about 25% of patients previously treated with chemotherapy (partial response in approximately 41%).[99] Tositumomab, another monoclonal antibody against CD20 with an added radionuclide, has also recently been approved by the FDA with similar response figures.

The final place for these agents is still not clear. The response rates and time to progression are fully comparable to conventional chemotherapy and the side effects are comparably mild.On occasion patients may experience a relapse with a more aggressive histology (known as transformation) and treatment must then be directed to the new histologic type.

Sustained complete remissions can in some cases be achieved with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support.[100,101] ■

A.5 BONE METASTASES

Summary

- Bone is, after the lungs and liver, the third most common location for metastases. Breast and prostate cancer are the most common cancers in which bone metastasis are seen. Increased survival in many cancers has led to an increased prevalence of patients with bone metastases.
- Until 20 years ago, bone metastases were treated with analgesics, external radiation therapy or surgery. Increased knowledge in osteoporosis and bone metabolism has led to the development of new drugs such as bisphosphonates, which have proved to be valuable in preventing and treating bone pain and hypercalcaemia and postponing skeletal complications in cancer patients.
- Radionuclides that target radiation to metastatic lesions in the bone have been also been developed. Improved surgical techniques, bone replacement materials and the development of multidisciplinary teams focused on treating patients with bone metastasis have also contributed to improved quality of life and reduced morbidity in this group of patients.
- The treatment of bone metastases is an example of a rapidly expanding field in oncology that aims to give patients best possible supportive care.

A5.1 Epidemiology

About 20-30% of patients diagnosed with cancer will develop bone metastases, most commonly to the spine, pelvis, femur, humerus and skull. Advanced breast (70-80%), prostate (70-80%), lung (40%) and renal cancers (40%) are the most common types of tumour in which skeletal metastasis are seen.[102,103] Only 20-35% of breast cancer patients with bone metastases will be treated for fractures[104] or paralysis (rare) but a majority of the patients will be affected to some degree by pain.[105]

A5.2 Pathophysiology

The development of bone metastases is a multi-step process requiring the tumour cells to have particular properties. Initially, the cancer cell must disengage physically from its primary site, then enter the vascular system, survive in the blood and finally be able to settle in a new tissue with other characteristics. Once a metastatic lesion has been established, the level and type of interaction between tumour cells and normal 'bone cells' (osteoblast and osteoclasts) determine the nature of the lesion. For example, many tumours have the ability to activate osteoclast activity that leads to increased breakdown of bone material around the metastatic lesion.

A5.3 Clinical presentation and diagnostic tests

The most common symptom of bone metastasis is pain. The pain may initially be well localised but may also be a diffuse migrating ache if the metastases are generalised in the skeleton.

Symptomatic hypercalcaemia with fatigue, lethargy, nausea, vomiting, anorexia and disorientation is seen primarily in advanced stages of bone metastasis.

Since the spine is one of the most common metastatic sites, pathological fractures and neurological symptoms due to spinal instability with pressure on the spinal cord have been fairly common presentations. Modern management with teams has reduced the risk of spinal cord complications like paralysis significantly.

Patients presenting with symptoms of bone metastasis usually undergo plain radiography and bone scintigraphy. MRI has proved to be a sensitive method for detecting bone metastases and may be of value if scintigraphy is negative. PET is a technique that is gaining ground, since it is as sensitive as scintigraphy but has far fewer false-positive findings.[106]

Laboratory tests include at least blood cell counts (to detect anaemia) and electrolyte analysis (to rule out hypercalcaemia). If the bone is found to be the first known metastatic site, verification by biopsy is strongly recommended.

A5.4 Prognosis

Prognosis depends on tumour type and localisation. Lymphoma, myeloma and breast cancer patients with bone metastases have the longest survival (2-4 years) and lung cancer the shortest (3 months).[107] Patients with skeletal metastases alone have an average survival of 12 months, compared to 3 months if both pulmonary and bone metastases are found.[108]

A5.5 Treatment

Current treatment is aimed to improve the patient's quality of life by focusing on pain relief, maintenance of function, reduction in local tumour burden and prevention of hypercalcaemic episodes. Optimal care of the patient requires insight in both systemic and local therapeutic options and multidisciplinary teams involving medical oncologists, radiation oncologists, anaesthesiologists and orthopaedic surgeons. There are three main treatment modalities that are often used in combination: medical therapy, radiation therapy and surgery. The intensity and choice of treatment depends to some extent on the prognosis and life expectancy of the patient.

A5.5.1 Systemic treatment

The aim of systemic therapy is an antitumour effect, pain relief, the prevention of hypercalcaemia and a reduction in the number of skeletal events. The cornerstones of systemic therapy are bisphosphonates, chemo-hormonal therapy and systemic radiotherapy, in the form of radionuclides.

Bisphosphonates inhibit the recruitment and bone-degrading activity of osteoclast cells. It has been shown that bisphosphonate treatment decreases skeletal morbidity, delays the onset of the first skeletal event (fracture) and decreases the risk of hypercalcaemia in patients with bone metastases.[109] Patients with breast cancer, prostate cancer and myeloma respond best to the treatment. In a trial with patients with microscopic metastatic breast cancer who received chemotherapy and a bisphosphonate the time to first skeletal event was delayed by 7 months.[110] This indicates that patients with bone metastases benefit from having bisphosphonate treatment at an early stage.

>>>

Of the commercially available bisphosphonates, the most data exist for zoledronate (zolendronic acid) and pamidronate (pamidronic acid). Zoledronate is at least as effective as pamidronate for breast cancer patients with bone metastases for various study end points.[111] However, in separate clinical trials in prostate cancer patients, zoledronate,[112] but not pamidronate,[113] reduced skeletal complications. Ibandronate, a new bisphosphonate, has also proven efficacy for preventing skeletal related events in breast cancer patients[114,115] and studies indicate similar efficacy as zoledronic acid for decreasing markers of bone resorption and formation in breast cancer patients.[116]

Chemotherapy options vary depending on the tumour type. In some malignancies, like many breast cancers and prostate cancers, bone metastases also respond to hormonal agents. Cortisone also alleviates pain in patients with bone metastases when the disease is no longer responding to usual hormone treatment.[117]
The use of radionuclides (strontium 85, strontium 89, samarium 153 or rhenium 188), which accumulate in bone tissue and deliver short-range radiation, is indicated in patients with breast and prostate cancer with pain due to widespread bone metastasis. The main effect of pain relief is achieved 2-4 weeks after treatment. Strontium is the most widely used radionuclide. A study in patients with prostate cancer show that a majority of patients experience pain relief even at 6 months post-treatment, as well as a decreased need of opioid pain medication and suggests of a direct antitumour effect.[118] Radionuclide treatment does, however, have limiting side effects such as bone marrow toxicity.

A5.5.2 Local treatment in single lesions
A5.5.2.1 Radiotherapy

Where bone metastases are limited to a single area, patients may be treated with external beam radiation or radionuclide therapy.
External beam radiotherapy has three indications: as pain relief when pain due to bone metastasis is localised; as prevention if there is increased risk of spontaneous fracture and there are signs of medullar compression; and as adjuvant treatment after surgery in order to prevent further tumour progression in the operated area. Studies indicate that post-operative radiotherapy decreases the need for orthopaedic stabilisation from approximately 15% to 3% and also results in a higher level of regained function.[119] Palliative radiotherapy has been shown to provide some relief in 80-90% of patients and complete relief in 50-85% of patients with localised skeletal disease.[120,121] Radiotherapy in combination with ibandronate seems to be even more effective.[122,123]

A5.5.2.2 Surgery

Surgery is indicated when there is need for biopsy at sites where there is an impending pathological fracture, if there is spinal instability or neurological deficit or in some instances when radiation has failed.
Pathological fractures do not heal properly and prosthetic replacements or internal fixation are therefore used to achieve pain relief and restore function. Surgery can allow for immediate weight bearing. The post-operative results are improved if adjuvant radiotherapy to the surgical area is given to diminish local tumour growth that would otherwise impede the surgical result.

Improved surgical techniques and replacement materials (including, for instance, injectable cement to reinforce fractured vertebrae[124]) have greatly increased the results and number of possible surgical interventions. ■

References

1. CANCERMondial. International Agency for Research on Cancer. 2005. Available at: http://www-dep.iarc.fr/.
2. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999; 49: 33-64.
3. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003; 289: 3243-3253.
4. Blackwood MA, Weber BL. BRCA1 and BRCA2: from molecular genetics to clinical medicine. J Clin Oncol 1998; 16: 1969-1977.
5. Claus EB, Schildkraut JM, Thompson WD, et al. The genetic attributable risk of breast and ovarian cancer. Cancer 1996;77:2318.
6. Whittemore AS. Risk of breast cancer in carriers of BRCA gene mutations. N Engl J Med 1997;337:788
7. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005; 365: 1769-1778.
8. Fisher B, Costantino JP, Wickerham DL, et al.: Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371-1388.
9. Kochhar R, Khurana V, Bejjanki H, et al. Statins reduce breast cancer risk: a case control study in US female veterans. Proc Am Soc Clin Oncol 2005; 23: abs 514.
10. Early Breast Cancer Trialists' Collaborative Group 2000 Trialists' Meeting at Oxford, September, 2000.
11. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 2000; 18: 1220-1229.
12. Gianni L, Valagussa P, Zambetti M, et al. Adjuvant and neoadjuvant treatment of breast cancer. Semin Oncol 2001;28:13.
13. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672
14. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687-1717.
15. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001; 19: 3808-3816.
16. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349: 1793-1802.
17. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005; 365: 60-62.
18. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350: 1081-1092.
19. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005; 352: 2302-2313.
20. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21: 1431-1439.
21. Piccart M. First results from the HERA trial. Presented at the annual meeting of the AmericaSociety of Clinical Oncology 2005. www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005816-00_21-001,00.asp

22. Romond EH, Perez EA, Bryant J, et al. Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 Positive Operable Breast Cancer. Presented at the annual meeting of the American Society of Clinical Oncology 2005. www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005817-00_21-001,00.asp
23. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol 2003; 21: 588-592.
24. Miller K, Wang M, Gralow J, et al. A randomized Phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Presented at the annual meeting of the American Society of Clinical Oncology 2005. www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005814,00.asp
25. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23: 792-799.
26. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27: 165-176.
27. Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel: an autopsy survey. Cancer 1979;43:1847.
28. DiSario JA, Foutch PG, Mai HD, Pardy K, Manne RK. Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men. Am J Gastroenterol 1991: 86; 941.
29. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000; 343: 162-168.
30. Whittemore AS, Wu-Williams AH, Lee M, et al. Diet, physical activity, and colorectal cancer among Chinese in North America and China. J Natl Cancer Inst 1990; 82: 915-926.
31. Burt RW. Familial risk and colorectal cancer. Gastroenterol Clin North Am 1996; 25: 793-803.
32. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al.: Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004; 350: 991-1004.
33. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996; 348: 1467-1471.
34. The Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004; 350: 2050-2059.
35. McNamara DA, Parc R. Methods and results of sphincter-preserving surgery for rectal cancer. Cancer Control 2003; 10: 212-218.
36. Wolmark N, Fisher B, Rockette H, et al. Postoperative adjuvant chemotherapy or BCG for colon cancer: results from NSABP protocol C0-1. J Natl Cancer Inst 1988; 80: 30-36.
37. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993; 11: 1879-1887.
38. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995; 345: 939-944.
39. Twelves C, Wong A, Nowacki M, et al. Updated efficacy findings from the X-ACT phase III trial of capecitabine (X) vs. bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer. J Clin Oncol (Meting Abstracts) 2005; 23: 251s, abs 3521.
40. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; 350: 2343-2351.
41. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336: 980-987.

43. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 2000; 18: 136-147.
42. Scheithauer W, Rosen H, Kornek GV, et al. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ 1993; 306: 752-755.
44. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355: 1041-1047.
45. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004; 22: 23-30.
46. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-2342.
47. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004; 351: 337-344.
48. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004; 240: 644-645.
49. Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. J Clin Oncol 1990; 8: 1885-1893.
50. Peto R, Chen ZM, Boreham J. Tobacco—the growing epidemic. Nat Med 1999; 5: 15-17.
51. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005; 16: 481-488.
52. US Environmental Protection Agency. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington: US Government Printing Office; EPA No. 600/006F, 1992
53. Khurana V, Kochhar R, Bejjanki HR, Caldito G, Fort C. Statins reduce the incidence of lung cancer: A study of half a million U.S. veterans. J Clin Oncol (Meeting Abstracts) 2005; 23: 107s, abs 1006.
54. Sundstrøm S, Bremnes R, Aasebø U, et al. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol 2004; 22: 801-810.
55. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2000; 2: CD002139.
56. Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994; 330: 153-158.
57. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994; 86: 673-680.
58. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and III non-small-cell lung cancer. J Clin Oncol 2002; 20: 247-253.
59. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non–small-cell lung cancer. N Engl J Med 2004; 350: 351-360.
60. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. Proc Am Soc Clin Oncol Late-Breaking Abstracts Booklet 2004; 23: 17, abs 7019.

61. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005; 352: 2589-2597.
62. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995; 311: 899-909.
63. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92-98.
64. Macbeth F, Toy E, Coles B, Melville A, Eastwood A. Palliative radiotherapy regimens for non-small cell lung cancer. Cochrane Database Syst Rev 2001; 3: CD002143.
65. Kelly K, Crowley J, Bunn Jr PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001; 19: 3210-3218.
66. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18: 2095-2103.
67. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589-1597.
68. Shepherd FA, Pereira J, Ciuleanu TE, et al. A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial. Proc Am Soc Clin Oncol Late-Breaking Abstracts Booklet 2004; 23: 18, abs 7022.
69. Herbst RS, Prager D, Hermann R, et al. TRIBUTE - A phase III trial of erlotinib HCI (OSI-774) combined with carboplatin and paclitaxel (CP) chemotherapy in advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2004; 23: 617, abs 7011.
70. Gatzemeier U, Pluzanska A, Szczesna A, et al. Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 2004; 23: 617, abs 7010.
71. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III Trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial - E4599. Proc Am Soc Clin Oncol 2005; 23: Abstr 4.
72. Herbst RS, Johnston DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. J Clin Oncol. 2005 23: 2544-2555.
73. Dinse GE, Umbach DM, Sasco AJ, Hoel DG, Davis DL. Unexplained increases in cancer incidence in the United States from 1975 to 1994: possible sentinel health indicators? Annu Rev Public Health 1999; 20: 173-209.
74. Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. Clin Lymphoma 2003; 4: 161-168.
75. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998; 16: 2780-2795.
76. Kaminski MS, Coleman CN, Colby TV, Cox RS, Rosenberg SA. Factors predicting survival in adults with stage I and II large-cell lymphoma treated with primary radiation therapy. Ann Intern Med 1986; 104: 747-756.
77. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998; 339: 21-26.
78. Glick JH, Kim K, Earle J, et al. An ECOG randomized phase III trial of CHOP vs. CHOP + radiotherapy (XRT) for intermediate grade early stage non-Hodgkin's lymphoma (NHL). Proc Am Soc Clin Oncol 1995; 14: 391, abs 1221.
79. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005; 23: 4117-4126.

80. Pfreundschuh MG, Trümper L, Ma D, et al. Randomized intergroup trial of first line treatment for patients <= 60 years with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD20 antibody rituximab - early stopping after the first interim analysis. Proc Am Soc Clin Oncol 2004; 23: 556, abs 6500.
81. Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 1997; 15: 1131-1137.
82. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. N Engl J Med 2004; 350: 1287-1295.
83. Shipp MA, Abeloff MD, Antman KH, et al. International Consensus Conference on high-dose therapy with hematopoietic stem-cell transplantation in aggressive non-Hodgkin's lymphomas: report of the jury. Ann Oncol 1999; 10: 13-19.
84. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333: 1540-1545.
85. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92: 1927-1932.
86. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 2453-2463.
87. Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000; 18: 1316-1323.
88. Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. J Clin Oncol 2003; 21: 2474-2480.
89. Kelsey SM, Newland AC, Hudson GV, Jelliffe AM. A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkins lymphoma. Med Oncol 1994; 11: 19-25.
90. Seymour JF, Pro B, Fuller LM, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol 2003; 21: 2115-2122.
91. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol 2004; 22: 1454-1459.
92. Hainsworth JD, Litchy S, Burris III HA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-Hodgkin's lymphoma. J Clin Oncol 2002; 20: 4261-4267.
93. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005; 105: 1417-1423.
94. Hochster HS, Weller E, Ryan T, et al. Results of E1496: A phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL). Proc Am Soc Clin Oncol 2004; 23; 556, abs 6502.
95. Hiddemann W, Forstpointner R, Dreyling M, et al. Rituximab maintenance following a rituximab containing chemotherapy significantly prolongs the duration of response in patients with relapsed follicular and mantle cell lymphomas: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol (Meeting Abstracts) 2005; 23: 566s, abs 6527.
96. Kaminski MS, Tuck M, Estes J, et al. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 2005; 352: 441-449.

97. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004; 104: 3064-3071.
98. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood 2004; 104: 2667-2674.
99. Witzig TE, White CA, Wiseman GA, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol 1999; 17: 3793-3803.
100. Bastion Y, Sebban C, Berger F, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J Clin Oncol 1997; 15: 1587-1594.
101. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J Clin Oncol 1995; 13: 1726-1733.
102. Plunkett TA, Rubens RD. The biology and management of bone metastases. Crit Rev Oncol Hematol 1999; 31: 89-96.
103. Galasko CS. Skeletal metastases. Clin Orthop Relat Res 1986; 210: 18-30.
104. Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer: implications for management. Eur J Cancer 2000; 36: 476-482.
105. Diel IJ, Solomayer EF, Bastert G. Treatment of metastatic bone disease in breast cancer: bisphosphonates. Clin Breast Cancer 2000; 1: 43-51.
106. Bury T, Barreto A, Daenen F, Barthelemy N, Ghaye B, Rigo P. Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastasis in patients with non–small cell lung cancer. Eur J Nucl Med 1998; 25: 1244-1247.
107. Finkelstein J, Zaveri G, Wai E, Vidmar M, Kreder H, Chow E. A population-based study of surgery for spinal metastases. Survival rates and complications. J Bone Joint Surg Br 2003; 85: 1045-1050.
108. Marco RA, Sheth DS, Boland PJ, Wunder JS, Siegel JA, Healey JH. Functional and oncological outcome of acetabular reconstruction for the treatment of metastatic disease. J Bone Joint Surg Am 2000; 82: 642-651.
109. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999; 17: 846-854.
110. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998; 16: 2038-2044.
111. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003; 98: 1735-1744.
112. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004; 96: 879-882.
113. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol 2003; 21: 4277-4284.
114. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003; 14:1399-1405.
115. Body JJ, Diel IJ, Lichinitzer M, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 2004; 90: 1133-1137.

116. Body J-J, Lichinitser M, Tjulandin SA, et al. Effect of oral ibandronate versus intravenous (i.v.) zoledronic acid on markers of bone resorption in patients with breast cancer and bone metastases: Results from a comparative phase III trial. J Clin Oncol (Meeting Abstracts) 2005; 23: 12s, abs 534.
117. Nishimura K, Nonomura N, Yasunaga Y, et al. Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. Cancer 2000; 89: 2570-2576.
118. Porter A, McEwan A, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Radiat Oncol Biol Phys 1993; 25: 805-813.
119. Townsend PW, Rosenthal HG, Smalley SR, et al. Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilization of impending or pathologic fractures due to metastatic disease. J Clin Oncol 1994; 12: 2345-2350.
120. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the study by the Radiation Therapy Oncology Group. Cancer 1982; 50: 893-899.
121. Vargha ZO, Glicksman AS, Boland J. Single-dose radiation therapy in the palliation of metastatic disease. Radiology 1969; 93: 1181-1184.
122. Micke O, Berning D, Schaefer U, Bruns F, Willich N. Combination of ibandronate and radiotherapy in metastatic bone disease – Results of a randomized study. Proc Am Soc Clin Oncol 2003; 22: 759, abs 3052.
123. Vassiliou V, Kalogeropoulou C, Solomou EK, Kardamakis D. Combination of radiotherapy and ibandronate for the treatment of bone metastases: clinical evaluation and radiological assessment (Abstract). Support Care Cancer 2005: 13; 467, abs 21-160.
124. Fourney DR, Schomer DF, Nader R, et al. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. J Neurosurg 2003; 98 (Suppl): 21-30.

APPENDIX B

Country	Variable	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Austria	Total	27,640	32,909	37,572	44,758	60,807	60,506	72,028	80,550	92,854	116,342	134,818	153,839
	<1993	26,161	29,754	33,178	35,980	43,007	36,514	38,765	39,829	38,576	37,543	36,685	35,159
	1993-1998	1479	3155	4395	8778	17,800	23,992	33,262	40,477	51,772	65,729	79,432	92,165
	1999-2004	0	0	0	0	0	0	0	244	2507	13,070	18,701	26,515
Belgium	Total		47,167	53,811	61,020	64,120	75,148	92,180	105,322	117,197	140,343	176,623	201,474
	<1993		47,073	53,276	57,822	59,359	64,471	70,955	75,278	78,571	75,285	64,421	63,277
	1993-1998		94	535	3198	4761	10,677	21,225	30,042	37,877	59,790	83,852	100,862
	1999-2004		0	0	0	0	0	0	2	750	5269	28,350	37,335
Czech Republic	Total	1494	1657	3313	7513	7993	19,997	23,252	31,871	39,725	49,494	60,511	77,334
	<1993	1494	1657	3228	6603	6315	13,989	13,559	15,083	15,588	17,502	19,346	21,712
	1993-1998	0	0	84	909	1678	6008	9692	16,788	23,980	29,674	36,424	46,195
	1999-2004	0	0	0	0	0	0	0	0	157	2318	4740	9426
Denmark	Total		9938	10,759	12,243	14,827	16,803	20,908	23,999	31,790	46,460	61,355	76,295
	<1993		8921	8875	9823	10,728	10,805	11,978	12,999	13,531	15,556	17,552	17,511
	1993-1998		1016	1884	2420	4099	5997	8931	10,981	17,910	26,812	37,025	47,554
	1999-2004		0	0	0	0	0	0	19	349	4091	6778	11,230
Finland	Total		13,552	14,658	18,556	22,687	25,348	29,148	34,101	42,371	53,843	65,030	81,562
	<1993		12,123	12,954	14,919	16,417	17,132	17,782	18,438	19,163	18,946	18,017	19,949
	1993-1998		1430	1704	3638	6269	8215	11,367	15,658	22,869	30,767	39,529	50,910
	1999-2004		0	0	0	0	0	0	5	339	4129	7485	10,704
France	Total	195,020	220,332	248,763	281,675	331,354	377,170	450,629	538,663	679,195	822,675	959,480	1,288,844
	<1993	195,020	210,705	229,859	233,970	244,277	240,412	259,176	285,178	310,725	303,312	299,977	325,924
	1993-1998	0	9627	18,904	47,705	87,077	136,758	191,454	253,372	359,290	459,034	553,251	795,794
	1999-2004	0	0	0	0	0	0	0	113	9179	60,329	106,253	167,126
Germany	Total	216,841	252,039	305,069	367,045	405,116	461,433	531,399	595,970	683,818	844,892	972,564	1,191,208
	<1993	216,841	243,444	286,199	320,040	309,474	311,499	319,638	322,023	329,714	329,664	325,440	581,819
	1993-1998	0	8596	18,870	47,005	95,642	149,934	211,761	267,851	334,466	431,153	499,230	265,790
	1999-2004	0	0	0	0	0	0	0	6097	19,638	84,075	147,894	343,599
Greece	Total	9917	9880	10,810	13,422	13,037	14,085	21,925	28,023	35,904	48,137	60,792	70,986
	<1993	9917	9880	9530	10,895	11,131	8720	11,927	13,165	13,884	15,448	16,846	22,729
	1993-1998	0	0	1280	2527	1906	5365	9998	14,857	21,192	25,168	30,224	35,352
	1999-2004	0	0	0	0	0	0	0	0	828	7520	13,721	12,904
Hungary	Total		3450	7737	15,409	15,961	26,757	35,973	43,953	60,054	70,842	91,099	107,259
	<1993		3450	7737	15,157	15,410	22,714	28,465	33,131	37,982	41,967	43,536	43,451
	1993-1998		0	0	252	551	4043	7508	10,821	21,945	24,723	36,900	46,494
	1999-2004		0	0	0	0	0	0	2	127	4153	10,663	17,313
Ireland	Total		2609	3016	3696	4656	5281	5831	6785	8025	11,722	15,035	18,689
	<1993		2605	2966	3315	3962	4260	4357	4590	4898	5098	5436	5943
	1993-1998		4	50	380	694	1021	1475	2168	3007	4245	6341	8432
	1999-2004		0	0	0	0	0	0	27	120	2378	3258	4314
Italy	Total	151,756	150,104	142,461	185,380	235,212	279,542	325,270	504,576	608,554	746,662	816,842	904,348
	<1993	151,756	150,104	137,689	163,212	177,353	193,695	206,138	255,128	264,682	253,904	215,526	207,315
	1993-1998	0	0	4772	22,168	57,859	85,847	119,132	246,583	336,600	448,059	473,898	542,121
	1999-2004	0	0	0	0	0	0	0	2865	7272	44,700	127,418	154,913
Netherl.	Total	34,854	40,348	46,836	53,625	60,307	68,180	83,615	92,156	107,473	133,581	169,978	207,824
	<1993	34,508	39,046	43,128	44,230	43,925	48,543	51,860	52,979	55,442	58,285	63,581	65,302
	1993-1998	346	1302	3708	9395	16,382	19,637	31,631	38,538	51,004	66,428	89,121	118,392
	1999-2004	0	0	0	0	0	0	123	639	1027	8869	17,277	24,131

Country	Variable	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Norway	Total					14,642	17,247	21,593	26,676	31,922	37,435	42,456	51,500
	<1993					10,487	11,347	12,524	13,326	13,731	13,209	12,070	12,203
	1993-1998					4155	5899	9069	13,337	17,790	21,717	26,241	33,081
	1999-2004					0	0	0	14	401	2509	4145	6216
Poland	Total	8727	12,632	14,114	15,698	23,313	51,349	47,677	60,438	73,282	90,523	106,789	124,553
	<1993	8727	12,632	14,078	15,578	22,084	42,996	40,101	49,720	60,191	64,654	67,658	68,125
	1993-1998	0	0	35	120	1229	8353	7576	10,718	13,090	23,853	32,661	46,158
	1999-2004	0	0	0	0	0	0	0	0	2	2016	6470	10,270
Portugal	Total	2086	2523	2896	3154	3023	2983	3087	2928	3050	3086	2977	2849
	<1993	2086	2523	2896	3154	3023	2953	2979	2737	2759	2726	2560	2393
	1993-1998	0	0	0	0	0	30	108	184	280	354	409	443
	1999-2004	0	0	0	0	0	0	0	7	11	5	8	13
Spain	Total	54,781	57,406	65,140	75,297	89,540	107,573	273,684	317,989	370,163	453,009	545,372	648,935
	<1993	54,781	57,406	65,112	74,732	80,278	89,085	143,623	144,448	148,306	153,905	153,368	148,825
	1993-1998	0	0	29	565	9262	18,488	130,062	173,279	219,486	269,489	322,012	399,621
	1999-2004	0	0	0	0	0	0	0	262	2371	29,614	69,992	100,489
Sweden	Total	22,524	30,606	36,588	43,739	45,386	54,675	61,844	70,654	71,749	101,124	117,730	138,006
	<1993	21,904	27,845	31,812	35,892	32,830	35,871	36,591	36,589	36,916	34,073	33,088	32,824
	1993-1998	620	2761	4776	7847	12,556	18,804	25,253	33,855	33,855	55,585	66,847	82,515
	1999-2004	0	0	0	0	0	0	0	210	978	11,467	17,795	22,666
Switzerland	Total	21,596	24,207	26,987	30,627	36,060	45,319	55,939	74,081	96,227	117,677	133,327	162,413
	<1993	21,596	22,692	23,937	26,360	28,822	32,056	33,524	37,813	41,334	46,346	44,779	44,312
	1993-1998	0	1516	3050	4267	7239	13,262	22,398	35,700	52,322	64,331	73,226	90,555
	1999-2004	0	0	0	0	0	0	17	569	2571	7000	15,322	27,546
UK	Total	97,710	118,688	146,851	166,793	192,425	219,314	276,391	322,938	382,766	457,846	564,332	665,838
	<1993	97,710	114,547	142,296	143,805	158,823	171,808	203,498	221,116	230,805	232,269	248,814	255,921
	1993-1998	0	4142	4555	22,988	33,602	47,507	72,893	101,383	147,613	194,402	259,163	325,645
	1999-2004	0	0	0	0	0	0	0	440	4348	31,175	56,355	84,273
All	Total	844,947	1,030,049	1,177,381	1,399,649	1,640,465	1,928,709	2,432,374	2,961,676	3,536,117	4,345,692	5,097,112	6,173,756
	<1993	842,501	996,407	1,108,751	1,215,487	1,277,705	1,358,870	1,507,439	1,633,570	1,716,797	1,719,691	1,688,701	1,974,695
	1993-1998	2446	33,642	68,630	184,162	362,760	569,839	924,794	1,316,592	1,766,348	2,301,314	2,745,786	3,128,078
	1999-2004	0	0	0	0	0	0	140	11,514	52,972	324,687	662,625	1,070,983

Tabel B1. Sales in Europe based on first introduction date in Europe (€000s).

In Table B.1 the date of potential first access to the drug is defined according to first date of introduction in any of the European countries included in the study.

In Table B.2 the date of potential first access to the drug is defined based on the introduction date in each country. Note that in Table B.2 there may be some sales for a certain drug before the formal date of introduction in each country, which can be explained by the fact that they are sold on a special licence prior to authorisation.

Country	Variable	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Austria	Total	27,640	32,909	37,572	44,758	60,807	60,506	72,028	80,550	92,854	116,342	134,818	153,839
	<1993	26,161	29,754	33,178	35,980	42,980	36,423	38,619	39,638	38,358	37,334	36,505	35,015
	1993-1998	1479	3155	4395	8778	17,827	24,083	32,682	38,356	44,449	55,620	65,467	75,293
	1999-2004	0	0	0	0	0	0	727	2556	10,047	23,388	32,847	43,530
Belgium	Total		47,167	53,811	61,020	64,120	75,148	92,180	105,322	117,197	140,343	176,623	201,474
	<1993		46,815	52,968	57,000	58,092	62,748	68,653	72,297	75,583	72,556	61,820	60,381
	1993-1998		94	568	3776	5790	12,159	20,385	24,734	26,865	36,949	45,596	52,499
	1999-2004		258	275	244	238	241	3142	8292	14,749	30,837	69,206	88,593
Czech Republic	Total	1494	1657	3313	7513	7993	19,997	23,252	31,871	39,725	49,494	60,511	77,334
	<1993	1258	1385	2619	5176	5297	11,113	10,775	12,149	12,558	14,397	15,549	17,094
	1993-1998	236	272	693	2337	2696	8884	12,260	17,566	20,814	24,530	28,264	34,575
	1999-2004	0	0	0	0	0	0	217	2156	6354	10,568	16,698	25,665
Denmark	Total		9938	10,759	12,243	14,827	16,803	20,908	23,999	31,790	46,460	61,355	76,295
	<1993		8738	8655	9615	10,560	10,534	11,571	12,427	12,444	14,144	15,872	15,896
	1993-1998		1199	2104	2628	4267	6269	9318	11,264	17,964	24,688	33,119	41,616
	1999-2004		0	0	0	0	0	20	308	1381	7627	12,364	18,784
Finland	Total		13,552	14,658	18,556	22,687	25,348	29,148	34,101	42,371	53,843	65,030	81,562
	<1993		11,796	12,402	14,149	15,511	16,196	16,742	17,150	17,820	17,426	16,507	18,602
	1993-1998		1757	2256	4407	7176	9152	12,343	16,714	22,881	29,225	36,074	45,574
	1999-2004		0	0	0	0	0	64	237	1670	7191	12,450	17,386
France	Total	195,020	220,332	248,763	281,675	331,354	377,170	450,629	538,663	679,195	822,675	959,480	1 288,844
	<1993	178,556	194,084	211,339	215,171	225,640	223,309	242,659	268,344	291,012	280,818	276,701	300,944
	1993-1998	16,464	26,249	35,698	63,088	102,256	149,259	203,710	262,134	356,145	445,052	528,473	754,852
	1999-2004	0	0	1726	3416	3458	4602	4260	8185	32,038	96,805	154,306	233,048
Germany	Total	216,841	252,039	305,069	367,045	405,116	461,433	531,399	595,970	683,818	844,892	972,564	1,191,208
	<1993	216,841	243,444	286,199	318,818	305,657	304,255	311,122	313,017	320,058	316,809	310,979	497,411
	1993-1998	0	8596	18,870	48,228	99,241	155,367	209,264	243,778	275,396	341,476	391,003	214,215
	1999-2004	0	0	0	0	218	1811	11,013	39,175	88,364	186,607	270,582	479,582
Greece	Total	9917	9880	10,810	13,422	13,037	14,085	21,925	28,023	35,904	48,137	60,792	70,986
	<1993	9917	9880	9530	10,895	10,966	8519	11,342	12,491	13,023	14,175	15,481	21,347
	1993-1998	0	0	1280	2527	2072	5566	9688	12,427	15,049	18,295	19,641	24,846
	1999-2004	0	0	0	0	0	0	895	3104	7831	15,667	25,670	24,793
Hungary	Total		3450	7737	15,409	15,961	26,757	35,973	43,953	60,054	70,842	91,099	107,259
	<1993		2676	4908	9403	9088	12,395	14,571	16,577	17,944	18,774	18,859	18,198
	1993-1998		773	2829	5708	6581	14,016	21,028	26,205	37,290	42,193	50,643	57,292
	1999-2004		1	0	298	292	346	374	1171	4819	9875	21,597	31,770
Ireland	Total		2609	3016	3696	4656	5281	5831	6785	8025	11,722	15,035	18,689
	<1993		2603	2965	3314	3956	4253	4349	4578	4890	5095	5434	5941
	1993-1998		6	50	381	699	1027	1482	1931	2337	3283	4806	5925
	1999-2004		0	0	0	0	0	0	276	797	3344	4795	6823
Italy	Total	151,756	150,104	142,461	185,380	235,212	279,542	325,270	504,576	608,554	746,662	816,842	904,348
	<1993	150,264	146,907	134,473	159,741	174,259	190,695	201,885	250,294	259,907	249,561	211,818	204,110
	1993-1998	1492	3197	7988	25,639	60,953	88,847	121,938	225,463	268,345	324,239	316,612	342,366
	1999-2004	0	0	0	0	0	0	1446	28,819	80,302	172,862	288,412	357,872

Country	Variable	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Netherl.	Total	34,854	40,348	46,836	53,625	60,307	68,180	83,615	92,156	107,473	133,581	169,978	207,824
	<1993	34,508	39,046	43,128	44,230	43,925	48,543	51,860	52,979	55,442	58,096	63,309	64,948
	1993-1998	346	1302	3708	9395	16,382	19,637	30,960	36,842	46,625	54,611	67,061	83,761
	1999-2004	0	0	0	0	0	0	794	2335	5406	20,874	39,609	59,115
Norway	Total					14,642	17,247	21,593	26,676	31,922	37,435	42,456	51,500
	<1993					9957	10,421	11,103	11,584	11,623	11,271	10,672	11,264
	1993-1998					4685	6825	10,491	14,937	19,569	23,045	26,691	32,397
	1999-2004					0	0	0	155	731	3119	5094	7840
Poland	Total	8727	12,632	14,114	15,698	23,313	51,349	47,677	60,438	73,282	90,523	106,789	124,553
	<1993	3673	4979	4875	4759	7124	12,443	11,006	11,963	14,890	15,565	18,694	19,188
	1993-1998	3029	5174	6714	7827	12,999	35,605	34,278	45,451	54,938	61,080	64,037	71,994
	1999-2004	2025	2479	2525	3113	3189	3301	2393	3024	3454	13,878	24,058	33,371
Portugal	Total	2086	2523	2896	3154	3023	2983	3087	2928	3050	3086	2977	2849
	<1993	2086	2523	2896	3154	3023	2953	2979	2737	2759	2726	2560	2393
	1993-1998	0	0	0	0	0	30	76	76	123	133	142	192
	1999-2004	0	0	0	0	0	0	32	115	167	226	275	264
Spain	Total	54,781	57,406	65,140	75,297	89,540	107,573	273,684	317,989	370,163	453,009	545,372	648,935
	<1993	54,713	57,328	65,013	74,622	79,913	88,397	129,160	126,998	129,292	136,286	143,384	141,518
	1993-1998	68	78	127	675	9627	19,176	124,817	153,460	166,158	184,643	211,248	247,577
	1999-2004	0	0	0	0	0	0	19,707	37,531	74,713	132,080	190,740	259,840
Sweden	Total	22,524	30,606	36,588	43,739	45,386	54,675	61,844	70,654	71,749	101,124	117,730	138,006
	<1993	21,573	26,771	30,561	34,170	31,340	34,064	34,822	34,729	35,056	32,238	31,094	30,838
	1993-1998	951	3835	6027	9569	14,046	20,611	25,986	32,153	32,153	48,029	56,016	66,195
	1999-2004	0	0	0	0	0	0	1036	3772	4540	20,858	30,620	40,973
Switzerland	Total	21,596	24,207	26,987	30,627	36,060	45,319	55,939	74,081	96,227	117,677	133,327	162,413
	<1993	21,596	22,692	23,711	25,706	27,943	30,895	32,314	36,352	39,575	44,335	42,811	42,348
	1993-1998	0	1516	3275	4921	8117	14,423	22,797	30,632	42,537	50,580	55,128	67,422
	1999-2004	0	0	0	0	0	0	828	7098	14,115	22,762	35,388	52,643
UK	Total	97,710	118,688	146,851	166,793	192,425	219,314	276,391	322,938	382,766	457,846	564,332	665,838
	<1993	88,495	102,969	126,868	126,027	137,679	143,252	167,139	177,935	182,497	179,168	194,793	202,443
	1993-1998	7811	14,013	17,977	38,832	50,706	69,435	98,084	128,778	166,822	211,244	259,383	303,438
	1999-2004	1404	1707	2006	1934	4041	6628	11,168	16,225	33,446	67,434	110,157	159,957
All	Total	844,947	1,030,049	1,177,381	1,399,649	1,640,465	1,928,709	2,432,374	2,961,676	3,536,117	4,345,692	5,097,112	6,173,756
	<1993	809,642	954,389	1,056,288	1,151,929	1,202,909	1,251,409	1,372,671	1,474,239	1,534,733	1,520,774	1,492,843	1,709,878
	1993-1998	31,876	71,216	114,561	238,715	426,121	660,370	1,001,589	1,322,900	1,616,459	1,978,916	2,259,402	2,522,029
	1999-2004	3429	4444	6532	9005	11,436	16,929	58,114	164,536	384,925	846,002	1,344,867	1,941,849

Tabel B2. Sales in Europe based on introduction date in each country (€000s).

APPENDIX C

INAHTA members		
Agence d'Evaluation des Technologies	AETMIS	Canada
Agencia de Evaluación de Tecnologías Sanitarias	AETS	Spain
Agencia de Evaluación de Tecnologías Sanitarias de Andalucía	AETSA	Spain
Alberta Heritage Foundation for Medical Research	AHFMR	Canada
Agency for Healthcare Research and Quality	AHRQ	USA
L'Agence Nationale d'Accréditation et d'Evaluation en Santé	ANAES	France
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical	ASERNIPS	Australia
Catalan Agency for Health Technology Assessment and Research	CAHTA	Spain
Canadian Coordinating Office for Health Technology Assessment	CCOHTA	Canada
Comité d'Evaluation et de Diffusion des Innovations Technologiques Assistance Publique Hôpitaux de Paris	CEDIT	France
Centers for Medicare and Medicaid Services	CMS	USA
Center for Medical Technology Assessment	CMT	Sweden
Centre for Reviews and Dissemination	CRD	UK
College voor Zorgverzekeringen	CVZ	The Netherlands
Danish Centre for Evaluation and Health Technology Assessment	DACEHTA.	Denmark
German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information	DAHTA @DIMDI	Germany
Danish Institute for Health Services Research and Development	DSI	Denmark
Unidad de Tecnologias de Salud	ETESA	Chile
Finnish Office for Health Care Technology Assessment	FinOHTA	Finland
Health Council of the Netherlands	GR	The Netherlands
Unit of Health Economics and Health Technology Assessment	HunHTA	Hungary
Israel Center for Technology Assessment in Health Care	ICTAHC	Israel
Instituto Nacional de Higiene Epidemiologia y Microbiologia	INHEM	Cuba
Unit of the Institute of Technology Assessment	ITAHTA	Austria
Belgian Federal Health Care Knowledge Centre	KCE	Belgium
Medical Services Advisory Committee	MSAC	Australia
Medical Technology Unit, Federal Social Insurance Office Switzerland	MTUFSIOS	Switzerland
National Coordinating Centre for Health Technology Assessment	NCCHTA	UK
National Horizon Scanning Center	NHSC	UK
NHS Quality Improvement Scotland	NHSQIS	UK
National Institute for Health and Clinical Excellence	NICE	UK
Norwegian Knowledge Centre for the Health Services (formerly SMM)	NKCHS	Norway
New Zealand Health Technology Assessment	NZHTA	New Zealand
Basque Office for Health Technology Assessment	OSTEBA	Spain
Swedish Council on Technology Assessment in Health Care	SBU	Sweden
Unidad de Evaluacion de Tecnologias Sanitarias	UETS	Spain
VA Technology Assessment Program	VATAP	USA
The Netherlands Organisation for Health Research and Development	ZonMW	The Netherlands
Other international Health Technology Assessment organisations		
BlueCross BlueShield Technology Evaluation Center	BCBS	USA
Canadian Task Force on Preventive Health Care	CTFPHC	Canada
The Centre for Clinical Effectiveness	CCE	Australia
HAYES Inc.		USA
Institute for Clinical Evaluative Sciences	ICES	Canada
The Institute for Clinical Systems Improvement	ICSI	USA
Malaysian Health Technology Assessment Unit	MHTAU	Malaysia
Technology Assessment Unit of the McGill University Health Centre	MUHC	Canada
Ontario Ministry of Health and Long-Term Care		Canada
Swiss Science and Technology Council/Technology Assessment	TASWISS	Switzerland
TNO Prevention and Health	TNO	The Netherlands
University HealthSystem Consortium	UHC	USA
Wessex Institute for Health Research and Development: STEER Reports (edited by Bazian Ltd)	WIHRD	UK
West Midlands Health Technology Assessment Collaboration	WMHTAC	UK
Washington State Department of Labor and Industries	WSDLI	USA
Agencies that are now closed		
British Columbia Office of Health Technology Assessment	BCOHTA	Canada
Health Services Utilization and Research Committee	HSURC	Canada
Health Technology Advisory Committee	HTAC	USA
Office of Technology Assessment	OTA	USA
Scottish Health Purchasing Information Centre	SHPIC	UK

INAHTA = International Network of Agencies for Health Technology Assessment

Tabel C1. Health Technology Assessment agencies included in the Health Technology Assessment database (1990-2004).

NOTES

NOTES

Karolinska
Institutet