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Review

Federation of European Cancer Societies. Full Report. Economic evaluation in cancer care: questions and answers on how to alleviate conflicts between rising needs and expectations and tightening budgets

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Abstract

All Western countries have experienced a fast growth in their healthcare expenses over recent decades. It is expected that pressure for such growth will continue in the future. But spending an ever larger share of our nation's resources on healthcare cannot be afforded. As a consequence, making choices will become more and more inevitable, even in cancer care. Economic evaluation is a very supportive tool for such decisions. This position statement concludes with recommendations for providers and healthcare policy-makers, to safeguard and further improve good clinical decision making and healthcare policy in cancer care under tightening budgets. © 2000 Published by Elsevier Science Ltd. All rights reserved.

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1. Growing scarcity of resources

1.1. Cancer poses a major burden on society

Cancer poses a major burden on society. One in four deaths can be attributed to cancer and it ranks second on the list of causes of death, after cardiovascular disease. It has been estimated that in the European Community in 1990, some 1 351 100 incident cases of all forms of cancer (excluding non-melanomatous skin cancers) were diagnosed, almost equally distributed between men and women. In men, the major forms of cancer were cancer of the lung (21%), large bowel (13%), prostate (12%), bladder (7%) and stomach (7%). In women, major forms were cancer of the breast (28%), large bowel (15%), lung (6%), uterine corpus (5%) and stomach (5%) [1]. These figures vary widely from one country to another, from developing countries to industrialised countries and even from one region to another within the same country.

For most cancers, with the exception of stomach and cervix, the incidence is still rising for a number of reasons such as ageing of the population and smoking [2]. It is estimated that, without action, one in three European citizens will suffer from cancer. Taking only the impact of ageing into account, it is estimated that the number of cancer patients will have increased by 20% during the 1990s. Despite this gloomy picture, it should be kept in mind that, with the current state of medical knowledge, on average 40% of cancer patients are cured. This average shows wide variations depending on the tumour site and ranges from a relative 5-year survival rate of as high as 93% for testis carcinoma [3] to an average of approximately 40–45% after colon and rectum cancer [4] and to as low as 4% after pancreas cancer [5]. This group of cured citizens, however, may face serious problems of social and professional rehabilitation and reintegration after cure and of restoration of physical, mental and social health, a problem all too often ignored.

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1.2. Treatment modalities

Several treatment modalities exist against cancer: surgery, radiotherapy, chemotherapy, immunotherapy or a combination of these.

Surgical removal of the tumour tissue, usually applied to relatively limited tumours, is at present the most generally successful mode of cancer treatment (60% of all cures). Radiotherapy is given to approximately 1 in 2 patients and is involved in approximately one-third of the cures. Chemotherapy was initially mainly used in patients with metastatic disease, as symptomatic treatment. A number of curative indications have progressively developed especially in haematopoietic malignancies, germinal tumours and paediatric tumours. Finally, chemotherapy is increasingly used in adjuvant settings where it is aimed at microscopic metastatic localisations in combination with the other treatment modalities which are aimed at controlling the primary tumour. As such, chemotherapy is estimated to play a role in approximately 10% of cancer cures while it is also used in a vast number of patients in a symptomatic setting.

Immunotherapy, although still in its infancy, has only been shown to be promising against relatively small numbers of cells and will thus need to be used in combination with other treatment modes. Hormonal therapy is effective for tumours growing in organs under hormonal control (e.g. tamoxifen in breast cancer).

1.3. Progress in science and technology boosts opportunities for cancer care

The previous decades have witnessed an explosive growth in scientific know-how, especially in cancer biology, resulting in a rapidly increasing availability of new drugs, equipment, materials and other technologies that are, or are expected to be, beneficial in the struggle against cancer [6, 7]. Moreover, many more new developments in medical technologies are expected for the future. Indeed, based on data from the National Cancer Institute, Bethesda, MD, USA it can be calculated that the share of cancer spending in total pharmaceutical research spending has increased from 9% (in the late 1970s) to 15% in the late 1980s and many more clinical research projects are underway in cancer than in any other area of medicine [8]. Twice as many new projects are underway in cancer care than in paediatric medicine or in cardiovascular medicine; two and a half times as much as in AIDS research, and four times as much as in obstetrics and gynaecology or in arthritis. Under the Biomedical and Health Research Programme of the European Union, cancer research takes up more than 20% of the research funds [9].

1.3.1. Chemotherapy

In chemotherapy, new and more expensive cytostatic drugs, such as docetaxel and paclitaxel have become available and many of the existing ones are now used in combination and/or in higher dosages resulting in higher exposure and levels of toxicity. For example, the use of 5-fluorouracil (5-FU) combined with low-dose leucovorin is increasingly advocated for the treatment of advanced and metastatic colorectal cancer. It has been observed in clinical trials that this combination has some therapeutic gain (longer survival and improved objective regression) in comparison with 5-FU alone [10, 11]. Autologous bone marrow transplantation, and even more the use of peripheral stem cells, has also allowed dose intensification. For example, peripheral blood progenitor cell reinfusion can considerably alleviate bone marrow toxicity resulting from high-dose melphalan in treating multiple myeloma [12]. The range of indications for which chemotherapy is being administered is widening, for example more diseases, more second- and third-line therapy and more types of treatment, such as neo-adjuvant therapy. Since 1989, combined levamisole and 5-FU chemotherapy has been advocated as an adjuvant treatment for stage III colon cancer by the US National Cancer Institute [13] (http://www.nci.nih.gov/). For non-small cell lung cancer (NSCLC), surgery is often inadequate as treatment due to existing micrometastases. Therefore, different chemotherapeutic agents, like cisplatin + vinca alkaloid and cyclophosphamide + doxorubin + cisplatin, are being tested for their ability to lower the incidence of metastases and to palliate disease-related symptoms [14]. This higher treatment intensity also requires additional monitoring of patients (sometimes patients must be hospitalised) and additional supportive therapies to counter the side-effects. For these side-effects, new drugs, such as antiemetics against nausea and growth factors to prevent episodes of febrile neutropenia and fever, have been developed (for example, 5-hydroxytryptamine$_3$ receptor antagonists), and these latter products are sometimes even more expensive than the cytostatics. Jones and colleagues [15] examined the budgetary impact of 5-HT$_3$ receptor antagonists in the management of chemotherapy-induced emesis as compared with conventional antiemetics. They found that the new antiemetics cause an increase in total hospital costs for these patients of 12–34% when used for delayed emesis (variation depending on the antiemetic treatment strategy considered). As of yet, the clinical benefits of this treatment policy are, however, still uncertain.

1.3.2. Radiotherapy

In radiotherapy, more sophisticated equipment, such as three-dimensional planning systems, enabling more accurate calculation of the target volume and planned dose and multileaf collimators, allowing more accurate

delivery of the dose, is being developed. The possibilities of accelerated radiotherapy as a means of delivering a shortened course of radical radiotherapy are being explored [16].

Much attention has been devoted to the development of quality assurance procedures such as *in vivo* dosimetry, portal imaging, immobilisation devices and verification systems. All these allow improved treatment precision, a crucial factor for both maximising tumour control and minimising damage to healthy tissue thereby enhancing long-term survival. It has been estimated, based on data collected in one university hospital in Belgium in the early 1990s, that introducing these quality assurance procedures into routine practice amounts to, on average, an overall one-time increase in treatment costs of at least (i.e. assuming that there is almost no excess capacity in terms of equipment) 5% [17–19].

1.3.3. Surgery

In surgery, improved treatment opportunities have come from the development of (more expensive) endoscopic equipment resulting in less invasive surgical procedures thereby reducing hospital stays (lower cost) and the use of disposable materials (higher costs). The effectiveness of some endoscopic resection techniques is, however, still under investigation [20, 21].

1.3.4. Combination therapies

Furthermore, increased use of combination therapies is also under investigation. It has become standard to administer adjuvant chemotherapy after primary surgery or radiotherapy in certain cancers, for example, colorectal cancer. It has been shown that for rectal carcinoma a combined adjuvant treatment of radiation or surgery and chemotherapy provides markedly better results than either therapy alone [22]. 5-FU + levamisole as an adjuvant therapy of surgery for stage III colorectal cancer provides considerable survival advantages and lowers the risk of recurrence by 40%. Additional drug use carried a price tag of approximately US$ 1565 per patient in 1989 [10].

Neo-adjuvant chemotherapy as the initial treatment offers advantages in the management of locally advanced solid tumours. For instance, some argue that neo-adjuvant chemotherapy in conjunction with surgery for regional advanced stage III NSCLC can provide considerable benefits in terms of disease-free survival. Results from clinical trials were initially conflicting, which was often due to different study designs [23], but more recent data confirm the cost-effectiveness of such combined treatments [24].

1.3.5. Chemoprevention

Moreover, the current use of drugs in chemoprevention (for example anti-oestrogens, retinoids, beta-carotene, alpha-tocopheral) is presently under review. It has been demonstrated that for some tumour types, patients cured of their primary tumour have a higher risk of developing a second primary tumour. For these patients the use of chemoprevention, involving the reversal, suppression or prevention of carcinogenesis, is under investigation. Also gene therapy, involving the replacement or addition of a single specific gene in tissue, and vaccination by means of custom-made vaccines from the patient's tumour, are under investigation for applications in cancer treatment. Since it is increasingly believed that some cancer patients have inherited a defective cancer suppressor gene, secondary prevention through genetic screening is a potential new option. The use of improved diagnostics such as the use of magnetic resonance imaging (MRI) in addition to mammography for breast cancer screening is also under investigation.

1.3.6. Follow-up

Improved, and more expensive, diagnostic procedures for follow-up after treatment are also being discussed. New imaging techniques such as MRI, biological tumour markers and molecular pathology tests (for example, polymerase chain reaction, PCR; fluorescent *in situ* hybridisation, FISH) yield additional information compared with traditional techniques, not only for tumour diagnosis but also for determining residual tumour mass and hence for determining the intensity and frequency of follow-up of patients after primary treatment for cancers. Developments in information technology allows medicine to be practised 'at a distance'. Tele-medicine will facilitate access to national and international cancer experts in the future [25, 26].

1.3.7. Psychosocial care and rehabilitation

Finally, demands and opportunities not only result in an increase in direct medical care. There is also a growing awareness that psychosocial care and rehabilitation should not be neglected either. These aspects remain important even after patients have, medically speaking, been declared 'cured'. These former patients may suffer from fatigue, difficulties with social reintegration, for example after a long absence from work and social activities, and may face financial problems, not only due to elevated treatment costs and temporary loss of income from work but also because of the difficulties of applying for private loans, mortgages and life and (private) healthcare insurance, due to 'pre-existing conditions'. Having cancer may be associated with the loss of a bodily part or function and such loss may lead to a reduction in self-esteem. This needs to be addressed in order to achieve as fully as possible restoration of physical as well as social and mental health. Therefore, adequate rehabilitation will typically require a multidisciplinary approach [27]. Since 40% of cancer patients are cured, this represents a large population whose problems of rehabilitation have received only limited attention.

Table 1
Healthcare expenses, as % of GDP (in selected OECD countries, 1960–1997)

Country	1960	1980	1995	1997	Index of growth 1960–1997 (1960 = 100)[a]
Belgium	3.4	6.6	8.0	7.6	2.2
Canada	5.5	7.3	9.5	9.3	1.4
France	4.2	7.6	9.9	9.9	2.3
Germany	4.8	8.4	9.6	10.4	2.1
Greece	2.4	3.6	5.4	7.1	3.0
The Netherlands	3.8	7.9	8.8	8.5	2.2
Spain	1.5	5.7	7.6	7.4	4.4
Sweden	4.7	9.4	7.7	8.6	1.6
UK	3.9	5.6	6.9	6.7	1.5
USA	5.2	9.2	14.5	14.0	2.7
Average	3.94	7.12	8.79	8.95	2.3

Source: OECD [28].
[a] Index growth = ((expenses 1997/expences 1960)$^{1/37}$−1)×100

Table 2
Real expenditure per capita at Purchasing Power Parity (US$, 1990 = 100 for price index)

Country	1960	1980	1994	Index of growth 1960–1994 (1990 = 100)
Belgium	323	1144	1350	4.3
Canada	640	1435	1642	2.8
France	439	1389	1524	3.7
Germany	555	1566	1527	3.0
Greece	98	373	489	4.8
The Netherlands	420	1353	1341	3.5
Spain	85	648	821	6.9
Sweden	549	1693	1101	2.1
UK	469	885	989	2.2
USA	860	2053	2872	3.6
Average	444	1254	1366	3.7

Source: OECD [28].

1.4. Healthcare budgets are limited

This rapid increase in knowledge, resulting in new medical technologies, together with many other factors such as an ageing population, increasing patient demands, extensive health insurance coverage, etc. has caused a rapid growth in healthcare expenses—faster even than the growth of countries' gross domestic product (GDP). Table 1 illustrates that the share of GDP devoted to healthcare has, on average, more than doubled in Organisation of Economic Cooperation and Development (OECD)[1] countries over the period 1960–1997 [28].

This observation, however, easily leads to underestimation of the actual growth level of healthcare costs, since real GDP (i.e. corrected for inflation) has also grown substantially over that period. Table 2 shows that real healthcare expenses per capita in a number of OECD countries, have more than tripled over the period 1960–1994.

Although it is quite difficult to assign healthcare expenses to diagnostic groups and thus come up with reliable estimates of the 'burden of cancer' on the overall healthcare budget, (the scarce) available data fairly consistently suggest that cancer takes up to 4.5–6% of the total healthcare budget.[2] In a number of countries, including the USA, Sweden and The Netherlands, healthcare expenses have been assigned to the 17 international classification of diseases (ICD)-groups. In these countries oncology is ranked as the fourth to eighth biggest spending group after other groups such as mental illness, cardiovascular diseases and diseases of the digestive system [29]. In all respects, the share of cancer in total direct healthcare costs is very low, compared with its share in mortality and morbidity in society and in grief and pain both for patients and family members.

In the literature it is noteworthy that very few data are available to enable forecasting of the impact of routine use of new technologies on total cancer care expenses. Most of the articles that report cost data focus on the providing institution or patients; very few attempt to estimate the aggregate expense impact (i.e. for all institutions and patients in a given country). There are exceptions, however. For instance, in studying the cost-effectiveness of several cervical cancer screening programmes, Koopmanschap and colleagues [30] have also reported the aggregate expense implications for The Netherlands. It is only when expenses are reported to be growing, that potential causes are investigated.

All countries are confronted with the continuing development of new health technologies and an ageing population, increasing the need for healthcare resources. However, governments face tighter budgetary restrictions, imposed by lower levels of economic growth since the 1980s compared with the first three decades following the Second World War, the Maastricht norms for the Monetary Union within the European Union (EU), which put limits on the governmental debt and annual deficit, and threats from international competition, hampering increasing fiscal pressure. Governments are forced to impose tighter budget constraints on many sectors including education, science, culture, defence and healthcare. Healthcare spending is becoming one of the main target areas of cost containment for many European governments since it takes up a large and steadily growing amount of

[1] OECD Health Care: http://www.OECD.org//els/health/info.htm
[2] Other sources [for example National Cancer Institute (NCI)] have estimated a much higher share: 15% (in 1990), expected to increase to 20% of total expenses by the next millennium. But these estimates probably not only include direct healthcare expenses, but also indirect costs due to morbidity and mortality.

national resources. New and expensive treatments are especially becoming subject to more scrutiny and critical appraisal.

1.5. There is 'no free lunch': scarcity requires choices

It is sometimes assumed, or at least hoped, that sufficient resources would be available to provide all possible care to all patients who could benefit from it. This is of course a fallacy. Choices have to be made all the time in healthcare. Since resources are limited, awareness that 'there is no free lunch', that these choices have to be made, is increasing. Resources (for example, physician time, equipment time) that are devoted to one cancer patient cannot be devoted to another or to patients with other diseases. Spending more money on healthcare inherently implies that fewer resources are available for the education of children, preventing environmental pollution, culture or defence. Awareness is growing that priorities must be set.

As long as budgets were expanding, the main focus was on which issues should be put first. Hence identifying priorities was much easier before budget cuts were required. With shrinking budgets, choices do hurt. The pressure to ensure that additional resources, if available, are used to their best effect and that cutbacks, if they have to be implemented, only occur where they do least harm, is increasing [31].

2. Priority setting is the answer

2.1. Priority setting occurs continually—overtly or covertly

Sometimes this process of priority setting is explicit, for instance when no reimbursement is provided for certain types of care or interventions (for example, organ transplantation for Medicaid patients in Oregon, USA, dental care for adults, plastic surgery for cosmetic purposes). More often, this selection process is much more implicit.

Implicit selection occurs when public or private health insurers impose budgetary restrictions on healthcare. These can take several forms. In many countries, the introduction of fixed global budgets, at several levels in the system, has been an important mechanism, or at least attempt, to contain costs. For instance, since the early 1990s the Belgian government has allowed the total healthcare budget to grow annually only at the rate of 1.5% above inflation. Global budgets, imposed by the national government, are also in place in the UK and The Netherlands. In other countries, global budgets are imposed by the regional governments (e.g. Sweden and Canada), by non-governmental statutory agencies (Germany and France) or by private for-profit companies (e.g. the USA). In some countries, these budgets cover the entire public health sector (e.g. the UK and Sweden), in other countries, budget ceilings are imposed only on specific sub-sectors, such as hospitals (e.g. The Netherlands), ambulatory physician visits and pharmaceuticals (Germany)—see Schwartz and colleagues [32] for an overview. Budgets seem to be applied more often for hospitals than for physician services in many countries [33].

The financing systems used for different healthcare-providing agents in the system have also been changed, which will be illustrated for hospital care. Traditionally, compulsory health insurance systems have paid hospitals either through an annual budget (to cover all running costs) or through a daily rate. In those days there were no incentives to use resources efficiently. In case of a per diem payment, hospitals have a strong incentive to 'produce' many stay days. Hospitals receiving a budget were not encouraged to economise, for fear of budget cuts.

Under the increasing pressure to economise, those countries that already used to pay their hospitals through a budget, are tightening their budgets, and combine these tighter budgets with incentives to encourage efficiency (to reduce length of stay, to adopt more cost-effective interventions). In OECD countries where hospitals were paid per diem, a switch can be observed towards some forms of case-related payments. In others, where per diem payments remain in place, budgets have been imposed since the late 1980s or early 1990s [34, 35]. Since 1983, American hospitals receive a case payment per diagnosis related group (DRG) for hospitalisation of Medicare patients (government health insurance for the elderly). Some free-standing cancer research centres and quasi-independent cancer centres (separate cancer hospitals, located at university medical centres) have been exempted from this system. Many other cancer centres supported by the NCI have not been exempted. Such a lack of exemption might reduce quality of care, lead to refusal to admit patients with severe illness and reduce access of patients to the newest types of care [36]. In Germany, public hospitals are reimbursed on the basis of a general per diem rate, a special per diem rate (for example, for paediatric oncology) or case payments (for example for bone marrow transplantation) [37–39].

All of this implies that the reimbursement for hospitals is shifting gradually from a retrospective, cost-based system (i.e. all proven hospital costs were, almost automatically, reimbursed by the health insurance) towards prospective financing whereby the hospital receives a fixed payment from which all operating costs (and sometimes also capital costs) have to be covered [40]. In some countries (for example, France, Portugal, Spain), this shift occurred only for public, and not for private hospitals.

Although the fee-for-service payment system may sometimes have led to over-consumption, it gave more

guarantee that all necessary steps were taken for high-quality diagnosis, treatment and follow-up than prospective payment. Prospective financing might permit easier cost containment, but will necessitate steps to guarantee the quality of the process and the required outcome, as well as access to care. These, and many other, healthcare reforms shift the financial responsibility to patients (higher co-payments), industry (lower profits) and providers [41, 42]. Providers are supposed to keep on delivering high-quality care for their patients, while simultaneously being confronted with tightening financial resources. So far no studies have attempted to evaluate precisely the effectiveness of such budgetary restrictions to contain costs [33].

Implicit priority setting also occurs when governments place restrictions on the number of centres, availability of equipment or of certain types of medical and allied health staff. For instance, the number of residencies in certain medical (sub)specialities can be restricted. In the USA, CON (certificate of need) legislation was used to try to restrict the diffusion of expensive new technologies [43]. This system often implies very unbalanced methods of rationing: heavy infrastructure is strictly programmed nearly everywhere, while the multiplication of other services (e.g. use of drugs, medical services) is left much freer. This has led to important distortions between the means spent on the various treatment modalities in cancer care. Also within the field of drug treatments, the proportions of money spent are in no way correlated with effectiveness but more with the ease of administration, allowing widespread use. The resources used for follow-up after treatment are often greater than those allotted to treatment itself. By their nature they remain largely hidden within the global packages of laboratory testing, nuclear medicine and medical imaging.

Implicit priority setting also prevails when patient out-of-pocket payments such as deductibles or co-payments are introduced or increased. In this situation access to the best available care is made dependent on patients' ability and willingness to pay [44].

Priority setting can be even more hidden if, for instance, requirements for pre-admission certification, procedure approval or demands for extensive supporting documentation and for physician communication with the health insurance administration are introduced, mainly in private insurance systems, such as in the USA. It is quite likely that fewer services will be delivered if the healthcare provider is not paid or has to go through excessive paperwork [7].

A study comparing waiting times for radiation treatment of different tumour sites in Canada and the USA revealed that for all but one type of treatment (emergency treatment for cord compression) waiting times were longer in Canada than in the USA ($P < 0.0001$) [45]. Part of these differences was explained by the higher case load per planning machine and treatment machine in Canada. The authors assume that this difference may also be related to differences in healthcare financing and organisation, thereby illustrating this process of implicit prioritisation. In Canada, unlike the USA, radiotherapy centres compete less for patients since they serve a geographical region; they are financed by means of a global budget (hence more patients only imply more costs but not more income) and Canadian physicians face fewer threats of litigation than their American colleagues. Moreover, when they were asked about 'acceptable' delays before treatment, Canadian physicians were clearly willing to accept longer waiting times, revealing that what medical doctors think is acceptable is partially determined by what is possible. This example clearly illustrates how priority setting and subsequent patient selection may permeate into routine medical practice in a way that goes unnoticed even for most physicians.

2.2. Need for explicit priorities

Although priority setting is not new, what is new is the (demand for) open discussion of the fundamental values on which priority setting is based [46]. A number of countries, such as The Netherlands [47], the UK [48, 49] and Sweden [50, 51] have issued official documents addressing explicitly the issue of choices in healthcare.

If priority setting occurs implicitly, it is not made clear for which types of care or interventions society is or is not willing to pay, although it is obvious that not all possible care can be covered from a limited budget. Implicit prioritisation carries the danger that the responsibility for setting care priorities is shifted silently towards lower levels of decision making, for example, regions, hospitals or other healthcare institutions, departments within institutions or even single healthcare providers (for example, a group of physicians having to decide on how to spend their annual budget for pharmaceuticals). The risk of such an implicit approach is that patient access to different care options may vary from one care provider to another or from one region to another, because of divergent priorities, all within the confines of a single country's healthcare system. This may happen for numerous—both defensible and irrelevant—reasons [46]. For instance, in one hospital, cancer care may be considered strategically less important than cardiovascular care and hence the management might not be willing to devote a large part of the budget to a cancer centre. In another hospital, the radiotherapists may have better bargaining and lobbying skills, and hence receive more resources to set up a radiation treatment facility with all the latest equipment.

In The Netherlands, where the hospital budget also has to cover all drugs used by patients during their

hospital stay, the Sickness Fund Council (http://www.ziekenfondsraad.nl/) found that the use of paclitaxel in patients with ovarian cancer or metastatic breast cancer differs widely between hospitals. A survey in February 1997 among all Dutch hospitals, with a response rate of 92.5%, revealed that there are large differences in the use of taxoids, for given indications. In 12 hospital sites, no taxoids were used, in 4 for financial reasons. Approximately half of the hospitals put a ceiling on the use of taxoids, either in terms of allowable expenses or in terms of a maximum number of patients. Hospitals attempt to broaden their financial base for providing taxoids by means of special deals with health insurance companies, patient out-of-pocket payments and industry support.

There is evidence of 'under-use', in the sense that almost 20% of the hospitals report using stricter indications than those for which paclitaxel and docetaxel have been granted registration in The Netherlands. All of this is a clear illustration of inequalities in access to care. In response to these findings, the Dutch government decided to grant an additional budget of 50 million fl. for 1997 and 1998, to reimburse for taxoid use up to 90%, provided that taxoids are administered according to the 'Guidelines for taxoids in oncological practice' and that patients are included in studies to evaluate the impact of taxoids on survival [52]. This example illustrates that a situation where the problem of political/administrative prioritisation is shifted towards individual institutions, may lead to unacceptable random differences in the level and nature of the available services, depending on, for instance, patients' residence or private health insurance company and thereby seriously hampering the quality of care provided.

As long as it was fairly easy to obtain additional resources for healthcare, there were at least no negative financial incentives for providing optimal care. In the current cost containment environment, there is a danger that providers will be penalised when providing optimal care to their patients because of financial restrictions. Hence, in order to avoid waste and safeguard equal access to different treatment modalities, not only for cancer care but also for other diseases, priorities must be determined explicitly. Explicit priority setting, the willingness to state and discuss priorities openly, is required to sustain confidence of the general public in healthcare [46, 51].

2.3. Role of providers

Providers have an essential role to play in this area because of their superior knowledge about appropriate care. Their knowledge, skill and experience in the field means that cancer care professionals are best placed to determine the priorities in this area. In order to avoid governments or others, such as private health insurance companies or hospital managers, imposing restrictions on cancer care, it is time that the cancer care professionals started giving suggestions on how to set such priorities. Hence, providers should be familiarised with the tools to make more rational choices in healthcare, such as evidence-based medicine, economic evaluation studies and health technology assessment.

2.4. Role of patients

The role of patients in priority setting should also be recognised. In this process, patients will always need advice and guidance from healthcare professionals because of their limited information. For a typical cancer, the physician may be best placed to judge which treatment is most effective and hence which treatment option should get priority. However, the patient may be better able to judge how this treatment will affect his quality of life and, therefore, needs detailed information about the effects of different treatment options [53]. However, why and how patients want information should be investigated.

A number of American studies have shown that most patients—approximately 95%—want detailed information about diagnosis, treatment and possible outcomes [54] but only 60% want to be actively involved in decision making [55]. The other 40% prefer expressing their autonomy by opting not to make a decision. Offering choice of treatment to patients apparently has both positive and negative sides. Although choice may lead to a higher level of satisfaction in the patient and hence to a higher quality of life [56], offering choice may also place a heavy burden of responsibility on the patient [57]. Moreover, if the chosen treatment proves unsuccessful, the patient may experience intolerable feelings of regret and self-blame and hence quality of life deteriorates [58]. Analogous feelings might be induced, however, when the treatment proves unsuccessful and no choice was offered: the physician might then be blamed for the failure of the treatment and the patient might feel regret about not having been able to choose [56]. Good communication skills are of paramount importance to elicit patients' preferences with respect to decision making about treatment. This is, however, not easy since, up to now, little is known about the influence on patients' preferences of type of cancer, cancer stage and the nature of the risk involved in different treatment options. Richards and colleagues [54] pooled the data from a British and a Canadian survey and concluded that persons who are closer to a potentially life-threatening illness, such as cancer, are more inclined to delegate the decisional responsibility to the doctor than healthy householders or persons with benign disease. Fallowfield and colleagues [59] observed that the way in which the surgeon communicates the treatment options

to the patient plays an important part in the patient's psychological health state. Breast cancer patients who had explicitly been given choice of treatment had less psychiatric morbidity than those whose physicians clearly preferred either mastectomy or lumpectomy. However, patients who had not been given a choice because of technical considerations had actually no difference in levels of anxiety or depression than those who had been. It thus seems that patients only want detailed information about why one treatment is recommended as opposed to another, rather than wanting to take decisions themselves.

3. Economic evaluation is a supportive tool for priority setting

3.1. Tools for rational decision making

To identify the most desirable ways for efficiency improvements and priorities, different methods can be used. Making rational choices ideally demands input from many viewpoints, not only medical knowledge, experience and ethical considerations but also economic aspects, organisational, social and other elements.

Improving scientific evidence on effectiveness of health interventions is the typical focus of evidence-based medicine. Advocates of 'evidence-based medicine' argue that the use of many healthcare interventions in routine clinical practice is not sufficiently based on solid scientific evidence but too much on tradition, habits and beliefs. The concept of 'evidence-based medicine' was developed at the McMaster Medical School in Ontario, Canada, where during the 1980s a new method of clinical education was developed.

> Evidence-based medicine is the conscientious, explicit and judicious use of the current best evidence to support decision making towards individual patients. The practice of evidence-based medicine implies an integration of individual clinical expertise with the best available external clinical evidence, based on systematic research [60].

Typical of economic evaluation is that different medical interventions (for example several ways of screening for breast cancer, follow-up strategies for cancer patients, modes of organisation of palliative care) are compared, not only in terms of their clinical efficacy and effectiveness, but also in terms of the costs entailed in generating this outcome.

Finally, the broadest scope is offered by health technology assessment, whereby health interventions are evaluated in all their societal consequences [43]. Whereas the target population for evidence-based medicine consists mainly of healthcare professionals, health technology assessment attempts to support decisions at the level of healthcare policy making.

3.2. Economic evaluation to support, rather than replace, clinical decision making

As economic evaluation studies are becoming more widespread, resistance against such studies is also increasing, especially in the medical field. Part of this resistance is due to the fact that economic evaluation is often perceived as primarily concerned with cutting costs and prohibiting access to new, expensive technologies, or even expensive care in general [61]. It is easy to understand those fears, especially since many healthcare policy-makers have only started showing interest in economic evaluation when they were forced to contain costs. But it is important to point out that the results of such economic evaluations are not intended to replace medical decision making or suppress professional autonomy. On the contrary, patient care and professional judgements can only improve, and not deteriorate when based on more solid information about the effects and costs of medical interventions. They are solely intended to support cancer care professionals in their decision making about the most appropriate types, levels and combinations of care for their patients, taking into account the fact that, at the societal level, the limited resources for cancer care will never be sufficient to provide all possibly beneficial cancer care. Such evidence is not intended to dictate choices or substitute individual decision making but to support it, to help professionals make better-informed decisions [31]. Economic evaluations yield information on how to improve efficiency but do not incorporate ethical, legal and equity considerations, whereas these aspects may in some instances be decisive. In a study by Ubel and associates [62], it was investigated whether prospective jurors, medical ethicists and experts in medical decision making would make decisions on the basis of evidence of cost-effectiveness if this would lead to an inequitable situation. It was found that approximately half of the respondents in every group would choose the less cost-effective alternative if this would lead to a more equitable situation.

4. Necessary conditions to work with these tools

In the near future, cancer care providers will encounter an increasing number of papers dealing with economic evaluation in cancer care, which are comparing costs and effects of different types of cancer prevention, diagnosis, treatment and rehabilitation. However, these papers are likely to differ substantially in terms of methodological quality. Providers should possess the skills to evaluate the quality of the studies and especially the usefulness of the results. Care should be taken not to implement invalid recommendations.

Brief descriptions of methods of economic evaluation in healthcare illustrate how accurate data on effects,

costs and a combination of costs and effects of interventions in cancer care may support decision making and help to use the limited budgets in the best possible way, i.e. such that most benefit for patients is realised out of a given budget. This paragraph concludes with the identification of some necessary conditions that must be fulfilled before such efficiency reasoning can be implemented in routine practice. They mainly concern the availability of sufficient data.

4.1. Some concepts and methodological aspects of economic evaluation studies

Economic evaluation is intended to support decision making about healthcare interventions on the basis of their efficiency (i.e. effectiveness relative to costs) relative to other interventions. This evaluation by its very nature involves a comparison of alternative care strategies (where one alternative can be 'doing nothing'). It is a characteristic of economic evaluations that not only the clinical benefits (i.e. efficacy and effectiveness) of the alternative interventions are considered but these clinical data are also related to the costs for achieving these outcomes. Economic evaluation is about comparing 'value for money' of several care options.

4.1.1. Methods

Several methods of economic evaluation can be distinguished. All these methods have in common that they compare costs as well as outcomes of alternative care options but they differ in the way in which outcomes are measured (see Table 3).

If treatment options are a priori known to have similar effects, it is sufficient to compare their costs: the least cost option is the preferred alternative. In this case a cost-minimisation analysis (CMA) is performed. If the outcome of different interventions can be compared in terms of one relevant natural unit, such as life-years gained, or number of days until complete recovery, a cost-effectiveness analysis (CEA) is done [64].

Often, however the outcome of several interventions cannot be compared in terms of a single measure, for example, one option yields better survival, but the other improves quality of life in terms of ability to function without pain or other physical and psychological symptoms (for example laryngectomy versus radiotherapy in patients with laryngeal cancer). In this case these several outcome dimensions (survival and quality of life) have to be weighed against each other. This can be done by converting all outcome aspects into monetary units, as is done in cost–benefit analysis (CBA). Since this is inherently a difficult problem (for example, a monetary value must be put on life-years), this method is not very popular in healthcare evaluation. An alternative consists of attaching 'utility values' to outcomes, for instance by calculating 'quality adjusted life-years' (QALYs), which attach a quality index, ranging from 0 (worst possible health state) to 1 (perfect health) to each post-treatment life-year which is the case in cost–utility analysis (CUA). Numerous instruments to describe quality of life have been developed (e.g. [65]). They include generic instruments, which measure all health dimensions and are applicable to a wide range of diseases, such as the Nottingham Health Profile, the Sickness Impact Profile and the Rand Medical Outcome Study questionnaire (http://www.qlmed.org/general.htm) and disease-specific instruments which measure in more detail the specific quality of life effects associated with a particular disease (see [66, 67] for an evaluation and a comparison between different types of instruments). For instance, in cancer care, the Rotterdam Symptom checklist can be applied to all types of cancer [68], while the Breast Cancer Chemotherapy Questionnaire is more specific to breast cancer [69]. Not all health status questionnaires can be used as outcomes for economic evaluation. A prerequisite for quality of life measures to be useful in economic evaluation is that they generate a single index, reflecting the utility in particular health states.

4.1.2. Identification of study perspective

Any economic evaluation should clearly state the perspective from which the analysis was performed. Ideally, each study should include an evaluation from the societal perspective, which implies that the costs and benefits of the considered alternatives, accruing to all members of society, including all patients and their families, providers, etc., are compared.

This does not imply that comparisons from a narrower perspective, such as the hospital or the insurer are worthless. On the contrary, such analyses from a more limited scope yield useful insights, but it should be kept

Table 3
Methods of economic evaluation

Methods	Measures used to compare outcomes of interventions
CMA (cost minimisation analysis)	None
CEA (cost effectiveness analysis)	Natural units (for example, disability days)
CBA (cost–benefit analysis)	Outcome expressed in monetary units
CUA (cost utility analysis)	Outcome expressed in 'utility' terms (for example Quality Adjusted Life Years)

Source: [63].

in mind that such comparisons may reflect only part of the entire picture that is relevant for policy-making. However, if all data are collected to compare interventions from the societal perspective, they can also be used to make comparisons from more limited viewpoints without requiring many additional data collection efforts.

4.1.3. Identification of comparators

In designing an economic evaluation study, sufficient attention should be given to the alternative care interventions that will be compared. Ideally, all current alternative treatment options or nursing interventions for the patient population under study should be included. In practice, sometimes not all options are included due to a lack of data on some treatment options or interventions (if this is the case, the investigators should mention it explicitly), or due to the limited perspective of a study. In order to obtain results of relevance for decision-makers, one treatment arm that should definitely be included in the study, is the 'usual' or 'standard' available care, but this may differ from centre to centre or from region to region.

4.1.4. Identification of cost categories

In an economic evaluation from a societal perspective, the following cost categories should be included: the costs of the medical treatment for the providing institutions, the costs for patients (including out-of-pocket payments and time investment in treatment and recovery) and the costs of informal care and support for family and friends (for example, travel time, time lost from work), including the 'intangible costs' (for example, psychological costs due to pain and suffering) (e.g. [70]). In some economic evaluation methods, these aspects are incorporated on the outcome side, as negative effects for patients and their environment.

The medical costs and patient out-of-pocket payments are often referred to as the direct costs of treatment, while the cost of informal care and support are summarised under the heading 'indirect costs'. Costs outside the healthcare sector, for instance transportation costs, should not be ignored as they may be an impediment to receiving the necessary cancer care [71]. Obviously, especially for life-saving interventions affecting younger people, the indirect costs of medical interventions may outweigh the direct costs many times. This is yet another reason why each economic evaluation should be very explicit about which cost categories have been incorporated. Moreover, it should be kept in mind that the costs of care by providing institutions should be measured in terms of the actual use of resources, rather than in terms of (fee-for-service) charges (reimbursed fees). The latter are financial returns for the providers, often bearing little resemblance to their true resource costs; they are 'costs' only from the viewpoint of healthcare financing/insuring organisations.

4.1.5. Additional aspects

Many additional aspects determining the methodological quality of economic evaluations of healthcare interventions are relevant. These include discounting, sensitivity analysis, modelling approaches, measurement of quality of life, linking economic evaluations with clinical trials and issues of external validity of medical and costing evidence. These will not be discussed in this paper. The interested reader is referred to the more specialised technical literature, dealing with economic evaluation in healthcare in general [63] or cancer care specifically [61, 64, 65, 70, 72, 73].

How reliable effectiveness, cost and combined cost-effectiveness data will lead to improved cancer care, either by reducing costs to obtain a given (or improved) outcome, or—and this is at least equally important—by justifying the use of increasing expenses to achieve larger benefits, is discussed below.

4.2. Interpreting data on efficacy and effectiveness

Accurate data on efficacy and effectiveness of care are an important source of information for improving routine clinical practices. The following applications show the need for more and more accurate data on the effectiveness of healthcare interventions.

4.2.1. Screening for carcinoma of the prostate

Screening for prostatic cancer in asymptomatic males can be performed by several diagnostic methods, such as digital rectal examination (DRE), transrectal ultrasonography (TURP) and prostate-specific antigen (PSA). In the USA, an active screening approach is already being advocated by the American Cancer Society (http://www.cancer.org/bottom.html), driven by the expected benefits of earlier diagnosis in prolonging survival. Alternatively, the Advisory Group of the European School of Oncology (ESO), in reviewing the European Code Against Cancer (http://telescan.nki.nl/code/l6_intro.html) after its initial use over a 6-year period [2], recommends suspending any screening recommendations until prospective randomised studies provide more reliable evidence on screening efficacy. In this disease, it is argued that the current evidence is limited to demonstrating the possibility of early detection and this is not sufficient to recommend screening as best current practice.

Without going into the full detail of all of the arguments proposed by different authors, it can be concluded at least that the evidence is not yet convincing enough to recommend a uniform screening strategy [74, 75], although in some countries a lot of resources are already being spent on these diagnostic investigations. In Belgium, for instance, the number of PSA tests has risen more than 60%, while healthcare expenses for PSA testing have more than doubled over the period

1993–1996, despite the lack of more conclusive evidence on its effectiveness. In Australia, the annual number of males tested increased 5-fold in the period 1989–1996 [76].

4.2.2. Self-care in cancer patients

Negative side-effects of cancer therapy, such as loss of hair, weariness and nausea may give rise to patients experiencing serious problems in coping with such therapies. Sometimes it may even be necessary to stop the therapy or alter the treatment schedule, while some patients may refuse any further treatment. Self-care is known in the nursing literature as an activity of patients to prevent or alleviate symptoms of disease, in this case symptoms of negative therapeutic side-effects. Some authors state that self-care has a positive influence on the patient's well-being [68, 77]. Others have shown that self-care activities are only moderately effective [78–80]. Whilst there is still a lot of uncertainty about the effectiveness of such interventions, there is increasing pressure to implement them in routine practice. In this area too, more accurate data on the effectiveness of these interventions are needed for rational decision making.

4.2.3. Role of diagnostic techniques in cancer screening, staging, treatment and follow-up

New imaging techniques (for example, MRI rather than mammography in breast cancer screening) and molecular pathology tests (for example, PCR, FISH) yield additional information compared with the traditional techniques for tumour diagnosis. However, although the additional information has proved useful in some patients, it is still not yet clear what the added value of that information is: at the population level, to what extent does it affect treatment patterns and hence expected survival, quality of life and/or costs?

Even for the more standard imaging techniques, there is a wide geographical variation in the extent and type of radiological evaluations, even for the common forms of cancer. Of course, this may depend on local availability and expertise, but even in centres with comprehensive facilities, different authorities champion several radiological techniques. For example, Bruinvels [81] observed wide variability in imaging techniques used for the follow-up of patients with colorectal carcinoma between a number of Dutch hospitals. Techniques used were history taking and physical examination, colonoscopy, carcinoembryonic antigen assay, chest radiography, liver function testing, liver ultrasonography, barium enema, faecal occult blood testing and computed tomography of the abdomen. Bruinvels [81] attributes this lack of uniformity in follow-up to insufficient knowledge about the effectiveness of these different follow-up procedures and about the benefits of follow-up itself.

4.3. Interpreting data on costs of care: cautious support for decision making

A number of examples are given to illustrate how the availability of cost data may improve routine clinical practice. At the same time, these examples contain a warning: before cost data are used to support decision making, the external validity of the data must be checked very carefully. Readers must check whether the reported cost data are applicable in their own setting and their own geographical area. The reader will notice that up to now, the literature has mainly focused on new and costly interventions.

4.3.1. Granulocyte-colony stimulating factor (G-CSF) administration in cancer patients

The administration of growth factors during chemotherapy is expected to reduce the number of episodes of febrile neutropenia, thereby reducing costs of hospitalisation and of antibiotics for treating this complication.

A number of studies [82–89] addressed relevant cost issues, for different types of tumours and different kinds of growth factors. The main message of most of these papers is that the administration of growth factors frequently leads to a reduction of direct medical hospital costs in chemotherapy patients. Cost savings are demonstrated, because hospitalisation soaks up the largest share of costs, and hence a small reduction in length of stay results in a substantial overall cost reduction. Moreover, quality of life of patients is likely to improve, due to fewer complications and consequent episodes of hospitalisation. Can it then be concluded from these studies that routine administration of growth factors should be advocated?

It can easily be shown that it is too early for such an optimistic conclusion, since these results only hold under the—quite restrictive—circumstances and assumptions described in each of the papers. Firstly, a number of assumptions made in some of the papers tend to increase the probability that the growth factor treatment results in lower costs than the non-growth factor treatment and that moreover costs would be lower in routine clinical practice than under trial conditions, especially for the non-growth factor treatment option [90]. Only some of these assumptions are mentioned here, to illustrate the argument. In some studies (for example, [83]), the growth factors themselves are valued at zero cost. In routine practice, dose reduction (and hence diminution in cost of chemotherapy), rather than growth factor administration, may be another way to cope with neutropenic episodes, but only a few studies [84, 89] include this option in their comparison. The costing-model used is another factor determining the results of a study. Glaspy and colleagues [82] distinguished between a baseline model, a charge model, a Medicare model and a cost model. In the baseline

model, the hospital rates and charges as observed in three different US centres were used. In the charge model, the hospitalisation rates for all patients in the trial were used, but charges were the same as those under the baseline model. The Medicare model used the same hospital rates as the charge model but charges were based on DRG payments. The cost model finally calculated 'true costs' incurred by the hospital by multiplying each hospital's charges by its overall cost-to-charge ratio listed in Medicare cost potential values. It should be noted that this is not a reliable way to obtain 'cost' data. Great discrepancies between the net savings/extra costs associated with the use of G-CSF were found with each of these scenarios. When compared with Glaspy's baseline model, the Medicare model suggests that filgrastim therapy results in an incremental cost of US$ 602 per patient per cycle. The cost model also found an additional cost per cycle of chemotherapy, but significantly less than the Medicare model (US$ 138). The charge model, on the other hand, yields a net saving of US$ 1250 per chemotherapy cycle, again compared with the baseline.

Secondly, the trials have not yet given full evidence of improved survival or improved quality of life in these patients. The current results are limited to 'intermediate' quality of life aspects, such as reduced hospitalisation during treatment and reduced therapy-related toxicity. Moreover, the reported results are based on small patient samples with different types of tumours and consider several types of growth factors.

Thirdly, administration of growth factors in routine clinical practice will not yield the cost savings proposed in a number of studies. At the societal level, total costs may increase as indications for this type of treatment are broadened. Even at the individual patient level, costs per patient need not decrease as proposed, if the reduction in febrile neutropenic episodes leads to dose intensification, with the aim of improving patient outcomes. Dose intensification will in turn increase costs of chemotherapy and the costs of treating complications associated with dose intensification. To conclude, all these studies have their merits, in that they show promising results both in terms of efficacy (improving outcomes) and efficiency (lower costs) of using growth factors during chemotherapy in several types of tumours. Simultaneously, careful analysis of the results and underlying methods reveals that the results are still too preliminary to justify routine use of growth factors. Two recently published studies, modelling cost-effectiveness of G-CSF in small cell lung cancer [89] and early stage breast cancer [88], even showed that routine use of growth factors was, in certain circumstances, not justified by clinical benefits, improved patient comfort or economic considerations. Silber and colleagues [88] demonstrated that the administration of G-CSF in the most needy 10% (as defined by first cycle blood counts) was most cost-effective (US$ 23 748 per life-year saved), although the administration in the most needy 50% yields a still acceptable cost-effectiveness ratio (US$ 34 297 per life-year saved). Use of G-CSF in 90% of the patients would result in a cost-effectiveness ratio that is far beyond those of other common medical problems.

Hence, it would not be acceptable to follow this strategy. According to Chouaid and associates [89], G-CSF prescription is never justified in patients with small cell lung cancer. A lower level of discomfort and lower costs were found in patients whose chemotherapy dose was reduced after an episode of febrile neutropenia without administration of growth factors, compared with patients who were given G-CSF.

4.3.2. Cost distribution across episodes of treatment

It is interesting to obtain more information on the distribution of cancer care costs across the different episodes of treatment, such as screening, initial therapy, follow-up, symptomatic therapy and palliative care. Such data are useful because they give some indication as to where cost containment opportunities may be available. They are also indispensable for evaluating the cost-effectiveness of screening activities, where it is often alleged that improved outcomes and savings on treatment costs can be realised by earlier detection of tumours.

Typically, costs across episodes of treatment follow a U-shaped pattern: initial treatment is relatively expensive, costs are lower during an intermediary period and peak again at the end of life. Table 4 illustrates this U-shaped distribution in terms of healthcare charges (excluding prescribed drugs) across initial treatment (first 3 months after diagnosis), terminal care (6 months prior to death) and monthly continuing care (interval time period) for a number of cancer sites for patients surviving more than 9 months after initial diagnosis, as well as total charges for patients surviving less than 9 months after initial diagnosis, for Medicare cancer patients in the USA followed during the period 1974–1981 [91]. This U-shape has also been documented in other studies, independently of the length of the survival period (e.g. [92]).

In order to be able to evaluate potential cost savings due to screening, treatment costs should be related to tumour stage. Table 5 illustrates the effect of stage at diagnosis on the costs of treating one type of cancer, colon cancer [93]. Costs are summarised for initial, continuing and terminal phases of care for members of a health maintenance organisation (HMO) in the USA. 'Initial care' is defined as the treatment given in the first 6 months after diagnosis, 'continuing care' as the treatment given between 6 months after diagnosis and 6 months before death and 'terminal care' as the treatment given in the last 6 months of the patient's life. Initial care costs as well as terminal care costs are calculated for 6 months, whereas continuing care costs are

Table 4
Charges for Medicare cancer patients, in 1984 (US$)

Cancer site	Cancer phase (more than 9 months survival)			0–9 month survivors
	Initial (3 months)	Continuing (monthly)	Terminal (6 months)	All phases of care
Colorectal	14 190 (96.5)[a]	572	15 776 (222.3)	21 602 (245.2)
Lung	12 916 (147.1)	690	15 565 (273.1)	17 957 (159.5)
Prostate	8112 (69.4)	560	14 613 (283.2)	16 324 (272.3)
Breast	7606 (58.1)	483	15 136 (301.9)	17 256 (380.1)
Bladder	8470 (122.2)	766	18 577 (447.3)	22 670 (557.0)
Leukaemia	9068 (307.7)	676	19 777 (692.9)	18 929 (470.1)
Pancreas	14 009 (468.5)	677	14 790 (737.9)	17 876 (302.8)
Stomach	14 443 (314.7)	660	16 132 (639.5)	21 058 (455.1)
Uterine corpus	9260 (134.8)	424	17 623 (741.2)	21 479 (866.9)
Kidney	12 608 (241.1)	670	19 302 (994.2)	21 861 (685.7)
Ovary	11 055 (272.5)	647	18 650 (867.9)	20 643 (638.8)
Uterine cervix	8979 (269.6)	493	16 414 (924.6)	17 505 (900.9)
Melanoma	6954 (201.8)	488	16 194 (905.9)	16 618 (1021.5)
All sites combined	10 039 (35.1)	578	16 280 (98.7)	19 109 (81.5)

Source: [91].
[a] Standard error of the mean.

calculated for a 3-month period. The reason is that the variability in the length of continuing care per case precludes an estimate of the standard error of costs for longer periods (6–22 months). Since the study runs over a 2-year period only, no cost data for longer continuing care were gathered. Instead, the cost figures for continuing care were estimated by means of the experiences of individuals 1.25 to 17 years after diagnosis. The mean number of years in continuing care for patients with colon cancer is 4.3 years. Hence, the average total cost of continuing care for all case subjects can be calculated, being US$ 22 670. This implies, for instance, that total costs for an average patient with local colon cancer, who has 4.3 years of continuing care, amount to US$ 20 296.

Terminal care is, all stages at diagnosis considered together, almost as expensive as initial care. However, the distribution of costs is quite different for various stages of the tumour at diagnosis: for cancer *in situ* (CIS) at diagnosis, terminal care takes up a very large share; in case of distant metastases at diagnosis, continuing care is relatively more expensive. Although terminal care costs of colon cancer do not vary significantly with stage at diagnosis, total costs of initial and continuing care increase remarkably with stage at diagnosis. Continuing care costs in particular, increase sharply as stage at diagnosis worsens. This should be kept in mind when considering screening for colon cancer.

4.3.3. Costs of PVC versus Orfit® fixation masks in radiotherapy patients

A study performed in the University Hospital Leuven, Belgium, compared the precision and costs of plastic versus Orfit® masks for patient head fixation during radiotherapy. It was found that both types of masks allowed the same degree of precision. Hence, decisions to use one or the other type of fixation devices could be

Table 5
Total costs of care for colon cancer patients (US$, 1992): average total cost[a] of care by stage at diagnosis and treatment phase

	Initial care			Continuing care			Terminal care		
	n	Cost[a]	SEM	*n*	Cost[a]	SEM	*n*	Cost[a]	SEM
All case subjects	290	14 968	748	868	1318 (22 670)	69	157	12 110	870
Stage									
CIS	20	9041	2716	88	820 (14 104)	204	8	16 544	3677
Local	74	13 848	1442	378	1180 (20 296)	99	38	14 145	1731
Regional	139	15 398	1060	373	1424 (24 493)	102	69	10 777	1273
Distant	53	17 223	1886	25	4632 (79 670)	460	39	12 195	1854
Unknown	4	N/A	N/A	4	2283 (39 268)	1075	3	N/A	N/A

N/A, not available; CIS, cancer *in situ*; SEM, standard error of the mean.
[a] Includes average cost of care of cancer and all other conditions for all case subjects in the phase of treatment shown (1992 US$; initial care (6 months), continuing care (cost per 3 months and per average number of years in continuing care (parenthesis) and terminal care (6 months)).
Source: [93].

based on cost factors solely. Taking all relevant costs into consideration, it was found that for most departments usually the Orfit® masks will be a cheaper alternative than the plastic masks. If several masks are used in many patients, the conclusion may be reversed [19].

4.4. Combination of cost and effectiveness data enable improved routine clinical practices

Sometimes cost data in themselves, or outcome data already yield useful information to guide clinical practice. Most often, however, considering cost and outcome evidence simultaneously, as in CEA, CBA and CUA (cf. Table 3), yields additional insights, as will be illustrated by some examples.

It is striking to note that only a limited number of studies have been conducted to evaluate the cost-effectiveness, or cost-utility of any type of cancer therapy. The majority of published studies have focused on screening and drug treatments. Few studies have dealt with staging, treatment other than with drugs, follow-up and palliative care [94].

4.4.1. Screening for cervical cancer

A study performed by Koopmanschap and coworkers [30] assesses the potential cost-effectiveness of screening, in this case, cervical cancer screening in The Netherlands. The aim of the study was, if cost-effective, to provide recommendations on the appropriate age-groups to be screened and on time intervals between screens. A comparison between the prospective costs of four screening policies and the prospective costs of 'no systematic screening' was made. 'No systematic screening' means that no explicit screening schedule was recommended and implemented. Hence screening is not absent, but occurs only spontaneously. The four policies were 7, 10 or 16 screening invitations in a woman's lifetime, differing in age-range and interval between screens, and spontaneous screening. Cost categories included were screening, diagnosis, primary treatment and terminal treatment. Social costs like time and travel costs were also considered for the screening programmes in addition to direct medical costs. The costs of treatment and diagnosis, however, were approximated by fees charged in The Netherlands (in 1987). On the benefits side, the number of life-years gained in the screening options was compared with that of the baseline option (no systematic screening).

Results are presented in Table 6. Screening clearly takes the largest share in the total costs for all policies (ranging from 55 to 69%). Furthermore, screening induces costs for diagnosis, since more screening inevitably leads to more positive test results and thus further diagnostic testing. Screening with seven invitations leaves the cost of primary treatment almost unaltered in comparison with the no-screening policy. More intensive screening policies induce higher primary treatment costs, since screening increases the number of women with diagnosed precancers and thus the number of treated women because women with spontaneously regressing lesions, which would never have become invasive, will also be treated. Terminal costs decrease with more intensive screening because of the reduction in invasive cancers and thus mortality.

Despite the high cost of screening, it can be shown that systematic screening is worthwhile and is more cost-effective than spontaneous screening. Table 7 shows the incremental costs per life-year gained for the three organised policies and the spontaneous screening option. The figures reflect the cost of adding one life-year to a patient's life. The lower the cost per additional life-year gained, the more cost-effective the procedure is. More tests per lifetime increase the costs per life-year gained. Spontaneous screening is shown to be less cost-effective than all the other policies. The reason for this rather remarkable result is that in a spontaneous screening programme some women, especially younger women, are screened very frequently, whereas the target group is in fact rarely screened. Hence, health benefits are rather limited and expenses are high. This implies

Table 6
Present value for 1988 of social costs of screening, diagnosis, treatment and incremental costs for three efficient policies, spontaneous screening and no early detection in millions of US$

	Efficient screening policies[a]			Spontaneous screening	No early detection
Costs	7	10	16		
Screening	659.7	935.8	1402.7	1173.3	0
Diagnosis	54.8	79.2	109.6	95.4	14.2
Primary treatment	334.9	369.5	389.8	406.0	330.9
Terminal treatment	158.3	148.2	138.0	170.5	205.0
Total costs (1988–2088)	1207.7	1532.7	2040.1	1845.2	550.1
Total incremental costs	657.6	982.6	1490.0	1295.1	–

[a] Number of lifetime invitations for screening.
Source: [30].
Period 1988–2088. Discount rate 5%.

Table 7
Present values for 1988 of incremental social costs (1988–2088), life-years gained and cost-effectiveness of three efficient screening policies and spontaneous screening

	Efficient policies			Spontaneous screening
	7	10	16	
Incremental social costs (millions US$)	657.7	980.5	1492.0	1295.1
Life-years gained (×1000)	13.3	17.2	20.1	13.4
Costs per life-year gained (×1000 US$)	49.5	57.0	74.2	96.6
Marginal costs per life-year gained (×1000 US$)	49.5	82.8	176.4	–

Source: [30].
All outcomes are compared with the zero-option. Discount rate 5%.

that substantial savings could be made by discouraging spontaneous screening and implementing one of the efficient policies.

4.4.2. Quality and costs: is there a trade-off?

Sometimes a trade-off has to be made between quality of life and costs. A more expensive treatment would then only be worthwhile if it enhances the patients' quality of life sufficiently in comparison with other treatment modes (for instance, breast conserving surgery versus mastectomy in breast cancer patients) [95]. But a trade-off does not have to be made in all instances. Enhancement in quality of life is sometimes accompanied by cost savings. In that case, the financial interests point in the same direction as the medical interests and the cheaper treatment should be preferred.

For example, most studies comparing ABMT (autologous bone marrow transplantation) with PBPC (peripheral blood progenitor cells) transplantation find that PBPC is cheaper than ABMT [85, 96–99]. Further arguments in favour of PBPC are usually based upon the improvement of clinical quality of life, that is, the physical health status of the patient: accelerated time to recovery of granulocytes and reticulocytes, accelerated time to platelet engraftment, reduction in platelet and red blood cell transfusion requirements and reduction in episodes of fever. These are very interesting features, both for the treatment of haematological malignancies and solid tumours. Traditionally, ABMT was only used after high-dose chemotherapy in haematological malignancies, such as leukaemia, to accelerate haematological recovery. However, increasingly ABMT, as well as PBPC, are also used for reconstitution in patients with solid tumours after myeloablative chemotherapy. This is done with the hope that a 1- or 2-fold dose escalation made possible by subsequent ABMT or PBPC could lead to an improvement in therapeutic efficacy [100]. Solid tumours in which stem cell transplantation has been applied are, in decreasing order of frequency, lymphomas (±50%), breast cancer (±40%), neuroblastomas (±10%), testicular cancer, ovarian cancer and brain tumours [101].

It should be noted that such measures are only intermediate quality of life indicators. Long-term effects, as well as patients' feelings about different health states or treatment procedures, have not yet been brought into the picture, but are nevertheless important in assessing the overall cost-effectiveness of PBPC versus AMBT.

4.4.3. Practice variations

Sometimes large practice variations are observed in routine clinical care. These are obviously associated with substantial variations in cost. Furthermore, it can be shown that these practice variations are associated with large differences in quality and outcome of care. If variations in practice are associated with different outcomes, economic evaluation techniques can be very helpful in deciding which practices are most appropriate, both from the clinical and the financial viewpoint.

Gerber and associates [102] describe variations (sometimes small, sometimes large) in treatment preparation and planning for radiation treatment of prostate carcinoma (672 cases) in US healthcare centres (23 academic centres, 26 hospital-based and 26 free-standing centres); in frequency and type of imaging procedures (bone scan, chest, pelvic computed tomography (CT), abdominal CT, ultrasound, intravenous pyelography (IVP), pelvic MRI); in laboratory studies (creatinine/blood urea nitrogen (BUN), acid phosphatase, alkaline phosphatase, chemistry screen, pretreatment PSA, prostatic acid phosphatase); in contours chosen for treatment planning (target volume, rectum, bladder) and in contrast used during large field and boost simulations. Torfs and Pocceschi [103] illustrated substantial variations in resource utilisation for treatment of advanced (stage III and IV) colorectal cancer in eight cancer centres, spread over five European countries. It should be noted, however, that these studies did not link these practice (and hence cost) variations to outcome, nor to severity of illness.

In a study comparing use of radiotherapy in advanced and metastatic cancer in the UK and the USA, Maher [104] even found evidence of disagreement on the aim of treatment (palliation versus cure) for a given type of

patient. Maher [104] also showed that variations in treatment became larger as prognosis worsened and that the type of treatment offered (surgery, radiotherapy, chemotherapy) seemed to be affected by which specialist the patient saw first.

Gillis and Hole [105] have compared survival outcome of breast cancer patients after care by specialist (918 patients) versus non-specialist surgeons (2868 cases) in West Scotland. 'Specialised' surgeons were defined on the basis of four indicators of specialist interest: setting up dedicated breast clinics; having planned collaboration with pathologists and oncologists; organising and facilitating clinical trials and maintaining a separate record of all breast cancer patients in the practice. The study revealed that the 5-year survival rate was 9% higher and the 10-year survival rate 8% higher for patients cared for by specialist surgeons. A 16% reduction in risk of dying was found after adjustment for age, tumour size, socioeconomic status and nodal involvement. This benefit of specialist care was apparent for all age and socioeconomic groups and for small and large tumours, with and without node involvement.

In a study of the potential benefits of specialised cancer care, many examples have been given of variations in practice, associated with differences in outcome [106]:

- For childhood leukaemia, treatment within nationwide clinical trials was found to be associated with better outcome than treatment outside a trial, irrespective of the number of cases treated in each hospital and the location or type of hospital [107].
- Patients treated for testicular cancer in centres with strict adherence to protocol-defined treatment doses or high case load have been shown to have a survival advantage in Norway [108, 109].
- It has been documented for Sweden that local control and freedom from local recurrence in soft-tissue sarcoma is determined by the skill of the surgeon [110].
- Treatment of ovarian cancer in teaching hospitals, by specialised gynaecologists (rather than general surgeons) has been shown to improve survival in the UK [111–113].
- Perioperative mortality has been shown to be higher in hospitals that do fewer oesophagectomies [114, 115]
- Mortality has been shown to be negatively correlated with case load after pancreatico-duodenectomies (performed between 1988 and 1993) in 39 American hospitals. 271 out of 502 operations were done at one regional hospital. The remaining 46% were done at 38 other hospitals, with the number of operations ranging from 1 to 20 per hospital. Mortality ranged from 2.2% at high volume hospitals to 19.1% at hospitals which operated on 5 patients or fewer annually [116].

On the basis of such data, more appropriate patterns of care resulting in improved outcomes and less wasted resources could be identified.

4.5. Solid scientific evidence

An absolute prerequisite for making reliable claims about the expected societal returns of investing in cancer care is solid data both on the effectiveness, costs and other implications of cancer care. As long as these data are lacking, the debate will be limited to opinions, rather than facts [94], yielding the danger that governments will blindly and randomly cut budgets and that professionals will take wrong decisions.

This urge for more scientific evidence as a basis for healthcare decision making, is the driving force behind evidence-based medicine as well as health technology assessment.

This increasing interest in evidence, broader than clinical effects, can be illustrated by the gradual shift in regulatory requirements for the registration of new drugs. Until quite recently, governments only used evidence on the efficacy of treatments in policy-making in the field of new drug approval ("Does the treatment cause a response and does it have a specific function in comparison with existing treatment possibilities?"). In a number of countries, such as Australia and Canada, governments are asking now for cost-effectiveness evidence, before approving registration of new drugs [94]. In fact, the focus is now on the question "Does the treatment increase survival or quality of life enough to justify the money spent on it, compared with alternative use of the same money, such as on other forms of treatment, or even other forms of healthcare, such as treatment of hypertension, smoking cessation, or education and culture?" [94]. It is quite likely that demands for such cost-effectiveness evidence to support future healthcare decision making will increase.

Evidence can be generated in many ways. Basically, a distinction can be made between observational and experimental methods. In observational research, patients are observed and the researcher manipulates data that are already available or are collected for the purpose of the study. Qualitative research, surveys and case–control studies are examples of observational research methods. Alternatively, in experimental research, the same intervention is performed as a result of planning by the researcher. The randomised controlled clinical trial (RCT) is the most powerful type of experimental design ([117], p. 71). (Cohort studies can either be observational or experimental; systematic reviews can be performed on any type of data, but the concept most often describes reviews of randomised controlled trials.)

In an RCT, patients who might benefit from the intervention studied are randomly allocated to a 'treatment

group' (patients who receive the intervention) or a 'control group' (patients who receive a placebo or standard treatment). Both groups are followed-up at prespecified intervals. The assessment of outcome should be done by an assessor who is unaware of the group to which each patient belongs ('blind' study). Sometimes it is possible that both patients and assessors are unaware of the group to which patients belong 'double blind' study ([117], p. 78). In a case–control study, the individuals selected for the control group have the same characteristics as the patients in the treatment group, except for the factor which is the subject of the study. In a cohort study, a group of individuals is followed over a pre-specified period of time and all changes in health status during this period are reported ([117], p. 89).

There have been strong disputes about the benefits and disadvantages of both types of research designs, but this focus on areas of disagreement has obscured the fact that there are many areas of agreement and that these two types of study design are complementary. Although the RCT has long been regarded as the gold standard for demonstrating effectiveness, awareness is growing that this research method also has its limitations, e.g. due to too small sample size, poor randomisation strategies and failure to blind assessors of outcomes as well as failures in follow-up [118].

4.6. Outcome data

In order to be able to make decisions on improved care, more data on final patient outcomes after care interventions should be collected [119]. Necessary conditions for achieving this aim are support for: (a) clinical research organisations that operate on an international scale and that are able to collect data on large patient samples and organise long follow-up studies; and (b) for cancer registries to allow assessment of changes in survival for entire populations.

Evidence on the efficacy and effectiveness of interventions (for example, screening, treatment) should preferably be presented in terms of endpoints related to final patient outcomes rather than intermediate outcomes, cancer outcomes or process measures. Survival remains the most important measure of success, especially for recommending adjuvant therapy. In the case of metastatic cancer, treatment can also be recommended if it does not improve survival, but ameliorates quality of life, including global quality of life as well as its physical, psychological and social dimensions. The impact of rehabilitative care should also be assessed in terms of quality of life. Because of its subjective nature, assessment of quality of life during and after treatment should in principle include an evaluation by the patient or his representative. Many research projects investigate quality of life in cancer care, but the suitability of these measures for day-to-day patient care in clinical settings has not yet been established. Short- and long-term toxicity are also of vital importance, especially in children. Moreover, it is often advisable to consider multiple outcome measures because no single indicator accurately describes the overall results of care.

Cancer outcomes (for example, tumour response, biomarkers) are of less value for guiding treatment. Their value depends on their ability to predict patient outcomes or to influence treatment decisions. Obviously, cancer response rates do have their merits, especially in guiding research efforts such as for new drugs, and in pointing out promising future treatment opportunities. Evidence on improved cancer outcomes, even without proof of improved survival or quality of life, which might take a long time to acquire, is, however, very hard for physicians to ignore. Recently, the Food and Drug Administration (FDA) has proposed accepting data with a category 'no progression', rather than 'partial or complete remission' as evidence of efficacy to approve new drugs. If such outcome measures are allowed to guide treatment decisions, despite lack of evidence of improved survival or quality of life, healthcare expenses may rise without improving the health status of the population. If even the FDA is accepting 'no progression', it will become very difficult to avoid large-scale diffusion since physicians would have a very hard time to deny such promising-but-not-yet-fully-proven interventions to their patients.

Moreover, it should be recognised that for several reasons it is often very difficult to collect data on final patient outcomes. Once intermediate endpoints reveal the superiority of a new treatment over standard available care, it becomes very difficult to randomise patients to a treatment arm where outcomes are expected to be inferior. Furthermore, long-term follow-up is required to obtain solid data on final patient outcomes (for example 5-year disease-free survival), and such long-term follow-up is expensive to organise. In the meantime, other new interventions may have been developed, so that there is already a switch in treatment patterns, before the superiority of the previous new treatment has been proven according to the statistical rules of the game. Cancer treatment is complex. Outcome is determined by many parameters, including accuracy of diagnosis, staging, combination of therapies and intensity of follow-up. Hence many more parameters need to be monitored than those under study in one trial, and large patient samples will be required to prove the beneficial effect of a single aspect of treatment.

4.7. Cost data

It is often very difficult to compare cost data from different studies due to a lack of uniformity in the kind of cost components included in the study (for example, due to differences in perspective or in the way costs

are defined) or the way in which the identified cost components (for example, indirect costs) are measured. It is also more difficult to transfer data on patterns of care and their associated costs across country borders than it is to export data on clinical efficacy and effectiveness.

For example, a study of breast cancer screening options in France, The Netherlands, Spain and the UK revealed that using country-specific data on disease incidence, tumour stage distribution, demography, healthcare prices and the organisation of screening activities yielded very different estimates of the cost-effectiveness of screening programmes in these countries. Uniform European recommendations based on the details of the study in one country only would therefore have yielded quite misleading conclusions [120].

Goodwin and colleagues [121] pointed out that the results of a study based in the USA, concluding that radiotherapy is a cheaper treatment option than surgery for patients with oesophageal carcinoma [122] might not hold in the setting of some Canadian hospitals where typically the surgical option would be relatively cheaper (because of shorter hospital and intensive care stay for similar levels of complications and shorter operating theatre time).

The accuracy and reliability of economic data can substantially be improved by standardising the methodology for economic evaluation studies. Analogous to the Good Clinical Practice (GCP) guidelines, for clinical efficacy research, standards for economic evaluations in healthcare are being developed [70, 123]. For instance, a number of countries, including Australia and Canada have issued guidelines for the economic evaluation to be submitted when applying for registration of a new drug. Research projects, co-ordinated across countries and disciplines, are directed specifically towards this aim of standardisation. Examples are the HARMED project, a BIOMED concerted action on harmonisation of economic evaluation methods and the Expert Panel on CEA in the United States of America, which aimed at establishing a consensus on appropriate methods for standardising the conduct of cost-effectiveness analysis for use in policy arenas [123].

Being explicit about all the assumptions underlying an economic evaluation is an important prerequisite for being able to investigate the transferability of data from one setting to another.

5. Towards evidence-based clinical decision making and policy-making

On the basis of all of these findings, a set of recommendations is suggested for healthcare policy-makers and providers, to further improve clinical decision making and policy-making in cancer care under tightening budgets. Such recommendations will help to ensure that, in future, cancer patients continue to/will have access to the best available care given the resources that society is willing and able to spend on this care. They are also intended to ensure that cancer care professionals and policy-makers are well equipped to select the best possible care out of a number of possibilities in circumstances where not all possible care options can be made available to all patients.

5.1. Implementation of the available evidence

Generating the evidence alone is not sufficient; it should also be implemented in routine practice. Ample examples can be given that making—even rigorous scientific—evidence available through scientific journals alone brings no guarantee of widespread implementation. For instance, in a study investigating the choice of fractionation schedules used in lung cancer among British radiation oncologists, it was found that the data from clinical trials influenced the choice in only 1–5% of the cases [124]. In palliative radiation treatment of bone metatases, although single doses have been shown to provide similar rates of pain relief as fractionated schedules [125], the latter are still used in many centres. When asked why, the overriding reasons given by Scandinavian and British radiotherapists were training and institutional policy, not scientific evidence based on comparative clinical trials [102].

All of this shows that explicit strategies will have to be designed to guarantee the wide-scale implementation of scientific evidence into routine practice. Awareness of this problem has only emerged recently and since the early 1990s, several approaches to encourage implementation of research findings have been developed [117].

With a pro-active approach, the new evidence is promoted strongly to guarantee rapid incorporation into clinical practice. Some of the pilot projects show that all key players, both clinical and managerial, have to be involved early in the process. Frequent communication with clear messages is necessary. Much effort must be put into presenting the results in user-friendly ways. This also implies that the message must be adjusted, according to the target audience. While a pro-active approach is to be preferred, sometimes a reactive approach (e.g. when a cost-ineffective intervention is already diffused into routine practice and must be down-scaled or withdrawn) is necessary.

Some [117] argue that managed care environments provide fertile ground for the implementation of evidence-based healthcare. Managed care systems indeed have strong incentives for not providing cost-ineffective care, but the US experience shows that they also bring disadvantages and potential threats to our European healthcare systems, such as patient selection, narrowing

down of the basic healthcare insurance package and too strong a focus on pure cost-containment, rather than cost-effectiveness.

Peer review can be a powerful tool for implementing new scientific evidence. The observation of what colleagues, experts or respected others are doing, may impact more on physicians' awareness of new findings and their practice policies than reading a published article. Consequently, physicians in a certain region may converge in their practices. This offers at least a partial explanation for some regional practice variations. If healthcare policy-makers encourage peer review among professionals within a country, for instance, through financial support and through accreditation, intra-country practice variations may ultimately disappear.

Given the fast evolution of medical science and technology, continuing medical education will play a strong role and will also be an important channel for distributing new evidence and facilitating its implementation.

One possible strategy is to reward providers of care for engaging in 'good clinical behaviour' and to 'punish' (i.e. by withholding rewards) them for not doing so. The most obvious examples of such a strategy can currently be found in the third party reimbursement policies (e.g. refuse or restrict reimbursement for (cost-)ineffective procedures), sanctions by peer review and accreditation of healthcare providers and institutions, e.g. based on proofs of continuing education, peer review, continuous quality improvement efforts, etc. which can all be seen as (indirect) evidence of good clinical practice. Potosky and colleagues [126] showed that healthcare coverage may have a positive impact on the use of cancer screening tests. However, if patients and healthcare providers are not convinced of the usefulness of the procedure, reimbursement policies may have no effect on the actual implementation of the intervention [127].

Another strategy is active participation in development and dissemination of consensus recommendations. The dissemination through publication in both general medical and specialised journals and through press conferences appears to have little impact on physicians' practices, even though this technique is often moderately effective in reaching the appropriate target audience [128]. An important element for implementation, however, is that clinicians should be actively involved in the development of detailed practice guidelines and their dissemination. The participation of experts in the evaluation of scientific evidence may make practice guidelines more credible to providers than the scientific literature from which they are derived. Engaging clinicians in the dissemination process (e.g. through interaction in a seminar) motivates them to reflect more seriously on the quality of arguments rather than on the quantity. Furthermore, to be effective, practice recommendations should be set in a clinical context, such that the clinical relevance and importance becomes immediately clear to the provider. Peer influences play a very important role in the implementation of new clinical evidence. The dynamics of this influence are, however, still not very well understood. Further studies are needed to determine the impact of peer influence on various practice settings.

The emerging field of 'evidence-based medicine', not only attempts to generate more solid evidence, but also to make it more easily accessible for healthcare providers, as for example through specialised journals, such as *Evidence-Based Medicine*, which summarise the results of methodologically sound studies and draw the appropriate conclusions for routine practice, thereby facilitating implementation in routine practice. The Cochrane collaborations (http://hiru.mcmaster.ca/cochrane/default.html) are very active in this field and illustrate well the advantages of international collaboration in this area.

5.2. Diffusion on the basis of evidence

In order to avoid wasting scarce resources on new interventions with expected—but not yet fully proven—effectiveness, the large-scale diffusion of such interventions into routine clinical practice should be postponed until sufficient evidence is available. For instance, cisplatin-containing chemotherapy for advanced gastrointestinal malignancy spread rapidly into routine practice, on the basis of preliminary evidence. However, when the results of randomised trials became available, no clear overall superiority of the combination chemotherapy could be demonstrated. A randomised prospective clinical trial [129] comparing 5-FU + cisplatin with 5-FU + doxorubicin + mitomycin C and with 5-FU alone, revealed that the 5-FU–cisplatin regimen did produce higher response rates and that the median time to progression was longer in this study arm. However, no statistically significant difference could be observed in the duration of response and overall survival between the different treatment groups. A possible explanation for this seemingly contradictory result may be that most responses were partial remissions (47%), whereas the proportion of complete responses was rather small (4%). Analogous results were found by Cullinan and colleagues [130] comparing a 5-FU–doxorubicin combination with 5-FU + doxorubicin + mitomycin C and with 5-FU alone.

Although in practice it is not easy nor desirable to entirely block patient access to promising interventions, it may be possible to control access. For instance, the application (and reimbursement) of new interventions may be temporarily restricted to a small set of designated centres until further convincing evidence becomes available, while allowing 'investigational medicine' studies in the meantime. For instance, in The Netherlands, research on the cost-effectiveness of new interventions

can be funded for a period of up to 3 years, by the Fund for Investigational Medicine (http://www.ziekenfondsraad.nl/inv-med/index.html). The purpose is to evaluate medical technologies, by looking prospectively at efficacy, costs, social, ethical and legal implications in order to support healthcare policy decisions (for example, regarding reimbursement, redefining indications, admission to the benefit package). During the study period, the intervention is, in principle, only accessible for patients through institutions participating in the study. In many countries, however, no such structure is available in which new developments can be 'parked' until their exact impact and optimal frame for application can be determined.

It is very difficult to prevent wide-scale diffusion of new technologies once 'preliminary' evidence shows promising results, since routine use is often pushed by both supply (manufacturers) and demand (patients) forces. Therefore, the evaluation of medical interventions should happen rapidly—preferably on an international scale.

5.3. Independent research

To be credible, research on the consequences of health technologies should be performed by independent organisations and not only through trials funded by those having a large financial stake in their rapid and widespread adoption.

At present, much research on new technologies is sponsored by the industry, which is obviously not neutral with respect to the outcome of the research projects. By their very nature, commercial firms may tend to support mainly those projects with expected favorable outcomes, independent of costs. Many commercially sponsored research projects are trying to provide evidence for modifications in cancer care, linked to more intense, and often more expensive interventions. Given their for-profit status, commercial enterprises will not be interested in sponsoring research to identify ineffective, outdated interventions that should be discarded. Typically, many 'phase IV' studies are intended to widen drug indications or increase dosage of drugs that are already on the market, i.e. such studies aim exclusively at market expansion.

Independent, (for example, government) research funding is required as a counterbalance to commercially sponsored research. Funding should be available to allow evaluation of new as well as established healthcare interventions. Although funding of investigational medicine will in the short-term generate additional expenses, governments should be aware that this investment is worthwhile since it will generate high returns in future. By discarding ineffective interventions and targeting interventions more accurately to subgroups of patients who are expected to benefit, substantial cost savings can be made. For instance, following a study on the appropriate use of preoperative routine tests by the Swedish Office of Technology Assessment (SBU) (http://www.sbu.se/), annual healthcare expenses on these procedures could be decreased by 50 million crowns annually, an amount 5 times higher than the annual research budget of SBU at the beginning of the 1990s [43].

Furthermore, many other societal benefits may be realised. These include an increase in know-how, better targeting of future research, development of research skills, improved information bases to support policy-making, improved quality and equity in healthcare delivery and wider economic benefits, resulting from the commercial exploitation of innovations and a healthy workforce [131]. Unfortunately, in most EU countries funds are insufficient to allow independent assessment studies aimed at decreasing cost. Owing to the scarcity of such data, the phasing out or replacement of less effective procedures is too slow, leading to a waste of resources. Perhaps more international collaboration in this area would yield improvement.

Such independent evaluative research should not be funded from within the healthcare budget for routine patient care but from funds specifically designed for this purpose. As routine patient care has to be implemented under tightening budgetary ceilings, the motivation to finance research projects in routine patient care settings is absent, or at least decreasing.

The results of evaluative research carried out by cancer care professionals should be used to support clinical decision making (individual patient level) as well as healthcare policy-making (societal level). 'Research should precede the policies and politics' [94].

5.4. International collaboration between research teams

Since research budgets are limited in every country, international collaboration should be encouraged for research into the effectiveness, costs and other societal implications of healthcare interventions. International collaboration facilitates larger research projects, recruiting larger patient numbers to obtain robust data on effectiveness and other consequences of health technologies more quickly, and hence during an earlier phase of development. International collaboration promotes efficient use of research money, since unnecessary duplication can be avoided. Through pooling of research funds, the opportunities for independent research are also enhanced.

In the area of health technology assessment for instance, a number of countries have set up an Institute for Health Technology Assessment (http://www.epi.mh-hannover.de/%28vierzu%2Cdreizu%2Czweizu%2Ceng%2Ceinzu%29/hta-intern-links.html) (e.g. the UK, Sweden, France, Catalunya, the Basque Country,

Australia, Canada) to give independent advice to healthcare policy-makers. Since the early 1990s, international collaboration, through the exchange of information, collaboration in research projects and joint evaluation of health technologies has been growing through channels such as INAHTA (http://www.inahta.org) (International Association of Health Technology Assessment Agencies), and EUR-ASSESS (Health Technology Assessment in Europe). The Cochrane collaborations (http://hiru.mcmaster.ca/cochrane/default.html) are also active in this area.

5.5. Action programme to enhance evidence-based cancer care

An action programme is needed to encourage evidence-based cancer care and economic evaluation of cancer care throughout the EU.

A necessary first step is to increase awareness and knowledge of evidence-based medicine among cancer care professionals and policy-makers. Familiarity with these concepts is absolutely vital to increase willingness to work with them. Wide-scale implementation requires specific tools and sustained efforts among all parties involved. A higher awareness of the benefits of evidence-based healthcare among the general public may also facilitate the implementation of the best evidence in cancer care.

Secondly, practice variations, and more importantly, variations in outcome, should be documented for all cancer sites, across all regions in the EU. This requires major follow-up efforts. Documentation of these variations and establishing clear links between outcomes and patterns of healthcare utilisation is a prerequisite for creating willingness to change practice, which will ultimately improve outcomes.

Thirdly, scarce resources for cancer care should be used more efficiently, by selecting best practices and eliminating (cost-)ineffective cancer care. This will reduce outcome variations across the EU. If waste of resources can be avoided, more resources are freed to spend on (cost-)effective interventions.

Finally, special attention should be devoted to the actual implementation of these best practices in all cancer care centres across Europe.

Such an action programme will ensure continuous improvement in outcomes of cancer care, while keeping the economic burden of cancer care within reasonable limits.

6. Conclusion

The shift to cost-effective healthcare provision may seem threatening to healthcare professionals. It should not, however, since this change also brings new opportunities, by helping policy-makers and individual providers determine the most beneficial use of scarce healthcare resources for current and future cancer patients. Since the number of new clinical technologies will increase faster than healthcare budgets, providers will have to choose which of these new technologies will be implemented and which outdated interventions can be discarded to free resources to spend on new, promising interventions.

Finally, care should be taken that the mechanisms in place to audit the system do not absorb the cost savings generated by the process of rationalisation.

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