Chapter 1

SUMMARY

This report addresses the role of radiotherapy for treating tumors. It describes the current use of radiotherapy in cancer treatment, reviews the scientific basis for using radiotherapy to treat solid tumors, and estimates the costs associated with radiotherapy. The report is intended primarily for decision makers at various levels, both practitioners and administrators.

The review of the scientific literature is based on results from nearly 1 700 studies published through 1993, involving more than 700 000 patients. All referenced studies are cited in the two volumes comprising this report. However, no reference citations appear in the following introductory summary, the content of which is based solely on information from the two volumes of the report.

Background[1]

Cancer diseases represent a serious public health problem since they affect many people, involve severe symptoms, and are a frequent cause of death. Many people experience these diseases as being more frightening than other conditions that may have a worse prognosis. Approximately 40 000 people are diagnosed with cancer each year in Sweden, and 20 000 die from some type of cancer. This implies that one in three Swedes now living will be affected by, and one in five will die from, some type of cancer. Most are affected at relatively advanced ages, but cancer also affects many young people, and is therefore a major contributor to years of life lost to premature death.

Tumors may appear in virtually any organ. Benign tumors are limited in growth, and cause only local symptoms, while malignant tumors are able to infiltrate adjacent tissues and can metastasize to other organs. Malignancies are usually called cancer, although the term "cancer" actually represents numerous disease types, depending on the type of cell from which the tumor emanates. This, along with the grade of tumor maturity (differentiation) determines its ability to grow, invade adjacent tissues, and spread throughout the body. Tumor spread (stage), type, and differentiation are generally the most important factors for determining the prognosis and choice of treatment.

The goal of treatment is to remove or incapacitate the tumor and help patients function as well as possible, for as long as possible. To assess treatment results, scientific studies have focused on survival and the local presence of tumors (primary tumor healing, relapse-free survival). The intent of *curative treatment* is to remove all tumor cells and heal the tumor. The intent of *palliative treatment* is to reduce symptoms such as pain, difficulty in swallowing or breathing, and circulatory obstructions. Palliative treatment may be used to treat metastases or wide-spread primary tumors where curative treatment is not possible. For example, radiotherapy can ameliorate pain from bone metastases, prevent bone fractures, and promote local healing of skeletal lesions. Preferably, treatment should neither interrupt the function of the organ where the tumor is located nor reduce the patient's general health status.

A general practitioner may be the first person to suspect cancer in a patient, and may initiate an investigation. Depending on the location of the suspected tumor, its diagnosis and primary management may involve representatives from surgical specialties, internal medicine, or oncology. When tumors are diagnosed, their spread is often limited and local treatment methods such as surgery, radiotherapy, or a combination of these methods can be used.

If the risk is high that the tumor has spread, complementary medical treatment, ie, adjuvant treatment involving anticancer drugs (cytostatic agents) and/or hormones can be used for some tumors. Generalized tumors, ie, tumors which have spread to other organs, can be treated by various systemic approaches, often in combination with local methods.

An EU expert panel found that 22% of patients were cured by surgery alone, 12% by radiotherapy alone, and 6% by combination therapy. Adjuvant medical treatment has rather limited effects, and can cure only a few unusual types (5%) of generalized tumors. However, different methods may slow the progression and even result in the gradual regression of tumors, thereby ameliorating symptoms. This can substantially improve the quality of life and general situation for the patient.

Advancements in recent decades have increased the opportunity for effective treatment via improvements in all three forms of, mainly in combination. Treatment of many

[1] 1 U.S. dollar (USD) = 6.67 Swedish knonor (SEK).

cancer diseases has thus become highly multidisciplinary, ie, requiring the involvement of numerous medical specialties. These advancements mean that more patients with different types of tumors can be cured, but mainly better opportunities exist for meaningful alleviation of symptoms and life-prolonging treatment in patients who cannot be cured. The latter involves a humanization of cancer care. Given adequate treatment, few patients with incurable cancer today need to suffer from severe pain or typically degenerative cancer lesions, no one needs to be suffocated by a tumor, few need to experience disfiguring surgical intervention or crippling bone fractures due to tumor growth. Modern radiotherapy, along with advanced organ-conserving and reconstructive surgery, often preserves organ functions.

Most cancer patients receive primary treatment at surgical departments. All curative, and nearly all palliative, radiotherapy is delivered at general oncology departments (at seven county hospitals, at eight regional hospitals in Sweden) and at gynecologic oncology departments (at seven regional hospitals). Even more advanced drug therapy for solid tumors is delivered at, or in cooperation with, these departments. Oncology may include investigation, diagnosis, and followup of patients with tumor diseases. Since radiotherapy is a technology-intensive activity, these departments collaborate closely with the departments of radiophysics which, in addition to participating in daily patient-related activities, are also responsible for service and quality control of equipment and radiation protection of patients and staff.

A questionnaire survey by SBU shows that approximately one third of all cancer patients in Sweden receive radiotherapy, either alone or as an integral part of combination therapy, usually with surgery. Few patients are admitted to hospitals in conjunction with radiotherapy, while chemotherapy more often requires hospitalization.

Radiotherapy has drawn particular interest because it is associated with ionizing radiation, which is viewed as having some risks, and also since radiotherapy involves a substantial capital investment. Therefore, it is important to assess the efficacy of radiotherapy, how it is used, and what costs are actually involved.

Considerations and Conclusions

This document reviews, classifies, and grades the scientific literature on cancer radiotherapy, describes the practice of radiotherapy in Sweden, compares practice to scientific knowledge, and analyzes the cost of radiotherapy in Sweden. The report also projects the trends in cancer diseases until the year 2010. A multidisciplinary project group has been responsible for this effort. The group used external experts and an independent international reference group comprised of researchers from eight countries and representing different scientific disciplines.

The extensive body of scientific literature was reviewed according to a model developed by the project group, based on criteria that reflected the scientific weight of the literature. Seventeen experts representing different disciplines (oncology, surgery, internal medicine, see Chapter 6) participated in the literature review. Each section of the report was discussed within the project group and was reviewed by at least one, but usually two to three, researchers from the international reference group. For the final evaluation to be as close to the objective truth as possible, a concerted effort was made in this project to guarantee objectivity and thorough assessment of current knowledge about the effects of radiotherapy on different cancer diseases. The literature review covered types of tumors for which 89% of all cancer patients receive radiotherapy in Sweden.

A wealth of scientific literature has been published on cancer therapy. The review presented here is, however, limited to scientific studies judged to be important for evaluating the effects of *radiotherapy on solid tumors*. Assessments of the content and quality of these studies, and a critical summation of the results, has never before been done in this way. The engagement of international experts to evaluate the assessments has enabled the greatest possible objectivity.

The survey of practice involved all 22 departments of general and gynecologic oncology in Sweden having resources for radiotherapy. During the 12 weeks of the survey, all patients with the diagnoses concerned who began radiotherapy, and all costs for radiotherapy (excluding inpatient services) were registered. The study included 3 000 patients and nearly 50 000 treatments during the survey period, corresponding to 13 000 patients for one full year.

The working group's conclusions may be summarized by the following ten points:

1. A study of practice in Sweden shows that somewhat less than one third of all cancer patients receive radiotherapy, a lower figure compared to other countries for which data is available (Table 3, Chapter 12).
2. Comparing the literature with practice shows that curative treatment is usually readily available in Sweden, and may be overutilized in some cases.
3. A review of the literature shows that radiotherapy plays an essential role in palliative treatment for cancer. Radiotherapy for palliative and symptom-relieving purposes appears to be underutilized in Sweden.
4. The total number of cancer cases in Sweden will increase by about 18% by 2010. This will lead to a greater need for curative radiotherapy. Furthermore, neglected but urgent needs for palliative radiotherapy must be met. Some efficiencies in radiotherapy are possible (eg, reducing the number of fractions in palliative radiotherapy). Advancements in surgery may

also reduce the need for radiotherapy. Hyperfractionation has been justified scientifically, but its use in Sweden is limited. Consequently, the need for radiotherapy is expected to increase until the year 2010.

5. Nothing appears in the literature to suggest that other methods for treating cancer would replace radiotherapy in the foreseeable future.
6. The total cost of radiotherapy in Sweden, including capital costs but excluding inpatient costs, is estimated at approximately 330 million Swedish kronor (SEK) per year.

   Radiotherapy requires a substantial capital investment and is therefore perceived as being relatively expensive. The high investment costs often lead to an intense debate concerning need. However, capital investments in radiotherapy can provide service for many years (shielded treatment rooms, 30 to 40 years; radiotherapy equipment, 12 to 20 years). In contrast, decisions to use new drugs or other types of and diagnostic methods are made by individual physicians, and the increased costs resulting from these decisions are observed only after a relatively long time. Without receiving much attention, pharmaceutical costs for a single drug can far exceed the costs for capital-intensive activities.
7. High capital costs yield low marginal costs. Increasing the utilization of a high-voltage device from 8000 to 12 000 fields per year reduces the unit cost per treatment by about 20%, although the increased utilization requires an increase in staff. Departments with fewer treatment devices often meet accessibility needs, but are at risk for having higher unit costs.
8. There is a need to specialize and centralize the care of uncommon types of tumors and certain interventions that may be rare, yet important for patients. In principle, this concerns all types of cancer therapy.
9. Clinical protocols or guidelines can be applied much more widely. A need also exists for controlled clinical trials, which should also include studies on patients' quality of life in conjunction with cancer treatment. This knowledge is essential for determining future recommendations, and choosing among alternative forms of treatment.
10. New forms of treatment should be subjected to controlled studies to determine their efficacy before they become routine. It is essential to consider both patients' quality of life and the economic consequences when assessing new forms of treatment. Such studies in many cases require international collaboration. Particular attention should be given to opportunities for collaboration within the European Union (EU).

Cancer trends until 2010 (Chapter 5)

All cancer types have been registered nationally in Sweden since 1958. Consequently, there is substantially more information on cancer prevalance, survival, and mortality than on any other disease group. For the 30-year period during which cancer has been registered in Sweden, Sweden's population has increased from 7.5 to 8.6 million inhabitants, and the average life span has increased from 75 years to 80 years in women and from 72 years to 75 years in men. This increase is expected to continue, which means that the percentage of elderly people will continually rise. From 1970 to 1990 the number of persons over 65 years of age increased by nearly 40% while the number of persons 80 years of age and older nearly doubled. Since cancer diseases affect older people more frequently than younger people, the number of cancer cases will continue to increase.

Incidence and prevalance of cancer

The most recent statistics show that 41 138 cases of primary tumors were registered in Sweden in 1992, 20 868 cases in men and 20 270 cases in women. During the time that cancer registers have been kept, the absolute number of primary cancer cases has increased by approximately 2% per year among men and women alike, thus the figure doubled from 1958 to 1992. More than half of the increase can be attributed to the changing age structure of the population, but other factors are responsible for 0.8% in men and 0.5% in women. Part of the increase is the result of better diagnostic methods, but part is due to actual increases in several types of cancer. Some geographic differences in the annual incidence of cancer can be found among the different regions in Sweden.

Usually the prevalence figure for cancer (number of cases at a given time) indicates how many people in the population have, or have had, cancer, regardless of whether or not the tumor has been removed. At the end of 1989, approximately 237 000 persons were living in Sweden who had one or more cancer diagnoses. Prevalence increased by 8% between 1984 and 1989, due in part to successful, life-extending treatment.

Mortality from cancer

Diseases affecting the circulatory organs are the most common cause of death (more than one half of all deaths) in both men and women, followed by cancer diseases (approximately 22% of all deaths). In men, tumors in the prostate or lungs are the most common causes of cancer death. In women, breast cancer is the most common cause of death. In both men and women, colorectal cancer is the second most common cause of death—corresponding to approximately 12% of all cancer deaths.

Expected trends until 2010

The number of cancer cases will continue to increase. Incidence is expected to increase by approximately 1% per

year, corresponding to 6 300 more new cases in 2010 than in 1992 (Table 2, Chapter 5). Cancer of the stomach, cervix, and uterus will decrease while most other types of cancer will increase, particularly lung cancer in women, skin cancer, cancer in the head and neck, breast cancer, prostate cancer, and some lymphomas. Mortality is expected to increase by 0.8% per year, resulting in 4 000 more deaths in 2010 (Table 3, Chapter 5). The difference between the increase in incidence and mortality suggests an expected increase in prevalence. In 2010, nearly 360 000 people in Sweden are expected to have, or have had, cancer (Table 4, Chapter 5). Screening or other preventive measures against certain types of cancer are not expected to reduce cancer diseases during the period.

What is radiotherapy? (Chapter 3)

The objective of radiotherapy is to deliver a defined radiation dose to a specific tissue volume—including the tumor and adjacent tissues where tumor cells might be found—with the intent to kill tumor cells while minimizing irradiation of surrounding, healthy tissue. Planning and delivering external radiotherapy (using an external irradiation source, usually an accelerator) is a complex process and involves taking into consideration for each individual patient: definition of the treatment volume, decisions on total dosage and fractionation schedule, choice of appropriate radiation quality and treatment method (Figure 1, Chapter 3).

First, the tissue volumes to be irradiated and tissues to be protected must be defined. This usually requires extensive diagnostic information, involving clinical examination and diagnostic imaging such as x-rays, ultrasound, and nuclear medicine. Dose planning follows, whereby the direction and field of the radiation beams are configured to achieve a dose distribution that corresponds as closely as possible to that desired. The advancement and refinement of dose planning and equipment has made it possible to better focus on tumor tissue, avoiding irradiation of normal organs. This permits greater precision, but increases dependency on new methods yet being developed.

To optimize dose distribution, a range of different radiation types and energies are needed. In practice, this means that a given department must have access to several different treatment devices, and the equipment for dose planning and simulation (a method to transfer the dose plan to the patient). A patient's position on the treatment table must be exact and reproducible since the position and settings must be repeated, perhaps up to 36 times. This may require some form of fixation device, continuous checks of dose measurements, and verification films. Geometric precision of ± 5 mm and dosage within $\pm 5\%$ to 7% are necessary.

Another form of radiotherapy involves placing the radiation source near or in the tumor, ie, brachytherapy (intracavitary treatment, if the radiation source is placed in a body cavity, or interstitial treatment if the radiation source is implanted in the tumor tissue). Treatment is usually delivered only on one, or a few, occasions at a relatively high dose. Radiation shielding problems have promoted the development of special devices (for afterloading). The need for precision is high, even with brachytherapy. Dosage is not as equally well-distributed with brachytherapy as with external radiotherapy. Brachytherapy is often combined with external radiotherapy.

During intraoperative radiotherapy—IORT—radiation is delivered during surgery, while the tissue to be irradiated is exposed. This method is considered experimental.

Radiotherapy is a team effort requiring close collaboration among oncologists, radiophysicists, and oncology nurses. Various quality control systems must be built into the entire process, such as regular supervision and checking of the equipment's performance, checking that the correct field geometry is used during each treatment, and that the correct dose is delivered. A program for standardizing dosimetry has been developed in Europe. Dosimeters (devices that measure irradiation) are exposed to given conditions at different clinics and are read centrally. Several countries have introduced this program on a trial basis, and consideration should be given to introducing the system in Sweden to further improve precision.

Description of radiotherapy practices in Sweden (Chapter 7)

The planning and delivery of radiotherapy at all oncology departments in Sweden was studied during the autumn of 1992. For 12 weeks, all patients who received radiotherapy for certain predesignated diagnoses were registered. During the study, 2 988 patients started radiotherapy. An inventory from Radiumhemmet the same year indicated that the diagnoses covered by the study included 82% of all patients receiving radiotherapy.

The study showed that a maximum of one third of all patients diagnosed with cancer in Sweden (13 000 patients in 1992) receive radiotherapy at some stage during the disease. Slightly over two thirds of the radiation treatments are provided at regional hospitals, and one third at county hospitals. Most patients receive only external radiotherapy, a few receive brachytherapy or both external therapy and brachytherapy.

One half of the patients receive curative radiotherapy, consuming nearly 75% of the resources. Only one fourth of the resources are used for palliative treatment for the remaining one half of the patients. (Table 5, Chapter 8). More than one third of the patients treated with curative radiotherapy had breast cancer, approximately 10% had tumors in the head and neck, and 10% had rectal cancer. Most of these patients also received other forms of treatment, mainly surgery. The gynecologic oncology depart-

ments differed by virtue of delivering a higher percentage of curative treatment.

In Sweden, approximately half of the patients with breast cancer, malignant lymphomas, and lung cancer received radiotherapy, and one third of the patients with prostate cancer received radiotherapy—in the two latter groups mainly for palliative purposes. Patients with bone metastases were the largest single group to receive radiotherapy (25% of all treated patients).

Cost of radiotherapy in Sweden (Chapter 8)

The cost of treating cancer patients can be divided into costs for general care (including hospitalization), costs related to diagnosis, and costs for specific types of treatment, eg, surgery, radiotherapy, or drugs. This study identifies and estimates the costs specifically associated with radiotherapy itself.

International studies that estimate the cost of radiotherapy often neglect to present the underlying assumptions. A relatively reliable study showed that the capital costs for radiotherapy are nearly 30%, and personnel costs are nearly 60%, of the total cost. This estimate corresponds well with estimates in the present report on the situation in Sweden.

This project included a survey of all departments that provide radiotherapy in Sweden, and data concerning staff resources, material, equipment, and facilities were collected on site from various sources. Thereby, adjustments could be made to increase comparability among the departments. All data, including the annual financial reports from the departments, were used as a basis to analyze the cost of external radiotherapy in Sweden (Table 7, Chapter 8).

The total cost of external radiotherapy in 1991 was approximately 260 million Swedish kronor (SEK). The cost for brachytherapy was estimated at approximately 36 million SEK. Costs averaged 499 SEK per irradiated field, 1 125 SEK per fraction (treatment occasion), and 17 200 SEK per patient for a complete radiotherapy series. These costs varied widely among the diagnostic groups. The cost for a series of breast cancer treatments was approximately 31 000 SEK, while the cost for treating bone metastases totaled about 7 000 SEK. These estimates do not include costs such as hospitalization associated with treatment, or other costs to the patient or society in conjunction with treatment. Most radiotherapy in Sweden is delivered on an outpatient basis. The cost of radiotherapy (330 million SEK per year) can be viewed in relation to the total cost for treating patients with cancer, approximately 6 900 million SEK in 1993 prices. The latter figure includes nursing costs. This can be compared with the cost of treating moderately elevated blood pressure, estimated by an SBU report to be 1 600 million SEK per year.

In 1991, the estimated value of equipment and facilities for external radiotherapy in Sweden totaled approximately 840 million SEK, whereof equipment was estimated at 490 million SEK, and facilities at 350 million SEK. The need for reinvestment in equipment and facilities is estimated at approximately 55 million SEK annually, whereof equipment represents 43 million SEK.

Current knowledge on radiotherapy for specific cancer types (Chapter 6)

Procedures for evaluating the scientific literature

In planning this project, it was decided to review the scientific literature covering diagnoses that accounted for at least 80% of all radiotherapy in Sweden. This goal was achieved (89% coverage). A special subgroup (Chapter 6) directed the literature study, based on principles discussed and approved by the project group. Studies published during 1990 through 1993 were searched through MEDLINE and other appropriate data bases. Regarding controlled clinical trials, the data search covered the past 10 years. Some literature reviews were also studied. References cited in the reviewed literature were used to identify and review older, yet important, reports. Each publication was classified according to two systems:

- in relation to the type of study: meta-analysis (M), controlled clinical trial (C), well-defined prospective study (P), retrospective study (R), literature review (L), case report or other type of study that potentially concerned a random area such as radiobiology, radiotherapy technology, or cancer epidemiology (O), and
- in relation to the weight of scientific evidence, as judged by the referees on a three-grade scale: 1 = high, 2 = moderate, 3 = low. The review did not consider publications that were of poorer quality, with inherent deficiencies that did not permit the referees to judge the methods used, patient data, or results, nor were these publications included in the report. The reference list includes a notation for each publication to indicate how it was judged (Chapter 6). Each report concludes with a table summarizing the number of scientific studies reviewed, how they were classified, and how many patients were included in the studies.

Based on the uniform process described above, a primary reviewer identified and reviewed the appropriate literature for each cancer type and drafted a preliminary manuscript. The manuscript was then reviewed by one or more experts. The refined draft was then submitted to the project group, translated into English, and reviewed by one or more of the researchers in the international group (Chapter 6). In some cases the results were discussed in a meeting of the international group or at a joint meeting with the project group. The primary reviewer considered the comments received and finalized the report, which was then reviewed and approved by the literature group. All

reports were edited and summarized as follows. Table 2, Chapter 6 summarizes the classifications and rankings assigned to the 1 666 publications accepted for review, and which serve as the basis for this report. Table 1, Chapter 12 shows the number of publications, tumor group by tumor group, judged to be of high scientific value.

The literature presentation generally identifies cancers by stage (classification based on the spread of disease). Classifications systems can vary with time, and the results differ with variations in the methods used to examine patients and whether or not methods have been standardized. In presenting the literature for each tumor type, the stages were grouped from early to advanced cancer. Since tumor staging is not uniform, the project group decided to use the 1992 survey to gather information on curative and palliative treatment. These groupings generally correspond to the stages in the literature, but the difference presents a weakness when comparing the literature with practices in Sweden.

In reality, it is impossible to completely avoid subjective values when evaluating scientific literature. However, with the process used here, this risk has been minimized by repeated review of manuscript drafts by domestic and international experts representing different disciplines and fields of interest.

The literature review shows that curative effects are often achieved for certain types of tumors (head and neck tumors, breast cancer, malignant lymphoma, rectal cancer, cervical cancer, and uterine cancer). For other types of tumors, radiotherapy often extends life and prevents symptoms—but treatment seldom results in definitive cure (ovarian cancer, most brain tumors, lung cancer, prostate cancer, and sarcoma). In yet other situations, radiotherapy is used for purely palliative purposes (bone and brain metastases, various forms of advanced tumors, and often treatment of relapse).

Head and neck tumors (Chapter 6, Section 4)

Approximately 1 000 cases involving tumors in the head and neck are diagnosed annually in Sweden, and approximately 400 patients die from these tumors. Head and neck tumors are relatively unusual, but represent a major health problem. These cancers are often painful, are accompanied by other local symptoms, and are not infrequently disfiguring. Treatment must often be combined with reconstructive and rehabilitative procedures.

On early diagnosis, local tumor control and good 5-year survival can often be achieved by radiotherapy alone, but radiotherapy is frequently combined with surgery. The prognosis for more advanced tumors is worse, and 5-year survival in this patient group is somewhat less than 50%. Surgery does not infrequently result in pronounced functional disability, and therefore radiotherapy can be advantageous. For example, surgery and radiotherapy have similar curative effects on tumors in the larynx, but radiotherapy offers better retention of voice. Metastases that frequently appear in regional lymph nodes in the neck can be irradiated with good results if detected early. Treatment of recurrence must be individualized, and frequently involves radiotherapy alone or in combination with other forms of treatment.

Summary. The literature review shows that radiotherapy alone or in combination with surgery plays a decisive role in treatment of these tumors. The survey indicates that approximately 90% of these patients receive radiotherapy, somewhat more than one half of whom receive radiotherapy alone. Curative treatment is delivered to 80% of the patients. Recent advancements in technology make it possible to define radiation fields more precisely, lowering the risk for side effects. The value of hyperfractionated radiotherapy for this type of cancer is documented in the literature. However, few patients in Sweden receive this type of treatment, and almost none receive interstitial brachytherapy. About one half of the patients receiving curative treatment would benefit from hyperfractionated treatment. This, however, would require more treatments per patient, and thereby more resources.

Expected trends. Because surgery has advanced technically, some patients who currently receive radiotherapy can expect to be treated by surgery alone. Concurrently, hyperfractionation will substantially increase the need for more radiation treatments. A 25% increase in the number of patients with head and neck cancer is expected by 2010.

Breast cancer (Chapter 6, Section 6)

Breast cancer accounts for 14% of all cancer cases and is the most common type of cancer in Sweden, with approximately 5 300 new cases and 1 500 deaths per year. Total survival is approximately 70% after 5 years and approximately 50% after 10 years (breast cancer can often reappear 10 to 15 years after it debuts). Primary treatment is usually surgery, either by removal of the entire diseased breast (mastectomy), or partial removal (breast-conserving surgery). Radiotherapy is usually given postoperatively to reduce the risk for relapse and metastases. Radiotherapy alone, or in combination with drug therapy, is given for inextirpable tumors and palliative treatment.

Numerous randomized studies were conducted from 1940 to 1980. These studies investigated 17 000 patients and analyzed the value of radiotherapy in combination with mastectomy. All studies found a reduction in local relapse in the irradiated group—with modern radiotherapy methods to less than one fourth that of surgery alone. If radiotherapy is started after relapse has been diagnosed, local tumor control is seldom lasting. Two studies that used modern radiotherapy methods (1 185 patients) observed a significant reduction in the number of patients with distant metastases, however only in patients with

lymph node metastasis in the axilla. These studies also showed a 5% to 10% improvement in long-term survival, but the difference was not statistically significant, ie, it is not shown scientifically that radiotherapy improves total survival.

Radiotherapy in conjunction with breast-conserving surgery was studied in several randomized trials, including approximately 7 000 patients treated by different surgical methods. Four randomized studies found a 9% to 43% lower risk for relapse in radiotherapy patients, dependent on patient selection, followup time, and surgical method.

Earlier studies observed increased mortality from cardiac complications and side effects following irradiation of lymph nodes in the axilla. These complications seldom appear with modern methods.

Summary. Radiotherapy following mastectomy of patients at high risk for local recurrence, eg, with demonstrated lymph node metastases in the axilla, leads to a substantial improvement in relapse-free survival, and even a reduced risk for distant metastasis. The benefits in patients without confirmed lymph node metastases are substantially lower, and radiotherapy can be motivated only in exceptional cases, eg, large tumors or uncertain surgical radicality. Radiotherapy, as a complement to breast-conserving surgery, involves a significantly lower risk for local recurrence. Radiotherapy, chemotherapy, and various forms of hormonal therapy can be used for advanced, inextirpable tumors, in many cases with good results. Palliative radiotherapy is also beneficial treatment for distant metastases, mainly in the skeleton or brain.

The SBU survey shows that approximately 37% of breast cancer patients receive curative local radiotherapy, usually following surgery. Approximately 60% of breast cancer patients receive radiotherapy at some time during the course of their disease, some of them for relapse or palliation. Swedish practice generally follows protocols based on information in the literature.

Expected trends. The number of breast cancer patients is expected to increase by slightly more than 20% during the next 15 years. Trends will probably continue toward earlier detection of smaller tumors and fewer patients with lymph node metastases in the axilla, further reducing the number of high-risk patients needing radiotherapy following surgery. On the other hand, an increase is expected in the proportion of patients who will be candidates for breast-conserving surgery and who, according to current treatment traditions, may need postoperative radiotherapy. Studies are under way to identify subgroups of these patients at low risk for local recurrence and who do not need postoperative radiotherapy. These studies are expected to result in a reduced proportion of breast conserving surgery patients needing postoperative radiotherapy.

The expected 20% increase in cases during the next 15 years will be offset by a reduction in the proportion of patients needing radiotherapy. At best, the need for radiotherapy for breast cancer in 2010 will not increase but will remain at current levels.

Cancer of the uterus

These tumors can emanate from the cervix (cervical cancer) or the body of the uterus (corpus cancer). Treatment results are presented every third year in reports that include summaries from over 100 specialized departments that uniformly follow and register their patients (so-called "Annual Reports"). These reports, presenting treatment results from thousands of patients, enable generally valid comparisons among different treatment strategies.

Cervix uteri—cervical cancer (Chapter 6, Section 9)

In 1992, 515 new cases of cervical cancer were diagnosed in Sweden, and 171 deaths were attributed to this form of cancer. Two randomized studies compared the results between surgery and radiotherapy in patients with stage I tumors. No differences in treatment results were observed. The results from most studies based on retrospective data suggest that surgery alone yields results similar to combination therapy at early stages, and small tumor volumes. In Sweden also, these patients are treated by surgery alone, thereby preserving ovarian function in younger women. Either radiotherapy or combination therapy can be considered at early stages with large tumor volumes. Treatment for more advanced stages of cervical cancer, in Sweden and internationally, consists mainly of radiotherapy alone. However, chemotherapy is being tested experimentally at the most advanced stages. This approach is supported in the literature.

Summary. Surgery is used as primary treatment at early stages with small tumor volumes, but postoperative radiotherapy can be motivated for lymph node metastases. At advanced stages, radiotherapy is the dominant treatment method for cervical cancer. The SBU survey shows that over 60% of the patients receive curative radiotherapy. This is given as external radiotherapy in 44%, intracavitary brachytherapy in 26%, or a combination of both in 30% of the cases. The literature supports the use of radiotherapy in this high proportion of patients. Development of new methods continues, mainly to improve radiation protection for staff.

Expected trends. The number of new cancer patients is expected to decrease by 15% over the next 15 years. The percentage of patients receiving external or intracavitary radiotherapy will remain unchanged. To improve protection from radiation, the trend toward using high-dose-rate brachytherapy will continue, involving additional, although shorter, treatments. This trend will reduce the need for inpatient beds but increase the number of treatments.

Corpus uteri—endometrial cancer (Chapter 6, Section 10)

In 1992, Sweden registered 1 199 new cases of endometrial cancer. Endometrial cancer is radiosensitive, and it was shown early that approximately 70% of the patients who receive radiotherapy alone at an early stage of the disease are cured. Later research shows combined surgery and radiotherapy yield even better results. The literature provides no clear guidance regarding whether primary surgery or primary intracavitary brachytherapy is preferable at stage I. At the time of the SBU survey in 1992, some patients were receiving preoperative brachytherapy. To enable surgical staging of the disease, there has been a shift during the past two years in Sweden toward using primary surgery in all operable patients.

Most patients receiving primary surgery now receive postoperative radiotherapy, depending on surgical findings, either vaginally or combined with external radiotherapy. According to the literature, recurrence and inoperable endometrial cancers at stages III and IV should be treated with radiation.

The 114 institutions that reported to the Annual Report (No. 21) gave radiotherapy to 83% of the 18 412 patients registered. Most patients were given radiotherapy in different combinations with surgery, while 16% were given radiotherapy alone.

Summary. Endometrial cancer is radiosensitive, and many patients can be cured by radiotherapy at different stages in the disease. Surgery, however, is used as primary treatment in most cases of endometrial cancer, followed by postoperative radiotherapy in most surgical patients. The value of radiotherapy is documented: a) at early stages in high-risk patients with lymph node metastases or other unfavorable prognostic factors, b) at advanced stages of the disease, and c) on relapse. The SBU survey found that over 80% of the patients with endometrial cancer received radiotherapy either by intracavitary brachytherapy, external radiotherapy, or a combination of the two.

Expected trends. During the next 15 years, the number of endometrial cancer cases is expected to decline by approximately 3%. The percentage of patients receiving external radiotherapy will remain unchanged. The use of intracavitary brachytherapy will decline, and will be reserved for patients with advanced disease and for postoperative treatment in selected cases.

Ovarian cancer (Chapter 6, Section 11)

Approximately 900 new cases of ovarian cancer are diagnosed annually in Sweden, whereof over 70% are detected at late stages. Attempts are being made to detect tumors earlier using ultrasound or markers, but no evidence has shown that this type of screening can reduce mortality.

The literature in this field is comprehensive and includes several controlled randomized studies that suffer from high drop-out due to severe side effects. Ovarian cancer is a difficult cancer to treat because of its location and early spread, mainly in the abdomen. Radiotherapy alone is not successful.

Generally, it can be argued that primary surgery is necessary, eg, as a basis for planning further treatment and sometimes for a "second look" following a period of chemotherapy and/or radiotherapy. Studies that have used similar treatment strategies have shown contradictory results. However, the literature reports evidence that radiotherapy following primary surgery has beneficial effects, although only in patients with very small—possibly microscopic—tumor residuals.

Summary. Ovarian cancer is often detected at late stages and is difficult to treat. Primary surgery is considered necessary as a basis for further treatment, but postoperative treatment emphasizes chemotherapy. The value of radiotherapy for ovarian cancer is unclear, and the results of apparently well-designed studies are often contradictory. Radiotherapy following primary surgery where small tumor residuals remain, or as consolidation therapy following successful chemotherapy may be motivated. The SBU survey found that slightly less than one fourth of ovarian cancer patients receive radiotherapy.

Expected trends. Ovarian cancer is expected to increase about 4% during the next 15 years. It appears that radiotherapy will play some role in selected cases postoperatively as consolidation therapy and in some cases as palliative treatment. Based on the review of the literature, the number of patients receiving radiotherapy should fall despite an increase in the total number of cases in Sweden.

Rectal cancer (Chapter 6, Section 7)

In 1992, 1 876 cases of rectal cancer were reported in Sweden (slightly more than 4% of all cancers in Sweden) and 753 deaths were attributed to rectal cancer. The literature shows good results from radical surgery at early stages. However, it appears that the incidence of relapse varies with a surgeon's experience and the radicality of surgery. When appropriate, attempts are made to limit the scope of surgery to avoid the need to construct an intestinal opening in the abdomen (colostomy).

The literature shows that preoperative radiotherapy reduces the risk for relapse. The effects are not as good with more radical surgery, but are better at more advanced stages and increase with the size of the radiation dose. However, no studies (through 1995) show that radiotherapy extends life. Preoperative radiotherapy in older patients (over 80 years of age) increases the risk for circulatory disease in conjunction with surgery. A randomized study found that preoperative treatment is more effective than postoperative. Preoperative treatment is often

given as a short series of five treatments within the course of one week, while postoperative therapy involves 5 weeks of daily treatment.

In locally advanced cancers, radiotherapy has enabled surgical resection of tumors even if they were initially judged to be inextirpable. Followup times remain short, and few of these patients have been reported as relapse-free after longer observation periods.

Relapse, as with locally advanced cancer, involves major suffering, severe radiating pain, urinary bladder dysfunction, etc. Several reports show radiotherapy to provide good relief in approximately 90% of patients, and regression in even very locally advanced tumors.

Summary. Preoperative radiotherapy reduces the risk for recurrence and prolongs the time before patients relapse. Studies have been unable to confirm that radiotherapy extends survival. On recurrence and with advanced cancer, radiotherapy provides effective pain relief and pronounced tumor shrinkage. Combinations with chemotherapy, intraoperative radiotherapy, and treatment with other radiation sources must be considered experimental. The SBU survey shows that in Sweden approximately one third of patients with rectal cancer receive radiotherapy, whereof one third receive palliative treatment and two thirds receive curative treatment, usually combined with surgery.

Expected trends. The number of cases of rectal cancer is expected to increase by 17% by 2010. A comparison between current practices and the literature suggests that radiotherapy is underutilized, mainly as palliative treatment (the survey shows that 10% of rectal cancer patients received palliative radiotherapy). The proportion of patients treated postoperatively with multiple fractions is expected to decline from the figure in the 1992 survey, with a potential corresponding increase in preoperative therapy using fewer treatments per patient. The need for this radiotherapy may decline somewhat with increased specialization of surgery.

A surgical procedure (described by Heald) involving the mesorectum (the tissue behind and lateral to the rectum) can reduce local recurrence to 5%. This procedure is being generally adopted among treatment centers in Sweden. If such a low recurrence rate can be achieved, preoperative radiotherapy will be offered only to patients with particular risk factors or locally advanced tumor growth. Less local recurrence can further reduce the need for later palliative radiotherapy.

The net effect of these changes is difficult to judge. At best, the level of need for radiotherapy of rectal cancer would remain unchanged until 2010.

Malignant lymphomas (Chapter 6, Sections 12 and 13)

Malignant lymphomas are divided into two basic types, Hodgkin's lymphoma (approximately 200 new cases per year) and non-Hodgkin's lymphoma (slightly over 1 300 new cases per year). Both types are sensitive to radiotherapy and chemotherapy. Treatment results have improved substantially during the past two decades. The literature is extensive and includes a relatively large number of controlled trials based on randomized patient data.

Approximately half of *Hodgkin's lymphoma* cases are diagnosed at stages I and II. Radiotherapy using relatively modest doses leads to complete remission in approximately 95% of these cases. Up to one third of the patients relapse. Relapse may be treated by chemotherapy alone or in combination with radiotherapy, yielding new remission in 75% to 90% of the cases and long-term survival in approximately 70% of patients who relapse. Long-term survival for the group as a whole is approximately 80% to 85%. Several randomized studies and two extensive meta-analyses show that chemotherapy combined with primary radiotherapy may somewhat reduce the risk for recurrence, but for many patients this represents unnecessary overtreatment.

At stages III and IV, primary chemotherapy provides better results, even complete remission at stage IV in 60% to 90% of the cases. The addition of radiotherapy increases relapse-free survival—but research has not confirmed any increase in total survival. Radiotherapy involves large, anatomically complicated fields, and requires good shielding of adjacent, non-tumorous tissues.

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of tumors. At stage I, radiotherapy leads to local control of low- and high-grade malignant lymphoma in over 90% of the cases, with long-term survival in about 50%. No studies show that results improve with combination chemotherapy. Primary chemotherapy is the dominate treatment for high-grade malignant tumors. Retrospective and randomized studies show that adding radiotherapy prolongs relapse-free survival, but do not confirm extended total survival. Radiotherapy is of little value at more advanced stages. Recent randomized studies show a substantial improvement in treatment results by alternating chemotherapy and radiotherapy and using whole-body irradiation, but this approach must be considered experimental.

Radiotherapy holds a well-documented place in the treatment of some more unusual lymphoma types, and at certain uncommon sites (eg, orbit, thyroid gland).

Summary. Hodgkin's lymphoma is highly radiosensitive. Primary radiotherapy dominates at early stages, while chemotherapy dominates at more advanced stages. Even at more advanced stages, radiotherapy represents an important complement in selected cases in conjunction with the primary therapy and for later recurrence. Treatment results are very good.

The literature shows that radiotherapy alone is superior for both low-grade and high-grade malignant forms of NHL in stage I. In other groups, its value has been demonstrated in selected cases and as a palliative method.

The SBU survey shows that approximately half of the patients with malignant lymphoma receive radiotherapy at some point during the course of their disease, and in half of these patients it is the only treatment method. This appears to be a reasonable figure, based on the literature review.

Expected trends. The number of malignant lymphoma cases is expected to increase by approximately 25% during the next 15 years, whereof non-Hodgkin's lymphoma is estimated to increase by approximately 30% and Hodgkin's lymphoma is expected to decline by approximately 5%. The number of patients receiving radiotherapy will probably remain unchanged, or possibly decline somewhat with continued advancements in chemotherapy. The potential decline can hardly be expected to compensate for the large expected increase in the number of new cases.

Primary brain tumors (Chapter 6, Section 3)

Brain tumors may be either primary, ie, emanating from tissue in the central nervous system including meninges, or secondary, ie, a result of metastases from tumors in other organs. Somewhat over 1 200 new cases of primary intracranial tumors are registered annually in Sweden. The most common tumors are glioma, followed by meningioma.

High-grade glioma (glioblastoma) represents approximately half of the primary brain tumors. The literature is extensive, with several prospective randomized studies that mainly investigate the value of radiotherapy following primary surgery. These studies show that postoperative radiotherapy can extend survival by weeks to months, and is more effective than chemotherapy. However, one can question the value of subjecting patients to prolonged and often arduous postoperative radiotherapy to extend life only a few weeks. As short-term palliative treatment, radiotherapy relieves severe headache and other symptoms in some patients. The survey shows that radiotherapy is used relatively seldom to treat these tumors in Sweden.

Low-grade glioma (astrocytoma) is relatively rare and has a prolonged course—more than half of the patients are alive 5 years after diagnosis. The primary treatment is surgery. Several retrospective studies found that postoperative radiotherapy leads to slow, but prolonged tumor regression. Half of the studies showed prolonged survival, but the others did not. Two studies found a relationship between radiation dose and survival time. There is no evidence that radiotherapy alone, or postoperatively, can lead to definitive cure. Based on the literature, postoperative radiotherapy for these patients is justifiable.

Meningioma, which emanates in the meninges, represents 30% of brain tumors. Primary treatment is surgery. Curative, postoperative radiotherapy is indicated when it is uncertain whether surgery was radical, but not following a macroscopic, radical operation. Two good-quality, retrospective studies demonstrated a substantial reduction in the risk for relapse (from approximately 80% to 20% after 10 years), limited however to patients where the tumor was not radically resected.

Summary. The value of postoperative radiotherapy has been scientifically demonstrated after non-radical surgery for meningioma and low-grade malignant glioma (astrocytoma). It can be justified for high-grade malignant glioma only as short-term palliative therapy in selected patients with pronounced subjective symptoms such as severe headache. The SBU survey shows that approximately 30% of patients with primary brain tumors are candidates for radiotherapy. Since curative radiotherapy is frequently included in primary treatment, and glioma is the dominant tumor type, this figure appears to be higher than that supported by the literature.

Expected trends. The number of patients with primary brain tumors is expected to increase approximately 15% during the next 15 years. The number of patients with high-grade malignant glioma who are offered postoperative radiotherapy should decline. Instead, palliative treatment should be used to a greater extent in selected cases with pronounced symptoms.

Lung cancer (Chapter 6, Section 5)

Lung cancer is one of the most common types of cancer in Sweden, with approximately 2 500 new cases annually. The two main types, small cell and non-small cell lung cancer, react differently to radiotherapy.

Small cell lung cancer (SCLC) accounts for approximately 20% of the cases. Surgery alone has discouraging results. If the spread is confined, remission can be achieved with either radiotherapy or chemotherapy, however relapse is rapid and survival poor (nearly all patients have died within 2 years). The results of individual randomized studies have been somewhat contradictory, but two meta-analyses based on 12 randomized studies and 2 103 patients showed 3-year survival of approximately 9% with chemotherapy alone. When combined with radiotherapy, 3-year survival increased to approximately 14%, and the most recently published studies have shown a 3-year survival of 30%. Relapse later than 2 years following treatment is unusual. The prognosis for extensive disease is worse, and published data have not shown that radiotherapy improves survival.

For non-small cell lung cancer (NSCLC) at stages I and II, surgery is the first treatment choice, and the literature provides no evidence to support the value of postoperative radiotherapy. Radiotherapy becomes an alternative only if surgery is ruled out for technical reasons. Stage III tumors are primarily inextirpable. Radiotherapy, possibly combined with chemotherapy, marginally improves 2-year to 3-year survival rates, but does not improve 5-year survival. Considering that the dose for curative radiotherapy can

cause severe side effects while offering the patient only limited improvement, one must question the routine use of radiotherapy for stage III NSCLC. Palliative radiotherapy may be indicated for symptoms caused by tumor growth.

Summary. Chemotherapy is the basic treatment approach for SCLC. If tumor spread is limited, the addition of radiotherapy reduces the incidence of local relapse and prolongs survival, a strategy supported by the literature. Surgery is the basic treatment approach for early stage NSCLC, and radiotherapy may be used in patients who are inoperable for technical reasons. In stage III NSCLC, radiotherapy has a demonstrated value only among selected cases as palliative treatment for pronounced symptoms from tumor growth, such as persistent cough, larger hemorrhages, severe pain, and respiratory or circulatory disorders. Curative radiotherapy for lung cancer is of value for limited SCLC and for palliative, symptom-relieving treatment.

Expected trends. The SBU survey showed that the need for palliative radiotherapy has not been met, eg, only 9 of 2 500 new lung cancer patients received palliative radiotherapy for brain metastases. The need for palliative treatment will expand with the projected 26% increase in lung cancer by the year 2010.

Prostate cancer (Chapter 6, Section 8)

Prostate cancer is the most common type of cancer in Swedish men, accounting for approximately 5 000 new cases and approximately 2 000 deaths per year. Prostate cancer grows slowly, and since it is most common in older men, other diseases play a major role in the prognosis. Survival figures, even 10 and 20 years following treatment, must therefore be compared with trends in untreated patients. No such studies on randomized patient data have been published. Therefore, it is difficult to draw conclusions about the curative effects of the various treatment methods. The palliative value of treatment may be estimated from closely monitored series of patients where, in addition to survival, symptoms that influence quality of life (pain, urinary obstruction, major hemorrhage) have been registered.

Radiotherapy at early stages has not been studied relative to observation alone. In more advanced tumors, external radiotherapy is of documented palliative value in selected cases. It is difficult to judge whether any patients have been cured or whether life has been prolonged. Prolonged freedom from symptoms of a cancer that was symptomatic prior to treatment is, however, of considerable value to patients.

Summary and expected trends. Given current knowledge, it must be questioned whether any form of treatment is indicated for prostate cancer at early stages, except in less common and poorly differentiated tumors that are generally radiosensitive. The SBU survey shows that 6% received curative radiotherapy and 35% received palliative radiotherapy.

Sarcomas—tumors in bone and connective tissue (Chapter 6, Sections 14 and 15)

Bone sarcomas—primary tumors in the skeleton—are rare. In Sweden, 60 new cases were diagnosed in 1992. The value of radiotherapy as an integral part of primary treatment has been scientifically demonstrated only for Ewing's sarcoma, and is less certain for chondrosarcoma.

Soft tissue sarcomas are a heterogeneous group of tumors. Based on the literature, the value of radiotherapy alone is limited to selected patients with locally advanced, inoperable, recurring or metastatic disease, mainly for palliative purposes. It is not scientifically motivated following radical surgery of the cancer, but can be considered pre- or postoperatively for non-radical surgery. Several retrospective studies, and one randomized study found that the frequency of local recurrence after combination therapy ranged between 7% and 28%, which is substantially lower than for surgery alone. Combination therapy is therefore scientifically justified in a substantial proportion of such cases. The SBU survey shows that approximately 90% of the patients with soft tissue sarcoma received radiotherapy, most for palliative reasons. This figure is probably higher than that justified by the scientific literature.

Expected developments. During the next 15 years, the number of patients with soft tissue sarcoma is expected to increase by 15%. Overall, the number of patients receiving radiotherapy should decline, despite the total increase in the number of cases.

Skeletal metastases (Chapter 6, Section 16)

In one half of the most common tumor types in Sweden, symptomatic, usually multiple, bone metastases appear in advanced disease, often followed by rapid bone degradation. Median survival following diagnosis is 3 to 12 months, but some patients live for several years. Dominate symptoms include pain, fracture, and hypercalcemia (approximately 10%). Pathological fractures in long bones, a common site for metastases, cause severe symptoms. Metastases in the spine lead to vertebral fracture with compression of the spinal cord, and irreversible paralysis. Radiotherapy is intended to relieve pain, prevent fracture, provide patients with pain-free mobility, and ameliorate other symptoms. Complete freedom from pain or substantial pain-relief is achieved in virtually all irradiated patients, the effects are rapid and long lasting.

Different ways of fractionating radiotherapy for bone metastases have been attempted with varying success. The literature consists mainly of retrospective studies where the criteria for evaluating effects, and other aspects in report-

ing, vary. Reduction in the number of treatments (fractions), using larger doses each time, simplifies treatment and saves resources. More fractions and a higher total dosage provided greater pain relief in a large randomized study, but this result was not replicated in several smaller studies. The optimal fractionation for bone metastases is therefore uncertain. Pending the results from ongoing studies, treatment should be individualized according to the site and expected survival time. Moderate radiation doses yield desired effects, and with such doses treatment can be repeated.

The most important conclusions that can be drawn from a review of the literature are:

- Irradiation of bone metastases effectively relieves pain
- Side effects are minimal
- Optimum dosage and fractionation of treatment is not established. In some cases, the number of treatments can be reduced and the dosage per treatment increased.

Summary. Based on the SBU survey, less than 11% of all cancer patients receive radiotherapy for bone metastases. Radiotherapy is probably underutilized in these cases, particularly considering that it effectively relieves pain. On average, eight fractions are used per treatment series, suggesting a minor deviation from earlier routines of 10 fractions per series, and a margin for further potential reduction in the number of treatments per patient. Reducing the average number of fractions to 5.65 across Sweden would save resources equivalent to half the cost of one treatment device.

Expected trends. Total tumor cases are expected to increase approximately 18% by the year 2010, leading to additional cases of bone metastases. Many of these cases will require radiotherapy. Even if fewer fractions, with larger doses per fraction, are used, this will probably not compensate fully for the expected increase in the number of cases. Increased demand for palliative treatment of bone metastases can therefore be predicted.

Brain metastases (Chapter 6, Section 3)

The brain is one of the three most common sites for metastases. The literature shows that metastases are found in 15% to 20% of all cancer patients, which in Sweden corresponds to between 6 000 and 8 000 patients per year. Patients develop a range of symptoms caused by increased intracranial pressure, ie, severe headache, blindness, balance disturbances, and other injury to cerebral function, which left untreated is generally progressive. Average survival time, according to the literature, is 4 to 8 months, and may be much longer in some patients.

Several publications report that symptoms are effectively relieved by radiotherapy in approximately 70% of the patients with brain metastases. Several prospective and randomized multicenter studies, involving a large patient database, demonstrated a palliative effect in 80% of the patients. The effects were relatively long-term, even following a few high-dose treatments. For solitary brain metastases, which are rare and where surgery is judged to be meaningful, several retrospective and prospective studies have been able to show that postoperative radiotherapy leads to longer survival than surgery alone. For smaller, solitary brain metastases, precision stereotactic irradiation using extremely high single doses can lead to lasting regression and years of survival.

Summary. Patients with symptomatic brain metastases experience rapid relief following radiotherapy of the whole, or large parts of, the brain, and this effect often lasts for the remainder of a patient's life. No evidence shows that survival is prolonged, except for postoperative radiotherapy for solitary metastases. No information is available in the Cancer Registry concerning the number of cancer patients with brain metastases.

Expected trends. The number of cancer cases in Sweden is expected to increase by slightly more than 18% during the next 15 years, and the number of cases with brain metastases are expected to increase substantially. This suggests that 7 000 to 9 000 patients will develop brain metastases by the year 2010. Most patients do not require the relief offered by radiotherapy. The SBU survey shows that only about 400 patients currently receive this type of treatment. In the future, more resources will probably be needed for palliative treatment, even if each patient requires only a few treatments.

Quality of life and radiotherapy

Treatment may have a positive impact on a patient's quality of life by influencing cancer and its effects, but treatment may also cause some undesirable side effects. These side effects are addressed to a greater or lesser extent by individual publications and in the literature review conducted for the present study. There is a need to systematize these observations, and the negative and positive effects of a therapy must be weighed when assessing its value. This is a relatively new, difficult-to-penetrate research field, and the literature is sparse. Several international cancer organizations and the European Union have been working toward developing common measurement instruments and a uniform nomenclature. These developments have progressed slowly, and uniform measures have been introduced to only a limited extent. The British Medical Research Council and several cancer funds require that quality of life issues be addressed in the studies of therapies which receive support from these organizations. This presumes the development of appropriate measurement instruments.

The literature search identified many (approximately 600) publications between 1988 and 1994 that more or less specifically addressed quality of life issues. However, most

of these focus mainly on methodological problems. Only 55 articles that addressed quality of life in relation to cancer treatment met the criteria for review, and of these, only a few specifically addressed the effects of radiotherapy. However, several well-controlled studies are planned or under way. One problem in interpreting the results concerns distinguishing the specific side effects of treatment from the effects of the cancer itself, and even the impact that notification of a cancer diagnosis has on a patient's quality of life.

Specific side effects of radiotherapy were studied in a series of patients who were classified according to the organ treated. In more than half of the patients, irradiation of the thorax and head and neck caused tiredness, skin irritation, loss of appetite, sore throat, and coughing, while irradiation of gynecologic or urologic cancer, in addition to tiredness, generated symptoms in the gastrointestinal tract, including nausea and diarrhea. Symptoms diminished after a few months, and could not be confirmed after one year. How these symptoms influenced quality of life in the short and long term was not described.

Summary. Studies of quality of life in patients with cancer, and the influence that radiotherapy has on quality of life, remain in the initial phases. The studies that are available do not, as a rule, address the most obvious advantages of radiotherapy, eg, maintaining organ function, preventing recurrence, and prolonging life. Future assessments of the different cancer therapies must address their short-term and long-term effects on quality of life. Such assessments require the further development of methods for studying quality of life in cancer patients, and the application of these methods in controlled clinical studies.

The literature: general comments

In assessing the literature, the project group adopted a systematic design whereby all studies were critically reviewed and ranked according to scientific strength. Prospective, randomized controlled trials are commonly looked upon as the best scientific evidence of effectiveness ("Golden Standard"). This, however, does not mean that other approaches toward studying treatment methods cannot be valuable for assessment. It is important, however, to rank the scientific basis for judging a method's relative effectiveness, and in such a ranking, randomized studies receive the highest scores. Prospective, well-executed observation studies, possibly with historical controls, are not far behind. Not all randomized studies have been sufficiently well designed and well executed, and their results cannot be accepted without scrutiny. Obviously, when rating the value of studies it is important to review and evaluate the merits of each one individually.

The effects of some methods are so obvious that clinical observation alone is sufficient. A common example would be penicillin, but the same would apply to many types of surgery, and radiotherapy for certain indications (eg, treating bone metastases).

Great care was taken in this project to assure an objective and thorough evaluation of current knowledge about the effects of radiotherapy on cancer. The involvement of domestic and international experts and engagement of external referees was intended to guarantee that the conclusions reached by this process would be as close to the objective truth as possible.

The greatest difficulty in judging the effectiveness of different types of curative treatment is that very long observation times are required before final judgments can be rendered on the results. In most cases it takes many years, which often leads to reporting the results as 5- or 10-year survival. Over time, oncologists have become used to treatment results based on this time horizon.

Sometimes interim judgments are needed, based on results that can be interpreted following shorter periods. For example, did a treated primary tumor shrink or completely disappear. Even if it is possible to observe local changes, experience shows that even the complete removal of a tumor does not guarantee that it will not return. Therefore, long-term survival is the best measure for comparative studies of different types of treatment, among different cancer types, etc. Clinical findings and mainly subjective symptoms may be sufficient for judging the results of palliative treatment.

In addition to scientific studies of a particular hypothesis, many large institutions also publish ongoing reports of their activities, often reporting treatment results as 5-year survival. These studies also compare different types of treatment, among different institutions, and even countries. However, due to their character we cannot use these comparisons to draw reliable conclusions on the relative advantages of different types of treatment. The underlying patient data may, however, be highly descriptive with respect to staging, tumor differentiation grades, and similar information. Nevertheless, it is impossible—because of the complex situation in which cancer patients find themselves—to define fully comparable patients, much less groups of patients.

Different types of cancer treatment can be justly compared only by randomly distributing patients to different treatment strategies. This has seldom been done with multiple types of cancer, partly because of the very long followup time required before we can interpret the results, and partly because certain types of treatment are traditionally used for certain conditions, and other types for other conditions. Treatments that are compared—radiotherapy and chemotherapy alike—are also complex, making it difficult to develop routine strategies.

Not infrequently, a particular institution or a particular group, often under a charismatic leader, will develop and consistently use a particular treatment design that they

subscribe to on theoretical grounds. Comparing that group's results with results from another group is nearly impossible since the patient data is not comparable from the start. This is not to say that such reports have no value. Many provide well-supported conclusions on different treatment results. In combination with other, more rigorous, scientific, studies they provide a solid basis for collaborative conclusions on the relative value of certain types of treatment. To the extent possible, the project group has attempted in this report to give balanced consideration to the full range of knowledge.

The randomization requirement may seem too strict when randomizing patients with life-threatening tumors to different treatment strategies. It may also be difficult to motivate patients to participate in such studies. Assessment of treatment effects must, however, rest on sound scientific judgment. Controlled trials are the only scientifically acceptable way to compare treatment results. This is particularly true in treating diseases such as cancer that vary widely in terms of prognosis and clinical routines.

It should be noted that 5-year survival is often about 90% for most forms of cancer that are diagnosed at an *early stage*, regardless of the type of treatment given. In treating these early forms of cancer, considerations other than prognosis should enter into assessing the value of a treatment method. Side effects of treatment, influences on quality of life, and costs must also be considered. A comprehensive assessment places greater demands on randomizing patients in treatment studies. Often, only such rigorously-controlled studies permit definitive conclusions about which method of therapy is most beneficial.

Future opportunities for treating solid tumors by radiotherapy and other methods (Chapters 10 and 11)

Optimizing current radiotherapy technology

Recent technological advancements have provided major benefits to radiotherapy, including methods for more exactly diagnosing tumors and defining their spread (eg, computerized tomography and three-dimensional imaging), the ability to more exactly calculate radiation dosage, and refinements in treatment devices. These advancements permit a better concentration of radiation on tumors, avoiding unnecessary irradiation of surrounding normal tissue. New knowledge in radiophysics and radiobiology enables better fractionation of the radiation dose. Several fractionation patterns are being tested:

- Hyperfractionation involves a smaller radiation dosage per treatment, two or three times per day, yielding a higher total dose within the same time as conventional fractionation,
- Accelerated fractionation involves several radiation treatments per day up to a normal total dose but during a shorter total treatment time,
- Hypofractionation involves higher doses per treatment and fewer treatments.

Treatment methods are still being adapted to better apply these new opportunities, but quality improvements should—even with current knowledge and equipment—be able to improve treatment results. Estimates suggest that a reasonable expectation in Sweden would be to increase 5-year survival for radiotherapy patients by approximately 10% during the next decade. Since slightly more than 30% of all cancer patients in Sweden receive radiotherapy, this would imply that an additional, approximate 3% of all cancer patients could be treated with curative results. An EU report (CEC 1991) estimated that it should be possible to improve curative results by approximately 5%.

New forms of radiotherapy

Neutron therapy is expensive due to the high cost of equipment. The method remains at the experimental stage, without being able to show fully convincing results, although it has been tested on approximately 20 000 patients. Any further research should be conducted at institutions that already have the appropriate equipment. Proton irradiation, in some situations, offers better dose distribution. The Institute of Radiation Sciences in Uppsala has acquired this type of equipment and can be expected to continue such studies, which require a major investment in equipment. The establishment of a collaborative facility for radiotherapy using light-weight ions is being discussed in EU, and detailed plans have been developed with active Swedish participation.

By binding radionuclides to antibodies specific to a particular tumor, an attempt is being made to concentrate radiation on tumor cells. Clinical studies, however, have been unable to reproduce the successful results from animal trials. Boron atoms collect in certain cells, mainly in brain tumors. If tissues containing boron are irradiated by neutrons, strong local ionization can be achieved in the cells. However, this method must still be viewed as an experimental line of research.

Work is being done to individualize radiotherapy through better radiological definition of tumor cells and normal tissue. Several groups are attempting to change the radiosensitivity of both tumor cells and normal tissue by supplying various substances. Results that can be applied in practice have yet to be presented.

Along with changes in fractionation, combining radiotherapy with other treatment methods appears to be the most promising. Although theoretically attractive, the combination of chemotherapy and radiotherapy has not demonstrated the improvements hoped for. The combination of surgery and radiotherapy has, however, proven successful in different situations and for several types of cancer. Continued study is needed to determine when it is

better to give radiotherapy before or after surgery, radiation dosage, etc.

Summary. It is improbable that new types of radiation will be routinely adopted in the foreseeable future. Radiosensitizing substances and the concurrent use of radiotherapy and chemotherapy have yet to meet research expectations. However, radiation combined with surgery and the application of new fractionation patterns have become accepted, valuable strategies that have already been successfully applied and will be developed further.

Advancements in the field of radiotherapy can lead to the application of radiotherapy in new patient groups, for other indications, and with new technology. It is important to assess the introduction of new treatment principles within the framework of controlled clinical trials on sufficiently extensive and representative patient data, using appropriate research methods. To the extent that assessment deals with incremental improvements in existing technologies, the well-designed, randomized study will often provide the most important instrument.

Development of other treatment methods

Surgery is the primary treatment method for most cancers, and also for later removal of tumor residuals or recurring tumors. Palliative surgery that relieves pressure is of major value, where appropriate. Surgery constitutes primary treatment when a solid tumor is detected early enough to be well differentiated. Recent experience has demonstrated the benefits of combining milder interventions with some other type of treatment, usually radiotherapy. Milder techniques are being developed in some areas of tumor surgery, particularly concerning the breast and the head and neck region. In other areas, eg, stomach cancer and rectal cancer, surgery is moving toward more extensive local intervention, eg, greater lymph node evacuation. In liver surgery, for example, the trend is toward smaller and milder interventions for some types of tumors, and toward more extensive resection for others. Recent experiences with laparoscopic surgery and endoscopic interventions have opened new opportunities for cancer surgery. In several areas, eg, esophageal cancer and colon cancer, laparoscopic procedures and conventional surgery are being combined in ways to make surgery easier on the body while achieving comparable surgical results. Endoscopic procedures, with or without laser technology, may be used to a greater extent, mainly in palliative situations. Microsurgery reconstruction methods and neurosurgical interventions aimed at relieving pain will further improve the overall results. Surgery will not, to any great extent, replace established treatment methods. Nor will these treatment methods make surgery less necessary in cancer therapy.

Treatment using *anticancer drugs* has existed since the 1940s, but became widely used during the 1970s and 1980s. Currently, 40 different anticancer drugs are registered in Sweden. Almost without exception, different agents are combined in treatment. Chemotherapy has been successful for certain types of tumors. The general effects on solid tumors have been less beneficial, except for some less common types. Intensive research is under way in the field, eg, to develop predictive tests that indicate the best substance for a particular patient, and to overcome the resistance developed by tumor cells.

Treatment with *hormones* and hormone-like substances has been important for hormone-sensitive tumors, mainly cancers in the breast, prostate, thyroid, and body of the uterus. During the next decade, important advancements are expected to further refine hormonal treatment.

Biological treatment refers to a general concept involving the attempts to treat cancer by engaging the body's own natural systems. Important approaches include strengthening the immune defense, stimulating new blood formation, and anticipated opportunities in genetic therapy. The rapid development of this field is characterized more by the expansion of knowledge than by definitive breakthroughs of major importance for treating cancer patients.

Summary. Treatment for many types of tumors has become more complex, involving a range of strategies. For the foreseeable future, the local forms of treatment, surgery and radiotherapy, will serve as the basis for all curative—and, to a large extent, palliative—cancer treatment. Surgery can be expected to become milder, and radiation therapy will be optimized. More cancers will be diagnosed at early stages, thereby increasing the demand for locally effective methods and for curative treatment.