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Swedish Cancer Society Radiation Therapy Research Investigation

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In an investigation by the Swedish Cancer Society, the present status, critical issues and future aspects and prospects were described by an expert group for each of nine major areas of radiation research. A summary of the investigation is presented in this report. A more extensive summary (in Swedish) can be found at www.Cancerfonden.se. It is concluded that radiation therapy plays an increasingly important role in curative and palliative tumour treatment and presents a considerable challenge to research. Several suggestions are made that could improve the possibilities for high-quality radiation therapy research in Sweden.

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INTRODUCTION

In the past decade we have seen a succession of advances in radiation therapy. New diagnostic techniques are increasing the possibilities of tumour delineation, and the potential for rapid and adequate 3D treatment planning has been refined. With new techniques in external radiation treatment, intensity-modulated radiation beams are able to confine the high therapeutic doses to the target tissues. Taken together, these developments imply increased possibilities for augmenting the effect on the tumour while at the same time reducing the risk of adverse effects in normal tissue.

New research in radiation biology has lead to an increased understanding of the effects of radiation on tumour and normal tissue, e.g. the significance of fractionation. Rapid advances in our knowledge of molecular pathways of cell cycle regulation and growth control, oncogenes, DNA damage surveillance and repair and stress response genes influencing genomic instability indicate the prospects for future combined molecular and radiation therapies. New advances in molecular biology are also augmenting the possibilities of individual radiation sensitivity assessment and early assessment of treatment efficacy. Dose-response relations for multiple low-fraction doses have been quantified in greater detail than before, and further knowledge has been gained concerning receptors and carrier molecules of importance for target seeking.

In 1994 and 1995, a Swedish Cancer Society radiation therapy research investigation group presented a number of proposals, and developments have rapidly continued since then, both in Sweden and abroad. This field needs delimitation and renewed scrutiny, and consequently a new radiation research investigation has been initiated.

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REMIT OF THE INVESTIGATION

The investigation group should draw up a long-term programme to encourage development and the national coordination of research initiatives in the field of radiation therapy.

In particular, the following issues should be discussed:

A. Medical imaging for improved tumour characterization, delineation and treatment verification.
B. Treatment planning, dose distributions, beam shaping and intensity modulation.
C. Radiobiological response to radiation.
D. The use of sensitizing and protective substances in radiation therapy and predictive assays.
E. Therapy with radiopharmaceuticals.
F. Radiation therapy through activation of stable nuclides.
G. The potential of proton and light ion beams in radiotherapy.
H. Interactions between chemotherapy, endocrine therapy and radiation.
I. Research and development of radiation therapy in clinical routines.
J. What is research, development, quality assurance, quality control and clinical routine in radiation therapy?

The group took the remit to infer that for each of the points A–J it was important to compile a strategic (not systematic) overview of the present status to identify the main critical issues and then to discuss them and describe the future potential of the field for both continued research and clinical benefit.

To encourage development in radiation therapy, the group described each subfield separately and in such a way that the text would also be of international interest. This is a summary of the report. The other subfields will be presented in separate articles in this and a forthcoming issue of *Acta Oncologica* (1–9).

SUMMARY OF THE REPORT

Radiation therapy is highly important for both curative and palliative treatment of tumours

Cancer is usually treated with surgery, radiation therapy and drugs. In recent decades we have gained increasing knowledge on the manner in which growth is regulated in normal cells and cancer cells and the genetic changes that cause malignant transformation. In the future this can lead to entirely new and, it is hoped, improved methods of treatment, not least if they are used in combination with present-day methods.

Ten years ago a EU panel of experts (10, 11) estimated that 22% of cancer patients were cured by surgery alone, 12% by radiation therapy alone and 6% by a combination of surgery and radiation. Tumour medication at that time was of relatively limited efficacy (5%). Both the cancer panorama and the treatments have changed since the 1980s, when the last assessment was made, and the proportion of patients cured has risen (12, 13). To some extent the improvement in survival that has occurred in recent decades can be ascribed to improved knowledge concerning various combination treatments, above all knowledge pertaining to surgery and various pharmaceuticals. The relative importance of medical tumour therapy has therefore increased. However, two reports from the Swedish Council of Technology Assessment (SBU)—one on radiation therapy, published in 1996 (14) and the other on cytostatic therapy, published in 2001 (15)—refer to the above-mentioned EU panel and consider its assessment as still valid.

The importance of radiation therapy as a curative treatment has not diminished. A further SBU study of radiation treatment is currently in progress. A group of experts within the European Society for Therapeutic Radiology and Oncology (ESTRO), headed by Dr Walter van den Bogaert, Brussels, has recently estimated that 50% of those who are cured of their tumours receive radiation therapy. About 60% of these receive radiation therapy only, while the remainder are given radiation therapy combined with surgery and/or medical tumour treatment. Between 50 and 60% of cancer patients undergo radiation therapy at some point during the clinical course. Half of all radiation treatments are said to be given for curative purposes. Similar estimates have been made in the USA and Canada (16, 17). Evidence-based estimates have found that about 66% of breast and lung cancer patients develop one or more indications for radiotherapy at some point in the course of the illness (18, 19). The majority of these patients require radiotherapy in their initial treatment. The proportion of patients receiving radiation therapy on one or other occasion appears to be smaller in Sweden (32% in 1992 (14), 43% in 2001 (SBU, unpublished results)) than in the USA and the other European countries, partly because radiation therapy in Sweden is under-utilized as a palliative treatment method (14).

The present investigation group has reviewed current treatment principles for all common forms of tumour and still finds it probable that radiation therapy alone, or in combination with other methods, cures at least 20% of newly diagnosed cancer patients. Given a total 'curability' today of just over 50% (13), this means that radiation therapy is significant for about 40% of the cancer patients who are cured (in the above calculations we have equated cure with 10-year survival). Radiation therapy will likely continue to play a prominent part in curing cancer. The new tumour and molecular biology will lead to improved and more effective treatments, which will probably have a favourable effect mainly on disseminated, usually microscopic disease. It is not likely that new treatment methods within the foreseeable future (20 years) will become so

effective as to be capable of exterminating as many tumour cells as are present in a clinically manifested tumour (10^9–10^{11} cells). Local treatment methods such as radiation therapy and surgery, which are capable of accomplishing this task, will therefore continue to be important.

The value of local treatment methods will increase as systemic treatment of microscopic disease becomes more effective (20, 21). At the same time this calls for further development in both surgical and radiation treatments and for less radical treatment than at present. Some of the development in progress in the field of radiation therapy is aimed at increasing its accuracy and (accordingly) making it gentler on normal tissue. Other developments are aimed at using radiation to cure cancer that has spread throughout the body. Both lines of development, as well as that aimed at making both external and internal radiation therapy more efficacious against the tumour, are assessed in the report. Taken together, these developments indicate that the value of radiation therapy will not only be undiminished but will likely increase, also for reasons of high cost-effectiveness.

Radiation therapy has long been extensively used for alleviating various troublesome tumour symptoms such as pain, bleeding, stenosis and secretion. In the previous SBU radiotherapy report (14) it was pointed out that too little palliative radiation therapy was being given in Sweden in relation to what would be desirable, given the knowledge about the efficacy. As a consequence of those observations, in Sweden and elsewhere radiation therapy departments are now being enlarged at several hospitals in order to make palliative radiation therapy more readily available. In a new survey, carried out in 2001, the number of patients receiving palliative treatment was found to have increased by approximately 40% during the past decade (SBU, unpublished results).

Radiation therapy presents important challenges to research

In the background to this report, the Swedish Cancer Society provides a good description of the challenges which radiation therapy research is now facing. The present group concurs with that description. The explosion of knowledge occurring in several fields, cellular and molecular biology not the least, and the great technical advances that have been made are opening up substantial possibilities for diagnosing and characterizing tumours, improving existing treatments and developing entirely new ones in which the effects of radiation on tumour cells are utilized. Improvements in other tumour treatments, above all medical ones, also imply new challenges, in terms of harnessing the benefits and minimizing the drawbacks of the method concerned. There is a greater likelihood of finding new positive synergies than of finding new drugs eliminating radiation therapy. Increased knowledge of what happens in both tumour cells and normal cells will mean greater possibilities of designing appropriate combination treatments.

The breadth and depth of the challenges to research are reflected in the host of critical issues identified in each section. The issues we have raised do not purport to be an exhaustive description, and it is possible that other issues are or will be of greater relevance than those mentioned.

Developments in medical oncology also hold positive implications for radiation therapy at the same time as medical oncology itself is a major competitor for researchers and research funding. In recent decades we have seen a quantitative explosion of research in medical oncology. Equally important, clinical initiatives have been taken in radiation therapy research, not least regarding improvements to accelerators and treatment planning systems. However, radiation therapy research investments have progressed more slowly. We cannot judge whether it has remained static or actually diminished in absolute terms, nor is this an important question to address. In budgetary terms, its relative extent has definitely diminished, which in itself is a major problem. Regrettably, there are indications that Swedish radiation therapy research has diminished in importance. There are also signs of activity in several fields failing to keep up with current international developments. Sweden has the great challenge of keeping well to the fore in fields where great advances can be expected in terms of knowledge and results. On the other hand, we must not seek to recover lost ground unless the field concerned is judged of intrinsic importance. It is essential that clinically important front-line research in our country will be sufficiently supported for us to keep up with the rapid international developments.

At one time, Swedish research in classical radiobiology was highly esteemed, but has conspicuously lagged behind. New knowledge in cellular and molecular biology has meant entirely new ways of processing radiobiological issues, and accordingly there is reason to strengthen this field again, above all by recruiting skilful researchers and by devoting resources to competent researchers/research groups in the field.

Medical radiation physics research in Sweden has been and remains internationally successful. Care must be taken to ensure that various measures in other fields do not impair the prospects for radiation physics research, given that this field is also vitally important for the devolvement of new methods of diagnosis and therapy.

Clinical radiotherapy research in Sweden has hardly been internationally eminent, apart from one or two isolated tumour diagnoses. This is unfortunately still the case. In the two surveys of radiotherapy practice in Sweden carried out in 1992 and 2001, only 3 and 4%, respectively, of the treatments were given within clinical trials (14) (SBU, unpublished results). The Swedish Cancer Society previously drew attention to the general problems of therapy research, especially radiation therapy studies for exam-

ple, and a number of measures have been proposed and partly implemented (22). Swedish researchers should participate more extensively than hitherto in international joint studies, e.g. those conducted by the European Organization for Research and Treatment of Cancer (EORTC). At the same time, it has to be pointed out that the results of radiation therapy for some tumours are indeed very good, with little room for further improvement. The long-term adverse effects of radiation therapy must be more adequately taken into account than has previously been the case. Better use than hitherto must be made of Sweden's unique opportunities for long-term monitoring of unselected groups of patients.

The development of new pharmaceuticals entails demands for preregistration Good Clinical Practice (GCP) for scientific documentation. The cost of this development is covered entirely by the pharmaceutical industry. No further investments are needed and the pharmaceutical is often introduced very swiftly, even when the clinical effects are limited. Since the development of new radiation therapy techniques has not been subject to any such requirements of official registration, good documentation has not always been available when a new treatment is introduced. The advancement of knowledge concerning the clinical value of a new radiation treatment often demands large investments, which, as a rule, have to be financed by the medical services. These include diagnostic equipment (CT, MR, PET), accelerators for therapy, the development of new software, various calculation and optimization algorithms and a comprehensive accumulation of knowledge by professionals. If the investments have been made, it can readily happen that the treatment is given even without adequate documentation. Unfortunately, this has often been the case, and remains so. As can be seen from the critical issues cited in several of the separate articles in this investigation (1–9), carefully planned studies are often needed in order to prove good clinical effects. There are a host of reasons for adequate studies not being performed, ranging from investigators being convinced, almost 'converted', to financial considerations. For all types of radiation therapy, undertaking conclusive studies is an important challenge, and so too is the procurement of substantial investments to make the patient studies possible.

The development of imaging techniques has been successful, resulting in better possibilities for planning, conducting and evaluating radiation treatments. The development now in progress has the potential for considerable improvement in radiation therapy, but efforts in this field have been limited in Sweden, where the introduction of new techniques in routine care has also moved slowly. There may be various explanations for the small number of research projects to optimize and develop imaging techniques for radiation therapy. In general, this type of research is not glamorous. One important factor may be that diagnostic and therapeutic radiology is organized in different hospital departments with, for the most part, good but still inadequate cooperation. Another factor is the difficult recruitment situation for both specialities, which has left insufficient time for research and development. Furthermore, the imaging equipment in the regular hospital environment is heavily used for routine clinical work. Clinical research involving imaging modalities such as CT, MRI, planar scintigraphy, SPECT and PET is largely hampered by limited availability and high costs. With the medical care of today the possibility of performing validation and optimization of imaging techniques as a clinical routine is limited. Medical imaging is one of the fields the group seeks to single out as being in special need of development.

A difficult recruitment situation

Compared with several other medical specialities, oncology has been relatively successful in recruiting physicians for specialist training, even though there is a shortage of oncologists in Sweden at present. Within oncology, however, radiation therapy has attracted less interest, and there are now far too few oncologists skilled in radiation therapy. The importance of radiation therapy in future cancer treatment has not been underlined, thus causing prospective specialists and researchers to look elsewhere. The greater interest in basic research and clinical research in medical oncology demonstrated by leading oncologists has also played a role. Support for clinical studies and opportunities to participate in international conferences are much more available in medical oncology than in radiotherapy. All these things taken together have resulted in a relative lack of interest in radiation oncology compared with other areas of oncology. This may also have inhibited the recruitment of students training to be medical physicists, radiation oncology nurses and accelerator engineers, with the result that Sweden is now short of these professional categories. The shortage of radiotherapy nurses, for example, is now so serious that several radiation therapy departments are operating below full capacity.

The shortage of clinically active individuals has had an adverse effect on research, development and education, with the result that not only are there quantitative constraints on feasible research and development but also an impending loss of quality. Knowledge and technology have developed rapidly, and unfortunately there are many instances to suggest that Sweden no longer occupies a prominent position on the international scene.

Improvements are needed in the training of oncologists specializing in radiation therapy (radiation oncologists)

In Swedish radiation therapy departments today, far too few oncologists have the necessary knowledge of radiation biology and radiation physics, and their age distribution is

unsatisfactory. As mentioned earlier, there has been insufficient cooperation in diagnostic radiology and other imaging specialities, which implies an inadequate standard of knowledge. The reduction in anatomical studies in the medical studies programme has limited oncologists' knowledge of anatomy in general, and no further training has been organized. Taken together, these factors have resulted in a variable, often low quality of target definition regarding both knowledge of what to include in the target and the ability to identify it in the individual patient. The group has discussed a number of measures that are needed in order to make radiation therapy and radiation therapy research more attractive and to raise the standard of knowledge among radiation oncologists and oncologists generally. Specialist training needs to be reviewed and must allow for subspecialization in radiation therapy. Both nationally and locally, a number of other measures are also needed to enhance the attraction of working with radiation therapy.

Wider competence in radiation therapy university departments

Most universities today have one or more departments/units focusing on radiation therapy, albeit they are differently structured. The group has studied these structures and the existing competence and, regrettably, has found deficiencies in many, if not all, locations. It was found that recruitment may sometimes be inhibited by the very name of the department/unit. It is neither possible nor particularly far-sighted to propose a uniform structure, but on the other hand, every university should review its organization and competence to optimize its structure to present and future challenges. The content of activities needs to be accurately described. If the name of the department/unit counteracts the recruitment of sufficiently competent staff, a change of name may be called for.

The fields of knowledge that are needed are numerous and include, for example, clinical oncology, radiation physics, radiation biology, diagnostic radiology, nuclear medicine, radiation chemistry and molecular biology. The group has found that knowledge of tumour biology and radiobiology is particularly deficient in the university departments. Another weakness concerns the integration of diagnostic information, above all from imaging techniques, with the radiotherapy process. We advise the Swedish Cancer Society to concentrate on three fields in particular, *radiation therapy research*, *molecular radiation oncology* and *tumour imaging*, *with special reference to radiation oncology*. Since the Swedish Cancer Society has already taken several measures to improve the possibilities for therapy research, particularly radiation therapy studies (22), the group does not presently propose further action. The difficult situation for radiation therapy studies must be closely monitored, and if rapid improvements are not seen, more powerful actions taken. Although the situation in radiation therapy is partly specific to Sweden and the other Nordic countries, it is worth being aware that the same problems also exist in other parts of the western world, though a number of prestigious centres are now being developed in Europe and elsewhere.

Wider competence facilitates the transfer of new knowledge and ideas between areas. Radiation oncology departments need to be influenced by molecular biology, pharmacology and physics. This is illustrated in the delayed introduction in Sweden of intensity-modulated radiation therapy (IMRT), considered by many to be one of the greatest advances in radiotherapy.

Special funding problems of radiation therapy research

Radiation therapy research, like any other kind of research, has to be both far-sighted and of high quality in order to qualify for research funding. There are, however, a number of circumstances—none necessarily unique to radiation therapy research—which, taken together, make it difficult to obtain full funding, even for high-quality studies.

In principle, the line of demarcation between research, development, quality assurance and quality control in radiation therapy is no different from that in other fields of research, but the practical consequences of inability to distinguish between the different aspects has created greater difficulties in the funding of radiation therapy research than in many other areas. Quality assurance/quality control (QA/QC) standards must be equally high in all research projects, but in practice they have become higher and, above all, much more expensive in radiation therapy research. Some of the requirements are defined in national and international rules and other agreements. Sometimes costly investments in equipment or extensive developments of methods are stipulated. Major research funding agencies have sometimes withheld research support because of heavy budget items for technical development, improvement in methods, methods validation, QA programme development and quality control. Since the projects relate to research, funding has also been difficult to obtain from county councils.

Translational research—meaning the transfer (translation) of new knowledge in a more basic field to an applied field—has usually come to be regarded as the transfer of basic molecular, cellular and tumour biological knowledge to clinical application. The same difficulties exist in the field of radiation therapy. But the difficulties also include other fundamental discoveries, physical not least, which are just as innovative as discoveries in molecular biology, even if they have not always been perceived in such a light.

In practice, radiation therapy studies are often more difficult to carry out than other therapy studies. Their conduct must of necessity be centralized to the localities where the technique is available. This can hamper patient recruitment. Industrial interest in and support for radia-

tion therapy studies, particularly those not involving any pharmaceuticals, have also been very low. Thus, no radiation therapy study has been able to induce a sufficient number of centres to ensure the completion of patient recruitment inside one or two years. Even though many centres eventually join the study, recruitment generally takes many years. Since the effects which are relevant after radiation therapy, usually long-term tumour control or survival, take much longer to observe than, for example, tumour response, which is of interest for many cytostatic drug studies (23), the time that elapses from the basic discovery and the formulation of the hypothesis to the results becoming available is, more often than not, a great deal longer than in other fields of oncology. Unfortunately, this delay causes the innovation level of the study, both when funding is applied for and when the report is published, to be perceived as reduced. Compared with medical oncology and some other medical fields, radiation therapy studies have greater difficulty in obtaining support from sources other than research agencies.

Even though the principal aim of radiation therapy research is to increase the proportion of patients cured, the aim is also to reduce the long-term adverse effects of a treatment that is sometimes already very good and can hardly be improved upon as regards tumour control. Around 9% of all radiation treatments result in substantial complications (grade III or IV). Studies of complications in radiation therapy differ from those in other treatment alternatives. The study of late complications only becomes relevant after successful treatment. Relevant complications following radiation therapy may be delayed, often for several decades. Corresponding complications following cytostatic treatment, for example, usually appear within 5 or 10 years (24). Thus very long observation times are more of a requirement in radiation therapy studies than in other studies. It is difficult to obtain information about such late-occurring complications, and experience has shown that it is also difficult to obtain funding for these types of studies, which involve long follow-up periods. An important project would be to create a nation-wide register containing this information. There should also be an obligation to report to this register and to analyse the data regularly. It is important that the Swedish Cancer Society initiates and supports such studies.

SUMMARY AND RECOMMENDATIONS TO THE SWEDISH CANCER SOCIETY

– Radiation therapy is playing an increasingly important role in curative and palliative tumour treatment.

Estimates show that radiation therapy in the western world, either alone or as an important part of treatment, helps to cure one cancer patient in five. Radiation therapy can also effectively alleviate many tumour-induced symptoms. The role of radiation therapy as a curative and palliative treatment is likely to increase in the foreseeable future.

– Radiation therapy presents important challenges to research.

Basic developments in radiation physics, biology and technology open up outstanding prospects of refining present-day methods of diagnosis and evolving completely new ones. Many examples of highly interesting developments are presented by the investigation group.

We describe the great challenges, but also the difficulties in radiation therapy research. Radiation therapy is a broad, vigorous field of research with a considerable development potential. In the separate articles of the investigation (1–9) we present a detailed description of the present state of knowledge, identify the main critical issues and offer points of view regarding future development possibilities and their potentialities.

– There has been no order of priority of the different research areas mentioned.

We have adopted a critical stance concerning the various research areas and have endeavoured to identify the most interesting issues and define their potential. Since some of the persons appointed by the Swedish Cancer Society to carry out this investigation are among the leading researchers in radiation therapy in Sweden and, moreover, the persons appointed to serve in the various working groups are active researchers in the various subsectors, there is obviously a risk that the text and, above all, the recommendations may be biased. To reduce this problem, the various summaries of facts presented have been processed by other members of the group, who have rewritten the text and worked out the recommendations on their own. All members were then given the opportunity to correct any factual errors in the text, but not to alter the recommendations. We did not find it reasonable to undertake an internal, intradisciplinary definition of priorities. This will have to be done within the Swedish Cancer Society in the customary manner or following consultation on international expertise. The examples given of exciting fields in which forces can be concentrated, and the proposals made concerning specific measures to be taken, refer to fields where the group does not have a strong active researcher. The fields that we have thus sought to highlight are certainly relevant, but it is possible that an external, independent group might highlight additional fields.

– A difficult recruitment situation prevails where researchers and clinically active personnel are concerned.

- The difficulties involved in recruiting sufficiently numerous and well-qualified radiation oncologists have hampered the recruitment of good researchers in this field.
- Training of radiation oncologists needs improvement in Sweden.
- The competence of university departments engaged in radiation therapy research needs to be broadened.
- The importance of viable radiation therapy research must also be highlighted locally, so that internal priorities in hospital and university departments will favour recruitment.
- There is difficulty in defining the delineation between research, development, quality assurance, and quality control. This difficulty may not be greater in radiation therapy than in other areas, but there are indications that the practical consequences of such difficulty have become larger in radiation oncology.
- The specific problems of radiation therapy research need to be given special consideration in the assessment of applications. Examples include difficulty in obtaining research funding from many agencies, extensive elements of technical and other development, quality assurance (QA) and quality control (QC)—the need for clinical work as well as for clinical studies in radiation therapy, difficulty in rapidly recruiting large numbers of patients for studies, and the long follow-up times required. Thus, clinical studies in radiotherapy should be stimulated and a systematic registration of late treatment complications promoted. This stimulation must relate not only to trials aiming at improving cure rates, but also to palliative radiotherapy trials. If the specific actions taken recently by the Swedish Cancer Society to support the infrastructure promoting clinical trials do not result in clear improvements, further measures must be taken. To improve the standard of radiation therapy, it is also desirable that the Swedish Cancer Society regularly supports nation-wide QA-programmes or regional QA-programmes of general relevance.
- Radiation therapy will be greatly influenced by technical innovations and an increased understanding of the biological principles that govern cell and tissue response to ionizing radiation. If clinicians and scientists involved in radiation therapy and radiation-therapy research are prepared to respond to advances in, e.g., imaging, dosimetry, engineering, computerization and molecular biology, there is likely to be a strong possibility of significant improvements in radiation therapy. Besides the specific problems of radiation therapy research, discussed above, the critical mass of knowledge needs particular reinforcement in the two fields:
  - Molecular radiation oncology
  - Tumour imaging, with special reference to radiation oncology
- Translation of current knowledge into clinical practice is a slow process. This partly reflects shortcomings in the continuing education of established specialists. Practice is influenced mainly by training and not by continuing education or published data. This has been observed in several areas and the Swedish Cancer Society has provided special support for translational research in, e.g., gene therapy. In the same way, it is a matter of urgency that translational research in radiation therapy should be stimulated.

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