RESEARCH INVESTIGATION REPORT

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Research and Development of Radiation Therapy in Clinical Routines

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In an investigation conducted by the Swedish Cancer Society, the present status, critical issues and future aspects and potentials were described by an expert group for each of nine major areas of radiation therapy research. In this report, research and development in radiation therapy clinical routines is described. The terms research, development, quality assurance, quality control and clinical routines in radiation therapy are also defined.

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INTRODUCTION

Radiotherapy is routinely indicated in a number of clinical situations, and there is generally good scientific evidence, or long clinical experience, of the gains that can be achieved. According to a survey performed in 1992, radiotherapy with curative intent in Sweden was basically on a level that was in accordance with the scientific knowledge, whereas palliative radiotherapy was considerably under utilized (1). The Swedish Council of Technology Assessment (SBU) group conducted a new survey in the autumn of 2001. Population statistics showed that in Sweden survival of patients treated mainly with radiotherapy after diagnosis is at a high level internationally (2).

However, although most of the radiotherapy in Sweden is given according to 'good scientific evidence' (1), there is a lack of precise knowledge of the most optimal radiotherapy in many clinical situations. This is due to the impact of recent developments not having been systematically investigated, for example improved imaging, better surgical techniques and better systemic treatments, together with greatly improved possibilities to deliver the prescribed radiotherapy accurately. These improvements influence clinical decision-making regarding, for example, whether radiotherapy should be given or not, in what doses and to which target volumes, and in what sequence in relation to other treatment modalities. Insufficient knowledge frequently prevents informed decisions being made based on recent developments. This knowledge is best attained in clinical, preferably randomized, trials but this is often impossible to achieve within a reasonable time. Radiotherapy trials often take a long time to complete, even for the most common types of cancer, as the relevant endpoints are often not seen until after long follow-up times. Therefore, decisions about the impact of new knowledge on present routines must be based upon extrapolations of other knowledge. Biological models based on the relation between dose-volume information and effect in tumours and normal tissues are used to estimate the impact of new developments (see (3)).

PRESENT STATUS

For the continuing development of radiotherapy in clinical routines, several key areas should be considered:

- The clinical decision process
- Dosimetric precision
- Geometric precision
- Competence

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The *clinical decision process* contains numerous steps where increased knowledge might affect outcome in both tumour control (or symptom control if the aim is palliative) and normal tissue complications (acute and late). Consensus has yet to be reached on a number of issues. For example:

- There is limited consensus on the definition of the tissue volume to be treated (the target) in many situations. The outlining of targets varies from centre to centre, and also within centres. Furthermore, the methodology for adding 'safety margins' around this tissue volume also tends to vary.
- The impact on survival owing to treatment of lymph node regions of clinically unproven involvements is not fully known for most tumour types. The data that to a large extent govern treatment policies today were established at a time when there were no accurate imaging methods. The more recent diagnostic tools, CT, ultrasound, MRI or PET have not yet changed the treatment policies to any major extent. Furthermore, recently gained knowledge from adjuvant chemotherapy trials (4, 5) has not always been incorporated in the decision-making process. More effective adjuvant treatments will normally reduce the requirement for elective irradiation, but the opposite is also possible; if the effects of systemic treatments are improved, the desire to treat larger volumes with radiation around the primary tumour and the most adjacent lymph nodes may increase in order substantially to improve survival (6). Non-small cell lung cancer may be an example of this (7). It is possible that in some patient groups unnecessarily large normal tissue volumes are treated, increasing the morbidity, whereas for other groups the volumes may be too small, thereby leaving regional disease behind.
- How long can a treatment be postponed because of lack of treatment resources without jeopardizing the treatment outcome? Can the loss in tumour control per week be calculated?

The *dosimetric precision* in radiotherapy is a multifaceted problem. The basic requirements such as machine output and radiation quality are probably being met today in all the Swedish radiotherapy departments. Three-dimensional treatment planning and dose calculation is also performed routinely. The amount of data that can be obtained from each patient is continuously increasing. However, this has not been accompanied by increased knowledge of the influence of dose variations in volumes of interest regarding effects on tumour control or normal tissue complications. Even the importance of changes in the prescribed dose and treatment time is not well known. A substantial portion of the existing data that is commonly referred to originates from patient materials collected at a time when the values of dose parameters may have been seriously flawed owing to considerable uncertainties in dose calculation.

Geometric precision is influenced by uncertainties that have several sources. One is the uncertainty in the delineation of tumour tissue by different imaging techniques; another is a relative lack of knowledge, especially on an individual basis, of the movements of the internal organ during radiotherapy. A third problem is the fixation, or identification, of the position of the patient for each fraction of therapy. With recent developments in dose delivery, enabling a sharp dose gradient for complex volumes of irradiation, the understanding of these uncertainties is becoming increasingly critical (see (8)).

Competence: The basic structural requirements for a high-quality radiotherapy department are:

- An environment that contains all the necessary competence and equipment for diagnostic work-up of patients to be treated with radiotherapy. The environment must also allow formation of multidisciplinary teams.
- Modern and well-maintained technical equipment.
- A sufficient number of competent radiation oncologists, medical physicists, engineers and radiographers/therapists.
- Support for adequate long-term clinical follow-up.

In general, Swedish hospitals housing departments of radiotherapy have a good 'diagnostic' environment. However, there are no specifications or regulations on the level of competence or equipment that should be available for diagnostic purposes. Probably all Swedish hospitals have access to CT, MRI, ultrasound, etc., whereas the availability of PET is limited. There are wide variations in policies for using these diagnostic tools between different hospitals. Many radiotherapy departments do not, however, have access to a diagnostic radiologist with a special interest and knowledge in tumour imaging.

PET using ^{18}FDG is considered to be an important method to identify viable tumour tissue and primary tumours, as well as metastases. It has, for example, been claimed that PET improves tumour coverage by identification of lymph node metastases not otherwise detected (9) and leads to a reduction in normal tissue irradiation (10) or avoidance of a redundant locoregional therapy for already generalized disease. Yet, the introduction of this technique has not been widely discussed and it is up to each hospital to decide on whether to invest in new equipment. In the near future such lack of congruence may lead to divergences between different departments with regard to the quality of radiotherapy.

Radiotherapy equipment, including accelerators, treatment-planning systems, simulators, etc., is generally modern and well maintained in Swedish hospitals. A national quality assurance programme is an important part of maintaining the high standard of radiotherapy that is common in this country.

The level of education and general competence of medical physicists, engineers and radiographers/therapists are

of a high standard in an international perspective. The availability of trained staff tends to be variable owing to changes in the employment market.

Palliative radiotherapy plays a crucial role in maintaining the well-being of many patients with advanced cancer. There is less need for technical precision than when long-term tumour control is the aim. Yet this treatment requires a high level of competence with respect to, for example, which patients to treat, the appropriate target volume and fractionation (11, 12).

Radiation oncology is a separate line of specialization in most EU countries and in the USA. In Sweden, the speciality does not exist as a unique entity but as a part of 'general oncology'. This term encompasses what is internationally known as radiation oncology and medical oncology. There is no minimum time for practical experience of radiation oncology stated as a requirement for gaining specialist status in 'general oncology'. The normal case seems to be that oncologists in Sweden have radiotherapy experience ranging from 6 to 12 months, but there are variations in both directions. There are no requirements that the physician responsible for a radiotherapy department should have experience of practising radiation oncology. In smaller clinics, with no close connections to larger departments, this might become a serious problem. In large radiotherapy departments, a few (usually 2–3) persons are occupied mainly with radiation oncology. This means that the total number of radiation oncologists in Sweden is small, which makes the speciality vulnerable and the potential for good research and development fragile.

WHAT ARE RESEARCH, DEVELOPMENT, QUALITY ASSURANCE, QUALITY CONTROL AND CLINICAL ROUTINE IN RADIATION THERAPY?

The regulations of the Swedish Cancer Society state that its task is to support research and development related to diagnosis, treatment and care of patients with cancer. Thus, the regulations state that not only research, but also development, can be funded. On the other hand, the task of the Society is not to provide financial support in sectors where the primary responsibility lies with the county councils.

What is research and what is development?—many and changing definitions

In the Swedish National Encyclopaedia, research is defined as 'a process that through systematic work may create new and increased knowledge'. Webster's Dictionary defines research as 'studious inquiry or examination, especially investigation or experimentation aimed at the discovery and interpretation of facts, or practical applications of such new or revised theories or laws'. These broad definitions are also used by 'Forskning 2000' (13), a governmental review, which also points out the absence of clear borders between different types of research. Accordingly, it considers the commonly used distinction between basic research and applied research as artificial.

In recent years, most people have adopted the definitions of various types of research given by the Organization for Economic Co-operation and Development (OECD) (14). In that report, the following definitions are used: *Basic research*: to systematically and methodologically search for new knowledge and new ideas, without any specific application in sight. Basic research is divided into *pure basic research*, which has no restrictions on the direction of the research, and *directed basic research*, where the aim is to create a base for what is supposed to be an application. *Applied research* is to systematically and methodically search for new knowledge and new ideas with a special application in sight.

The governmental review uses the term 'basic research', which is well known, and for most people is established as meaning an unbiased search for new knowledge. The definition 'research regarding special needs for society' is used for research that is motivated and evaluated with regard to its importance for various, more or less, precise problems in society. There is an important distinction between research managed by scientists and research managed by purchasers, and this should be considered.

In medical research, people often discuss in terms of 'clinical research' in contrast to 'preclinical research'. Preclinical relates to courses the students study before they have reached the clinical disciplines of medicine and surgery. Using this distinction, clinical can be connoted as 'patient-near', as the preclinical fields largely use non-patient-near research methods. In its review of clinical research, the Swedish Medical Research Council (MFR) (15) uses a broader definition of the term—as illness-oriented research, and thus clinical. On the other hand, the methods can be patient-near or not patient-near, which at least partly corresponds to the previous use of the terms 'clinical' and 'preclinical'.

Another important concept is development of which the intention is not to find totally new knowledge but to improve already established methods. Examples are i) implementation of research results into clinical practise, ii) development of methods and products, iii) evaluation of established clinical practice and transfer of knowledge. This type of work should also be supported by the Swedish Cancer Society, following the discussion above.

What is research and what is clinical routine?

The question 'What is research?' was also raised in an editorial in one of the leading international journals on radiation oncology (16). With reference to the principles of the Helsinki Declaration in the early 1960s and the reconfirmation in the Belmont Report of 1979, it was pointed out that many treatments given to patients are yet unproven, but that the results are systematically analysed and re-

ported publicly. This should thus be classified as research, and, as such, would require approval by research ethics committees. This also modifies the information necessary to give to the patients. Thus, there are problems in the precise delineation of what research is and what routine clinical care is. Much of the development discussed below definitely belongs to this 'grey zone'.

What is quality assurance and quality control?

An additional concept is *quality assurance* (QA), often defined as 'the level below development and including measures within the established routines' (17). The European School of Oncology defined quality assurance in medicine as 'the process through which we attempt to monitor the actual quality of care given to an individual patient, to a patient group or to a population (18). The term 'QA' refers to programmes aiming at defining the range of uncertainties of any action, and at detecting prospectively the potential causes of any failure to reach the objectives of that action (19, 20). Whether or not the Swedish Cancer Society should support this type of activity is not clear from its regulations.

QA in radiotherapy explores each step from the production of the radiation to the follow-up of the irradiated patient. *Quality control* (QC) is a 'mechanism', a procedure by which a particular objective of QA can be reached.

Practical implications of the delineation difficulties

In daily life, the definitions mentioned above (with the exception of the border between routine care and research) are of minor importance. Their main influence is in the contact between researchers and granting authorities and between different funding organizations when defining their different responsibilities. The definitions may also influence the priorities made by granting organizations and their individual reviewers.

The main support for medical research—with the exception of certain clinical trials that are initiated, run and funded by drug companies—comes from funding organizations where the influence of society dominates. From time-to-time conflicts arise when defining planned research using the definition described above. This is especially evident in the relation between the county councils, being responsible for healthcare, and the research funding authorities. A research foundation may classify a project as development, QC or a simple follow-up of a clinical material, all of which are assumed to be funded by the county council. The county council, on the other hand, may consider the project as the introduction and development of a new method, which is of major interest also for other hospitals, or even world-wide. Therefore, the project, in their view, should be supported by research funds.

This unclear situation has sometimes resulted in good projects falling between two chairs. For this reason, it would be important for the research community that these concepts are generally defined and properly used by the funding authorities. On the other hand, a clear delineation can never be reached and many projects contain research, development, quality and routine components. Of course, the relative contribution of each of these parts differs between projects. In radiation oncology, the components of development and QA/QC may not be fundamentally larger than in other oncological research areas, but they may appear so since the requirements are high, sometimes due to special regulations, and costs may be high. There is a risk that large granting authorities with well-defined scientific goals are tempted to stay away from research, which they consider as patient-near, with costly aspects of QA/QC, even though these are necessary components of the research project.

Granting authorities do not always realize that there are various types of QA programmes. A QA/QC programme that is connected to a research programme should be included in the project budget and funded with research money, since it is crucial for the value of the research. In addition, development of QA programmes is needed for completely new methods and new equipment introduced for clinical testing. The authorities should be able to finance this with research funding. On the other hand, QA programmes relating to the daily routines at the hospital are the responsibility of the hospital and the county councils. These programmes include, for example, routines for daily checks of instruments, equipment, dealing with patients and the development of regional or national guidelines.

The difficulties in running clinical studies have been widely discussed and are subject to special evaluations (15, 21). The scientific value of such studies has also been questioned, possibly because many clinical studies do not include the latest biological achievements. Clinical studies are often based on knowledge obtained as a result of basic studies carried out several years earlier. Since clinical studies often take a long time to complete and follow-up, the delay from the basic findings to knowledge of their outcome may take many years, or even decades. This necessary delay has to be considered in order properly to evaluate the scientific value of clinical studies. In medicine, there is usually a long interval between an innovation, proven to be an advance, and its acceptance. The time that elapses before it becomes standard practice, recommended in clinical guidelines or textbooks, is often even longer (22). To fully abandon clinical studies to commercial interests would put a stop to important research areas such as studies in radiation therapy and surgery, both of which lack industrial support. Moreover, commercial priorities are not always the same as scientific priorities—a situation that may lead to serious consequences. It is therefore of paramount interest that independent clinical research is performed in Sweden. Clinical trial results may be the ultimate proof of a hypothesis.

The main problem confronting county councils today is the high cost of hospital care and the councils' lack of money. Therefore it cannot reasonably be expected that they should fund research that has no local interest and that does not generate local money in the short-term perspective. There are also difficulties in receiving funding for projects in areas that the hospitals/county councils are likely to consider as basic research. Examples of such projects include dosimetry and development of new measurement techniques.

Concerning funds for research of a more fundamental character, there is another problem: The access to competent researchers varies widely between different county councils. Therefore the distribution of funds from this level is ineffective in a national perspective. Only larger funding authorities, such as the Swedish Cancer Society, possess sufficient knowledge to carry out accurate evaluations.

CRITICAL ISSUES

- Dose-response relationships for normal tissues and tumours utilizing three-dimensional information on tissue structures and absorbed dose distributions.
- Further development of immobilization devices and imaging techniques for correct identification of the position of the target volumes and critical structures during the course of radiotherapy.
- How to incorporate new knowledge from modern imaging techniques for better target definition and for further individualization of radiotherapy techniques.
- Using refined diagnostic techniques, and better clinical information from prospectively collected large patient materials, for optimizing the use of elective radiotherapy.
- Monitoring of treatment response during radiotherapy.
- Scoring of late adverse events, particularly the relevance of intermediate events not requiring the very long follow-up times.

Competence

- A limited number of oncologists dedicated to radiation oncology for maintaining a high level of competence, increasing development of new techniques, and translation of new knowledge into clinical routine. It is important to find ways of improving the status of radiation oncology.
- Establishing minimum requirements for a radiotherapy department in Sweden, with respect to clinical competence, equipment, environment, etc. It should be noted that the minimum requirement established by ESTRO could not be translated into the Swedish situation, since the requirements assume that radiation oncologists are always involved in the process. This is not generally the case in Sweden.
- Lack of continuous education programmes to keep the level of knowledge acceptable

FUTURE ASPECTS AND POTENTIALS

A major problem in modern radiotherapy is that a large proportion of the data on dose-response relationships for tumours and normal tissues was gathered several years ago. Most data were produced before the era of 3-D treatment planning and advanced dose calculation algorithms. The dose is better defined today along with better information on dose-volume relationships. Furthermore, the treatments of today are better monitored using a variety of quality assurance measures, and the immobilization devices have continuously improved. This means that a substantial part of the data on dose response is incomplete and was collected under different therapy situations than those of advanced therapy today.

A number of fairly simple but time-consuming projects could easily be set up to greatly increase knowledge on dose-response relationships. Rigorous registration of dose-volume data for all treated patients is required along with a close follow-up to monitor the outcome with regard not only to the disease but also to side effects, especially those that may only be obvious after 5 to 10 years, or even longer. Such data are most effectively gathered in conjunction with radiotherapy trials, but other possibilities must be sought since only a limited number of patients participate in trials (see also below).

'Geographical' errors leading to insufficient treatment of tumour tissue are likely to result in a poor outcome for the patient. It is also widely accepted that the inclusion of large volumes of normal tissue may lead to unacceptable side effects and/or hamper the possibilities for delivering a radiation dose large enough to eradicate the tumour. Thus, the ability to visualize tumours using different imaging techniques or precisely to locate tissues at risk of containing tumour cells will often determine the outcome of treatment. The integration and evaluation of new imaging techniques in radiotherapy are therefore an important part of future development. In order to utilize imaging techniques effectively, every department should have access to a diagnostic radiologist with a special interest in and knowledge of radiotherapy. Radiation oncologists will probably also need training in diagnostic procedures. The medical physicists of tomorrow, working with radiotherapy, will have to be trained in radiotherapy physics as well as in medical imaging.

There is presently great interest in the value of PET in the therapeutic process. Studies have shown superior results in the precision of staging and diagnostic accuracy using PET. Reimbursed indications for PET in the USA are regularly revised. In Europe, a recent review listed evidence-based criteria for FDG-PET examinations (23). In non-small cell lung cancer (NSCLC), studies have

shown improvement in the accuracy of tumour staging with consequential changes in treatment decisions in 20–40% of patients as a result of both upstaging and downstaging compared with CT-based staging (9, 10, 24, 25) (see Fig. 1). Of major practical importance for treatment decisions is the finding of distant metastases in about 20% of patients with NSCLC planned for curative treatment when utilizing PET (26). This is, for obvious reasons, of great benefit, and should be aimed at once the cost-effectiveness has been adequately assessed (26, 27). In a randomized trial of 188 patients, the addition of FDG-PET to conventional preoperative work-up prevented unnecessary surgery in one out of five patients with suspected NSCLC (28). It is likely that similar gains can be achieved prior to definite radiotherapy, but this remains to be studied. Fused PET/CT information, for target definition in radical radiotherapy of NSCLC, decreased the interobserver variability compared with only using CT information (29). The question of whether the functional information from PET images may result in changes in dose prescription and whether this will improve outcome has not been addressed.

The issue of variations in target delineation between different centres should be addressed specifically since this is a severe symptom of lack of basic knowledge (30). Simple measures including teaching efforts and precisely written clinical guidelines will probably help in increasing the conformity among specialists. The problem, however, lies not only in the dissemination of knowledge, and thus the duty of the hospitals and county councils, but also in a genuine lack of precise knowledge of what volumes should be included in the targets. This is a research issue. What then needs to be studied is, for example, what margins are needed around the visible tumour using various imaging techniques (CT, PET or MRI) in order to include all cancer cells. The margins may differ if other treatments are given in addition to the radiotherapy, particularly if tumour regressions have been seen. Other unresolved issues are how frequently, and to what extent, microscopic tumour cells are seen in a particular lymph-node station, depending upon primary tumour location and tumour characteristics, and in relation to the staging procedures performed. Again, other treatments such as chemotherapy may influence the risks. Because of the possibilities accurately to image also comparatively small tumour deposits, or to predict their existence and the improvements afforded by other treatments, radiotherapy must continuously evolve. This continuous evolution can only be reached in properly designed clinical trials or,

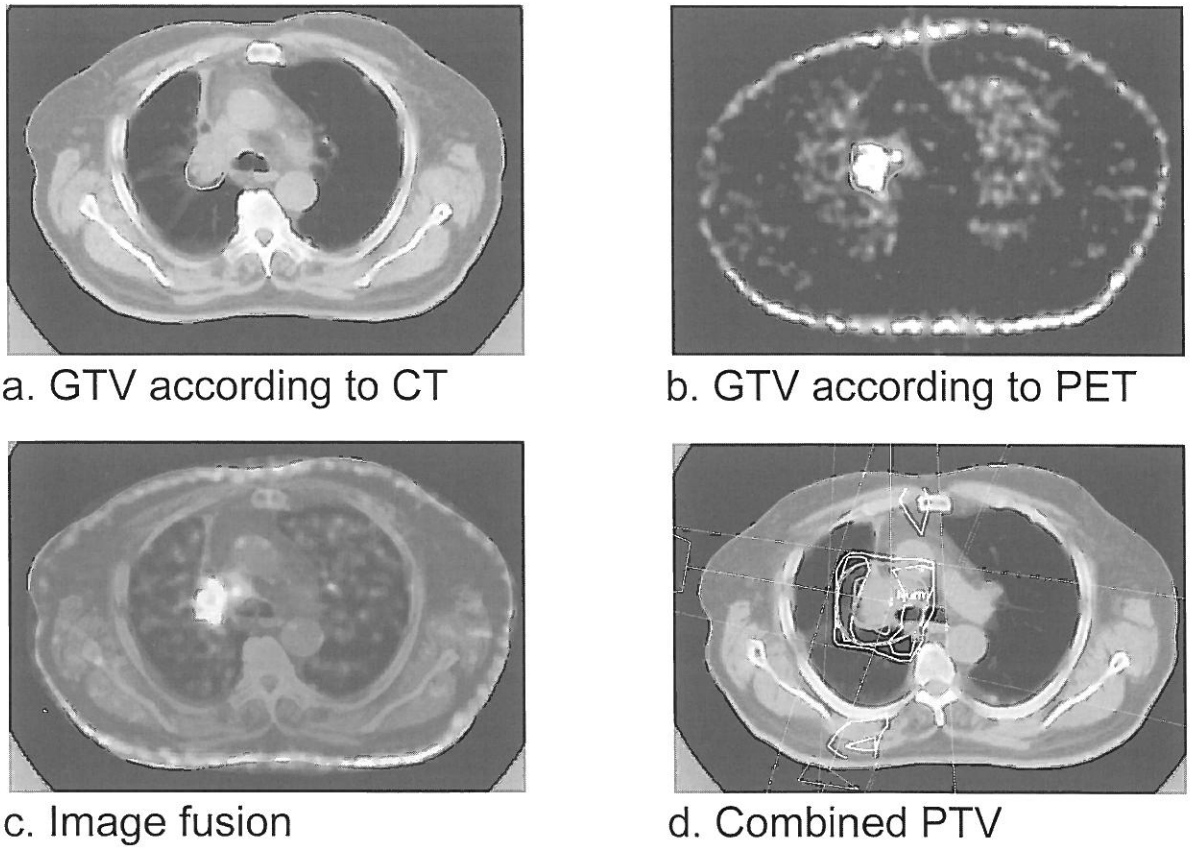

Fig. 1. Differences that can be seen when defining the gross tumour volume (GTV) from a conventional CT study (a) and from an ^{18}FDG-PET investigation (b) of a patient with a non-small cell lung cancer. The fused images are shown in (c) and the final PTV and dose plan in (d).

alternatively, by having a systematic approach to all radiation treatments given with prospective recordings of all relevant information. Clinical and dosimetric information must then be gathered in large databases together with careful recordings of sites of first failure, of whether treatment is unsuccessful and of late effects. These databases must preferably be national (or Nordic, etc.), since many tumour types are uncommon, and serious events are comparatively infrequent. Since the late effects may not appear until after a long follow-up period, better scoring methods of intermediate, albeit non-severe, events of relevance for the late effects must be developed. It must be recognized that long follow-up times are needed, from the closure of a radiotherapy trial to its evaluation, since long-term survival and serious late side effects are the main outcome measures.

Competence

This area is of crucial importance for the future. The success of radiotherapy research will ultimately depend on qualified people with the competence to perform radiotherapy and to apply new knowledge and techniques in clinical routines. Presently, the lack of physicians (radiation oncologists) seems to be the most limiting factor. It is important that the government does not delay in recognizing the need for education in order to ensure that there is a sufficient number of physicians trained in radiation therapy as well as competent medical physicists and nurses to satisfy present and future needs for staffing of radiotherapy departments.

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