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The Potential of Proton and Light Ion Beams in Radiotherapy

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In an investigation 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. The present report deals with the potential of proton and light ion beams in radiotherapy.

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PRESENT STATUS

Major improvements in dose delivery with conventional external photon and electron beams have been seen during the past decade. At present, intensity-modulated radiotherapy (IMRT) using photon and electron beams is being introduced as routine treatment at some radiotherapy departments (1, 2). Sophisticated beam delivery techniques, implementation of computer technology, and dynamic computer-controlled multileaf collimators have to be utilized for this purpose. Alternatively, the use of a combination of external beam radiotherapy and brachytherapy may to a large extent provide a highly conformal dose distribution to the tumour volume.

A further challenge is to improve conformal radiotherapy by using other types of radiation modalities than the conventional photon and electron beams. Heavier particles than electrons and photons, such as protons and other light ions, may have several advantages. The physical characteristics of proton and ion beams are such that less normal tissues will be irradiated. This increases the treatment tolerance of the patient and, in most instances, permits a dose escalation to the tumour and a higher probability of cure may be achieved. Protons as well as other ion beams have a well-defined range in tissues with a pronounced dose maximum in the region where the primary particles stop, the so-called Bragg peak. A conformal tumour dose can be obtained by modulation of the Bragg peak, and there are various techniques that can be used for this purpose. In the majority of situations, improvements in dose distributions compared with photon and electron beams are obtained. In this review, ion beams are divided into three groups according to the atomic number, Z: protons ($Z = 1$), light ions ($Z = 2–6$), and heavier ions ($Z \geq 7$). Examples of light ions of interest for radiotherapy are helium ($Z = 2$), lithium ($Z = 3$), and carbon ions ($Z = 6$). Heavier ions that have been used for radiotherapy are, e.g. neon ions ($Z = 10$).

Proton beam therapy

The possibility to use the Bragg peak of protons for treatment of deeply localized tumours was proposed in 1946. The first patients were treated in the early 1950s in Berkeley, CA, USA. Since then, more than 30 000 patients have been treated with proton beams at some 20 research facilities world-wide. Most of the treatments have been given at physical research facilities. Therefore, the treatments have typically only been possible during a few weeks per year. This time constraint has limited both the number of patients treated and the number of fractions possible to administer. Consequently, mainly phases I and II studies on patients with certain clinical diagnoses have been allocated to proton beam radiotherapy. One hospital-based proton facility (synchrotron) has been running in Loma Linda, CA, USA, since 1990. This centre has treated over 6 000 patients up until the present. Another hospital-based facility has recently been installed in Boston, USA. The first patient was treated in November 2001. At the previous physical

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research facility in Boston (the Harvard Cyclotron Laboratory), almost 9 000 patients have been treated since 1961. A hospital-based proton therapy facility is also presently in operation in Kashiwa, Japan. World-wide, there are several new hospital-based facilities under planning and installation. In Uppsala about 400 patients have been treated with proton beams. Seventy-three patients were treated at the The Svedberg Laboratory (formerly the Gustaf Werner Institute) between 1957 and 1976. Since the re-opening of the facility after reconstruction in 1989, more than 350 patients have been treated up until June 2002.

The majority of treatments with proton beams (as well as other ion beams) world-wide have been concentrated to small, demarcated sites in the skull and head-and-neck region. A considerable number of patients have had treatment also at other sites (3). Arteriovenous malformations (AVMs) have frequently been treated (4). Examples of tumours commonly treated are ocular melanomas (5), skull-base tumours such as chordomas, chondrosarcomas and meningeomas (6, 7). In these tumours, the physical dose distributions have resulted in favourable tumour control probabilities with few adverse effects. However, these results are only based on phase II studies. Randomized trials comparing different dose levels are ongoing, but investigations comparing proton beams with photon beams are limited.

Prostate cancer has been in focus for dose escalation studies, using either proton beams or conformal radiotherapy with photon beams. In a randomized trial in prostate cancer (T3-4, NX, NO-2 MO) photon beams of conventional dose were compared with mixed photon and proton beams of escalated dose. A significantly improved local control was seen in the subgroup of poorly differentiated tumours when a proton boost was applied. No difference in disease-free and overall survival was seen (8).

Potential advantages in terms of better dose distributions in model studies have been shown in a number of therapeutic situations for proton beams compared with photon and electron beams (9–24). Comparative dose-planning studies have been performed at a great number of tumour sites, revealing an advantage of using proton beams relative to classically delivered photon and electron beams. The dose distribution with proton therapy is also generally superior to the most advanced dose delivery of photons using IMRT. In the near future, intensity modulated proton therapy (IMPT) will be implemented. IMPT has been assessed in comparative dose-planning studies, and has shown to further improve dose conformality. Reductions in the treatment volume for IMPT in relation to IMRT have been demonstrated for many anatomic sites.

Concerning the relative biological effectiveness (RBE) for clinical proton therapy with the use of a spread-out Bragg peak (SOBP), experimental in vivo data have resulted in a value close to 1.1. Significant variability according to tissue type, dose per fraction or proton energy has not been revealed. However, there is a local hot region over the terminal few millimetres of the SOBP. This needs to be considered in treatment planning concerning the risk of increased damage to critical structures, and whether it might be beneficial for tumour curability (25, 26).

Light ion beam therapy

A possible potential in the development of radiation therapy is to use light ion beams. Light ion beam therapy may allow a somewhat better geometrical precision in dose delivery to the tumour compared with proton beams. The reason is that the penumbra and the width of the Bragg peak of an ion beam decrease with increasing atomic number of the ions. The linear energy transfer (LET) is determined by the atomic number and energy of the particles. Therefore, at the high-dose peak, ion beams have higher LET than the more sparsely ionizing electron, photon and proton beams. Therapy with light ion beams with atomic numbers in the range $Z = 2-6$ might be more advantageous than ion beams with $Z \geq 7$ (27, 28), particularly for the treatment of gross tumours. There are three major reasons for suggesting the use of light ion beams in radiotherapy instead of heavy ions.

First, for heavier ion beams such as neon ($Z = 10$), the LET value is fairly high (more than 20 eV/nm) also in the path through normal tissues including the first layers of tissue in front of the tumour volume. This LET is comparable with that obtained at therapy with fast neutron beams and may cause undesirable normal tissue toxicity.

Secondly, when traversing matter, heavy ions fragment into lighter ions that have ranges beyond the Bragg peak of the parent ions and produce a 'tail' in the depth-dose distribution. In this respect, heavy ions in particular, but also light ions, are less advantageous than protons, by deteriorating the longitudinal conformal properties of the dose distribution.

Thirdly, it became clear in the early 1990s (29), that there is an increasing risk that high-LET radiation could result in microscopic 'cold spots' in the dose distribution. This phenomenon can be relevant for the risk of tumour recurrence. It can be shown that, for low-LET radiation, the microdosimetric standard deviation of the dose to the cell nucleus (≈ 8 μm in diameter) is about 0.7% at the therapeutic dose level in classical electron and photon beams. However, with ions where $Z > 10$, this value could be as high as 10–15%. Accordingly, in a tumour consisting of 10^8–10^9 clonogenic tumour cells, many cells may be as much off in dose as 5 to 6 standard deviations, which correspond to 50–90% in a prescribed dose. Thus, even if a curative dose is expected, there may be many clonogenic tumour cells left causing the tumour to recur after the treatment. This will make the dose-response relationship at

therapeutic doses shallower for heavier ion beams ($Z > 10$) than for low-LET electron, photon or proton beams.

The RBE is dependent on LET. Both the energy of the ion beams and the atomic number have a considerable impact on the LET. The most important issues in the implementation of ion beam therapy are to take into account the steeper penumbra and the increased biological effectiveness in an appropriate way in the treatment planning process. Both the variable RBE through the beam path and the distal fragmentation tail have to be taken into account. To obtain homogeneous tumour sterilization, the energy and fluence of the particles have to be modulated to match the variable RBE in the Bragg peak volume.

RBE also varies with cell type, cell cycle phase and cellular oxygenation (30). The clinical complexity is further increased by the fact that RBE varies with the dose per fraction, because of the difference in the shape of the dose-cell survival curves for photon and ion beams. Therefore the final RBE has to be determined by calculations. For the clinical use of ^{12}C ions, the RBE is calculated from in vitro-determined parameters. This means that the RBE values applied today are subject to uncertainties and insufficient in vivo validation.

All these RBE-related issues make it uncertain to establish the biological equivalent doses for various tissues in the treatment volume. In particular, it is to be expected that various late-responding cell types such as endothelial cells, smaller muscle cells and fibroblasts will have RBE similar to that of radioresistant tumour cells. These cell types are responsible for the preservation of the tissue integrity of the tumour bed, including specific structures such as larger blood vessels, nerves, etc., and will determine the maximum dose level that can be delivered. Therefore, it is questionable whether the higher RBE of high-LET radiation will increase the therapeutic ratio significantly in situations where the tumour bed and normal tissue structures therein have to be conserved. This is a critical question for future research.

Hypoxic cells are less radioresistant to high-LET radiation than to low-LET radiation. Poorly oxygenated tumour cells are present in many tumours. There is strong evidence that hypoxic cells may reduce the probability of local tumour eradication by conventional radiation therapy (31, 32). In order to cure hypoxic as well as relatively radiation-resistant tumours (chordomas and chondrosarcomas of the skull base, prostate, non-small cell lung cancer (NSCLC)) and very resistant tumours such as glioblastomas, the idea is to utilize the high LET and the high RBE of the Bragg peak of the ion beam for conformal dose delivery to the tumour tissue. This is possible with the light ion beams of helium, lithium, beryllium and boron, and even with carbon ions, where the entrance part of the depth dose distribution is still of a relatively low LET. If the Bragg peak from such beams can be placed solely in the target volume, a high therapeutic effect on the tumour might be achieved, without serious impact on normal tissues. To that end high-LET neutrons have been tried in order to improve the curability of hypoxic tumours, but without clear success. The main reason why neutron radiotherapy was discontinued was the low tolerance of late-responding tissues (33). The same problem is assumed to appear also with high-LET ion beams concerning the integrity of the normal tissue structures within the tumour bed and its neighbourhood, as explained above. Therefore, the higher RBE might be of limited usefulness in a number of clinical situations.

The expectations from light ion beams are based on radiobiological studies in vitro, and to some extent on clinical information gathered with carbon ion beams and high-LET beams of neutrons. Theoretical model studies of clinical light ion beams regarding optimization of beam qualities and physical and biological dose distributions have been performed by the Darmstadt/Heidelberg (34) and the Karolinska research groups (35), respectively. Other research groups have performed in vitro RBE studies with carbon ion beams (36). However, there is a lack of RBE investigations for other types of light ion beams. Further studies are necessary to determine to what extent light ions are more efficient in eradicating hypoxic tumour cells than photons. A substantial body of in vitro and in vivo studies have to be performed before light ion beams can be translated into patient treatments. So far, only clinical feasibility studies have been performed for carbon ion beams.

The first clinical use of light ion (helium) beams was undertaken as early as in 1957 by the San Francisco Medical Center at the Lawrence Berkeley Laboratory in California, USA. In 1977, radiotherapy with heavier ion beams (neon) was also introduced at Berkeley. Carbon, silicon and argon ion beams were also used. These efforts were seminal, but were done with suboptimal ion beam delivery techniques. Modern 3D pencil beam scanning was developed, but too late to come into clinical use before the closedown of the accelerator in 1992. Since 1957, more than 3 500 patients have been treated world-wide. There are presently two ion facilities in operation: one in Japan and one in Germany. Recent clinical results are mainly obtained from the work done since 1994 at HIMAC (Heavy Ion Medical Accelerator Centre, Chiba, Japan), where about 1 400 patients have been treated with beams of carbon ions (37). The official reports available from this centre are, however, very limited and are mainly reported as abstracts. The interpretation is not clear-cut, owing to the lack of prospective phase II or III studies.

The review group of this chapter has had the possibility to interview Professor Seymour Levitt, who recently (March 2002) visited HIMAC. We have also seen the written report from this visit (Levitt & Sirzén 2002) and interviewed

Professors Hans Svensson and Bengt Lind, who also took part in the visit. About 1 400 sporadic patients have been treated with a fixed ^{12}C beam. Compared with conventional therapy, their results indicate better results using carbon ions than photon/electron beams for stage I NSCLC. Trends towards improvements were also seen for hepatocellular carcinoma, adenocarcinoma of the head and neck, melanoma of the head and neck and bone and soft tissue tumours, including skull base tumours. On the other hand, no benefit was seen for squamous cell carcinoma in the head and neck region, oesophagus carcinoma, glioblastoma multiformae or pancreatic cancer.

The second ion facility, available at the GSI laboratory in Darmstadt, Germany (34) has so far treated about 150 patients. Mainly tumours of the skull base and the head and neck region have been referred to treatment with a carbon ion beam (38). Some patients have been treated with ion beams only and others with mixed photon/ion beams. The first clinical results for chordoma and chondrosarcoma are promising. No acute toxicity of more than grade 2 has been observed. However, an observandum is that severe late complications have been seen in a few patients, as recently reported (ESTRO 2002).

In Japan, another facility for both proton and carbon ion beams is under commissioning. There are proposals and planning for new light ion beam facilities in Europe (including Sweden).

The various types of treatment beams are ranked with respect to some parameters of importance for radiotherapy in the Table 1.

Other high-LET beam therapy

Fast neutron beams have a dose distribution similar to that of photon beams, although the dose to adipose tissues is significantly higher and to bony structures significantly lower. The LET and RBE are much higher for neutron beams than for photon/electron beams. Pions, which are unstable particles, have also been used for radiotherapy. Beams of negative pions have physical advantages over neutron beams, but a lower LET. Randomized trials in prostate cancer using neutrons or pions have been performed (39–41). Improved tumour control rates and survival, but more normal tissue toxicity, were seen in one neutron trial (39). Mixed beam neutron and photon therapy has been advantageous, showing improved cure and/or reduced toxicity, indicating the potential of intermediate LET with a more conformal dose delivery (42). About 1 100 patients have been treated with pion beams and about 10 000 patients with fast neutron beams.

CRITICAL ISSUES

Protons

- We need to establish whether the dose-distribution advantages seen in a number of comparative dose-planning studies will translate as a substantial clinical gain in increased tumour cure or reduced normal tissue toxicity when investigated in controlled clinical studies. To reveal a benefit in tumour cure, a 5- to 10-year of follow-up is needed. To establish any reduction in normal tissue effects and a lower risk of induced malignancies, a follow-up of more than 10 to 15 years is necessary.
- We need fully to exploit the potential of protons, the technical development required for implementation of IMPT is necessary.

Table 1

Ranking of photon, proton, light and heavy ion beam therapy with regard to some parameters of importance for radiotherapy

Parameter	Photons, IMRT	Scanning beams		
		Protons	Light ions	Heavy ions
Absorbed dose distribution	1	1+	1++	1+
Microscopic dose distribution	1	1	1	1−−
Low dose hypersensitivity	1	1+	1+	1+
RBE—tumour	1	1(+)	1+(+)[1]	1++
RBE—normal tissue	1	1(−)	1−(−)[2]	1−−
OER—tumour	1	1	1+(+)	1++
Technical complexity	1	1−	1−	1−−
Clinical complexity	1	1+	1+	1+
Treatment planning	1	1	1−	1−−
Biological precision	1	1	1−	1−−

[1] ++ For resting tumour cells; +for proliferating tumour cells.
[2] − For resting normal cells (e.g. various cell types in vessels); − for proliferating normal cells.
Abbreviations: IMRT = Intensity modulated radiotherapy; RBE = relative biological effectiveness; OER = oxygen enhancement ratio.

Ion beams

- To increase our knowledge of the RBE for different cells and tissues and at various depths of high-LET ion beams, and for different types of light ions.
- Whether the potential advantages for the treatment of radioresistant and hypoxic tumours with high-LET ions will be achieved depends on the differential response of normal tissue structures in the tumour bed. A follow-up of 5 to 10 years is required to experience late complications.
- Evaluation of the impact of cold spots of ion beams for the tumour cure probability.
- Deterioration of beam precision in inhomogeneous tissues due to uncertainties in the lateral position of the beam; for example tumours in the lung, and tumours close to air cavities and bone. This may introduce larger deviations from the planned dose distribution for ion beams than for protons.
- The results of carbon ion therapy experienced at Chiba and Darmstadt for specific patient groups are promising. However, it is important to establish to what extent this is due to a better dose distribution or to the higher RBE.

General comments

The requirement in radiotherapy is that the biologic equivalent dose should be at least within $\pm 10\%$ of that prescribed. The figure seems to be high, but includes the effects of varying fractionation, RBE, etc. The physically absorbed dose should lie within $\pm 5\%$, or better. Today it is possible to fulfil these requirements with proton beams, but not with light ion beams. This is one of the reasons that light ion therapy still has to be considered as an experimental treatment. Moreover, we do not have enough knowledge of what is the best fractionation scheme. What is optimal depends on the RBE and its variation by a number of parameters.

To make all the necessary implementations, and to perform the necessary research and development, we need a large body of competence in radiation oncology, medical physics, technology, general oncology and nursing in order to use the advantages of this complicated beam. There is also a need for years of feasibility studies for a proper evaluation of the dose-limiting side effects in the use of light ions.

FUTURE ASPECTS AND CLINICAL POTENTIALS

Photon beam IMRT creates conformal dose distributions to the target volumes but at the cost of contributing to a low absorbed dose to large volumes of surrounding normal tissues (1, 2). The existence of the so-called low-dose hypersensitivity for some cell types may lead to more damage than generally considered when the conformal target dose is delivered by a large number of beam portals (43–46).

Proton and light ion beams can generate more favourable dose distributions with fewer beams compared with photon beams and without the large spread of low doses to large volumes of normal tissue. A significant long-term advantage for proton and ion beams is that the integral dose is approximately one-half that of photon beam therapy. It is well known from long-term follow-ups (i.e. > 10 years) that the risk of serious late effects at anatomic sites not only near to but also distant from the primary target increases with dose to the site (47). The effects would include atrophic or degenerative changes, as well as radiation-induced neoplasms. Therefore, it is important to avoid large volumes with low dose to normal tissues, particularly in children and young adults. Another relevant aspect is that keeping the volume of normal tissue as small as possible will provide a greater tolerance to chemotherapy. For example, this is important for large cohorts of patients with breast cancer.

A problem with high-LET ion beam therapy may be the phenomenon of microscopic cold spots. To circumvent this problem, one way is to include a significant low-LET dose component to compensate for the microscopic dose heterogeneity between the cold- and hot spots. This can be achieved by using mixed-beam therapy such as photon beams and neutron beams, electron and ion beams, as well as proton and ion beams. Light ion beams, however, already have a potentially useful combination of low- and high-LET dose components. This is one important reason that light ion beams in the range from helium to carbon are of greater potential interest to radiation therapy than heavier ions. There is still no experience at all with such mixtures of various low- and high-LET radiation modalities, with the exception of combinations of photons and neutrons.

For the clinical use of ^{12}C ions the RBE is today calculated from in vitro-determined parameters. This means that the RBE values applied are subject to large uncertainties and lack of in vivo validation. This makes it difficult reliably to establish the biological equivalent doses for various tissues in the treatment volume. In particular, it is to be expected that various late-responding cell types such as endothelial cells, smaller muscle cells and fibroblasts will have an RBE similar to that of radioresistant tumour cells, which might be an obstacle for achieving a therapeutic gain. Therefore, further in vivo and in vitro studies have to be performed before light ion beams can be translated into more widespread patient treatments.

With respect to fast neutron therapy, a previous committee of the Swedish Cancer Society did not recommend development of a therapeutic facility for neutron beams (48). These beams have the advantage of a high LET in the tumour, but limited geometric selectivity of the dose. The committee considered high-LET radiation as interesting,

and in urgent need of more basic research. These statements are still relevant.

Proton beams for radiation therapy have been implemented at many sites world-wide. There are many examples of improved dose distributions relative to what the most recent developments in photon/electron beam radiation therapy can achieve (47). In order fully to utilize the advantages of proton beams, a beam scanning system is needed. Such systems are not yet in widespread clinical use. Two scanning systems, although still very large, are in use today, one at PSI, Switzerland, using proton beams and one at GSI, Darmstadt, Germany, using carbon ion beams.

The previous committee stated that the development of proton therapy in Sweden should be supported (48). Specifically, the committee recommended further studies concerning:

- Evaluation of expected advantages using proton beams relative to other optimal radiation therapy in comparative dose-planning studies. Radiobiological models should be included in the comparisons. Models that simulate the effects of high LET should also be included.
- Optimal gantry construction with respect to safety, dose distributions, size and costs.
- Continuation of studies of high-energy proton beams to optimize dose–volume distributions in different tumours with RBE estimations in different tissues.
- Consideration of practical, humanitarian, socioeconomic and technical aspects prior to selection and centralization of certain patient categories to one or several units for proton beam therapy.

Light ion beams may allow a more conformal lateral energy deposition than proton beams because their multiple scattering is lower. The penumbra for proton beams at greater depths in the body is significantly wider than that for light ion beams. Moreover, the Z-value can be chosen in such a way that a uniform and sufficiently high LET is obtained in the tumour. Light ion beams might have the advantage of geometric dose delivery and biological effect compared with photon, electron and also proton beams. Light ion beams have the potential to deliver a defined tumour dose with fewer side effects than electrons and photons and in some situations more so than protons.

When bombarding organic targets with ^{12}C, β^+-emitting target fragments and projectile fragments are obtained. These positron emitters can be imaged with a positron camera. Since the distributions of the positron emitters and the absorbed dose do not match directly, the application of the PET technique to control the precision of the light ion therapy requires the prediction of the positron emitter distribution from the treatment plan. To do this, Monte Carlo codes have been developed for making a careful modelling of the production of the positron emitters and the detection of the annihilation γ-rays. PET seems to have a considerable potential for quality assurance (QA) of ion therapy (34), but the practicality of the technique has to be studied.

An interesting approach is the proposal to use ion beams (up to about neon) for a high accuracy boost in combination with standard low-LET electron and photon beams. This might give improved effects on a hypoxic or otherwise resistant tumour and remove the high-LET heterogeneity problem by delivering the major dose to the patient using standard or intensity-modulated techniques. However, the relative improvement in treatment outcome, compared with proton beam therapy, has not yet been established either on a theoretical basis or in experimental animal studies.

The role of ion therapy has still to be determined. There are limited short-term data, and almost no long-term follow-up data at all. The experiences from the operating facilities will be essential to identify the treatment sites that will benefit from ion radiation therapy, provided that the outcome is based upon rigorously designed clinical studies.

The investments for buildings, accelerators and treatment room facilities for both proton and ion beam therapy projects are high. However, the lifetime of these accelerators is expected to be long, up to 30 years at least. For IMRT therapy with electron and photon beams, the investment is lower, but the lifetime is shorter, and is assumed to be less than 15 years. Electron accelerators therefore have to be replaced frequently. The costs for maintenance, upgrading of equipment and QA for a daily, safe, high-quality function with high up-time performance are related to the investment in the equipment. For a proton therapy facility with five gantries, the cost per fraction is estimated to be about 2 to 3 times higher for proton beam therapy compared with electron/photon beam therapy with IMRT. For light ion beam therapy, the cost per fraction is estimated to be 3 times higher than that for protons and approximately 8 times higher than the cost of conformal electron/photon beam therapy.

Recent initiatives concerning highly specialized cancer treatment with protons/light ions

A national group of oncologists and medical physicists has forwarded the idea to investigate the possibilities for a national centre for advanced radiotherapy. The idea is that the university and regional hospitals could have access to time for their patients at a national centre. As a first step, it is important to develop this concept further in terms of organization and economy in order to be able to have some understanding of the realism of the project. This might be done within the ongoing national planning of the highly specialized medical care in Sweden. Uppsala University and Uppsala University Hospital have long experience of proton therapy and ongoing development for recruitment of new patient categories. This centre is evaluating the possibility of establishing a clinically dedicated proton

facility in Uppsala. The Karolinska Institute and Hospital has an advanced project in planning for a light ion therapy centre in Stockholm (35). The Karolinska Institute participates within an EU network operating for the establishment of other similar centres in Europe.

RECOMMENDATIONS TO THE SWEDISH CANCER SOCIETY

Photon and electron beams are under intensive development and can be foreseen to be the main sources for external radiation therapy for decades to come. This is valid for all types of tumour. New techniques that will improve the dose distribution, such as IMRT, are under implementation and clinical evaluation. Increased support and stimulation to research and development regarding new technology and evaluation of treatment results in the field of photon and electron beam therapy are highly warranted (49).

In the vast majority of cases, proton beams result in improved dose distributions relative to what can be obtained using the most recent developments in photon and electron beam radiation therapy. In order fully to exploit the potential clinical advantages of proton beams, a beam scanning system has to be utilized, as well as intensity-modulated proton beams. No doubt, proton therapy will become generally available for curative treatments within two decades (47).

Light ion beam therapy results in dose distributions similar to those found in proton therapy. The rationale for the clinical interest in light ion beams is based on their higher RBE per unit dose. The high RBE of ion beams is assumed to be beneficial with regard to eradication of both hypoxic tumours and common radioresistant tumours. The committee suggests substantial support for basic research in this area. In particular, basic studies in radiation physics and radiobiology should be stimulated to underpin various national and international initiatives. It is crucial that careful RBE estimations for the various ion beams are established for different tissues and organs. Furthermore, clinical implementation of light ion beams has to be preceded by animal experimental studies. In the case of convincing outcomes of the basic and experimental research on ion beam therapy, clinical introduction should be supported promptly. Meanwhile, the committee considers it important to conduct comparative dose-planning studies of ion beams, combinations of ion beam therapy and photon/electron radiotherapy, versus IMRT using photons and IMPT.

Clinical results obtained with ion beams in Japan and Germany should be reconsidered carefully. In particular, it is necessary to focus upon the occurrence of late normal tissue effects after high-LET treatments. The Swedish Cancer Society should actively support various types of cooperation between Swedish scientists and the few groups that use high-LET beams for radiotherapy at the moment. The most advanced technology and clinical applications of ion beam therapy have been developed in Darmstadt/Heidelberg. A clinical-dedicated facility is under construction in Heidelberg. The Swedish Cancer Society should also give active support to further investigations of possible organizations and the necessary economy for a national centre for advanced radiation therapy in Sweden.

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