Proton radiotherapy

Horizon scanning report
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Dear Minister,

I hereby have the pleasure to present to you the horizon scanning report on Proton Radiotherapy, which has been drawn up under the responsibility of the Committee on Radiotherapy of the Dutch Health Council. Drafting this report has been the work of a group of experts, bringing together expertise in the fields of radiotherapy, clinical oncology, physics, epidemiology and health technology assessment. At the request of the Committee, the Dutch Cochrane Centre has assisted in tackling the question what scientific evidence is available to assess whether proton radiotherapy could offer a benefit, and if so, for which patients with cancer. This issue carries particular importance since, in the case of proton radiotherapy, there have been several decades of experience with the clinical treatment of patients, but for different reasons there has been no systematic data collection and evaluation of treatment outcomes, where proton radiotherapy has been compared with currently available radiotherapeutic modalities. What has become clear so far on the basis of research, is that the extraordinary physical properties of proton beams allow a very efficient and accurate radiation of the tumour, resulting in only a very low radiation dose to the surrounding normal tissues and critical organs, compared to currently available radiotherapy techniques. This may hold out the prospect that proton radiotherapy could lead to the reduction or even prevention of acute and late side effects of radiation, including the occurrence of secondary tumours later in life. Children and adolescents in particular may profit from this.

As has been mentioned already, there is insufficient scientific evidence available today to make a fair assessment of the potential and consequences for future policy decisions of introducing proton radiotherapy for the treatment of Dutch cancer patients. This is precisely why the Committee on Radiotherapy recommends, on the basis of the horizon scanning report at hand, that – when the decision is taken to establish one or more proton therapy
facilities in this country –from the very start there should be emphasis on a combination of patient care and clinical research. I share this opinion and support the recommendations. In similar cases before the Health Council has made a plea to foster concentration of costly infrastructure and facilities, by applying the Specific Medical Procedures Act. A viewpoint that you clearly subscribe to, judging by your recently published Planning Document on Radiotherapy.

Finally, I would like to mention that this horizon scanning report has been reviewed by the Standing Committee on Medicine and by the Committee on Health Technology Assessment of the Health Council.

Yours sincerely,

(signed)

Professor J.A. Knottnerus
Proton radiotherapy

Horizon scanning report

to:

the Minister of Health, Welfare and Sport

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, Agriculture, Nature & Food Quality, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This horizon scanning report can be downloaded from www.healthcouncil.nl.

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Proton radiotherapy
Executive summary

What is proton radiotherapy?

Treatment with protons (a type of subatomic charged particle) is a promising development in the field of modern radiation oncology. The physical properties of protons allow a better dose distribution when compared to current photon (X-ray) radiotherapy. This has the potential to minimize the dose to normal tissues and significantly reduce acute and late side effects. The result may be a more accurate, more effective and less toxic radiation technique.

Why a horizon scanning report on protons?

In 2008 the Health Council of the Netherlands published an advisory report on the future need and planning of radiotherapy at the request of the Minister of Health, Welfare and Sports (WVS).* The Advisory Committee that prepared the report concluded, among others, that the clinical introduction of proton radiotherapy, an emerging radiation delivery technique using heavy charged particles, will require special attention in the near future. This was underlined by the fact that, in comparison to the currently used photon radiation, the clinical introduction of proton radiotherapy calls for complex infrastructural requirements with,

in addition, special expertise and far greater financial investments resulting in higher costs per treatment. Apart from the financial aspects, there is also discussion concerning the scientific validation of new radiation delivery technology in general and proton radiotherapy in particular. This debate focuses primarily on the role and feasibility of randomised controlled trials (RCT’s) to demonstrate the clinical value of proton radiotherapy. Because of this, it was felt that a separate and more comprehensive advisory report on proton radiotherapy was called for.

Potential benefits of proton radiotherapy

The use of proton radiation may result in significant benefits over current radiation techniques. First, radiotherapy with protons is associated with a substantial reduction of the integral dose deposited in tissues and organs both in the vicinity and at a distance of the primary target volume, as compared to photon radiotherapy. This benefit, based on the physical properties of proton beams, may clinically translate into a significant reduction of serious and frequently irreversible late side effects, and of the long-term risk of inducing (secondary) cancer. The lower radiation exposure to normal tissues with protons complies with the fundamental basis of safe radiation delivery, known as the ‘ALARA’-principle (‘as low as reasonably achievable’). Randomized controlled trials however may not be the most suitable approach to demonstrate this clinical advantage. Instead, clinically validated Normal Tissue Complication Probability (NTCP) models and dose planning comparative studies offer a more appropriate methodology in this case.

Secondly, in those cases where current radiation techniques do not achieve the delivery of higher doses due to unacceptable toxicity, proton radiotherapy, by virtue of its superior dose distribution, does permit dose escalation aiming to increase local tumour control rates and improve survival without enhancing side effects. Assessment of this type of clinical advantage requires robust comparative studies, preferably RCT’s.

Scientific validation of proton beam therapy

Evidence-based medicine has become the cornerstone of the clinical introduction of new treatment strategies. In this context, RCT’s are generally considered the gold standard for assessing differential benefits in clinical outcome between competing therapies. Thus an RCT approach is undoubtedly needed to demonstrate the potential and efficacy of a novel radiation technique, such as proton therapy, to improve local tumour control and patient survival. However, when
translating these requirements to the validation of new radiation technologies that primarily aim to reduce side effects and secondary tumours, one is confronted with certain methodological, practical and ethical problems. This is particularly the case for proton radiotherapy. Therefore, the critical assessment of the clinical benefits of proton radiotherapy requires an alternative methodological approach in addition to RCT’s. For the purpose of the current report, the committee decided to use the same approach and criteria as proposed in a (recently published) advisory report by the Dutch Health Care Insurance Board (College voor Zorgverzekeringen - CVZ), for the purpose of determining “the current status of science and clinical practice of proton therapy”.

Current and future indications for proton radiotherapy

On the basis of prospective phase I and II trials and observational and case-control studies, it has become clear that for some well-defined indications the benefit of proton radiation is substantial enough for proton radiotherapy to be considered an ‘accepted’ therapy, in addition to currently existing treatment options. And in selected cases there may even be a surplus value over conventional (radio)therapy, which could make proton radiotherapy the treatment of choice. These so-called ‘standard’ indications include: intraocular melanoma, tumours of the skull base and paraspinous tumours (chordoma, chondrosarcoma), and some paediatric tumours. In the Netherlands this group of patients will total around 252 annually.

Next, there is a relatively large and diverse group of tumours, where protons may be used to achieve dose escalation and subsequent improvement of local tumour control, resulting in increased treatment efficacy. This category includes lung cancer and prostate cancer. Proper RCT’s should be performed to demonstrate the potential benefit of protons for these indications. These tumours can be indicated as ‘potential indications’ for proton radiotherapy.

Another large group of indications comprises tumours for which protons can be used with the aim to reduce acute and late side effects of radiation (resulting in improved treatment quality). This consideration rests on (computer-based) individual planning comparative studies, simulating dose distributions of photons versus protons, and estimating and comparing the respective risk of side effects of each of these techniques. These so-called ‘model-based’ indications include: head and neck tumours, urologic tumours, breast and lung cancer as well as gynaecological cancers.

Finally, there is a relatively small category of cancer patients, for whom proton radiotherapy is expected to reduce the incidence of radiation-induced secondary tumours. These indications include breast cancer and haematological malignancies in young patients, as well as testis tumours (seminoma) in young males.

Estimated total number of patients for proton radiotherapy in the Netherlands

On the basis of the cancer incidence data available from the Dutch Cancer Registry (IKC), and data from Australian* and Swedish studies** on the percentage of cancer patients eligible for radiotherapy, it can be estimated that in total around 7,000 cancer patients in the Netherlands could potentially benefit from receiving proton radiotherapy (based on 2005 figures). This estimate is based on currently available in-silico studies and relevant expert opinion. Assuming that a proton facility in the Netherlands could be operational at the earliest by 2015, this number may have increased by then to around 9,400. The estimated numbers of patients eligible for proton therapy, as presented in chapter 6 of this report, should be interpreted – as is stressed by the committee – as maximum numbers. The actual number of patients to be treated with protons will probably turn out to be less, one of the reasons being that patients are not willing to travel longer distances for obtaining this specific treatment. In addition, it should be considered that, after starting up a proton facility, it will usually take a minimum of 3 years to reach its maximum capacity. The clinical introduction of proton radiotherapy in the Netherlands will therefore be a gradual process.

Current and future facilities for proton radiotherapy in Europe

In all there are now eight operational centres for particle therapy (protons and ions) in Europe. These centres have already treated more than 15,000 patients in the past years, and worldwide this number exceeds 50,000. Some centres (with low-energy accelerators) are dedicated to treatment of eye melanomas only, while others perform treatments (with both protons and carbon-ions) for a wider


range of indications, using high-energy accelerators. Most centres devote considerable time to research activities, apart from providing clinical treatment.

There are over ten initiatives in European countries today for additional proton/ion centres; some already under construction, others have been approved or are in the early stage of planning. Additional centres are planned in Germany (5), France (2), Italy (3) and Austria (1). Realization of these plans will eventually result in an eight-fold expansion of the capacity for patient treatment in Europe.

In the Netherlands there are at present explorative plans for proton radiotherapy facilities in Maastricht and Groningen and a proposal by a consortium including Leiden/Delft/Amsterdam/Rotterdam.

Prerequisites for a well-controlled introduction of proton therapy in the Netherlands

Based on the above mentioned considerations, and assuming that further validation studies prove successful, it is concluded that a substantial number of Dutch cancer patients could potentially benefit from future treatment with proton radiotherapy, resulting in less clinically relevant side effects, improvement of local tumour control, and prevention of secondary cancers. Well-planned and timely investments in proton radiotherapy in the Netherlands are called for to enable the future treatment of these patients and achieve the potential benefits. A number of prerequisites will have to be fulfilled to let this become a reality. The most important are:

- The centres that will take up proton radiotherapy must be embedded in an environment where clinical care, clinical research and technological development are naturally well-integrated.
- During the initial investigational phase an important part of the activities should be focused on the clinical validation of potential and model-based indications for proton radiotherapy, besides the treatment of patients with standard indications.
- Future capacity for proton radiotherapy should be sufficient to allow treatment of both patients with standard indications and patients with potential and model-based indications who will participate in validation studies, either observational studies or RCT’s. In a scenario favouring gradual and controlled introduction, proton facilities in the Netherlands could – in the longer run – reach a capacity to treat approximately 7,000 patients per year. In the initial phase however, emphasis should be on clinical validation involving prospective controlled and observational studies, where an important part of the patients eligible for proton treatment will take part in RCT’s comparing pro-
tons with photons. Therefore one can realistically expect that the capacity for proton therapy during this phase will show a gradual increase to finally reach a maximum of 4,000 patients annually at the end of this period.

- From the very start of the introduction of proton radiotherapy there should be reasonable prospects that the treatment cost of both patients with standard indications, patients treated with the intention to prevent secondary tumours, as well as patients enrolled in clinical validation studies of potential and model-based indications, will be covered.
- The introductory phase should see a well-controlled start, with proton therapy facilities in the Netherlands highly concentrated, if necessary on the basis of the Specific Medical Procedures Act (WBMV). Efficient referral of patients by Dutch hospitals is important to guarantee good utilization of the available capacity and sufficient enrolment in the validation studies.
- The Dutch Health Council committee that has prepared this horizon scanning report does not see pronouncement upon the number of proton facilities needed, or making recommendations on specific locations or centres as part of its assignment.
Chapter 1

Introduction

1.1 Advisory request on Radiotherapy

In 2008, the Health Council of the Netherlands was asked for advice by the Minister of Health, Welfare and Sports (VWS) whether radiotherapy should remain subject to the Specific Medical Procedures Act (WBMV), enabling the central regulation of radiation oncology departments and radiation equipment capacity. More specifically, the Minister asked which particular components of radiotherapy (e.g. new technological developments and methods, new indications) would continue to require legal regulation by the WBMV and which components (e.g. standard, routine care) could be excluded from this regime.

For this task, the Health Council assigned a special Committee on Radiotherapy, consisting of experts with different backgrounds in order to formulate answers and recommendations to these questions. During the meetings of this Committee, it became clear that the clinical introduction of proton radiotherapy, an emerging radiation delivery technique using heavy charged particles (protons), requires special attention. The reason being that the introduction of proton radiotherapy, in comparison to the currently used photon radiation, demands complex infrastructural requirements with special expertise and a much higher capital outlay resulting in higher costs per treatment. Due to the need for clinical proof of the effectiveness of proton therapy, and also because of these financial aspects, there is a lively discussion ongoing in medical literature regarding the scientific validation of particle therapy, and its introduction on a wider scale.
This discussion focuses primarily on the need for robust scientific evidence to demonstrate the clinical value of proton therapy, and on the necessity and feasibility of randomised controlled trials (RCT’s) in this process.\textsuperscript{1-7} Therefore, the Committee on Radiotherapy decided that a separate and more comprehensive horizon scanning report on proton radiotherapy was called for.

Evidence-based medicine has gradually become the cornerstone in the clinical introduction of new treatment strategies. To this end, RCT’s are generally accepted to be the gold standard for assessing differential benefits in clinical outcome between therapies. However, in the context of radiotherapy and in particular when validating new radiation technologies, the translation of the RCT requirements may pose some problems. There can be no doubt that the RCT approach is the appropriate method to assess the clinical benefits of a new radiation technique aiming to improve local tumour control and hopefully prolong survival. On the other hand, when new techniques primarily aim at a reduction of side effects, in particular of radiation-induced secondary tumours, one is confronted with a series of methodological, practical and ethical questions and problems, that may complicate the validation process of new radiotherapy developments. This is particularly the case for proton radiotherapy. Therefore, a critical assessment of the clinical benefits of proton radiotherapy requires exploration of an alternative methodological approach as a complement to RCT’s.

This discussion on validation methodology is also relevant in the context of decision making on health insurance coverage and reimbursement under the Dutch health insurance system, which is the responsibility of the Dutch Health Insurance Board. Therefore, it was decided that for the purpose of the current horizon scanning report the committee should adopt the same set of criteria that are proposed in a recently published advisory report on proton radiotherapy by this Health Care Insurance Board (College voor Zorgverzekeringen - CVZ), to fulfil the legal requirement of determining “the current status of science and clinical practice of proton therapy”.

1.2 State-of-the-art report on Proton Radiotherapy

This horizon scanning report describes various aspects of proton radiotherapy and its potential role in the treatment of cancer. In Chapter 2, a brief overview of the presently available photon radiation techniques is presented. Chapter 3 describes the main physical principles of proton radiotherapy. Chapter 4 focuses on the potential clinical advantages of proton therapy, and methods to validate this are further discussed in Chapter 5. Current and future treatment indications and patient selection criteria are explored and discussed in depth in Chapter 6.
while Chapter 7 sums up the main conclusions here. In Chapter 8 some tentative data on economic appraisal and cost-effectiveness of proton therapy are presented. Chapter 9 briefly describes the current status of proton radiotherapy in Europe. Chapter 10 describes the preconditions for a careful clinical implementation of proton radiotherapy in the Netherlands, and presents a global estimate concerning the present and future demand for proton radiotherapy in the Netherlands, based on the earlier discussed indications and the need for validation studies. Finally, Chapter 11 sums up the main conclusions and recommendations.
Chapter 2

Current status of radiotherapy

2.1 Role of radiotherapy

Between 40 and 50% of all cancer patients are treated with radiotherapy, either as single modality or as part of a combined approach (with surgery and/or chemotherapy). In approximately half of these patients radiotherapy is given with curative intent subsequently contributing to improved survival rates. As a result there is a large and expanding population of cancer survivors who have been previously exposed to ionising radiation. Some of these survivors will manifest the long-term effects of radiation on normal tissues. These include ‘deterministic’ effects, such as organ dysfunction resulting from vascular damage, fibrosis, atrophy and necrosis, as well as ‘stochastic’ effects such as radiation-induced secondary cancers. These side effects may cause serious distress to the patient and are too often refractory to treatment.

Early and late side effects following radiation treatment have been recognised ever since radiotherapy was clinically introduced over 100 years ago. Initially, these side effects were accepted as inevitable events, in an attempt to cure an otherwise fatal disease. Even today, radiation treatment continues to deliver significant but supposedly unavoidable radiation doses to normal structures, resulting in a certain, generally accepted risk of side effects and secondary cancers. With the presently available new treatment techniques however, some of these side effects should no longer be considered inevitable or even acceptable.
2.2 Technological developments

The past fifty years have seen a fast-paced development of the technology and physics of radiation therapy, all directed towards achieving more effective destruction of cancer cells, while sparing normal tissue. The most crucial change has been the replacement of outdated cobalt-60 and orthovoltage X-ray machines with the currently used linear accelerators generating high-energy photons and electrons. These are now the standard equipment in all radiotherapy departments in the Netherlands, and allow the use of sophisticated beam delivery systems such as (micro)multileaf collimation, intensity modulated radiation therapy (IMRT), image guided radiotherapy (IGRT), stereotactic radiosurgery, and tomo-therapy.

The advantages and the current status of the clinical implementation of these new photon techniques have been described in some detail in the advisory report Searchlight on Radiotherapy that has published before by the Health Council Committee on Radiotherapy.* Based on recent experiences, proton therapy could well be a challenging next step in this ongoing process of improved radiation treatment techniques.

2.3 Origin of proton therapy

The potential role of charged particles, including protons and carbon-ions, as an effective treatment for cancer was first suggested by the physicist Robert Wilson (then director of the US Fermilab) in 1946, who was at that time involved in the design and building of the Harvard Cyclotron Laboratory in the United States. He proposed to obtain a better conformal treatment in radiotherapy by exploiting the exceptional physical characteristics of proton beams, in particular the so-called ‘Bragg peak’ that occurs in particle radiation (resulting in reduced doses in front of and behind the tumour, compared to photon radiation). The first pioneering treatments on patients were performed using particle accelerators that were in fact built for physics research, especially in the Berkeley Radiation Laboratory (California, USA) in 1954, in Moscow, and in Uppsala (Sweden) in 1957. A clinically oriented collaboration was started in 1961 between the Harvard cyclotron facility and the Massachusetts General Hospital in Boston, focusing on proton therapy. This collaboration lasted till 2002 (when the old cyclotron facility was

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finally shut down), and involved over 9,000 treated patients. The first hospital based proton therapy facility in the world was established in 1990 at the Loma Linda University Medical Center in California, where over 13,000 patients have been treated so far. In Europe the first proton therapy centre was established in 1984 at the Paul Scherrer Institute (PSI) in Villigen (Switzerland), followed later by centers in Clatterbridge (UK) and Orsay (France).
3.1 Theoretical advantages of proton radiotherapy

From a purely physics point of view, charged particles such as protons have an evident advantage over gamma rays and x-rays: they deliver their destructive power with a higher precision than photons, resulting in better sparing of normal tissues. Whereas x-rays (photons) have their maximum dose near the surface (at entrance) followed by a continuously reducing dose with depth, protons deposit almost all of their radiation energy in the so-called Bragg peak (see Figure 3.1), a sharply defined peak at the point of greatest penetration in the tissue (i.e. the tumour). The exact depth of the Bragg peak depends on the energy given to the proton beam, and this allows for very precise targeting of the tumour. By varying the energy of the charged particles, one can spread out the Bragg peak and cover a well-defined region encompassing the tumour (Spread-Out Bragg Peak or SOBP). Because practically all protons are absorbed at the Bragg peak, normal tissues beyond the tumour receive very low to no radiation dose at all.
First of all, this offers the possibility to enhance the protection of normal tissue while the dose in the tumour is expected to remain the same. As a result, tumour control will be similar, whereas the treatment tolerance and quality of life of the patient will improve, due to reduced toxicity and incidence rates of secondary tumours. Secondly, because of its reduced toxicity, proton radiotherapy offers the possibility to improve local tumour control by increasing the dose, which may result in improved cancer-specific and overall survival.

The recent development of intensity modulation of photon beams (IMRT) has already led to a significant improvement in dose conformality to the tumour and sparing of normal tissues. However, the physical properties of currently used photon beams do not leave much room for further improvement. Figure 3.2 shows the example of a patient with a complex shaped tumour located in the vicinity of critical normal structures (brain tissue). Even when using the most sophisticated photon beam techniques, the location of normal structures near the target volume precludes further dose escalation. As can be seen from these computer simulations, this patient could certainly benefit from proton beam therapy because of the limited dose delivered to the healthy brain tissue.

**Figure 3.1** Proton beam absorption profile.
The observed dosimetric advantages of proton radiotherapy can be further enhanced with emerging technologies such as pencil beam scanning systems (see 9.2.2), intensity modulated proton beams (IMPT) and image guidance. These technologies require continuous monitoring and development by expert groups in the field.

Besides improvements in the physical dose distribution, further improvement can be expected through the use of other types of charged particles. Thus far, experience has been mainly gained using protons, but in principle a series of other charged particles can be used for radiotherapy. Further increase of the therapeutic ratio may be achieved by using high-LET radiations (e.g. carbon ions: $^{12}$C). This approach combines the physical advantages of charged particles with an enhanced relative biological effect (RBE), which is most pronounced in the Bragg peak (see Figure 3.3). Carbon ions are heavier than protons and have been shown to be particularly effective in the treatment of so-called radioresistant tumours. It has been shown that the differential radiosensitivity between poorly oxygenated (more radioresistant) and well-oxygenated (more radiosensitive) cells is reduced with high-LET radiations. Therefore, tumour sites that are prone to hypoxia might benefit most from high-LET radiations, as for instance with squamous cell head and neck cancer and non-small cell lung cancer. Although many issues remain to be resolved, $^{12}$C ions appear to be promising candidates for a future generation of particle therapy. However, the pros and cons of this treatment modality fall outside the scope of this report and therefore will not be discussed.
3.2 Potential disadvantages

Proton radiotherapy (in particular intensity modulated proton therapy - IMPT) has the potential to deliver highly conformal dose distributions. However, as the range of protons is finite, the actual delivered dose distribution is susceptible to some treatment-related uncertainties. Potential sources of error are the uncertainties in the CT Hounsfield units and the conversion to stopping power, artefacts in the CT image, but also changes in the anatomy of the patient. For example, many tumours (e.g. of the lung) move with the patient’s respiration, are at a different position each day, or change shape during the treatment course. If tumour motion and deformations are not handled correctly, the superior dose distribution of proton beams will inevitably be compromised. To minimize these dose-degrading effects the development of high-level image-guidance and dose-guidance techniques will be of utmost importance in the application of proton radiotherapy.

Another downside to proton radiation is the fact that (passive) modulation techniques applied to spread out the proton beams in such a way that the whole of the tumour is covered (e.g. passive scattering and collimation), inevitably also result in the patient getting exposed to a scatter of low dose of secondary high-energetic neutrons. These neutrons are generated through interaction of the accelerated protons with provisions placed in the beam line to achieve spreading (using scattering foil) and collimation to produce a field of useful size. Although we know that exposure to a low total-body dose of neutrons may indeed induce cancer, it is not yet clear to what extent this may result in an increased incidence of neutron-induced second tumours. What is certain however, is that the lifetime risk of secondary cancer in the young patient is more enhanced than in the older patient, and consequently this risk needs to be avoided in children and ado-
In the mean time we have now learned that this problem of neutron contamination may well be solved in practice by applying more sophisticated active scanning techniques (using pencil beam scanning, see 9.2.2). This method avoids placement of physical objects such as a collimator in the beamline, which places the energy-selection system (ESS) directly after the cyclotron; as a consequence the flux of neutrons is practically zero.

The committee, taking into account the generally high level of technological expertise in radiotherapy and the fast developing field of proton radiation today, considers it likely that the possible technical disadvantages of this therapy, indicated above, can and will be overcome in the near future. A crucial requirement is that proton radiotherapy must take place in a clinical and technological research setting of sufficient scale. This would improve the likelihood of a successful development and safe application of image-guidance and dose delivery techniques in the field of proton radiotherapy.
Based on the physical principles of proton beams described in the previous Chapter, there are three important areas where the superior properties of protons, as compared to photons, can – at least on theoretical grounds – be expected to produce a benefit for cancer patients. Evidence from their clinical application supports the assumption that these advantages of protons may be realistically exploited in clinical treatment strategies. These strategies are briefly introduced here and will be explored in more detail in Chapter 5.

4.1 Improvement of tumour control (treatment efficacy)

Patients treated with photon therapy not infrequently receive a radiation dose that is insufficient to fully eradicate the tumour, in particular when this tumour is located close to critical organs. By using protons however, the energy dose deposited in the tumour can be optimized without simultaneously increasing the dose to the critical organs. This strategy will be particularly useful when dose escalation can be expected to improve tumour control, e.g. in the case of non-small cell lung cancer\textsuperscript{12,13} and prostate cancer\textsuperscript{14-18}. For such indications, the primary aim of proton radiotherapy would be to improve treatment efficacy without aggravating the side effects.
4.2 Reduction of radiation-induced side effects (treatment quality)

Treating patients with photon radiotherapy bears the risk of causing damage to normal tissues, leading to subsequent radiation-induced side effects. These side effects can be subdivided into both acute and late effects. For virtually all critical organs or normal tissues, the probability of radiation-induced side effects depends on the radiation-dose distribution and the relative volume of tissue that receives a certain dose. Acute and, in particular, late side effects may have a major negative impact on health-related quality of life, as has been reported by patients\textsuperscript{19-22}, and cause an increased demand for health care and financial resources (e.g. because of reduced employment). Proton radiotherapy, because of its optimal dose distribution properties, can be used to reduce the dose to critical organs, which would benefit especially patients for whom side effects are clinically relevant (e.g. in head and neck cancer).

4.3 Reducing the risk of secondary tumours (prevention of late side effects)

Although radiotherapy is applied with the aim to cure or palliate cancer, radiation itself bears the risk of inducing secondary malignant tumours. Young patients in particular run a relatively high risk of developing secondary tumours after radiation therapy (approximately 5-10\% life-time risk for a 15 year old\textsuperscript{11,82,200}). Several studies have shown that the occurrence of radiation-induced secondary cancers increases with the total dose to normal tissues\textsuperscript{23,24}, in particular tissues in front of and beyond the tumour. Recent technological developments such as IMRT have contributed to a further reduction of the dose to the critical organs, but the dose to these organs and in the rest of the patient’s body is still not negligible. From a theoretical point of view, one might expect a reduction of secondary tumours after irradiation with protons.

4.4 Application of these strategies

In the next chapter the committee will explore to what extent there already exists scientific evidence for the claimed or expected benefits of proton therapy, aiming to achieve the above described clinical advantages in practice. Moreover, the methodology is discussed to validate the clinical appropriateness of these approaches.
Chapter 5

The need for scientific evidence of the clinical benefits of protons

5.1 Recent debate

In recent years, there have been profound discussions among radiation oncologists whether or not proton radiotherapy can and should be clinically introduced as a new standard of care, without formal confirmation as yet by proper randomized controlled trials (RCT’s). Indeed, the principles of evidence-based medicine dictate that new technologies’ claims to superior efficacy and quality over existing modalities must be underpinned and validated with scientific evidence obtained from robust comparative trials.

In the debate concerning proton radiotherapy some critics have – correctly – claimed that the use of protons for treating cancer has not yet been properly evaluated in RCT’s to the extent that is presently desired or actually required. This has been stated in many reviews and recent overviews of the literature. In summary, the authors of these reviews have come to the conclusion that ‘the evidence for clinical effectiveness, according to standard health technology assessment criteria is scarce and the data do not yet support the extension of these treatments as a major treatment modality except for certain rare tumour types’. As a consequence they do not recommend wider application of proton radiotherapy today.

On the other hand, proponents have argued that owing primarily to its particular beam properties, there is no denying that the dose distributions that can be
obtained with protons are, in almost all cases, superior to those feasible with photons with or without intensity modulation (a technique that can be applied with both photons and protons). This is particularly relevant when the new technology is primarily aiming to reduce the dose to critical organs, as well as the (integral) dose to normal tissues, and thus to prevent acute and (very) late side effects. They also point out that even recently improved radiotherapy technologies such as IMRT have been implemented without prior controlled clinical trials, but mainly on the basis of their perceived physical advantages. Clinical confirmation of their superiority over the standard treatment modality was in fact provided some years later, e.g. in breast cancer, prostate cancer and head and neck cancer. The significance of this issue is illustrated by the fact that recently patients themselves started to participate in this discussion, requesting their doctor for the lowest possible radiation dose to organs at risk, and stressing the importance of meticulous consideration of all possible pros and cons.

To answer the question raised why, in the case of proton radiotherapy, there is this striking lack of RCT-based evidence, and secondly, whether this precludes the clinical introduction of this new treatment modality, the committee will more closely explore the reasons for this situation.

5.2 Why are there so few RCT’s in proton radiotherapy?

One can think of a number of reasons to explain the virtual lack of evidence from RCT’s investigating the added value of proton radiotherapy. The main arguments are the following:

1. Until very recently, practically all proton (and carbon ion) treatments have been carried out at facilities intended and built for the purpose of physics research, which often severely reduced the clinical beam time availability and limited the use of beam modulation techniques. Most cancers are best treated with multiple fractions during several weeks, which has been practically impossible to achieve at most of these sites. A few dedicated centres for proton radiotherapy have been in operation in the United States now for nearly two decades, but all other dedicated centres did not start until a few years ago, or have not started as yet.

2. The technical radiation equipment used was not well suited for treatment of other than a few tumour sites. Sufficiently large field sizes, gantries or scanning possibilities have generally not been available. The full geometrical advantages of protons could thus not be realized. Any trial, even if it would have been reported, would have used an already out-dated technique in a rapidly developing area.
3 The structure and management of the institutions, often private or outside the general health care system, and their location, generally far away from a hospital, have severely restricted the possibilities for performing clinical trials.

4 The number of patients with a specific type of cancer has generally not been sufficient to allow a proper study at a single site, and, for sufficiently powered clinical trials to be performed, would have required close cooperation between centres far apart and often in markedly different health care and cultural environments. So far, this co-operation has not come off the ground in proton therapy. Even within the framework of the EORTC (European Organisation for Research and Treatment of Cancer), a phase III study would take at least 5 years with the participation of approximately 15 to 20 centres from different countries to achieve sufficient statistical power. Until now, this number of fully operational proton therapy centres was not available. From these data it becomes clear that RCT’s aiming to determine the added value of proton radiotherapy, will be feasible only when sufficient numbers of facilities are operational, preferentially within clinical research environments. Another prerequisite will be that these facilities work together in international collaborative groups. This situation will take more time to be realized.

5 Finally, the extra costs for proton radiotherapy, which are approximately twice that of photon therapy, are in most countries not yet (fully) reimbursed by the health insurance agencies. This causes difficult to solve problems for clinical researchers as proton facility providers are scarce and not able to provide on their own the financial resources needed to carry out large multicenter international clinical studies.

Despite the practical problems mentioned above, the committee takes the view that proton therapy, as any other novel medical technology, must demonstrate through robust comparative controlled research that it offers clinical advantages to patients over conventional treatment, before being introduced more widely in health care. However, it can be argued – as a number of authors on this subject have done – whether an RCT is, in all circumstances, the best appropriate methodology to validate the benefit of new radiation delivery techniques, in particular that of proton radiotherapy. In addition, if this would not prove to be the case, the question would arise what kind of alternative methodology could be applied to establish current and new indications for proton therapy. To address this issue, it is essential to make a distinction between the different strategies for translating the theoretically superior physical beam properties of protons into the expected clinical benefits that were already outlined in the previous chapter.
5.3 Clinical strategies for applying protons

The different strategies that can be applied to translate the superior physical beam properties of protons compared to photons into a clinical benefit were already identified in Chapter 4 as follows: 1) increasing local tumour control; 2) reducing the radiation-induced side effects, and; 3) reducing the risk of secondary tumours. In this section, the scientific and clinical underpinning for these strategies will be discussed, as well as the appropriate methodology available to validate them.

5.3.1 Improvement of tumour control (treatment efficacy)

It has been shown that when patients are treated with conventional photon therapy, the dose received is often not sufficient to effectively eradicate the tumour cells. In particular when the tumour is located close to critical organs, the dose given is limited due to the physical characteristics of photons. However, using protons allows one to optimize the energy dose deposited into the tumour, without increasing the dose to the critical organs or even with a reduced dose to the surrounding normal tissues. This strategy can be applied for those indications where local tumour control is now relatively hard to achieve, where dose escalation is likely to improve tumour control, and/or in cases where dose escalation to the tumour would result in an unacceptable risk of side effects, as for instance in the case of non-small cell lung cancer and prostate cancer. For these indications, it can be hypothesized that proton radiotherapy is superior to photon therapy as a result of higher escalation of the radiation dose to the tumour that can be achieved with protons, with an equivalent or lower radiation dose to the surrounding tissues. In other words, the primary aim would be to improve treatment efficacy.

There is virtually no difference in tumour response per unit dose between protons of therapeutic energies and photons, and therefore the potential benefit of protons in terms of local tumour control and subsequent overall survival will mainly be the result of physical dose escalation. Methodology-wise it is clear that in order to validate the value of protons for the purpose of improving local tumour control, conducting an RCT would be the most suitable and valid approach.
5.3.2 Reduction of radiation-induced side effects (treatment quality)

As mentioned before, patients treated with photon radiotherapy with the intent to cure cancer (as distinct from cases where radiotherapy is primarily used to control the cancer or to palliate symptoms), are at risk of developing normal tissue damage and subsequent radiation-induced side effects. Radiation-induced side effects can be distinguished as both acute and (very) late side effects. Acute side effects occur during or immediately after the course of radiation and are clinically relevant as they limit the dose that can be administered. In some cases, acute side effects progress into late side effects (so-called ‘consequential’ side effects). Late side effects can occur up to several months or sometimes even decades after completion of the radiation course and may prove to be irreversible or even progressive over time, e.g. the development of cardiovascular events after irradiation of the chest. Generally, the risk of developing side effects increases with the total dose delivered to the critical organs and their irradiated volume. Although these side effects are often considered inevitable consequences of radiotherapy, there is increasing evidence that both acute and particularly late side effects do have a major negative impact on health-related quality of life as reported by patients.\textsuperscript{19-22} As a result, radiation-induced side effects may increase the overall demand for health care and financial resources (e.g. additional costs for medical care and social costs because of incapacity to work).

The favourable beam properties of protons, as compared to photons, can be used in this approach to reduce the dose to critical organs without escalating the actual dose to the tumour. This is particularly beneficial for those indications where dose escalation is not expected to improve tumour control as such, but where reducing or preventing side effects is clinically relevant (as, for instance, in small cell lung cancer and head and neck cancer). This approach may thus result in reducing adverse side effects even further than is now possible with IMRT.

5.3.3 Reducing the risk of secondary tumours

Although radiotherapy is intended to cure or palliate the patients’ cancer, radiation itself bears the risk of inducing secondary malignant tumours. This risk of radiation-induced secondary tumours is most pronounced in younger patients, since the incidence of secondary cancers does markedly increase when radiotherapy is administered at a younger age, and also increases with the number of survival years.
A number of reports have reported on late side effects after irradiation, including the induction of secondary cancers. All tissues close to and particularly in front and beyond the target area (tumour) are exposed to unwanted irradiation and are therefore at risk of developing secondary cancers. This has been demonstrated e.g. in the Hiroshima and Nagasaki atom bomb survivors. Recent technological innovation such as IMRT has contributed to a further reduction of the dose to the critical organs, but the dose to these organs and to the remainder of the patient is still not negligible.

From a physical point of view one might expect that protons will bring about a reduction of secondary tumours after irradiation as the beam properties of protons result in a lower dose to the critical organs in front of and beyond the tumour, as well as in a lower integral dose. A recent study has indeed revealed a significantly lower risk of a second malignancy after proton radiotherapy when compared to photon therapy.

5.4 What methodology to validate the effect of protons?

Several authors have argued that applying an RCT approach for the appraisal of new radiation technologies that aim primarily at the reduction of side effects (including secondary tumours), is actually based on the wrong paradigm. They point at the fact that the original ‘rules of evidence’ (as formulated by the prominent clinical epidemiologist David Sackett) were in the first place intended to evaluate evidence pertaining to the differential benefits of competing therapeutic interventions, that is: treatment efficacy (in radiotherapy: e.g. improvement of local tumour control). These rules appear to be less well suited for evaluating evidence pertaining to the risks of exposure to potentially avoidable hazards, such as ionizing radiation (that is: treatment quality). Another approach is to be preferred in this case. This starts from the observation that for virtually all critical organs or normal tissues, the probability of radiation-induced side effects depends on the radiation dose distribution and the relative volume that receives a certain dose. These dose-volume-effect relationships can be described mathematically in so-called Normal Tissue Complication Probability (NTCP) models (see Figure 5.1). The prognostic value of these dose-volume parameters has been found to be consistent in numerous prospective cohort studies, and for some side effects has also been confirmed by systematic reviews (providing level I evidence for prognostic factors).

This background knowledge with respect to dose-volume-effect relationships, as applied in NTCP models, is already widely exploited in daily practice of radiation oncology. Whenever available, radiation oncologists and patients will
choose the radiation technique that yields an equivalent dose to the target volume with the lowest dose to critical organs, when that reduced dose to critical organs will result in a profound and clear reduction of radiation-induced side effects. In the case of proton therapy, applying the standard RCT methodology would result in randomizing patients between two radiation delivery technologies that yield the same tumour dose distribution but where one technique would result in a clear left-shifted (unfavourable) dose-volume histogram in critical organs at risk. This would not be consistent with the general ethical principle of ‘equipoise’ (balanced uncertainty). As a consequence, RCT’s investigating the added value of protons compared to photons with regard to reduction of side effects, run the risk of being ethically compromised. This may partly explain the present absence of RCT-based data (in addition to the reasons already explored in paragraph 5.2).

Concluding that RCT’s in proton therapy are currently not available and, more importantly, not the most suitable methodology for validating proton radiotherapy aiming at reduction of side effects, the question arises what kind of approach should in fact be used to determine the potential benefit of a new radiation technology such as protons. For the purpose of this report, the committee reviewed the literature using the 3-step methodology described below (which has now also been adopted by the Dutch Health Insurance Board - CVZ). This methodology consists of two consecutive phases: phase α (consisting of 3 steps) aiming at the definition of cohorts of patients who may benefit from protons using the combination of NTCP-models and planning comparative studies, and phase β aiming at the clinical validation of these model-based indications, either through RCT’s or prospective observational cohort studies using historical comparisons as a reference, whenever appropriate.

5.4.1 Phase α: Model-based indications

Step 1: Normal Tissue Complication Probability (NTCP)

The basic principle in the development of new radiation delivery techniques is the existence of validated relationships between dose distributions in critical organs and the probability of radiation-induced side effects (i.e. Normal Tissue Complication Probability - NTCP). In general, the NTCP-value will increase with increasing dose and increasing volume that receives a certain dose (see Figure 5.1).
Step 2: Planning comparative studies (*in-silico* studies)

With respect to reduction of side effects, the potential benefit of proton radiotherapy is mainly based on the assumption that this new technique achieves a better optimized dose distribution, resulting in an at least equivalent dose to the target volume with a lower radiation dose to critical organs, compared to photons. In cancers where radiation is part of a treatment with curative intent, protons are likely to prove sufficiently better than photons for a given proportion of patients. These subgroups must be identified from computer-based studies in which the dose distributions that can be achieved with the new technique are simulated and compared with the current standard in the same cohort of patients. These kinds of studies are referred to as *planning comparative studies* or *in-silico studies* (see Figure 5.2). It should be emphasized that conclusions from *in-silico* studies regarding the added value of protons can only be justified in case of straightforward comparisons with photons, meaning that the reference technique should at least include the most advanced and currently available photon techniques, such as intensity modulated radiotherapy or tomotherapy.
The need for scientific evidence of the clinical benefits of protons

Figure 5.2 Example of a ‘planning comparative study’ or ‘in-silico study’ comparing 3D-conformal radiotherapy (photons) with intensity modulated radiotherapy (IMRT) with photons and intensity modulated proton therapy (IMPT). Presented is a case of a oropharyngeal tumour (dark area). The red area represents the high dose area. The light green structures on both sides represent the salivary glands. These structures should be spared as much as possible to prevent lifelong xerostomia. With 3D-CRT the dose to the parotid glands is highest. A significant reduction can be obtained with photon IMRT (current standard). The blue area represents the lowest radiation dose. Further reduction can be achieved using proton IMPT. Source: A.J. Lomax, 2008.

Another important prerequisite for a proper design of in-silico studies is the definition of appropriate endpoints, i.e. the most relevant dose-volume parameters following from NTCP-modelling studies, and to use these parameters with properly chosen dose constraints for treatment planning optimisation for all techniques included in the analysis. Only in this way can the results coming from in-silico studies be used to translate the dose distribution advantages of protons compared to photons into a clinical benefit.

Step 3: Model-based studies

The final step in phase will be to determine to what extent the optimised physical dose distributions will translate into a clinically relevant beneficial effect, using the combination of data from existing NTCP-models and planning comparative studies which is illustrated in Figure 5.3.
The methodology outlined above, using existing NTCP-models combined with the results of published data on planning comparative (in-silico) studies, will enable one to make a valid estimation of the proportion of patients per indication that will benefit from proton radiotherapy, and is therefore advocated by the committee. These indications are referred to as model-based indications. In Chapter 6, some examples of model-based indications will be discussed in more detail, including head and neck cancer, lung cancer, prostate cancer, breast cancer and meningeoma.

5.4.2 Phase β: Clinical validation

When proton radiotherapy is available at a treatment centre, the aforementioned approach could also be used on an individual basis as a tool to determine whether a given patient is expected to benefit or not from proton therapy, in comparison to the available photon radiotherapy technique, and thus to select this patient for one of three different strategies (see Figure 5.4).
The need for scientific evidence of the clinical benefits of protons
this context, it should be emphasized that proton radiotherapy is now a rapidly evolving technology where further improvement can be expected to occur within relatively short periods of time. Therefore, when proton radiotherapy is predicted to significantly reduce the risk of such complications based on phase α-step 3 results, patients should be treated with protons if this facility is available, provided that these patients will participate in prospective observational study programs. The same applies to patients for whom proton radiotherapy is indicated with the aim to reduce the risk of secondary tumours, as these are also expected to occur after relatively long latency times.

b In some patients, the individual planning comparative analysis may reveal a substantial predicted difference in NTCP-value between photons and protons for a given side effect, while the dose to the target volume stays the same, e.g. an expected difference in severe swallowing dysfunction after radiotherapy of the head and neck region. Enrolling this patient in an RCT would not be consistent with the general ethical principle of ‘equipoise’ (balanced uncertainty)², in particular when the expected side effect would significantly impact on health-related quality of life. When clinically available, these patients should be offered proton radiotherapy within the framework of a prospective observational study. The same applies even to relatively small differences in observed NTCP-values, when this particular side effect is expected to have major impact on health-related quality of life, e.g. radiation myelopathy with total paraplegia or radiation retinopathy with severe visual impairment or complete blindness.

c For some radiation-induced side effects the precise association between the dose-volume parameters is less clear, and therefore the translation of observed differences in dose distributions between protons and photons into clinical benefits remains to be determined. In such cases, conducting an RCT is probably the best methodology to test the clinical benefit of protons over photons. The same approach applies to relatively mild side effects, where other issues, such as cost-effectiveness, may become increasingly important.

5.4.3 Prospective observational studies

As stated in the previous paragraph, for some model-based indications their clinical validation by means of prospective observational study offers a more suitable approach. However, in order to allow for a reliable (historical) comparison between photons and protons, the primary and secondary endpoints should be assessed in a consistent and standardised way. This implies among others: pro-
spective assessment of baseline data (e.g. potential confounders such as demographics and tumour stage), of treatment-related variables, of acute and late radiation-induced morbidity and tumour follow-up, and possibly also data on quality of life of patients that are currently treated with photons, all done in a standardised way. For radiation oncology departments in the Netherlands to effectively introduce new developments such as proton radiotherapy, they should be encouraged to start or extend such programs for collecting standardised follow-up data.
Chapter 6

Treatment indications and patient selection

6.1 Clinical effectiveness of proton radiotherapy

As stated before, based on its physical properties proton radiotherapy offers improved dose distribution resulting in significantly lower doses to critical structures and surrounding tissues, when compared to the most sophisticated photon treatment techniques currently in use. Comparative dosimetric studies show that this advantage can be expected to result in less toxicity and a reduction of side effects, contributing to a better quality of life. For some patients this dosimetric benefit will translate into an escalated dose to the tumour, bringing prolonged survival within reach. However, until now the number of studies that have systematically analysed this therapeutic benefit in clinical practice – be it in a randomized, controlled prospective approach or in a retrospective design – is rather limited.213 Moreover, the scientific quality of some of these studies (in particular their methodological design, and the manner of reporting) does not stand up to scrutiny. Rather disappointing is the paucity of evidence that demonstrates incremental value of proton radiation therapy over conventional photon therapy, based on comparison of contemporary treatment strategies. More comparative studies in general are needed to document the assumed theoretical advantages of protons in specific clinical situations.213

In 2007 Lodge and co-workers published what is, till today, the most comprehensive and thorough systematic literature review on the clinical effectiveness and
cost-effectiveness of proton therapy (including also irradiation with light- and heavy-ions).\textsuperscript{29}

In this review they included 773 (out of a total of 7,209) articles that met their search and quality criteria (such as: studies with a minimum of 20 patients and a follow-up of at least 2 years). The results of this review are here summarized in Table 6.1.

To get an up-to-date overview of the most recent developments in proton radiotherapy since the systematic review by Lodge c.s., the committee undertook a review of all research data published after 2006, with the help of the Dutch Cochrane Centre (DCC). The aim was to establish to what extent these new study results would confirm or change the judgement of the aforementioned authors concerning the clinical effectiveness of proton therapy. In the following paragraphs these outcomes and judgements are grouped in four major categories: a) standard indications; b) potential indications; c) model-based indications; and d) indications where treatment is aiming to prevent or reduce secondary tumours. For each category the recent research literature is summarized and the resulting judgements are given. A more detailed overview of this literature and the analysis by the committee can be found in Annex C1-C4 of this report.

The following comment should be made with regard to the given percentages and the number of patients eligible for proton therapy, as shown in this chapter and in the accompanying tables: these are all maximum numbers based on the available comparative in-silico studies, as well as on expert opinion in the field of radiotherapy. Patients with metastases and specific groups of patients who are a priori non-eligible for proton therapy, are not included in this analysis.

| Tabel 6.1 Outcome of systematic review: effectiveness of proton therapy compared with conventional therapy, grouped according to tumour site (Lodge 2007). |
|-----------------------------|-----------------|-----------------|-----------------|
| tumour site                | number of studies | number of patients | outcome         |
| head and neck              | 2                | 62               | no firm conclusions |
| prostate                   | 3                | 1,751            | protons similar to photons |
| eye                        | 10               | 7,708            | protons superior to photons |
| gastro-intestinal          | 5                | 369              | no firm conclusions |
| lung (NSC)                 | 3                | 156              | no firm conclusions |
| CNS                        | 10               | 839              | protons similar to photons |
| base of skull chordomas    | 3                | 302              | protons superior to photons |
| sarcoma's                  | 1                | 47               | no firm conclusions |
| pelvis                     | 3                | 80               | no firm conclusions |

50 Proton radiotherapy
6.2 ‘Standard indications’

For a limited number of clinical situations the benefit of proton therapy is substantial enough – as was demonstrated first in comparative dosimetric studies, but now also in prospective phase I/II trials and observational case series – for radiation oncologists to reach a consensus that proton radiation in those cases can be considered an ‘accepted’ form of therapy, in addition to currently existing treatment modalities. This is not to say that all patients with these indications should necessarily be treated with protons, but rather that they have this option available to them.

In certain cases however, there is good reason (e.g. because of a more favourable risk profile with equal effectiveness) to consider proton radiation as the optimal form of therapy, and therefore as the treatment of choice. Such cases may be defined as ‘standard indications’ for proton radiotherapy. These standard indications will be discussed in the following paragraphs and can be grouped as follows: intra-ocular melanoma (plus certain other cancers of the eye), skull base tumours and paraspinal tumours, and certain paediatric tumours. All of these are relatively rare tumours: it is expected that in the Netherlands approximately 252 patients per annum with these standard indications will be eligible for proton radiotherapy (see Table 6.2).

6.2.1 Intra-ocular melanoma

Around 120 patients annually in the Netherlands are diagnosed with intraocular melanoma (including uveal melanoma, and melanoma of the choroid and ciliary body). Treatment depends on the size and location of the tumour, and may consist of: enucleation (complete removal of the eye), laser photocoagulation (transpupillary thermotherapy), plaque brachytherapy with a radioactive template (radioisotopes Iodine-125, Ruthenium-106 or Palladium) sutured to the base of the tumour, or proton radiotherapy. Removal of the eye is usually necessary in case of metastases. Brachytherapy is effective in case of melanomas up to 15 mm diameter and 5 mm thickness. Especially for larger tumours (diameter >15 mm, and thickness >8 mm), and those located closely to the iris or optic disc and optic nerve, proton therapy can offer an attractive alternative, because the only other effective treatment in this situation is enucleation of the eye.
Proton radiation for the treatment of intra-ocular melanoma has been applied already since 1975, but the number of studies set out to evaluate the effectiveness and safety of this treatment modality is still small. The majority are observational studies, and mostly without controls present. The advantage of proton irradiation compared with photon irradiation is the highly localized and uniform radiation dose distribution, based on the physical characteristics of protons. This permits tumours that are close to the macula and optic nerve to be irradiated, leaving visual potential better intact. To evaluate the effectiveness of proton therapy for intra-ocular melanoma the relevant outcomes are: eye function (visual acuity), eye sparing (avoiding enucleation), and incidence of side effects, rather than survival as such. There is already widespread clinical experience with thousands of these patients treated in different centres around the world, and good local control and eye retention rates are reported.51-54 There certainly is a need for robust assessment of its role and indications for its use.

Table 6.2 Estimated percentage and number of patients for whom proton therapy can currently be considered ‘standard’ treatment.

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Number of patients treated with radiotherapy in NL (2005)</th>
<th>Total number of cancer patients in NL 2005a</th>
<th>Percentage of patients treated with RTb</th>
<th>Number of patients treated with RTc</th>
<th>Estimated percentage of ‘standard’ indicationsd</th>
<th>Estimated number of ‘standard’ indicationse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracranial Tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-ocular melanoma</td>
<td>120</td>
<td>47%</td>
<td>56</td>
<td>80%</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Base of skull/paraspinal tumours</td>
<td>70</td>
<td>90%</td>
<td>63</td>
<td>100%</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>Paediatric tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>60</td>
<td>50%</td>
<td>30</td>
<td>80%</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Other brain tumours</td>
<td>300</td>
<td>50%</td>
<td>150</td>
<td>80%</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>550</td>
<td>299</td>
<td>252</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Total annual number of patients with specific type of cancer in the Netherlands, based on the Dutch Cancer Registry 2005.

b Estimated percentage of patients with specific type of cancer to be treated with radiotherapy based on CCORE report and adapted in the NVRO report.

c Estimated number of patients with specific type of cancer to be treated with radiotherapy based on CCORE report and adapted in NVRO report = total number of cancer patients in NL 2005 x% of patients treated with RT.

d Estimated percentage of patients with specific type of cancer with ‘standard’ indication for proton radiotherapy, based on available in-silico studies and expert opinion.

e Estimated number of patients with specific type of cancer with ‘standard’ indication for proton radiotherapy, maximum numbers based on available in-silico studies and expert opinion.


controlled – if possible randomized – studies that directly compare the currently existing treatment modalities (brachytherapy, sophisticated photon therapy and proton therapy). However, chances that such a study will still be feasible are slim, in view of the good results that are now achieved with proton radiation.\textsuperscript{55}

It is estimated that around 40-50 patients with intra-ocular melanoma may be eligible for proton treatment each year in the Netherlands.

6.2.2 Recent studies of proton therapy for intra-ocular tumours

Since Lodge et al published their systematic review of proton therapy studies in 2007, a number of publications have appeared that present both new proton research as well as long-term outcomes of earlier treated patients. 2009 saw the publication of a comprehensive new systematic review focusing on the application of proton radiation in tumours of the eye.\textsuperscript{56} The general conclusion of this review is that proton therapy is effective and has become the treatment of choice for patients with intra-ocular melanoma and other high-risk indications of the eye (although side effects can be significant). Proton radiotherapy results in good local tumour control and, in many cases, achieves better eye retention rates and improved visual acuity, also long-term. Table C1 in Annex C summarizes these studies and the outcomes.

6.2.3 Other indications of the eye

Besides treatment of melanoma, proton radiotherapy finds application also for other indications of the eye, e.g. choroid hemangioma and choroidal neovascular membranes (CNVM) caused by age-related macula degeneration (AMD). This treatment proved generally effective, but the outcomes were not significantly better than with photon radiation or brachytherapy.\textsuperscript{56}

Complications after proton radiation for intra-ocular tumours

As major side effects after proton radiation are listed: glaucoma, optic disk neuropathy, symptomatic dry eyes, cataract, retinal detachment, rubeosis (abnormal neovascularization) and maculopathy (side effects prevalent in up to 66\% of patients).\textsuperscript{56} Glaucoma appeared to be an important reason for secondary enucleation of the eye. Scleral necrosis following radiation is a rare side effect and does not threaten the eye (and needs no treatment). The frequency of most side effects after proton therapy is generally lower than with photon therapy.
6.2.4 Base of skull tumours and paraspinal chordoma and (chondro)sarcoma

This concerns a group of rare tumours. Surgical resection is seen as the preferred form of treatment, but radical surgery is usually not possible, and high radiation doses are needed in that case to achieve local control in the non-radically operated patient. Due to the vicinity of the medulla oblongata, the brainstem, the spinal cord and other dose-limiting structures (e.g. optic nerve, optic chiasm, and pituitary gland), the possibilities for radiotherapy with photons are usually limited. The superior dose distribution of protons enables the application of higher doses of radiation, leading to good local control rates with low toxicity, as reported in several series. Postoperative radiation using protons after maximum surgical resection now seems to establish itself as the treatment of choice for chordomas and chondrosarcomas. Good local control is generally reported, whereas a combination of photon (IMRT) and proton treatment is also documented as giving superior results. Table C2 in Annex C gives an overview of recently published studies (since 2006).

It is estimated that approximately 60-65 patients with base of skull and paraspinal chordoma and (chondro)sarcoma may be eligible for proton therapy annually in the Netherlands.

Complications after proton radiation of base of skull tumours

The most frequently reported side effects after proton radiation of base of skull tumours are cranial neuropathy, radiation necrosis and pituitary dysfunction. Proton treatment generally resulted in minimal symptomatic damage to the brain. And although evaluation with MRI showed a higher incidence of radiation-induced brain changes (RIBC), there were usually no apparent clinical symptoms. In some patients damage to the temporal lobes, resulting in epilepsy, has been reported as a late side effect.

6.2.5 Other intracranial and spinal/paraspinal tumours

Besides base of skull chordomas, a number of other intracranial tumours are eligible for radiotherapy and could benefit from proton therapy, including meningioma (benign but locally destructive tumour of the cerebral membrane). Table C3 in Annex C presents an overview of recent studies investigating proton radiation for this group of tumours. This research shows that these tumours can be
effectively treated with protons, giving results that are equal or even better than with conventional radiotherapy.

Complications after proton radiation of intracranial tumours

Some serious side effects after radiation of intracranial tumours with protons have been reported: with meningeoma late damage to the optic nerve may sometimes occur, leading to complete blindness; in one case the development of an anaplastic glioma in a patient with chondrosarcoma 13 years after combined proton and photon radiation was reported.

6.2.6 Paediatric tumours

Some 500 children annually are diagnosed with cancer in the Netherlands. Leukemias, lymphomas, central nervous system (CNS) tumours and sarcomas of bone and soft tissues occur most frequently (according to the SKION Registration). Survival for paediatric cancer has improved markedly over the last decades with cure rates nowadays around 60-70%. Due to these improved chances of cure however, late complications of treatment are observed more frequently. Long-term follow-up studies in the United States (Childhood Cancer Survivor Study) have shown that, after having been treated during their childhood, a significant number of these patients experience serious chronic and even life-threatening disorders in later years.

Assessment of adverse health outcomes in a cohort of more than 1300 Dutch long-term survivors of childhood cancer indicates that at a mean age of 24 years, a high or severe burden of illness due to adverse events was observed in 55% of survivors who underwent radiotherapy. Late side effects after irradiation include growth disorders, cognitive disorders, hearing impairment, endocrine, renal and gonadal dysfunction, as well as induced secondary tumours. Clearly the risk of suffering these side effects is affected by the total volume of normal tissue exposed to irradiation and by the dose administered.

Comparative dosimetric studies have shown that proton radiation generally achieves a significantly lower integral dose (i.e. the median dose in the total body, which is relevant for the risk of secondary tumours), and leads to better sparing of normal tissue and critical structures. It is now widely acknowl-

* SKION – Stichting Kinderoncologie Nederland (Dutch Foundation for Paediatric Oncology): national registry of late cancer treatment effects.
edged that this may offer a significant benefit to children who need radiotherapy because of CNS tumours, intracranial tumours (e.g. medulloblastoma, ependymoma), (rhabdomyosarcomas), retinoblastomas and lymphomas.

A recent comparative analysis of second malignancy risk in patients treated with proton therapy versus conventional photon therapy from Harvard Medical Centre indicates that the use of proton radiotherapy is associated with similar efficacy but with a significantly lower risk of a second malignancy, when compared to photon radiation therapy. In a similar comparative study, in which a craniospinal irradiation technique was successively simulated with conventional radiotherapy, photon IMRT, and proton radiation (using both passive scattering and spots scanning technique), the risk of secondary cancer using photons was demonstrated to be 6 times higher with IMRT and 11 times higher with conventional radiotherapy, when compared to proton therapy (using passive scattering). When the scanned beam technique was used, the advantage of proton therapy increased even more. This risk difference is particularly relevant to those who survive cancer in childhood and are then confronted with the prospect of developing secondary malignancy at a later age, suffering potentially serious and devastating physical and psychological consequences.

For reasons described above, when treating childhood cancer the efforts are particularly focused on developing strategies that reduce the exposure of normal tissues and critical structures to radiation. A possible approach would be to at least consider proton treatment for every child that is eligible for radiotherapy (whenever this modality is available). Weighing each patients’ personal options (based on comparative simulated treatment plans) one would then have to decide whether proton therapy could be expected to bring significant benefit. For obvious reasons, the cost of this treatment would also have to be considered when weighing these options. For the moment the cost-effectiveness of proton therapy has barely been studied at all. Lundkvist et al. performed a cost-benefit analysis of proton therapy for childhood medulloblastoma and the outcome of this analysis indicates that proton radiotherapy may be cost saving in comparison to photon therapy, mainly due to the reduction of late side effects. More detailed research however is needed to show whether this also holds true for other types of cancer.
6.2.7 Paediatric tumours eligible for radiotherapy

In childhood cancer a number of categories of (rare) malignancies that are eligible for radiotherapy, and potentially also for proton therapy, can be distinguished.80

- Bone tumours: low-grade sarcoma of the base of skull, fast-growing benign chondrosarcoma, Ewing sarcoma of the skull
- Soft tissue sarcoma, including rhabdomyosarcoma
- Head-and-neck tumours, including craniopharyngioma and orbital rhabdomyosarcoma
- Low-grade glioma, including optic pathway glioma
- Meningeoma
- Other brain tumours: medulloblastoma, ependymoma, low-grade astrocytoma
- Extracranial tumours, in particular neuroblastoma
- Ocular tumours, including uveal melanoma, retinoblastoma.

It is estimated that some 140-150 children annually may be eligible for proton radiotherapy in the Netherlands, based on the above mentioned considerations and criteria. Table C4 in Annex C presents a summary of the outcomes of recent studies into the clinical effectiveness of proton therapy, and of studies making dosimetric comparisons of protons versus conventional radiotherapy in childhood tumours. This overview shows that proton treatment is a valuable complement to existing treatment modalities targeting these diverse groups of tumours. For some of these, proton radiation even presents itself as the treatment of choice, in particular due to its potential for sparing normal tissues and critical organs. As a result, one may expect less late complications and a reduction of the risk of secondary tumours.

Complications following proton radiotherapy of childhood tumours

In general the acute radiation-induced side effects of radiotherapy in children are similar to those in adults (including: skin reactions, fatigue symptoms).81 However, it is rather the long-term complications of radiotherapy that cause particular problems. These side effects include: growth and bone development disorders (inhibited growth rate), hypothyroidism (diminished activity of the thyroid gland), impaired lung function, brain disorders, and neuropsychological disorders (learning deficiencies). In children the risk of developing secondary malign-
nancy carries particular importance, in view of the long-term survival and further course of life of children with cancer. The incidence of treatment-related secondary malignancy in children is approximately 14% after 10 years, 90% of which is radiation-induced. The development of advanced radiation techniques (such as 3D-CRT, IMRT) is also aiming to reduce these long-term risks.

Proton radiotherapy now proves to be a promising development, in particular for treating children, due to its exceptional physical properties, e.g. its superior dose distribution. There are definite indications that proton radiation may actually reduce the occurrence of long-term side effects. On the other hand proton radiotherapy carries a small risk of neutron contamination during the generation of protons (when using the currently prevailing passive scattering technique); this could cause e.g. the brain to be exposed to neutron radiation and potentially lead to radiation-induced secondary tumours and other late side effects. The development and application of the so-called spots scanning technique in proton radiation however, appears to provide a conclusive solution to this problem (see Chapter 9).

### 6.3 Potential indications (improvement of treatment efficacy)

‘Potential indications’ for proton radiotherapy include those cases for which protons may be specifically utilized to improve local tumour control (see Table 6.3). Two main categories can be distinguished.

The first category includes cases where the current ‘standard’ radiation dose can not be administered without delivering a certain amount of radiation to the critical organs, which carries an unacceptable risk of radiation-induced side effects. Some side effects are considered unacceptable as they lead to devastating impact on health-related quality of life (e.g. paraplegia, complete blindness) or may even result in death (e.g. from severe radiation pneumonitis). In such cases it is generally accepted that one should limit the radiation dose to the critical organs in order to avoid these side effects, but – inevitably – at the cost of a lower dose to the target volume and thus less chance of local control. These indications are specified as ‘individual’ in table 6.3.

The second category includes indications where RCT’s should necessarily be performed to investigate the potential benefit of protons in achieving dose escalation and subsequent improvement of local control. Therefore the total number of patients (in Table 6.3) has been divided by two assuming a two-arm RCT design. These indications are specified as ‘RCT’ in table 6.3 and are discussed in more detail in paragraph 6.3.1 (lung cancer) and paragraph 6.3.2 (prostate cancer). It is expected that approximately 1.200-1.250 patients per annum with
‘potential’ indications will be eligible for proton radiotherapy in the Netherlands. In table 6.3 the estimated number of patients to have been treated with radiotherapy for a specific indication in 2005, has been calculated according to the method presented in the report published by the Dutch Association for Radiotherapy and Oncology (NVRO) in June 2007 (‘Groei met kwaliteit in de Radiotherapie. Een vooruitblik tot 2015’). The percentage of patients eligible for proton radiotherapy has been estimated on the basis of available literature.

Table 6.3 Percentage and number of patients in the Netherlands eligible to participate in RCT’s aiming to investigate the potential of proton radiotherapy for dose escalation to improve local tumour control.

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Number of patients treated with radiotherapy in NL (2005)</th>
<th>Percentage of patients treated with RT</th>
<th>Number of RT patients</th>
<th>Research participation</th>
<th>Estimated percentage ‘potential’ indications</th>
<th>Estimated number ‘potential’ indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracranial tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant brain tumours</td>
<td>1,022</td>
<td>92%</td>
<td>940</td>
<td>RCT</td>
<td>25%</td>
<td>235 (118)</td>
</tr>
<tr>
<td>Re-irradiation</td>
<td>200</td>
<td>100%</td>
<td>200</td>
<td>individual</td>
<td>25%</td>
<td>50</td>
</tr>
<tr>
<td><strong>Head and neck cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranasal sinus tumours</td>
<td>147</td>
<td>100%</td>
<td>147</td>
<td>Individual</td>
<td>25%</td>
<td>37</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>120</td>
<td>100%</td>
<td>120</td>
<td>individual</td>
<td>10%</td>
<td>12</td>
</tr>
<tr>
<td>Salivary gland tumours</td>
<td>129</td>
<td>87%</td>
<td>112</td>
<td>Individual</td>
<td>10%</td>
<td>11</td>
</tr>
<tr>
<td>Re-irradiation</td>
<td>150</td>
<td>100%</td>
<td>150</td>
<td>individual</td>
<td>25%</td>
<td>38</td>
</tr>
<tr>
<td><strong>Urologic tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>8,773</td>
<td>60%</td>
<td>5,264</td>
<td>RCT</td>
<td>10%</td>
<td>526 (263)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2,616</td>
<td>58%</td>
<td>1,517</td>
<td>RCT</td>
<td>10%</td>
<td>152 (76)</td>
</tr>
<tr>
<td><strong>Intrathoracic tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>7,848</td>
<td>76%</td>
<td>5,964</td>
<td>RCT</td>
<td>20%</td>
<td>1,192 (596)</td>
</tr>
<tr>
<td><strong>Sarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retropertioneal sarcoma</td>
<td>56</td>
<td>100%</td>
<td>56</td>
<td>Individual</td>
<td>25%</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21,061</td>
<td></td>
<td>14,471</td>
<td></td>
<td></td>
<td>2,267</td>
</tr>
</tbody>
</table>

Total, assuming that 50% of patients enrolled in RCT’s are treated with protons 1,215

a Total annual number of patients with specific type of cancer in the Netherlands, based on Dutch Cancer Registry 2005.
b Estimated percentage of patients with specific type of cancer to be treated with radiotherapy based on CCORE report and adapted in NVRO report.
c Estimated number of patients with specific type of cancer to be treated with radiotherapy based on CCORE report and adapted in NVRO report = total number of cancer patients x % of patients treated with RT.
d RCT = patients eligible for RCT (the number is divided by 2 assuming a 2-arm RCT); Individual = patients eligible for proton radiation on individual criteria (to achieve the required escalated dose, without unacceptable risk of radiation-induced side effects).
e Estimated percentage of patients with specific type of cancer with potential indication for proton radiotherapy, based on available in-silico studies and expert opinion.
f Estimated number of patients with specific type of cancer with potential indication for proton radiotherapy. Numbers in parentheses are patients enrolled in RCT’s that are actually treated with protons. These are maximum numbers based on available in-silico studies and expert opinion.
6.3.1 Lung cancer

For most patients lung cancer is diagnosed when they are already in an advanced stage of the disease, and are therefore no longer candidates for surgery. Radiation therapy delivered with photons plays a fundamental role in the treatment of non-small cell lung (NSCLC) cancer, preferably in combination with concurrent chemotherapy. Its application in early stage disease is also extensively documented, since many patients are not suitable for surgery due to co-morbid conditions. For these patients, treatment with high radiation doses applied with stereotactic techniques using photons, yields local control rates comparable with surgical series, and with very few side-effects due to the relatively small volumes being treated.

Three studies have demonstrated similar high local control rates (compared to conventional radiotherapy) with hypo-fractionated treatment schedules using protons for stage IA-B disease, and with mild toxicity. From this point of view, looking at the already favourable therapeutic ratio of the stereotactic photon therapy, the added value of proton radiotherapy in early stage non-small cell lung cancer is probably quite limited. However, this may be rather different for locally advanced lung cancer. The loco-regional control rates achieved with photons in these cases remain poor, and the outcomes of a number of both randomized and non-randomized studies indicate that radiation dose escalation in NSCLC is associated with improved loco-regional tumour control. However, dose escalation in these patients is generally hampered by the dose to critical organs such as the lungs themselves, the oesophagus, heart and spinal cord. For these organs, dose-volume-effect relationships have been confirmed in numerous retrospective and prospective cohort studies. Because of this, higher dose conformity, i.e. applying a higher dose to the target volume while reducing the dose to critical organs, is clinically highly relevant.

The results of in-silico studies in lung cancer have indeed confirmed that the dose to critical organs can be reduced significantly with protons, as compared to advanced photon techniques (IMRT). In this way dose escalation to the tumour becomes feasible without increasing the risk of unacceptable toxicity, at the same time reducing the probability of severe side effects. In a study by Chang et al, typical stage III lung cancer patients were optimally planned using photons (3D-CRT or IMRT ) and protons respectively. In all cases, the dose to the lungs, spinal cord, heart, and oesophagus, as well as the integral dose was lower with proton therapy, even if compared with photon IMRT. Even with dose escalation to the target volume, proton treatment still significantly reduced the dose to
normal lungs, oesophagus, spinal cord, and heart. In addition, there was 33-61% absolute reduction of non-target integral dose with proton therapy. Proton radiotherapy with dose escalation in NSCLC may therefore result in better local control and increased survival without increasing toxicity, or with even lower rates of side effects. Currently, several ongoing phase I/II clinical trials are assessing the therapeutic efficacy and toxicity of proton radiotherapy, with or without concurrent chemotherapy, for patients with inoperable stages II/IIIA/B non-small cell lung cancer (see clinical trials archive NCT00495170, NCT00614484, and NCT00495040).

Several studies also deal with physical and technical challenges related to proton radiotherapy in lung cancer.95-99 Respiration-induced variations in tissue density lead to changes in radiologic path lengths and could result in geometric misses. Due to the finite range of protons, this effect is much more critical in proton radiotherapy than with photons. Using 4D-CT planning and tools like ‘smearing’ (see Glossary, Annex E), and reconstructed ‘average target volumes’, these technical challenges can be overcome.

In conclusion, the results of in-silico clinical trials in locally advanced lung cancer show that further dose escalation is possible by using protons instead of photons, without increasing the dose to organs at risk. As the results of numerous studies also demonstrate that in NSCLC loco-regional tumour control can be improved by escalating the dose, the use of proton radiotherapy has the potential to increase the therapeutic ratio (and therefore the chance of cure). So far, however, limited data are available on its application in clinical practice that support the outcomes of these plan comparison studies.99 Well-designed clinical trials (RCT’s) and prospective studies are needed to better evaluate and validate the benefits of proton therapy with respect to other high-precision radiotherapy modalities. These studies should adequately take into account the special technical requirements of proton radiation in lung cancer.

### 6.3.2 Prostate cancer

The beneficial effect of a higher radiation dose on prostate cancer control has been documented in several randomized trials, using 3D-CRT and IMRT with photons, and even in one trial combining photons and protons.100 The anterior rectal wall, located dorsally and in direct contact with the prostate, is the dose limiting critical organ in this tumour site. Dose planning studies and clinical experience from Mass General Hospital in Boston indicate that proton radiotherapy is able to deliver similar high doses of radiation to the prostate, and
achieves high levels of tumour eradication without any substantial increase in morbidity. Furthermore, proton therapy appears to reduce the volume of pelvic tissue receiving lower doses of radiation.\textsuperscript{101} It is not clear however, whether this advantage translates into worthwhile clinical differences. This should be evaluated in clinical trials, focusing on tumour control, but also, and maybe more importantly, on morbidity and health related quality of life.\textsuperscript{102} It should be stressed that for many patients with prostate cancer, brachytherapy offers a good alternative to external beam radiotherapy with either protons or photons. However, for those patients in whom brachytherapy is not feasible or not chosen for other reasons (e.g. patients own preference), protons could be used for dose escalation without increasing the dose to critical organs. Given the current availability of effective alternative treatment modalities in prostate cancer, the committee estimates that only about 10% of all prostate cancer patient treated with radiotherapy in the Netherlands may be eligible for such a study involving protons (see Table 6.3).

6.4 Model-based indications (improvement of treatment quality)

‘Model-based’ indications include those cases where protons will primarily be utilized to reduce side effects of radiation. In fact these patients should preferably be offered proton therapy, whenever clinically available, if individual planning comparative studies show that the risk of side-effects can be reduced significantly by using protons instead of photons. Clinical validation of this strategy should be carried out by prospective cohort studies with historical comparisons. It is estimated that approximately 5,000 patients in the Netherlands are eligible for proton radiotherapy for model-based indications (see Table 6.4). This number is again based on the number of patients that have actually been treated with radiotherapy, following the calculation method used in the before-mentioned NVRO report. In the following paragraphs, the most important model-based indications will be discussed in more detail.

6.4.1 Lung cancer

The main side effects of radiation in lung cancer include: a) swallowing dysfunction due to radiation oesophagitis, which may develop into long term and persistent dysphagia; b) radiation pneumonitis, and c) lung fibrosis, leading to long term and persistent loss of lung function. These side effects are frequently observed and are found to have a negative impact on health-related quality of
The risk of developing these side effects is strongly associated with the dose to the oesophagus\textsuperscript{105-107} and to the lungs\textsuperscript{91,108-110} respectively.

The number of in-silico studies systematically comparing currently used photon techniques with protons is as yet limited. However, these studies do show that in most cases the dose to organs at risk, such as the lungs and oesophagus, can be reduced significantly by using protons.\textsuperscript{111-113} Indeed, the first results of a clinical study comparing proton radiotherapy to IMRT in NSCLC (conducted in the M.D. Anderson Cancer Hospital in the US) show that the probability of radiation pneumonitis and oesophagitis was reduced significantly when using protons.\textsuperscript{112} Moreover, it was shown that the feasibility of and compliance with concomitant chemotherapy increased due to a reduction in haematological toxicity, which was explained by a reduced radiation dose to the bone marrow.

A preliminary conclusion might be that proton radiotherapy has little extra benefit to offer in the early stages of lung cancer (stage I), in view of the fact that local control is already excellent using stereotactic photon radiation, with minimal acute and long-term side effects. Based on the existing literature cited before, the greatest advantage is to be expected for the more advanced stages of the disease, eligible for chemo-radiation: in small-cell (limited disease) as well as in non-small cell lung cancer (stages II and III). This is mainly because of the expected reduction of side effects. The estimated numbers of patients in table 6.4 do not take include patients with metastatic NSCLC or extensive-stage SCLC.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Tumour site} & \textbf{Number of patients treated with radiotherapy in NL (2005)} & \textbf{Total number of cancer patients in patients treated with RT}\textsuperscript{a} & \textbf{Percentage of patients treated with RT}\textsuperscript{b} & \textbf{Estimated percentage of model-base indications}\textsuperscript{c} & \textbf{Estimated number of model-based indications}\textsuperscript{d} \\
\hline
\textit{Intracranial tumours} & & & & & \\
\text{-meningeoma} & 300 & 50\% & 150 & 50\% & 75 \\
\text{-re-irradiation} & 200 & 100\% & 200 & 25\% & 50 \\
\text{Head and neck cancer} & & & & & \\
\text{-paranasal sinus tumours} & 147 & 100\% & 147 & 50\% & 74 \\
\text{-nasopharyngeal carcinoma} & 120 & 100\% & 120 & 65\% & 78 \\
\text{-oral cavity cancer} & 904 & 78\% & 705 & 25\% & 176 \\
\text{-pharyngeal cancer} & 415 & 100\% & 415 & 70\% & 291 \\
\text{-laryngeal cancer} & 751 & 100\% & 751 & 50\% & 376 \\
\text{-re-irradiation} & 150 & 100\% & 150 & 50\% & 75 \\
\text{Urologic tumours} & & & & & \\
\text{-prostate} & 8,773 & 60\% & 5,264 & 10\% & 526 \\
\text{-bladder} & 2,616 & 58\% & 1,517 & 10\% & 152 \\
\hline
\end{tabular}
\caption{Estimated percentage and number of patients for whom proton therapy may be indicated with the aim to reduce the risk of side effects.}
\end{table}
6.4.2 Head and neck cancer

Survival in head and neck cancer is mainly influenced by rate of loco-regional tumour control, which requires high radiation doses to the tumour. Moreover, most tumours in the head and neck region are characterised by a high risk of occult metastases in the regional lymph nodes, which requires elective irradiation of the neck on both sides. The final result is that many patients will receive high radiation doses to large volumes of normal tissue, resulting in a large variety of side effects, such as dry mouth, swallowing dysfunction, dental caries, and hearing loss. Some side effects are considered unacceptable as they will have a devastating impact on health-related quality of life as reported by patients: in a single case causing paraplegia or complete blindness or exceptionally – when
taking a ‘calculated risk’ – even resulting in death (e.g. from brain necrosis). Among radiation oncologists, the generally accepted approach is that one should limit the radiation to these critical organs to a certain threshold, even at the cost of a lower dose to the target volume and thus a higher risk of local recurrence.

Recent analysis based on radiation quality assurance data collected within the framework of a RCT in head and neck cancer indeed showed that sub-optimal radiotherapy, resulting from under dosage in the tumour area, significantly reduced local control and eventually also survival (L. Peters, abstract EHNS-ESTRO 2009).

The risk of developing numerous radiation-induced side effects in the head and neck region is dependent on the radiation dose and irradiated volume of specific critical organs. For instance, the risk of xerostomia (permanent dry mouth) strongly increases with an increasing mean dose to the salivary glands, and the risk of swallowing dysfunction increases with the radiation dose to the muscles that are involved in swallowing. Because of this observed association, deliberate reduction of the radiation dose to these structures can be expected to decrease or even prevent the development of these side effects.

A number of in-silico studies have reported on the reduction of the dose in critical organs that can be achieved with protons, as compared to photons, demonstrating that the dose to critical organs can be significantly reduced when protons are used. This is particularly true for tumours originating in the pharynx and the paranasal sinuses, which will occur in head and neck cancer patients treated with bilateral neck irradiation, as is the case in the majority of these patients. Some studies revealed that a significant reduction of the risk of side effects, estimated in advance on the basis of existing and validated NTCP models, indeed occurred in approximately 70% of the cases.

6.4.3 Breast cancer

Patients with left-sided breast cancer have been shown to present a higher risk (16% vs 11.6%) for late cardiac morbidity than patients with right-sided breast cancer. This risk is further increased with the use of systemic anticancer agents and also in younger patients. As the incidence of breast cancer in younger patients increases by some 2% per year and the vast majority of these patients indeed receive adjuvant systemic treatment, this is an increasing concern. In addition, patients with locally advanced breast cancer or those treated with loco-regional radiotherapy, have an increased risk of radiation-induced toxicity to the lungs.
The results of in-silico clinical trials have shown that protons give less dose to the non-target normal tissues such as the heart and the lungs after (partial) breast irradiation\textsuperscript{131-133} as well as after loco-regional radiation therapy\textsuperscript{134}, in comparison to 3D-CRT and IMRT. In theory this should translate into lower long-term cardiac morbidity and mortality in these patients, and would often result in a longer life expectancy. Further studies are certainly needed to define more clearly which patients would benefit most. However, because of the prolonged interval between treatment and the appearance of late side effects, it will likely be several years before these outcomes are known. In the present absence of clinical data, cost benefit estimates may give some insight in the potential benefits for this large group of patients. Data from Sweden and the United States indicate cost-effectiveness with protons for selected patients with left-sided breast cancer.\textsuperscript{34,35,37}

6.4.4 Prostate cancer

As already stated in paragraph 6.2.2, the chance of prostate tumour control increases with higher radiation doses. This is accompanied however by an increased rate of mainly gastrointestinal and genito-urinary side effects.\textsuperscript{32,135,136} The use of modern photon radiation techniques can reduce this risk.\textsuperscript{32} Proton radiotherapy is theoretically able to deliver similar dose distributions around the prostate with lower dose to the non-target normal tissues.\textsuperscript{137-141} Although the results of in-silico clinical trials do indeed indicate lower dose to the non-target normal tissues, the role of protons in prostate cancer remains at least controversial\textsuperscript{142}, as the clinical relevance of these dose reductions is currently unclear and begs to be clarified, preferably in a RCT.

In more advanced stages of prostate cancer the pelvic lymph nodes are often irradiated. This leads to a substantial increase of the dose to the bowels. As the occurrence of side effects is directly related to the irradiated volume, it is likely that proton radiotherapy may further reduce the morbidity in these cases.

6.5 Indications aiming at reduction of secondary tumours

Despite its beneficial effects on tumour control, radiation at the same time bears the risk of inducing secondary malignancies. In particular younger patients run a high risk of developing secondary tumours after receiving radiotherapy as the occurrence of secondary tumours is especially increased when radiotherapy is administered at a young age.\textsuperscript{43,143,144} The higher risk of a second malignancy becomes manifest some 5 to 10 years after radiotherapy and has been shown to
persist for at least 30 to 35 years.\textsuperscript{42,144,145} Data from the WW II Japanese atomic bomb survivors show that radiation-associated excess risks persist for a lifetime.\textsuperscript{44} This information is particularly relevant for patients who have been treated with radiotherapy for childhood or adolescent malignancies: when cured their life expectancy is excellent, but this may be compromised by the elevated risk of second malignancies.\textsuperscript{145,146}

A series of reports, including Dutch studies, have reported on late side effects after irradiation, including the induction of secondary tumours.\textsuperscript{41-43,147,148} These studies have demonstrated that the risk of radiation-induced secondary cancers increases with the total radiation dose to the normal tissues.\textsuperscript{143,147,149,150} A linear dose-response relationship between radiation dose and risk of secondary cancer has been clearly demonstrated for breast cancer\textsuperscript{143,147,150}, lung cancer\textsuperscript{149,151}, stomach cancer\textsuperscript{152}, and sarcoma.\textsuperscript{153,154} All tissues that lie close to and particularly in front and beyond the target area (tumour) are exposed to unwanted irradiation and consequently are at risk of developing secondary cancers.\textsuperscript{43} Although some tissues and organs are more sensitive to developing radiation-induced tumours than others, there are no tissues that are totally resistant. Surveillance of Hiroshima and Nagasaki atomic bomb survivors has shown that even a very low acute radiation dose (integral dose) can induce secondary cancers.\textsuperscript{44} And although IMRT is now making an important contribution to the reduction of the dose to the critical organs, the dose to these organs and to the rest of the body is still not zero, and in fact with IMRT can be sometimes even higher than with conventional photon radiation at normal tissues further away from the target. In other words, with IMRT a larger volume of normal tissue receives a relatively low dose of radiation. A few studies have shown that a larger radiation volume with similarly dosed radiotherapy yields a higher risk of secondary cancers.\textsuperscript{155,156}

From a theoretical point of view, one can, after irradiation with protons, expect a reduction of secondary tumours as the beam properties of protons enable one to achieve a lower dose to the critical organs in front of and beyond the tumour as well as a lower integral dose. Indeed, a recent comparative analysis of secondary malignancy risk in 503 patients – treated with proton therapy between 1974 and 2001 at the Harvard Cyclotron in Boston – versus 1591 matched patients from the SEER cancer registry treated with conventional photon therapy, revealed a significantly lower risk of second malignancy after proton radiotherapy when compared with photon radiation therapy.\textsuperscript{45,157}

Table 6.5 shows the estimated annual number of patients eligible for proton radiotherapy in the Netherlands to reduce/avoid the risk of secondary tumours.
Table 6.5 Estimated percentage and number of patients for whom proton radiotherapy is indicated to reduce secondary tumours.

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Number of patients treated with radiotherapy in NL 2005</th>
<th>Total number of cancer patients in NL 2005</th>
<th>Percentage of patients treated with RT</th>
<th>Number of patients treated with RT</th>
<th>Estimated percentage of standard indications</th>
<th>Estimated number of standard indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>12,171</td>
<td>10,102</td>
<td>83%</td>
<td>6%</td>
<td>606</td>
<td></td>
</tr>
<tr>
<td>Haematol. malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Hodgkin</td>
<td>393</td>
<td>255</td>
<td>65%</td>
<td>10%</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>-Non-Hodgkin</td>
<td>2,713</td>
<td>814</td>
<td>30%</td>
<td>10%</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>590</td>
<td>118</td>
<td>20%</td>
<td>80%</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15,867</td>
<td>11,289</td>
<td></td>
<td></td>
<td>807</td>
<td></td>
</tr>
</tbody>
</table>

a Total annual number of patients with specific type of cancer in the Netherlands, based on Dutch Cancer Registry 2005.
b Estimated percentage of patients with specific type of cancer to be treated with radiotherapy based on CCORE report and adapted in NVRO report.
c Estimated number of patients with specific type of cancer to be treated with radiotherapy based on CCORE report and adapted in NVRO report (= total number of cancer patients in NL 2005 x % of patients treated with RT).
d Estimated percentage of patients with specific type of cancer with indication for proton radiotherapy to prevent secondary tumours, based on available in-silico studies and expert opinion.
e Estimated number of patients with specific type of cancer with indication for proton radiotherapy to prevent secondary tumours, based on available in-silico studies and expert opinion.
Chapter 7

Estimated number of patients for proton radiotherapy

In this Chapter an overview of treatment indications for proton therapy resulting in an estimated annual number of patients who are (potentially) eligible for proton therapy in the Netherlands, is presented (see Table 7.1). These estimates are based on the summary tables presented in the previous Chapter, and should be seen as maximum numbers.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Total number of patients with cancer in NL 2005(^a)</th>
<th>Number of patients treated with RT(^b)</th>
<th>Estimated number of patients eligible for proton radiotherapy(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard indications</td>
<td>550</td>
<td>299</td>
<td>252</td>
</tr>
<tr>
<td>Potential Indications</td>
<td>21,061</td>
<td>14,471</td>
<td>1,215</td>
</tr>
<tr>
<td>Model-based indications</td>
<td>52,795</td>
<td>34,697</td>
<td>4,824</td>
</tr>
<tr>
<td>Reduction of secondary tumours</td>
<td>15,277</td>
<td>11,171</td>
<td>807</td>
</tr>
<tr>
<td>Total</td>
<td>7,098</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Total annual number of patients with specific type of cancer in the Netherlands, based on Dutch Cancer Registry 2005.

\(^b\) Estimated number of patients with specific type of cancer to be treated with radiotherapy, based on CCORE report and adapted in NVRO report.

\(^c\) Estimated number of patients with specific type of cancer eligible for proton radiotherapy based on available *in-silico* studies and expert opinion.
7.1 **Standard indications**

Starting from the CCORE data*, the estimated number of patients in the Netherlands for whom proton radiotherapy is considered ‘standard’ treatment, totals 252 annually (i.e. approximately 0.6% of the total number of patients eligible for radiotherapy).

7.2 **Potential indications**

The estimated number of patients that could benefit from protons based on ‘potential indications’ (focusing on improving local tumour control), totals 1,215 (i.e. approximately 3.0% of the total number of patients eligible for radiotherapy).

7.3 **Model-based indications**

The largest category of patients eligible for proton radiotherapy is that with ‘model-based indications’ (focusing on reducing or preventing side effects), totalling 4,824 patients (i.e. approximately 12.1% of all patients eligible for radiotherapy).

7.4 **Reduction of risk of secondary cancer**

The estimated number of patients that should be treated with protons, with the aim of reducing the risk of secondary tumours, is 807 (i.e. approximately 2.0% of all patients eligible for radiotherapy).

7.5 **Total number of eligible patients**

The above estimates result in a total number of about 7,000 patients per year, based on the cancer incidence figures of 2005 for the whole of the Netherlands. Given the fact that it will take at least 4 to 7 years for a new proton facility to become fully operational, one should extrapolate this number of potential candidates for proton radiotherapy to 2010 and 2015, assuming an annual increase of

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the number of cancer patients of 3% per year. This would result in an estimated
total number of about 8,100 and 9,400 patients respectively, who are potential
candidates for proton radiotherapy in the Netherlands in the coming years.

These prospective figures, resulting from the Dutch Cancer Registry data,
can also be compared with the estimates presented in two other international
reports. On the basis of these studies, the total number of candidates for
proton therapy, when translated to the Dutch situation in 2005, would vary
between 6,000 and 11,500 patients annually.
8.1 Proton therapy versus conventional radiotherapy

Goitein et al have performed a cost comparison study for both proton therapy and advanced photon radiotherapy (IMRT). They found that the cost of proton treatment was approximately 2.4 times higher than that of photon treatment (€1,025 vs €425 per fraction, or €25,600 vs €10,600 per treatment). In this study both capital expenditure and operating costs were considered in detail. Capital expenditure (for construction of the facility) is the dominant factor responsible for this cost difference, but the average number of patients treated per year, number of treatment rooms and number of gantries also have significant impact. The authors expect a 25% decrease in cost if the facility would run a full treatment schedule of 14 hours a day, operates with 3 gantries, and once more experience is gained in machine maintenance and treatment delivery. Another study estimated the cost of light ion treatment to be at least 3 times higher than that of protons and approximately 8 times higher than photons.
8.2 Cost-effectiveness data

Lodge et al have performed a systematic review and identified 14 publications dealing with economic evaluation of proton therapy, of which 4 addressed cost-effectiveness in more detail. They found the quality of these studies to be rather variable and the outcomes difficult to compare. The most relevant and detailed are the following.

Lundkvist et al studied cost-effectiveness of proton radiotherapy in the treatment of childhood medulloblastoma, using a Markov simulation model to evaluate the consequences of radiotherapy for this group of patients. Children with medulloblastoma aged 5 years were followed during their treatment. These patients were at risk for a range of adverse events, most of them radiation-induced (e.g. hearing loss, growth and cognitive impairment, osteoporosis, cardiac disease, and secondary malignancy). The risk of these adverse events in a group of children receiving photon radiotherapy (IMRT) was calculated from existing studies (base-case analysis). Risk reduction with proton therapy was then simulated, using dose-planning models. Following this, costs and utilities for both the IMRT and proton therapy group were calculated. The total radiation costs were found to be €4.239 for conventional radiation and €10.218 for proton radiotherapy. However, proton therapy was estimated to save another €23.600 by better preventing adverse events. Proton therapy also resulted in 0.68 QALY’s (quality-adjusted life-years) gained, compared to conventional radiation. The overall conclusion from this study was that proton therapy can be cost-effective and cost-saving compared to conventional radiotherapy for this specific group of patients, if they are carefully selected (on the basis of their risk profile).

The same authors also studied cost-effectiveness of protons in other groups of patients, using the same Markov cohort simulation model (for prostate cancer, left-sided breast cancer and head and neck cancer). The outcomes of different radiation modalities in 55-year-old women with breast cancer were simulated; cost and QALY’s were the primary outcome measures. The cost per QALY gained was found to be €67.000 for the average patient with left-sided breast cancer treated with proton therapy. It was concluded that this amount would be significantly reduced if only patients with high risk of developing cardiac disease were selected.

Konski et al in 2007 compared proton therapy with current state-of-the-art radiotherapy in the treatment of adenocarcinoma of the prostate. Again, a Markov model approach was used, combining cost data, freedom from...
biochemical failure (FFBF), and utility data obtained from the literature and from patient interviews. The comparison focused on treatment delivered with proton beams (91.8 cobalt gray equivalent - CGE) versus IMRT with photons (81 CGE); the model was run for length of time after treatment, patient’s age, the probability of 5-year disease-free survival (FFBF) after proton and photon radiation, patient utilities and treatment cost. Analysis at 15 years post treatment for 60-70 year-old patients resulted in an expected mean cost of US$63,511 for proton therapy (resulting in 8.54 - 9.91 QALY’s gained) and US$36,808 for IMRT (resulting in 8.12 - 9.45 QALY’s gained). Focusing on proton therapy, the incremental cost effectiveness ratio (ICER) for a 70-year-old man was calculated at US$63,578 per QALY, and at US$55,726 per QALY for a 60-year-old man. The conclusion from this analysis was that, even assuming that using protons would allow a 10-Gy dose escalation in the prostate compared with IMRT, proton therapy is not cost effective for most patients with prostate cancer. Proton treatment could however benefit younger men with intermediate-risk prostate cancer, who have longer life expectancies and a longer time horizon to experience a recurrence of their cancer and undergo salvage treatment. For this group proton therapy may also be cost-effective. On the basis of this analysis the authors concluded that the number of proton treatments for prostate cancer in the United States should not be further increased, pending comprehensive evaluation. One criticism to this study is that the threshold for cost-effectiveness was arbitrarily set at US$50,000 per QALY.

In a recent study (2008) by the US Institute for Clinical and Economic Review (ICER) into the treatment of low-risk prostate cancer, comparing brachytherapy, IMRT and proton beam therapy, Ollendorf et al reached their conclusions based on a meta-analysis of existing clinical data. They reviewed 159 selected articles (from a total of 755): 136 on brachytherapy, 6 on proton therapy and 4 on IMRT, and another 13 on active post-treatment surveillance. All reports on proton therapy were based on either cohort or case-control studies or on non-controlled case series. Compared were the clinical effectiveness of the three treatment modalities, their toxicity profiles, and the expected costs, in an economic model based on a life expectancy of 17 years post treatment for a 65-year old man. The analysis showed almost equal clinical effectiveness for all modalities, relatively similar toxicity, and therefore only small differences in overall quality-adjusted life expectancy. On the other hand, large differences were observed in lifetime cost of treatment, with the brachytherapy overall cost being 30% lower than IMRT and 60% lower than proton therapy. Table 8.1 shows both costs and QALY’s for the different modalities.
With almost equal clinical effectiveness for all modalities, brachytherapy (both immediate and deferred treatment) emerges as the least costly and most effective strategy. Even under different scenarios (varying toxicity rates and toxicity-related utilities), because of the very small differences in QALY’s and the large cost differential between treatment modalities, the incremental cost-effectiveness rates for IMRT and proton therapy remain very high (>US $1 million per QALY). It must be stressed, however, that the outcome of this analysis is based on the assumption of no real difference in survival or biochemical recurrence among all three treatment modalities, which leads to very small differences in QALY’s produced in the model findings. In fact, the clinical data on toxicities are sparse and highly variable, especially for IMRT and proton therapy. This warrants further prospective comparative study.

The committee cannot but observe that these calculations are based on current treatment rates in the US, and not on the actual costs (probably considerably less). This practically precludes the realistic translation of such cost comparison data to the Dutch context.

### 8.3 Conclusions

Because of its high capital outlay, proton therapy is still considerably more expensive than photon radiotherapy. This leads to a cost increase factor of 1.5 to 2.5 for proton therapy, depending on the in- or exclusion of the initial capital investment, the capacity and the workload of a centre. The present peer-reviewed literature contains little robust evidence on the cost-effectiveness of proton therapy, as compared to other radiotherapy modalities. A realistic cost-effectiveness assessment or economic appraisal must also take into account any proven clinical benefits of proton therapy.\(^\text{165,166}\) This data will have to be generated and validated in the coming years. Such economic analyses of proton therapy as there are (e.g. in breast cancer, head and neck cancer, childhood cancers, medulloblastoma, and sarcoma) indicate that this treatment can indeed be cost-effective in well-selected patient populations for whom the reduction in toxicity, side effects and mortality offered by protons translates into a significant reduction in cost and gain in quality-adjusted life years.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>QALY’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachytherapy</td>
<td>$29,575</td>
<td>13.90</td>
</tr>
<tr>
<td>IMRT</td>
<td>$41,591</td>
<td>13.81</td>
</tr>
<tr>
<td>Proton therapy</td>
<td>$72,789</td>
<td>13.70</td>
</tr>
</tbody>
</table>
Chapter 9

Current development of proton radiotherapy

9.1 Facilities for proton radiotherapy

In general, a proton facility consists of a dedicated particle accelerator (cyclotron or synchrotron) and a beam line system for the transport of the protons to the treatment rooms. Various components in the beam line, such as energy degraders and deflection magnets, are used to give the beam the correct physical properties. Sophisticated beam monitoring systems are used to assure these properties.

Protons are commonly accelerated with the help of a cyclotron or a synchrotron. An important advantage of a cyclotron is that its beam intensity is very stable. The advantage of a synchrotron is its capability to accelerate a variety of other (heavy) particles. A single accelerator is able to supply proton beams to multiple treatment rooms for both clinical and research purposes. Protons can be aimed at the tumour either by a fixed beam or by a rotational gantry. A rotational gantry allows radiation treatment from all possible directions and offers maximal flexibility. Today, in most proton facilities both options are available: a stationary horizontal beam line is used for single-beam irradiations of for example eye melanomas, and one or more gantries for complex, multidirectional treatment plans. Imaging devices in the treatment room are required to assure the correct patient setup and location of the tumour with respect to the planned dose distribution. A typical proton facility has three treatment suites and may treat around 1000-1500 patients annually to achieve an economically feasible operation. Figure 9.1 shows the lay-out of a modern proton radiotherapy facility.
9.2 Methods for Proton radiotherapy

The size of the proton Bragg peak is narrower than the actual size of most tumours. Therefore two methods, namely ‘passive scattering’ and ‘pencil beam scanning’, are currently available to spread the dose of a proton beam effectively to match the volume of an individual tumour. In this way the maximum dose (hot spot) can be localized in the target volume in three dimensions (spot scanning). In the following paragraphs these techniques will be described in more detail.

9.2.1 Passive scattering

The classical method to broaden a proton beam in the lateral direction is with the so-called ‘scattering’ technique. With this technique foils in the beam broaden the relatively narrow beam coming from the accelerator. However, if the thus broadened beam is too wide, damage to healthy tissue surrounding the tumour could occur. Therefore, the broadened beam is collimated using a collimator of which the aperture matches the shape of the tumour, as seen from the direction of the beam.
In the depth direction, the Bragg peak is spread out by means of a rotating modular wheel with varying thickness that is placed in the beam line. This rotating wheel creates the so-called Spread-out Bragg peak (SOBP): an in-depth flat dose distribution. A range compensator is used to conform the dose distribution to the distal or proximal edge of the tumour.

Although the passive scattering technique is currently used in most proton therapy centres, it has several disadvantages. First, the dose distribution is not optimal. In the depth direction, the dose distribution is usually shaped to the distal tumour edge. If the dose is shaped to match the distal side, the proximal boundary of the dose distribution will have approximately the same shape as the distal boundary. As a result healthy tissue located in front of thinner parts of the tumour will receive the same dose as the tumour itself. A second major disadvantage is that the range compensator and collimator are patient-specific and field-specific. Furthermore, any items through which the proton beam passes will give rise to (potentially harmful) scattered neutrons.

9.2.2 Pencil beam scanning

A new sophisticated method to conform the beam to the shape of the tumour is the application of ‘pencil beam scanning’. With this technique the Bragg peak of a proton beam is scanned in the lateral direction by magnetic deflection, and in-depth by changing the energy of the proton beam (illustrated in Figure 9.2). By optimizing the exposure time of each individual pencil beam, a higher conformity than with passive scattering can be achieved. An additional advantage is that no patient-specific and field-specific hardware is required. A relative disadvantage of pencil beam scanning is the increased sensitivity to organ motion during the delivery of the dose. Motion that interferes with the scanning could lead to under- or over-dosage of the tumour and the surrounding healthy tissue. Repeated scanning lowers this risk. A major advantage of the scanned beam technique is also that risk of generating harmful scattered neutrons is highly reduced.
9.2.3 New systems

In addition to the currently commercially available and operational extensive proton therapy facilities, using cyclotrons or synchrotrons, and large size gantries and deflection magnets necessary to focus and direct the beams on to the patients, there are developments ongoing to produce a compact proton radiotherapy system that would fit in a standard radiation treatment bunker and does not require a large size cyclotron. This involves a linear accelerator of high field-strength (100 MV/m), equipped with a so-called high gradient dielectric wall accelerator (DWA). This concept has been developed by Lawrence Livermore National Laboratory in the US (as an outgrowth of weapons research). However, this development is still in the phase of ‘proof of concept’ and has not yet produced an operational prototype.

Another system from the US that has recently come on the market, is the so-called Still River system (Monarch 250 PBRT). Again this involves a compact system, where a mini-cyclotron is integrated with the treatment unit (gantry). The first patients are expected to be treated around end of 2010. The major disad-
vantage of this system is that it will only enable proton radiotherapy using the passive scattering technique, and not by way of dynamic spot scanning. As a consequence the most attractive features of protons (dose reduction proximal of the tumour, and the possibility to do intensity-modulated radiotherapy) can not be exploited. Another limitation concerns the need for patient- and field-specific hardware adaptations (brass beam shaping device, range compensator), which makes the treatment more costly, time-consuming and less flexible.

A ‘classic’ proton radiotherapy facility usually features three or more treatment units served by one cyclotron, because this is the most cost-effective setup. Indeed, only one cyclotron accelerator and trunk line system (including steering and bending magnet systems) is needed to transfer the proton beams to multiple treatment units and locations. The major advantage of the DWA and Still River systems is said to be the fact that one buys a totally integrated system, which results in a considerably lower capital outlay. One should however keep in mind that the cost per treatment is determined by multiple factors, of which the capital investment is but one. Other factors are the time needed per radiation treatment, the depreciation period, the cost of maintenance etc. In general the capital outlay for today’s customary proton facility is higher (€45M for 3 treatment units) than for the single-unit system (€20M for a single unit), but the write-off period for the former is much longer (25 versus 10 years).

The fact that many of the cost factors involved are not yet known for these new systems, makes it practically impossible to do a reliable cost comparison (per treatment) of these different systems and determine the potential differences in cost effectiveness.

9.3 Current status of proton radiotherapy in Europe and worldwide

Figures 9.3 and 9.4 show the current locations of established and planned centres for proton therapy in Europe and worldwide. In this paragraph the current situation and status of the centres in Europe is described in further detail.
In Europe there are currently eight operational centres performing particle therapy (including proton radiotherapy). Until now, these centres have treated more than 15,000 patients in total, and worldwide the number of treated patients is around 50,000. Four of these centres (Berlin, Catania, Clatterbridge and Nice) are suitable for the treatment of eye tumours only, since they have at their disposal an accelerator of low clinical energy (60-72 MeV). Of these four, only Nice is fully dedicated to clinical treatment. The other low-energy centres devote considerable time also to research activities.

In France, the Orsay facility has been in operation for several years. Recently, the number of treatment rooms has been increased and the equipment has been modernised. There are two other planned initiatives in France: in Caen (carbon-ion facility) and Lyon (carbon-ion and protons). Uppsala (Sweden) and Villigen (Switzerland) are locations with proton centres featuring higher energy (180-250 MeV) accelerators. Currently, the carbon-ion facility in Darmstadt (Germany) is the only operational centre of its kind in Europe. Orsay, Uppsala and Villigen (using scanning beam technique) are now in the process of significantly expanding their activities. The facility in Villigen is currently extending its capacity.
from two to three treatment rooms (one fixed base facility and two rotational gantries). The clinical activities in GSI Darmstadt will be terminated in the near future and patients are now being referred (as from November 2009) to the new centre in Heidelberg (Heidelberger Ionenstrahl-Therapiezentrum HIT).

### 9.3.2 Planned centres in Europe

Several new European centres are currently under construction or have been recently approved. Four of these centres will primarily focus on proton treatment: Essen and Munich in Germany, and Trento and Mestre in Italy. Six other centres will also undertake carbon-ion treatment: Heidelberg (in collaboration...
with GSI Darmstadt), Pavia, Lyon, Caen, Vienna, and Kiel. In addition, the Karolinska Institute in Stockholm is planning the establishment of a second generation ion particle treatment facility.

On completion of these new centres and with the expansion of the already existing centres, the capacity for treating patients with particle therapy could increase more than eightfold in the coming six years. Numerous other centres all over Europe are being proposed and in the early stages of preparation, but as the tender procedure for their construction has not yet started, their eventual realization remains uncertain. Most of these proposed centres are located in Germany (amongst them: Marburg, Berlin, Köln, Aachen, Dresden, and Erlangen).

In the Netherlands there are currently three initiatives in the early stages of exploration and preparation: Maastricht, Groningen and the Leiden/Delft/Amsterdam/Rotterdam consortium.

### 9.4 Relevant advisory reports in Europe

The committee would now like to summarize two recent advisory reports, focusing on the introduction of proton treatment facilities in some countries neighbouring the Netherlands, i.e. the UK and Belgium.

#### 9.4.1 Plan for proton treatment in the UK

In April 2006 the National Radiotherapy Advisory Group (NRAG) of the Department of Health published an extensive report describing the level of radiotherapy provision required to overcome national shortages of radiation oncologists and medical physicists, and insufficient hospital-based linear accelerators for radiotherapy in an ageing and more cancer-prone population. The report also considered the potential of particle therapy (both proton and carbon-ion treatment) and explored the advantages of particle therapies for a wide range of cancers. Currently the UK has at its disposal one particle accelerator facility, located at Clatterbridge Hospital (in Wirral). Although in fact the first hospital-based proton therapy facility in the world, this is now an ageing fixed beam device with rather restricted beam energy (62 MeV), which makes it capable only of treating eye cancers. For two decades it has successfully operated as the national referral centre for choroid melanoma (100-130 patients per year). However, this facility is now deemed insufficient for treating a wider range of cancer patients, on account of both the modest beam energy and the limited infrastructure. Because of this approximately 15-20 patients annually with other cancers
are referred for proton treatment abroad (by NHS hospitals, and an unknown number as private patients).

The NRAG report concludes that there is now wide support among British radiation oncologists for the further development of proton therapy, especially if the benefits of such therapy can be properly assessed within a wider research portfolio. A distinction is made between a) ‘high priority’ indications (mainly intra-ocular melanoma, base of skull chondrosarcoma, and some pediatric tumours), which are considered already validated and widely accepted indications for proton therapy (approximately 500 per year in UK), and b) ‘strong indications’ (meningoma, acoustic neuromas and patients with complicated anatomy or previous malignancy), for which referral for proton therapy is considered the preferred treatment (another estimated 900 patients per year). Other indications are seen emerging from the literature as ‘suitable for proton treatment’, but not yet validated. Here the results of clinical trials are awaited with interest (these include prostate cancer, left-sided breast cancer, oesophageal cancer, hepatocellular cancer and gynaecological cancers), and this is expected to increase the demand for proton therapy substantially.

The report recommends that, as a start, two modern proton treatment facilities and national referral facilities are set up in England; the patient numbers for accepted clinical indications are, according to the NRAG, sufficient to justify this. In addition, capacity must be allowed for clinical research. For the interim period, and for the initial phase of introduction of proton therapy, it is recommended that there should be an expert consultation group to ensure clarity about indications and ensure equity of access. This expert group should also establish criteria and procedures for patient selection, in particular for patients who will be referred for proton treatment to centers abroad. NRAG proposes to establish (without delay) a relationship with one or more proton/particle centers abroad, to work out practical arrangements and referral criteria.

9.4.2 Advisory report on hadron therapy in Belgium

In 2006 the Belgian Senate passed a resolution that asked for a study into the accessibility of hadron therapy (= particle therapy including proton and carbon-ion treatment) for cancer patients in Belgium. This study was published in 2007 by the Belgian Centre fédéral d’expertise des soins de santé (KCE) and was based on an extensive literature review and survey of operational centers worldwide. The main questions to be answered were: ‘Should hadron therapy be introduced and developed in Belgium? For which groups of patients; on what
scale, and what costs are involved?’ On the basis of the existing scientific literature (up to 2006) the authors concluded that ‘there is no convincing evidence available that hadron therapy (including proton therapy) for any indication results in improved local tumour control, increased disease-free survival or better general patient survival’. The KCE-report continues: ‘However, there are some indications that for a very limited group of rare tumours there could be an improvement of local tumour control: i.e. ocular melanoma, chordomas and chondrosarcomas of the base of skull and the spine, locally advanced adenoid carcinoma, and some rare pediatric tumours.’ The total number of patients with these indications in Belgium was estimated at 50-100 per year. Judging against the considerable capital outlay for a hadron therapy center in Belgium (estimated at €160 million), the authors concluded that this cost does not justify the establishment of such a center in Belgium. The option that should be considered, according to the KCE-report, is referral of selected patients to treatment centers in neighbouring countries (i.e. Switzerland, Germany), and negotiating contracts with these centers for a maximum number of patients. The report, however, ends with the observation that ‘although the scientific evidence does not justify this investment in a hadron therapy center at the expense of the federal health care insurance system, there could be other reasons to consider investing in such a center: i.e. stimulating biomedical research, innovation and support of technological industry. This capital should come from other sources than the health care system.’

So far today, there have been no cross border agreements between Belgian health insurance (RIZIV/INAMI) and foreign centers to accommodate the referral of patients. Some patients have been referred to foreign centers on an individual basis, and this has been paid for by the National Cancer Foundation and the Health Care Solidarity Fund, since proton and carbon-ion therapy have not yet been included in the nomenclature of the federal insurance system.

In 2008 a new National Cancer Plan was published by the Belgian federal Minister of Health. This plan promotes the establishment of (at least) one national hadron therapy center for Belgium, which should focus on both clinical treatment and scientific/technological research. The launching of a feasibility study for such a center in Belgium was announced in the plan. In addition it was announced that the reimbursement for hadron therapy abroad for Belgian patients, at the expense of the national health insurance system, should be expanded. An interesting fact is that the Belgian company IBA (Ion Beam Application SA) is one of the world wide leaders in the development and production of particle accelerator equipment for cancer treatment.
Chapter 10

Preconditions for clinical implementation of proton therapy

10.1 Technological development

Radiotherapy with photons (X-rays), as stated before, is one of the most effective treatment modalities in modern oncology and contributes in more than 50% of all cancer patients to their cure. Over the past decades it has evolved from a simple and relatively imprecise treatment into an extremely sophisticated and accurate technique allowing the delivery of high radiation doses with high precision (intensity-modulated and image-guide radiotherapy). Despite these technological developments the major dose-limiting factor in current radiation treatment regimens remains normal tissue toxicity, ranging from (temporary) organ dysfunction to radiation-induced secondary malignancies. Radiotherapy with protons takes advantage of the specific physical and radiobiological properties of these charged particles and allows the delivery of radiation with superior dose distributions. This provides the possibility to reduce the dose in normal tissues and/or escalate the dose in tumours, resulting in an increase in the therapeutic ratio.

Proton radiotherapy thus holds the promise of being a logical next step in the evolution of radiotherapy towards a complication-free curative treatment modality.
10.2 Prerequisites for the clinical introduction of proton radiotherapy

The following issues are considered by the committee as necessary prerequisites for a careful and successful introduction of proton radiotherapy in the Netherlands.

a Clinical introduction: a two-step approach

Clinical implementation of proton radiotherapy in the Netherlands should preferably be carried out in a careful, stepwise manner. As proton radiotherapy is still an emerging radiation technique, it is crucial that its initial introduction will take place within an environment that is dedicated to high standards of care and with a proven track record of highly integrated clinical and technological research and development. During this initial phase, the activities should be focused on the clinical validation of model-based and potential indications and on technological development of proton therapy in order to exploit its true potential. The information that will emerge from this initial phase will eventually be used to determine the ‘true’ indications and to estimate the number of patients that will significantly benefit from proton radiotherapy and, subsequently, to estimate the eventually required treatment capacity for the second phase of routine use.

It should be emphasized again that proton therapy is a not yet fully developed technology, e.g. until recently most patients undergoing proton therapy have been treated with scattered beams instead of fast-scanning beams. Further development and research are needed with regard to technical aspects, such as moving targets and the relevance of the spot size. Therefore, new proton facilities should preferably operate in close collaboration with institutions having specific expertise in the field of nuclear physics.

b Capacity during the initial phase

During the initial phase of introduction, the capacity for proton treatment should preferably be sufficient to ensure treatment of at least the ‘standard’ and most model-based indication patients as well as inclusion of patients who will participate in RCT’s. On the other hand, the inevitable uncertainties in the estimation of the number of eligible patients, balanced against the required high capital outlay and subsequent financial risk, call for the necessary restraint. Moreover, it is rather unlikely that all eligible patients will be actually referred and treated with the limited capacity for proton therapy that will be available in the initial phase.
due to unrecognized indications, patient refusal or other reasons. From this point of view, it seems reasonable to assume that a maximum of 50% of the estimated number of patients eligible for proton radiotherapy actually needs to be accommodated in available proton facilities. One should also keep in mind that, even after becoming operational, it will take several years for a proton facility to achieve its full technical and logistic potential.

Therefore, based on the findings of this report, the committee concludes that the introduction of proton radiotherapy in the Netherlands should start from a realistic growth model, allowing the actual number of treated patients to gradually increase to a maximum of 4000 per year. The number and capacity of proton radiotherapy facilities in the Netherlands in this phase should be geared to accommodate this number.

c  Staffing

The staff of a proton facility should consist of dedicated, well-trained specialists (radiation oncologists, physicists, radiation technologists, technicians and, last but not least, researchers). A jointly run, continuous program of education and training should ensure the required high level of specific expertise. In addition to patient care, a proton treatment facility should be in the forefront of innovative research and develop collaborative projects (e.g. physics, radiobiology, software development, and imaging tools).

d  Methodology and data collection

One of the crucial issues in the introduction of proton therapy relates to the methodology needed to demonstrate clinical benefits of proton radiotherapy over current techniques. To establish the clinical benefit of proton radiotherapy with respect to improved treatment efficacy (better tumour control and patient survival) an RCT approach is best suited. However, as already discussed in Chapter 5, to demonstrate a considerable reduction of the probability of late toxicity effects by way of prospective randomized trials, is hardly justifiable on ethical grounds. To conduct RCT’s as a means to demonstrate (very) late treatment-related side effects and secondary cancer induction is also rather impractical, in particular due to the long latency time of the study endpoints. Therefore the use of validated predictive NTCP-models in combination with *in silico* dose planning comparative studies represents a valid alternative: the so-called ‘model-based’ approach. A proton treatment facility should therefore keep an extensive and prospective patient- and treatment-related data registry in order to expand
the number of in-silico analyses and at the same time carry out solid confirmatory clinical observational studies. Prospective data collection should already commence before the actual start of proton therapy, in order to determine the results with regard to side effects, quality of life and other endpoints achieved with currently used radiation techniques, and create a base-line. Collaboration with other (both national and international) proton treatment facilities is pivotal and ensures the necessary exchange of expertise and data. Only in this way can identification of patients who will truly benefit from proton radiotherapy be achieved.

e Collaboration and referral

From the very start of the introduction of proton therapy in the Netherlands good cooperation with regional referring hospitals should be sought to ensure access of patients to proton treatment. To this end joint protocols should be developed. Efficient referral of patients is needed, also in the interest of initiating validation studies.
Chapter 11

Conclusions and recommendations

The following are the principal conclusions and recommendations of the committee regarding the current state-of-the-art of proton beam therapy, and its potential introduction in the Netherlands.

11.1 Conclusions

1. Proton radiotherapy is an emerging treatment modality for cancer that promises to bring certain advantages over conventional radiotherapy. Its superior physical properties – minimal dose to normal tissues resulting in reduction of acute and late side effects – offer the possibility of a better and safer radiation technique for selected indications.

2. Despite 30 years of clinical experience and over 50,000 patients treated, the evidence on clinical efficacy of proton therapy relies to a large extent on non-controlled studies, resulting in a low level of evidence according to current health technology assessment and evidence based medicine criteria. Consequently, there is an urgent need for robust clinical evidence to substantiate and validate the claims to better efficacy and less side effects of proton radiotherapy. Introduction of proton therapy in the Netherlands should be conditional on conducting these studies.

3. Based on treatment plan comparative studies in patients (in silico studies), it has been demonstrated that proton beam therapy has the potential to achieve a better conformality and dose distribution as compared to conventional
state-of-the-art radiation techniques. This may lead to a reduction of side effects, and/or increased local tumour control, but without an accompanying increase in late normal tissue or organ toxicity. In addition, it may result in reduced risk of secondary malignancies.

4 Systematic review of published studies as well as reported case studies support the conclusion that proton therapy already offers better treatment for patients with ocular and intracranial tumours, and paediatric tumours, and can be considered as the ‘standard’ treatment option for these selected indications.

5 A number of other indications may be eligible for proton therapy, but proper scientific validation in these cases is still lacking, and requires additional robust studies. While randomized controlled trials (RCT’s) are generally considered the gold standard for assessing differential benefits in clinical outcome between competing therapies (e.g. demonstrating improved treatment efficacy with protons versus photons), this however may not be the appropriate approach to demonstrate the very kind of outcomes that result from novel radiation technology such as proton radiotherapy: significant reduction of late side effects, and of the risk of secondary malignancies. Other approaches, such as a combination of validated normal tissue complication probability models (NTCP) and dose planning comparative studies, may offer a more appropriate methodology for this purpose. However, RCT’s would still be needed to demonstrate increased rates of local tumour control and improved survival with proton radiotherapy.

6 In order to make the introduction of proton beam therapy feasible in the Netherlands, and also in the interest of conducting validation studies, there should be reasonable prospect that the cost of treatment for both patients with ‘standard’ indications as well as patients with ‘potential’ and ‘model-based’ indications will be covered.

7 The data available from the Dutch Cancer Registry, combined with data from relevant Australian and Swedish studies on the proportion of cancer patients eligible for radiotherapy, allow a provisional estimation of the potential number of patients in the Netherlands that could benefit from receiving proton radiotherapy. Based on 2005 data, this number could be as high as 7,000, increasing to 9,400 in 2015. However, since for different reasons (including the need for randomized controlled studies) it seems unrealistic that all eligible patients will indeed be referred for proton therapy, the actual number of patients expected to receive proton radiotherapy in the initial phase would not exceed 4,000.
11.2 Recommendations

1 A substantial number of Dutch cancer patients could potentially benefit from treatment with proton therapy, and this justifies the realization of a limited number of proton therapy facilities in the Netherlands in the coming years. However, the committee does not see it as its task to pronounce upon the number of facilities, nor recommend specific locations.

2 The available capacity for proton therapy should allow treatment of both patients with standard indications, and patients with potential and model-based indications who will participate in much-needed validation studies. The introduction of proton radiotherapy should be planned in such a way that the number of patients that are referred and treated will gradually reach a maximum of 4,000 per year.

3 Facilities for proton radiotherapy should be located in institutions that optimally combine and integrate clinical, research and technological expertise and potential.
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Annexes

A The Committee
B Contributing experts
C Summary of recent research into standard indications
D Glossary of proton therapy terms
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The Committee

The Health Council Committee on Radiotherapy consisted of:

- **Prof. M. de Visser MD PhD, chair**
  Professor of Neurology/Neuromuscular diseases, Academic Medical Centre Amsterdam, vice-president of the Health Council of The Netherlands, The Hague

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Annex

Summary of recent research into standard indications

Intra-ocular tumours

Table C1  Summary of recent clinical studies concerning proton treatment of intra-ocular melanoma (including choroid hemagioma and macula degeneration – AMD).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Outcomes/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekkering et al⁷⁶</td>
<td>2009</td>
<td>Systematic review of studies up to 2007: protons for treatment of ocular melanoma and other eye tumours. Included are studies with at least 10 patients. Total of 37 studies included (5 controlled, 2 comparative, 30 case series).</td>
<td>One RCT and 12 case series of ocular melanoma: protons give better outcomes than photons, but also significant number of side effects.</td>
</tr>
<tr>
<td>Levy-Gabriel et al⁷⁷</td>
<td>2009</td>
<td>Retrospective review of treatment in 71 patients with choroidal hemangioma</td>
<td>Protons give good long-term and functional outcomes (recovery of vision due to retinal reattachment, and tumour regression). Side effects e.g. radiation-induced maculopathy.</td>
</tr>
<tr>
<td>Kacperek⁷⁴</td>
<td>2009</td>
<td>Review of 20 years proton radiotherapy in 1700 patients with eye tumours in Clatterbridge facility (UK 1989-2007).</td>
<td>Proton therapy superior for larger tumours (&gt;5 mm thickness), tumours close to optic nerve and fovea, and for melanoma of iris and ciliary body.</td>
</tr>
<tr>
<td>Radin et al⁷⁵</td>
<td>2008</td>
<td>Retrospective case series of 23 patients. Treated with plaque-brachytherapy or protons; analysis of evolution and management of scleral necrosis as side effect.</td>
<td>Scleral necrosis is rare side effect after radiotherapy (more frequent with brachytherapy, less with proton treatment). In 17/23 patients scleral necrosis remained stable needing no further treatment.</td>
</tr>
<tr>
<td>Munier et al⁷⁶</td>
<td>2008</td>
<td>Comparison photon-proton radiation; 6 pilot cases with retinoblastoma in children.</td>
<td>Protons equal to stereotactic conformal therapy (SCR), and superior when using spot-scanning technique</td>
</tr>
</tbody>
</table>

Summary of recent research into standard indications 115
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zytkovicz et al</td>
<td>2007</td>
<td>Dosimetric study</td>
<td>Patients with uveal melanoma; comparing CyberKnife, Gamma Knife and proton therapy.</td>
</tr>
<tr>
<td>Rundle et al</td>
<td>2007</td>
<td>Retrospective study</td>
<td>Patients with iris melanoma, treated with protons. Proton beam gives significantly less peripheral dose in (contralateral) eye and thyroid gland, compared to Gamma Knife and CyberKnife.</td>
</tr>
<tr>
<td>Desjardins et al</td>
<td>2006</td>
<td>Randomized study</td>
<td>151 patients with (large) uveal melanoma treated with protons versus combined protons and laser therapy, to prevent secondary enucleation.</td>
</tr>
<tr>
<td>Conway et al</td>
<td>2006</td>
<td>Retrospective, non-randomized cohort study</td>
<td>21 patients with large choroidal or cilio-choroidal melanoma, treated with protons. Proton treatment effective for inoperable iris melanoma (superior to brachytherapy): LC in 93% of patients (14/15); eye-sparing in 80% (12/15); no metastases during follow-up. Side effects: 50% glaucoma, 33% symptomatic dry eye.</td>
</tr>
<tr>
<td>Lumbroso-Le Rouic et al</td>
<td>2006</td>
<td>Retrospective review of 21 patients with iris melanoma, treated with protons as alternative for surgical resection.</td>
<td>Proton therapy resulted in 67% LC and 90% metastasis-free survival after 24 months. Also good eye-conserving option (retention eye and visual acuity improvement).</td>
</tr>
<tr>
<td>Höcht et al</td>
<td>2005</td>
<td>Comparative dose-planning study: photons versus protons in 10 patients with posterior uveal melanoma (high risk of complications with brachytherapy).</td>
<td>Proton therapy achieves superior sparing of critical structures (80% cases), that are relevant for visual acuity.</td>
</tr>
<tr>
<td>Hamrouni et al</td>
<td>2005</td>
<td>Retrospective study in 167 patients with uveal melanoma, treated with protons at least 10 years follow-up.</td>
<td>Superior long-term outcomes with proton therapy: good visual acuity in 50%; secondary enucleation in 13%. Survival: 63% after 10 years; metastases in 31%.</td>
</tr>
</tbody>
</table>

LC = local tumour control.
### Tumours of the base of skull and paraspinal chordomas and (chondro)sarcomas

Table C2 Summary of recent clinical studies concerning proton treatment of base of skull tumours and paraspinal chordomas and (chondro)sarcomas.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Outcomes/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amichetti et al</td>
<td>2006</td>
<td>Literature review of current clinical indications for proton radiotherapy</td>
<td>5-year LC reported with protons for chordoma, chondrosarcoma and meningioma of the base of skull superior to photons.</td>
</tr>
<tr>
<td>Brada et al</td>
<td>2009</td>
<td>Systematic review of 36 studies concerning proton radiotherapy and 15 studies involving ions.</td>
<td>The included literature sees proton radiotherapy as the therapy of choice for chordoma and base of skull tumours. This is based largely on the perceived theoretical benefit of protons; however this conclusion is not yet sufficiently supported by published outcomes of studies.</td>
</tr>
<tr>
<td>Torres et al</td>
<td>2009</td>
<td>Comparative dosimetric study in 5 patients with base of skull chordoma: treatment with protons, IMRT and combined protons+ photons.</td>
<td>Combined proton + IMRT treatment achieves best dose conformity and homogeneity. Protons alone result in better normal tissue sparing, but higher dose inhomogeneity. In future further dosimetric benefit could be achieved with IMPT (intensity-modulated proton therapy).</td>
</tr>
<tr>
<td>Delaney et al</td>
<td>2009</td>
<td>Phase II study: effectiveness of combined photon + proton irradiation in 90 patients with spinal sarcoma.</td>
<td>5-year LC of 78%; 5-year overall survival of 87%, and disease-free survival of 63%. Late side effects in 5 patients. Adding protons gives results superior to conventional treatment.</td>
</tr>
<tr>
<td>Yoneoka et al</td>
<td>2008</td>
<td>Retrospective study: long-term effectiveness in 13 consecutive patients with base of skull chordoma. Surgical resection and stereotactic radiosurgery (GammaKnife) compared with proton therapy.</td>
<td>5-year survival of 82%; 5 patients survived &gt;10 years. Similar results for resection + radiosurgery, and proton therapy.</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>2008</td>
<td>Literature review of role of proton therapy for patients with base of skull chordoma and chondrosarcoma.</td>
<td>Proton therapy allows dose escalation, and results in maximal sparing of critical structures.</td>
</tr>
<tr>
<td>Feuvret et al</td>
<td>2007</td>
<td>Comparative dosimetric study: treatment plans in 10 patients with base of skull tumours using protons alone versus combined photons + protons.</td>
<td>Protons-alone result in better radiation homogeneity and sparing of normal tissue and critical structures, but dose conformity of combined treatment and protons-alone is similar. Proton therapy is best suited for pediatric patients.</td>
</tr>
<tr>
<td>Rutz et al</td>
<td>2007</td>
<td>Retrospective study: effectiveness of post-operative proton radiotherapy (using spots scanning technique) in 26 patients with extracranial chordoma.</td>
<td>Overall survival after 3 years: 84%, and disease-free survival: 77%. 4 patients with radiation-induced late side effects. Protons give good LC: 86% after 3 years, 69% after 5 years (20% with conventional radiotherapy).</td>
</tr>
</tbody>
</table>
**Other Intra-cranial tumours**

<table>
<thead>
<tr>
<th>author</th>
<th>year</th>
<th>study design</th>
<th>outcomes/conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boskos <em>et al</em></td>
<td>2009</td>
<td>Retrospective study: effectiveness of combined protons + photons in 24 patients with intracranial atypical and malignant meningioma.</td>
<td>8-year LC of 47%, 8-year survival of 43% (similar or better compared to other treatment modalities).</td>
</tr>
<tr>
<td>Cochran <em>et al</em></td>
<td>2008</td>
<td>Study of radiation exposure of the optic lens in the treatment of 39 patients with craniospinal tumours using proton therapy (craniospinal radiation technique).</td>
<td>With proton technique the mean dose to the lens could be reduced by 50%. Significant sparing of the lens especially in young patients.</td>
</tr>
<tr>
<td>Cozzi <em>et al</em></td>
<td>2006</td>
<td>Comparative planning study in patients with benign brain tumours treated with proton therapy.</td>
<td>Similar effectiveness for different proton techniques, but lowest dose in normal tissue with spot-scanning technique, in comparison with passive scattering.</td>
</tr>
</tbody>
</table>

LC= local tumour control

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**Table C3** Summary of recent clinical studies concerning proton treatment of other intra-cranial tumours.

Pommier *et al* | 2006 | Retrospective study: effectiveness of proton therapy in 23 high-risk patients with adenoid cystic carcinoma of the base of skull. | LC after 5 year: 93%, after 8 years: 82%. Superior to conventional photon therapy (LC: 17-23%). Overall 5-year survival of 56% for patients <47 years, and 100% for patients >46 years. |

Noël *et al* | 2005 | Retrospective analysis of 100 consecutive patients with base of skull chordoma, treated with combined protons + photons. Definition of prognostic factors for local control and survival. | 2-year LC of 86%, 4-year LC of 54%. 2-year survival of 94% and 5-year survival of 80%. Local control and survival largely determined by success of surgical resection. |

Igaki *et al* | 2004 | Retrospective study: clinical effectiveness of proton therapy in 41 patients with base of skull chordoma. | LC after 5 years was 46%. |
### Table C4: Summary of recent studies concerning dosimetric and clinical research for paediatric tumours.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Outcomes/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habrand et al.</td>
<td>2009</td>
<td>General literature review and summary of proton therapy in 108 children in Orsay center (1994-2007).</td>
<td>Overall 5-year survival: 88%, 5-year disease-free survival: 74%. Proton therapy more and more seen as treatment of choice, especially for radiation-resistant tumours, and tumours close to critical structures. Proton therapy more and more seen as treatment of choice, especially for radiation-resistant tumours, and tumours close to critical structures.</td>
</tr>
<tr>
<td>Merchant et al.</td>
<td>2009</td>
<td>General literature review of proton therapy in children.</td>
<td>Proton therapy allows reduction of side effects, as well as dose escalation and optimal radiation technique.</td>
</tr>
<tr>
<td>Semenova</td>
<td>2009</td>
<td>Literature review on proton radiotherapy for central nervous system tumours.</td>
<td>Proton therapy leads to better sparing of normal tissues and critical organs, less cognitive and growth dysfunction, compared to conventional RT. Better curative potential with less late side effects. Risk of secondary tumours is halved.</td>
</tr>
<tr>
<td>Boskos et al.</td>
<td>2009</td>
<td>Retrospective study: effectiveness of combined proton + photon radiotherapy in patients with malignant meningeoma.</td>
<td>8-year LC of 47%; 8-year overall survival 43%.</td>
</tr>
<tr>
<td>Fogliata et al.</td>
<td>2009</td>
<td>Dosimetric planning study of 5 complex pediatric tumours, comparing protons (IMPT), and advanced photon technique (RapidArc, Helical Tomotherapy).</td>
<td>All 3 techniques give good dose distribution and conformity. Protons result in better sparing of normal tissue and critical organs. IMPT (especially spot scanning technique) is method of choice in pediatric patients.</td>
</tr>
<tr>
<td>Kozak et al.</td>
<td>2009</td>
<td>Dosimetric comparison of proton therapy and IMRT in 10 patients with rhabdomyosarcoma.</td>
<td>Both techniques result in adequate coverage of target volume (95% of dose in 99% of CTV); protons give better sparing of normal tissue due to superior dose conformity.</td>
</tr>
<tr>
<td>Levy-Gabriel et al.</td>
<td>2009</td>
<td>Retrospective study: long-term effectiveness of protons in 71 patients with choroid hemangioma.</td>
<td>Excellent anatomical and functional outcomes in the long run; retinal reattachment, complete tumour regression, and good visual recovery (if treatment takes place within 6 months). Radiation-induced maculopathy may occur after many years as side effect.</td>
</tr>
<tr>
<td>Fossati et al.</td>
<td>2008</td>
<td>Review of complications (toxicity) after current treatment of medulloblastoma in children.</td>
<td>Proton therapy could result in significant reduction of toxicity of craniospinal irradiation, due to optimal dose distribution with IMPT (using spot scanning technique). Clinical experience (published) is still very limited: 4 patients. Proton therapy could result in significant reduction of toxicity of craniospinal irradiation, due to optimal dose distribution with IMPT (using spot scanning technique). Clinical experience (published) is still very limited: 4 patients. Potential role of proton therapy.</td>
</tr>
<tr>
<td>Hillbrand et al.</td>
<td>2008</td>
<td>Dosimetric comparison of protons and sophisticated photon therapy in patients with abdominal cancer: 5 patients with neuroblastoma (NBL), 4 patients with Wilms Tumour (WT).</td>
<td>Treatment plans using protons result in favorable dosimetric parameters in NBL and WT patients, in comparison to photons (IMRT). Risk of secondary cancer was similar for both IMRT and protons (passive scattering), but lower when using IMPT (spot scanning).</td>
</tr>
</tbody>
</table>
Merchant et al\textsuperscript{205} 2008 Dosimetric comparison of protons and photon therapy in 40 patients (with optic pathway glioma, craniopharyngioma, ependymoma and medulloblastoma - 10 patients each per indication).

MacDonald et al\textsuperscript{206} 2007 Dosimetric comparison of protons (IMPT) with photon therapy (IMRT) in 17 patients with intracranial ependymoma. Analysis of clinical outcomes using protons.

Estimated outcomes at 5 years. Differences in dose distribution translate as clinical benefit with proton treatment (better sparing of cognitive function, less growth hormone deficiency, less hearing loss). Clinical outcomes proton therapy: LC after 2-year of 86%, overall survival of 89%, and progression-free survival of 80% (all superior to conventional treatment). Coverage target volume (CTV) was similar for both protons and IMRT. Sparing of normal tissue and critical organs better with protons (could be increased with IMPT). All patients alive after 3 years, with good LC. Late side effects in 3 patients (mild to moderate). Need for longer follow-up to determine risk of secondary cancer (5-10 years).

Rutz et al\textsuperscript{207} 2007 Assessment of clinical effectiveness of post-operative proton radiation (spotscanning and IMPT) in 10 patients with chordoma and chondrosarcoma.

Feuvret et al\textsuperscript{208} 2007 Dosimetric comparison of protons-alone with combined photons + protons in 10 patients with base of skull tumours.

Both radiation modalities give similar dose conformity. Protons-alone result in better sparing of normal tissues and critical organs: treatment of choice for children.

Timmermann et al\textsuperscript{209} 2007 Assessment of clinical effectiveness of spot scanning proton radiotherapy in 16 patients with inoperable soft-tissue tumours.

Rutz et al\textsuperscript{211} 2007 Assessment of clinical effectiveness of combined proton + photon radiotherapy in 15 patients (incl. 5 children) with craniopharyngioma.

Mean follow-up was 13 years. 4 patients died. Overall survival at 10 years: 72%; LC at 5 years: 93%, at 10 years: 85%. No tumour recurrence. No neuro-psychological disorders. Results with combined treatment similar to or better than with conventional radiotherapy. Outcomes in children superior to those in adults. Proton treatment resulted in better coverage of target volume and better sparing of normal tissue and critical structures, compared to photon therapy. Protons are therapy of choice for treating children.

Hoch et al\textsuperscript{212} 2006 Retrospective study: effectiveness and toxicity of proton therapy in 73 children and adolescents with base of skull chordoma.

Lee et al\textsuperscript{213} 2006 Retrospective analysis of clinical effectiveness and toxicity of proton therapy in 16 patients with craniopharyngioma.

Luu et al\textsuperscript{214} 2006 Retrospective analysis of clinical effectiveness and toxicity of proton therapy in 16 patients with craniopharyngioma.

Fitzek et al\textsuperscript{215} 2005 Retrospective analysis of long-term outcome of combined proton + photon radiotherapy in 15 patients (incl. 5 children) with craniopharyngioma.

Lee et al\textsuperscript{216} 2005 Dosimetric comparison of protons to other conformal techniques (3D-CRT, IMRT) in 8 patients with retinoblastoma, medulloblastoma and pelvic sarcoma.

LC = Local tumour control
The following studies involving proton radiotherapy are currently registered (via WHO Search Portal):

<table>
<thead>
<tr>
<th>Main ID</th>
<th>Public Title</th>
<th>Date of Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00969111</td>
<td>Postoperative or Salvage Radiotherapy (RT) for Node Negative Prostate Cancer Following Radical Prostatectomy</td>
<td>28-8-2009</td>
</tr>
<tr>
<td>NCT00915005</td>
<td>Image-Guided Adaptive Conformal Photon Versus Proton Therapy</td>
<td>4-6-2009</td>
</tr>
<tr>
<td>NCT00901836</td>
<td>Preoperative Proton Radiotherapy for Retroperitoneal Sarcoma</td>
<td>13-5-2009</td>
</tr>
<tr>
<td>NCT00881595</td>
<td>Proton Chemoradiotherapy for High-Risk Soft Tissue Sarcomas</td>
<td>13-4-2009</td>
</tr>
<tr>
<td>NCT00881712</td>
<td>Proton Therapy With Chemotherapy for Stage III Non-Small Cell Lung Cancer (LU02)</td>
<td>13-4-2009</td>
</tr>
<tr>
<td>NCT00875901</td>
<td>Proton Therapy for Stage I Non-Small Cell Lung Cancer (LU03)</td>
<td>2-4-2009</td>
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<tr>
<td>NCT00850200</td>
<td>Proton Therapy for Hodgkin Lymphoma</td>
<td>20-2-2009</td>
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<tr>
<td>NCT00763516</td>
<td>Proton Therapy for Resectable Carcinoma of the Pancreas</td>
<td>30-9-2008</td>
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<tr>
<td>NCT00713037</td>
<td>Hypoxia-Positron Emission Tomography (PET) and Intensity Modulated Proton Therapy (IMPT) Dose Painting in Patients With Chordomas</td>
<td>9-7-2008</td>
</tr>
<tr>
<td>NCT00693238</td>
<td>Proton Therapy for Low and Intermediate Risk Prostate Cancer</td>
<td>4-6-2008</td>
</tr>
<tr>
<td>NCT00614172</td>
<td>Proton Therapy for Early Stage Breast Cancer</td>
<td>26-12-2007</td>
</tr>
<tr>
<td>NCT00503932</td>
<td>Proton Therapy With Capecitabine for Rectal Cancer</td>
<td>17-7-2007</td>
</tr>
<tr>
<td>NCT00489814</td>
<td>Study of Quality of Life for Prostate Proton Therapy</td>
<td>19-6-2007</td>
</tr>
<tr>
<td>NCT00426829</td>
<td>Proton Therapy and Bevacizumab for Primary Liver Tumors</td>
<td>23-1-2007</td>
</tr>
<tr>
<td>NCT00976898</td>
<td>Proton Beam Irradiation for the Treatment of Unresectable Hepatocellular Carcinoma and Cholangiocarcinoma</td>
<td>11-9-2009</td>
</tr>
<tr>
<td>NCT00857805</td>
<td>Transarterial Chemoembolization Versus Proton Beam Radiotherapy for the Treatment of Hepatocellular Carcinoma</td>
<td>5-3-2009</td>
</tr>
<tr>
<td>NCT00831623</td>
<td>Study of Hypofractionated Proton Beam Radiation Therapy for Prostate Cancer</td>
<td>28-1-2009</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Title</td>
<td>Start Date</td>
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<tr>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>NCT00797043</td>
<td>Photon/Proton Beam Radiation Therapy for Carcinoma of the Skin of the Head and Neck</td>
<td>24-11-2008</td>
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<tr>
<td>NCT00797290</td>
<td>Photon/Proton Beam Radiation Therapy for Carcinoma of the Nasopharynx</td>
<td>24-11-2008</td>
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<td>Pilot Study of Lucentis Combined With Proton Beam Irradiation in Treating Wet Age-Related Macular Degeneration</td>
<td>15-8-2007</td>
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<td>NCT00496119</td>
<td>Proton Beam Therapy for Chordoma Patients</td>
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<td>Neoadjuvant Accelerated Short Course Radiation Therapy With Proton Beam and Capecitabine for Resectable Pancreatic Cancer</td>
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<tr>
<td>NCT00432445</td>
<td>Proton Beam Radiation Therapy for Intraocular and Periocular Retinoblastoma</td>
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<td>NCT00105560</td>
<td>Proton Beam Radiation Therapy in Treating Young Patients Who Have Undergone Biopsy or Surgery for Medulloblastoma or PNET/blastoma</td>
<td>15-3-2005</td>
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122 Proton radiotherapy
### Annex E

### Glossary of terms and abbreviations

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Active beam</strong></td>
<td>also called ‘scanning beam’ and referring to moving (or scanning) a proton beam across the height and width of the tumour volume. It also moves throughout the tumour’s depth to cover the whole of the treatment volume.</td>
</tr>
<tr>
<td><strong>ALARA principle</strong></td>
<td>as low as reasonably achievable’. Radiation protection principle on the basis of which patients should not be exposed to a higher than strictly necessary risk.</td>
</tr>
<tr>
<td><strong>Bragg Peak</strong></td>
<td>point of greatest penetration (deposition of energy) of proton (or other heavily charged particles) radiation in tissue. This point occurs at the end of the protons’ path. By varying the beam’s energy, one can spread this peak to match the contours of a tumour or other targets.</td>
</tr>
<tr>
<td><strong>CCORE study</strong></td>
<td>Collaboration for Cancer Outcomes Research and Evaluation (Sydney, Australia)</td>
</tr>
<tr>
<td><strong>Charged particles</strong></td>
<td>positively charged subatomic particles (protons, carbon-ions)</td>
</tr>
<tr>
<td><strong>Clinical proton therapy center</strong></td>
<td>a proton treatment facility located in, or in close association with, a hospital or cancer center.</td>
</tr>
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</table>
Coformal radiation therapy
radiation that is shaped (or ‘conformed’) to the shape of a tumour in all three dimensions. The ability to shape the beam helps to deliver the bulk of the radiation to the tumour and not to the surrounding tissue.

Collimator
technical provision to narrow or broaden a radiation beam, shaping it to the target.

CVZ
College voor Zorgverzekeringen (Dutch Health Insurance Board)

EORTC
European Organization for Research and Treatment of Cancer

Equipoise principle
The concept of uncertainty: a key ethical principle in research that holds that a subject may be enrolled in a randomized controlled trial only if there is true uncertainty about which of the trial arms is most likely to benefit the patient.

Gantry
A device for rotating the radiation delivery apparatus around the patient during radiation therapy. This motion is designed to treat from different angles.

Gray
A measure of absorbed radiation dose. One Gray equals 100 rads.

High-LET radiation
High linear energy transfer radiation

Hounsfield unit
Quantitative scale describing radiodensity; radiodensity of distilled water at standard pressure and temperature is defined as zero Hounsfield units (HU)

IGRT
Image guided radiotherapy

IMPT
Intensity modulated proton therapy

IMRT
Intensity modulated radiation therapy (photons)

In silico studies
computer-based planning comparative studies

Modular wheel
A spinning polycarbide wheel with vanes of variable depth. In proton radiation therapy, protons passing through the thinner vanes travel
farther into the body than those passing through the thicker vanes. Different wheels, with different vanes, can be used to shift the peak energy (the Bragg peak) to different depths of the tumour.

<table>
<thead>
<tr>
<th>NSCLC</th>
<th>Non-small cell lung cancer</th>
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<tr>
<td>NTCP model</td>
<td>Normal tissue complication probability model</td>
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<tr>
<td>NVRO</td>
<td>Nederlandse Vereniging voor Radiotherapie en Oncologie (Dutch Radiotherapy and Oncology Association)</td>
</tr>
<tr>
<td>PBT</td>
<td>Proton Beam Therapy</td>
</tr>
<tr>
<td>Photon therapy</td>
<td>gamma and X-ray irradiation using photons</td>
</tr>
<tr>
<td>Proton</td>
<td>A positively charged particle of an atom. The charged and relatively large mass (1800 times that of an electron) of protons accounts for the Bragg peak effect.</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative Biological Effectiveness</td>
</tr>
<tr>
<td>SEER Registry</td>
<td>Surveillance, Epidemiology and End Results database (US National Cancer Institute)</td>
</tr>
<tr>
<td>SBU</td>
<td>Swedish Council on Technology Assessment in Health Care (Stockholm, Sweden)</td>
</tr>
<tr>
<td>SKION</td>
<td>Stichting Kinderoncologie Nederland (Dutch Foundation for Paediatric Oncology)</td>
</tr>
<tr>
<td>Smearing</td>
<td>A technique to counter the detrimental effects of breathing motion on the dose to the clinical target volume (CTV), by adjusting the range compensator.</td>
</tr>
<tr>
<td>SOBP</td>
<td>Spread-out Bragg Peak (extended Bragg peak covering a region encompassing the tumour).</td>
</tr>
</tbody>
</table>
TCP
Tumour Control Probability

Tomotherapy
Radiation treatment in which the radiation is delivered slice-by-slice, instead of irradiating the entire tumour volume at one time.

VWS
Volksgezondheid, Welzijn en Sport (Ministry of Health, Welfare and Sport)

WBMV
Wet Bijzondere Medische Verrichtingen (Specific Medical Procedures Act)