
Executive summary

Health Council of the Netherlands. Proton radiotherapy. Horizon scanning report. The Hague: Health Council of the Netherlands, 2009; publication no. 2009/17

What is proton radiotherapy?

Treatment with protons (a kind of charged particles) is a promising development in the field of modern radiation oncology. The physical properties of protons allow a better dose distribution as 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 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,

^{*} Health Council of the Netherlands. *Searchlight on radiotherapy. A vision for 2015*. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/27.

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 induction of (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.

Second, 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 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 in 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 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 radiotherapy over conventional photon treatment 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 paraspinal 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'.

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 is based 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 these techniques. These so called 'model-based' indications include:

* CVZ Report 'Protontherapie', Publication nr. 273, March 9, 2009.

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 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,

* Deleany G, Jacob S, Featherstone C, et al. The role of radiotherapy in cancer treatment – estimating optimal utilization from a review of evidence-based guidelines. Collaboration for Cancer Outcomes Research and Evaluation – CCORE. *Cancer* 2005; 104: 1129-37.

** Möller TR, Einhorn N, Lindblom C, et al. Radiotherapy and cancer care in Sweden. *Acta Oncologica* 2003; 42: 366-75.

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, 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 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
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patients eligible for proton treatment will take part in RCT's comparing protons 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. 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.