Report

Indications for proton therapy (part 1):

- **Intraocular tumours**
- **Chordomas/chondrosarcomas**
- **Paediatric tumours**

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Summary

New technique

During the past few years a new radiotherapy technique has been developed which may offer advantages for certain indications in comparison with conventional radiotherapy techniques: proton therapy. In the Proton Therapy Report sent to the Minister of VWS in March 2009, the *College voor zorgverzekeringen* (CVZ) described the approach chosen to assess whether treatment with proton therapy meets the legal criterion 'established medical science and medical practice' in specific indications.
This criterion co-determines whether an intervention is included among the provisions insured under the Health. Insurance Act (*Zorgverzekeringswet*, Zvw).

'Standard indications'

At the end of December 2009, the Health Council of the Netherlands [*Gezondheidsraad,* GR] issued a horizon scanning report on Proton radiotherapy . In this report, the GR distinguishes between four different types of indication fields for proton therapy. One of these relates to the so-called 'standard indications'. Consensus exists among radiotherapists/oncologists that proton therapy is an accepted form of care for these indications, in addition to other, more common forms of radiotherapeutic treatment. These 'standard indications' are:

- intraocular tumours
- chordomas/chondrosarcomas
- paediatric malignancies[1].

Conclusion: insurable care

In this report, CVZ comes to the conclusion that proton therapy is included in the basic healthcare benefit package for the indications intraocular tumours, chordomas/chondrosarcomas and paediatric tumours, because the current statutory conditions have been fulfilled (it is care normally provided by medical specialists and the care fulfils the established medical science and medical practice criterion).

'Reasonably

This does not mean that every insured client with a disorder in

[1] This refers to malignancies that occur up to the age of 18 years.

dependent upon'

one of the indication fields mentioned is automatically eligible for reimbursement of the costs of proton therapy. For every individual insured client it must determined whether, in his/her case, proton therapy is the most appropriate form of radiotherapy in comparison with other radiation techniques. As far as health insurance is concerned, this is based on article 2.1, third paragraph, of the Health Insurance Decree [*Besluit zorgverzekering* Bzv]. This article determines that an insured person only has a right to the reimbursement of medical expenses if the person is reasonably dependent upon that form – and amount – of care. This will depend upon the individual circumstances of the patient.

Care only available outside the Netherlands

Proton therapy is not (as yet) available in the Netherlands. At the moment this care can only be obtained abroad. The question is: will an insured client who depends upon proton therapy and who undergoes it abroad, be provided with this care or, alternatively, a reimbursement of its costs? The reply to this question is 'yes', although – depending on the individual situation – conditions and limits may apply. CVZ provides an outline of these in this report.

Indication protocol

Furthermore, CVZ comments that the fact that the care is not (yet) available in the Netherlands (though it is considered a provision under the Zvw for the indications mentioned), compels the professional groups involved to make haste in drawing up guidelines indicating how patient selection will take place. We understand that the professional group of radiologists (the NVRO) are currently planning to draw up just such an indication protocol.
CVZ welcomes this and urges them to press on in the matter.

WBMV permit

To CVZ's knowledge, at the moment of issuing this report no centres in the Netherlands have definitely decided to set up a proton facility. There are three initiatives that are currently at an exploratory and preparatory stage. CVZ feels it would be

Uniform data registration

wise to limit the use of proton therapy – by making use of the Special Medical Procedures Act (*Wet bijzondere medische verrichtingen*, WBMV) – to a number of locations in the Netherlands and eventually to attach to the permit for using proton therapy (which will be granted to a number of hospitals), the condition that uniform data registration takes place within those centres.

1. Introduction

Proton therapy

During the past few years a new radiotherapy technique has been developed which can offer advantages for certain indications in comparison with conventional radiotherapy techniques: proton therapy.

Technical progress

The field of radiotherapy (RT) is characterised by a rapid succession of improvements in techniques, the aim of which is to improve tumour control, reduce side effects or both. Although such technical improvements are generally readily accepted in clinics, they are by no means always subjected to randomised, long-term clinical research. After all, these are mainly technical improvements, which do not alter the essence of the treatment, but rather its precision. Proton therapy is also a form of radiation treatment. However, the radiation is induced in a different way (using protons instead of photons), and this makes it easier to apply a higher dose to the tumour and a lower dose to surrounding organs. Introducing this treatment into the Netherlands, unlike the current photon radiation, involves complex infrastructural requirement, special expertise and considerably larger financial investments.

The *GR* recently published a horizon scanning report on Proton radiotherapy (1). This report can be consulted for a comprehensive scientific analysis.

Complex care, high costs

Due to the complexity of this new care form and the additional costs, it is important to know whether this treatment is – or will shortly – be included in the package insured under the Health Insurance Act [*Zorgverzekeringswet,* Zvw] and, if so, for which indications.

Established medical science and medical practice

Whether an intervention is included among the provisions insured under the Zvw is partly determined by the criterion 'established medical science and medical practice'. Last year, in their Proton Therapy report, CVZ described how they would set to work in assessing this new form of radiotherapy, taking into account the special circumstances involved in proton

therapy (2).

GR's classification of types of indications

The GR report (1) distinguishes between various types of indications for proton therapy. Firstly, the GR distinguishes 'standard indications', for which consensus exists among radiotherapists/oncologists that proton therapy is an accepted form of care alongside other, more common forms of treatment. The GR also distinguishes between indications that are 'based on models' and 'potential' indications, pointing out that, in order to determine clinical efficacy, a number of indications first need to be examined exclusively in a study setting, whilst models would be sufficient for a number of other indications.

'Standard indications'

In this report, CVZ examines whether proton therapy is care that belongs among the provisions insured under the Zvw for the 'standard indications'. An important test is – as mentioned earlier – the legal criterion 'established medical science and medical practice'. Proton therapy is already being used (often for many years) for the 'standard indications', due to the possibly severe consequences when using conventional radiation in patients with these indications. These are the following indication fields:

- intraocular tumours
- chordomas/chondrosarcomas
- paediatric malignancies[2].

CVZ has – as indicated in the above-mentioned Proton Therapy report – set up a proton therapy group of experts[3]. This group of experts discussed the assessment of established medical science and medical practice with regard to proton therapy for the indications mentioned above, and the conclusions in this report agree with the opinions discussed by the group of experts. The draft report – in as far as it relates to conclusions over established medical science and medical practice – has

[2] This refers to malignancies that occur up to the age of 18 years.
[3] The proton therapy expert group is comprised of a number of experts on the subject, an HTA expert and a representative of, respectively, the GR, NFU, ZN, ZonMw and NZa. A representative of VWS also attends meetings.

been presented to the associations of a number of professional groups[4].

Report layout

In section 2 CVZ first reflects upon the statutory provisions that are relevant to the assessment. This section also briefly discusses CVZ's views on their method for assessing proton therapy in relation to established medical science and medical practice, as described in their report dated 9th March 2009 (2). The remaining sections discuss an examination of the provisions per indication and the results of that assessment. Section 3 discusses the indication field intraocular tumours. Sections 4 and 5 discuss chordomas/chondrosarcomas and paediatric tumours respectively. Section 6 discusses a number of relevant issues/consequences that are related to/the result of outcome of the assessment.
Finally, in section 7, we discuss the consultation regarding this subject. What responses were received and how did CVZ respond to them?

[4] This relates to scientific associations of the professional groups: Radiotherapy and Oncology, Medical Oncology, Paediatrics, Surgery, Ophthalmology and Neurology. A copy of the draft document was sent to the Order of Medical Specialists.

2. Laws and legislation

Relevant legislation

The following provisions are relevant to the question as to whether proton therapy can be classified as a provision insured under the Zvw for the indication fields intraocular tumours, chordomas/chondrosarcomas and paediatric tumours.

Curative care

Curative care As stipulated in Article 2.4, first paragraph, of the Bzv, curative care includes care that is normally provided by medical specialists[5].

Established medical science and medical practice

Established medical science and medical practice
Article 2.1, paragraph 2, of the Bzv stipulates, where relevant, that the content and amount of forms of care are determined in part by established medical science and medical practice.

Working method

Working method
In their report "Assessment of established medical science and medical practice", CVZ described their working method for determining what can be regarded as established medical science and medical practice[6]. CVZ's working method adheres to the principles of evidence-based medicine (EBM). The EBM-method focuses on 'the careful, explicit and judicious use of the current best evidence'. Furthermore, CVZ's general point of departure is that the highest possible evidence must be available for a positive decision on the established medical science and medical practice criterion. CVZ can make a substantiated deviation from this requirement. If the assessment relates to an intervention that can be deployed as an alternative to a given standard treatment, then the intervention fulfils 'established medical science and medical practice' if its efficacy (in the broadest sense) is at least equal to that of the standard treatment. In that case, equal value is sufficient.

[5] Except for care that is normally provided by dental specialists.
[6] *College voor zorgverzekeringen*. Assessment of established medical care and medical practice. Publication number 254. November 2007. www.cvz.nl

Specific working method in assessing proton therapy
As mentioned in the introduction, in the March 2009 report on proton therapy (2), CVZ describes the planned working method for assessing proton therapy in relation to established medical science and medical practice considering the special circumstances involved in proton therapy.

Aim of the therapy

In the report CVZ stated, among other things, that the type of studies required for the assessment depends on the intended goal of the therapy. Controlled studies are required in a case of dose escalation that aims to achieve a higher cure percentage, and thus patient survival. After all, the goal of such studies is to determine the efficacy of the treatment. Randomised studies provide the greatest degree of certainty regarding the (added) value of a new form of treatment. However, if the aim of using proton therapy is to reduce (late) side effects, then RCTs are not the obvious choice for demonstrating this. Such side effects are generally rare and frequently occur only (many) years after treatment (e.g., cardiotoxicity, secondary tumours).
RCTs are too small and their follow-up is too short to be able to detect a difference in such side effects. Registration databases and observational studies are more suitable for demonstrating a reduction in side effects.

Model studies

Furthermore, CVZ's report describes how, in theory, for a number of proton therapy indications, it is possible to make statements about the effects/value of proton therapy on the grounds of model studies (planning studies and NTCP models). This applies in particular to what the GR refers to as 'model-based indications'. For a more detailed explanation, see CVZ's report dated 9th March 2009.

'Standard indications'

The report states that proton therapy is already being used for a number of rare tumours, for which it is crucial that the (surrounding) tissue remains unharmed. These are the so-called 'standard indications'.
This report focuses on those indications.

3. Intraocular tumours

3.a. Assessment of 'normal practice'

'Normal practice'

Care that is part of 'normal practice' is – in short – care that the professional group (in casu: the professional group of medical specialists) regard as being part of their accepted care arsenal. CVZ feels that this condition has been fulfilled with respect to proton therapy. Though this care is not available in the Netherlands, in practice, Dutch doctors have been referring patients with intraocular tumours, and for whom they have established that proton therapy is the most appropriate form of radiotherapy (in comparison with other forms of radiotherapy), to a foreign care-provider. In CVZ's opinion, this implies that the treatment is part of the accepted care arsenal for the professional group concerned. This leads to the conclusion that proton therapy 'is care that is normally provided by medical specialists'[7].

3.b. Assessment of 'established medical science and medical practice'

Working method

Initial comment on the working method

Among other things, CVZ used the above-mentioned horizon scanning report of the GR (1) to assess 'established medical science and medical practice', as well as a number of recent systematic reviews on proton therapy involving various indications (3-6). The conclusions of the reviews are not always identical, depending on – among other things – the review's inclusion criteria. For this reason, each review of the indication concerned is discussed individually, although they do overlap in part (even with respect to the authors).

[7] CVZ also drew this conclusion when publishing their report, the Importance of the 'normal practice' criterion and its assessment. Diemen: CVZ, 2008. Publication number 268. www.cvz.nl.

Assessment

Intraocular tumours

For a long time enucleation was the standard treatment for intraocular tumours, in particular for intraocular melanoma. Since the introduction of radiotherapy, preservation of the eye is possible in a number of cases. RT (photons or protons) is currently treatment of first choice. However, in the long term, photon radiation of surrounding tissue can lead to loss of vision due to gradual, progressive, occlusive vasculopathy. For this reason proton therapy is preferred above conventional radiotherapy for tumours located near the N. opticus or the macula: it reduces the radiation of richly vasculated regions essential for vision, thereby reducing the chance of late loss of vision. Proton therapy is also used on larger tumours, as it helps achieve improved local tumour control.

Aim: retained vision

Much experience

Proton therapy has been used for many years for these (rare) tumours: initial publications date from 1985.

The results of proton therapy on intraocular tumours were described in four recently published systematic reviews. These are discussed briefly below.

Systematic reviews

Lodge et al. (3) carried out a systematic review into the efficacy and cost-effectiveness of proton therapy on various oncological indications. They found ten studies relating to eye tumours: two prospective dose-escalation studies and eight retrospective studies. Weighted averages for local tumour control and 5-year survival (overall and disease-specific) were, respectively, 97% and 85%. Eye preservation was possible in 90% of the patients. Neovascular glaucoma (a complication of radiation of the eye) occurred in 12%. The efficacy of proton therapy is comparable with that of stereotactic radiotherapy with photons (the optimum 'conventional' radiotherapy for this indication), although there is a lack of data with a follow-up that exceeds 2 to 3 years for the stereotactic radiotherapy. The incidence of neovascular glaucoma is slightly lower after treatment with protons.

Brada et al. (4) updated this review and carried out additional analyses. As far as efficacy is concerned, the authors found no

indications that proton therapy was superior to conventional radiotherapy. They did not present any toxicity data.

Pijls-Johannesma et al. (5) published a systematic literature review in the NTvG (partly consistent with Lodge and Brada). As far as eye tumours are concerned, the authors concluded that the efficacy of protons is superior in comparison with optimal photon therapy.

Lastly, Olsen et al. (6) analysed 32 articles on the treatment of eye tumours with proton therapy. One of these was an RCT; the others were case series or cohort studies. The RCT compared two doses of proton therapy, which makes it of little use for assessing the actual efficacy of proton therapy. The authors refrained from expressing a clear conclusion, due to the low level of evidence (level C) for the efficacy of proton therapy on eye tumours.

GR

The GR's horizon scanning report (1) refers to proton therapy as 'standard therapy' for selected intraocular melanomas. These are the larger tumours, and those located near the macula and the optic nerve. For these tumours proton therapy is a good alternative because it means that enucleation can be avoided. The GR report states that extensive clinical experience has been obtained on thousands of patients and that good results have been reported in relation to local tumour control and eye preservation. The GR report contains an extensive review of medical-scientific literature on these indications.

CVZ's conclusion

From the available literature and the GR report, CVZ concludes that proton therapy complies with established medical science and medical practice for selected intraocular tumours. This is based on the following arguments:

- there are signs that, for selected patients, proton therapy is at least equal – and possibly superior – to optimal conventional radiotherapy, whilst causing fewer adverse effects in the long term. The cohort studies (with evidence level C) on which this is based can be accepted as

conclusive evidence, as the main aim of the therapy is to reduce/prevent late side effects (see section 2 on the relevance of the aim of the therapy);
- these are tumours that are rare (with a low prevalence), which explains the lack of studies that generate a higher level of evidence (e.g., RCTs);
- proton therapy has been used on such tumours for more than 20 years. International consensus exists that this can be the preferred treatment for selected tumours. For this reason, the generation of scientific evidence of a higher level is unlikely.

3.c. Outcome of assessment

In the previous two paragraphs, CVZ concluded that, for the indication field intraocular tumours, proton therapy is care normally provided by medical specialists and it complies with the 'established medical science and medical practice' criterion. This means that, for the indication field intraocular tumours, proton therapy can be regarded as a provision insured under the Zvw.

This does not detract from the fact that for each *individual* patient, one should determine whether proton therapy is indeed the most appropriate form of radiotherapy in comparison with other techniques, such as, for example, brachytherapy and intensity-modulated radiotherapy. This is discussed in more detail in paragraph 6.b.

4. Chordomas and chondrosarcomas

4.a. Assessment of 'normal practice'

'Normal practice'

Care that is part of 'normal practice' is – in brief – care that the professionals (in casu: the professional group of medical specialists) regard as being part of their accepted care arsenal. CVZ feels that this condition has been fulfilled for proton therapy. Though this care is not available in the Netherlands, in practice, Dutch doctors have been referring patients with the said indications, and for whom they have established that proton therapy is the most appropriate form of radiotherapy (in comparison with other forms of radiotherapy) to a foreign care-provider. In CVZ's opinion, this implies that the treatment is part of the accepted care arsenal for the professional group concerned. This leads to the conclusion that proton therapy 'is care that is normally provided by medical specialists.[8]

4.b. Assessment of 'established medical science and medical practice'

Working method

Initial comment on the working method

Among other things, CVZ used the above-mentioned report on Proton Radiation Therapy of the GR (1) to assess 'established medical science and medical practice', as well as a number of recent systematic reviews on proton therapy involving various indications (3-6). The conclusions of the reviews are not always identical, depending on – among other things – the inclusion criteria for the review. For this reason, each review of the indication concerned is discussed individually, although they do overlap in part (even with respect to the authors).

Rare tumours of the axial skeleton

Assessment

Chordomas are rare, slow-growing and localised aggressive

[8] CVZ also drew this conclusion when publishing their report, the Important of the 'normal practice' criterion and its assessment. Diemen: CVZ, 2008. Publication number 268. www.cvz.nl.

tumours that grow from bone tissue and which are mainly found at the base of the skull.[9] Treatment consists of surgery, followed by radiotherapy. Radical surgery is usually impossible due to localisation near the nerves of the brain, the brainstem or the spinal cord, and high doses of radiotherapy are required for local tumour control in patients who have not undergone radical surgery. The first studies with proton therapy for this indication date from 1989.

Systematic reviews

This indication was also discussed in the four systematic reviews on proton therapy:
From the data available, Lodge et al. (3) distilled the following results for, respectively, local tumour control and 5-years' survival:
Proton therapy: 63% and 81%.
Conventional RT: 25% and 44%
Stereotactic RT: local tumour control 50%
(C-ions: 72% and 83%; this treatment is not discussed here).
Based on the literature, the authors conclude that treatment with protons leads to improved local tumour control in comparison with treatment using photons.

Brada et al. (4) examined only 5-years' local tumour control and concluded that no clear superiority of proton therapy can be demonstrated.

Pijls et al. (5) discussed the skull base tumour, spinal cord chondroma and chondrosarcoma jointly and concluded that the results are comparable with the best published photon results.

Olsen et al. (6) assessed a case series involving a total of 500 patients and concluded that 5- and 10-years' survival after treatment with proton therapy is high and that the chance of severe toxicity is low. The level of evidence is low (level C).

[9] Chordomas typically occur in the axial skeleton: mostly in the base of the skull and in the sacral region, less frequently in the vertebral column (www.uptodate.com).

GR

According to the GR's report (1), these were rare tumours, whereby surgery is frequently not possible and the radiotherapy option is limited due to the proximity of the medulla oblongata, brainstem and spinal cord. Due to the favourable dose distribution of proton therapy, high doses of radiation can be given with good local tumour control and low toxicity, as demonstrated in various series. The GR report contains an extensive review of medical-scientific literature on these indications.

Chondrosarcomas

Chondrosarcomas are extremely rare malign tumours that develop in cartilage, and which are usually located at the base of the skull. They are closely related to the chordomas and are often discussed together with the chordomas in the literature.

Systematic reviews

Lodge et al. (3) concluded that the results achieved with proton therapy are comparable with those of conventional therapy. Brada et al. reached the same conclusion (4). Pijls et al. and Olsen et al. did not discuss the chondrosarcomas separately (5,6).

GR

The GR report did not discuss the chondrosarcomas separately either. However, the GR report does contain an extensive review of medical-scientific literature on these indications.

CVZ's conclusion

Based on the available literature and the GR report, CVZ concludes that, for selected chordomas and chondrosarcomas, proton therapy complies with established medical science and medical practice. This is based on the following arguments:

- there are indications that, for selected patients, proton therapy is at least equal – and possibly superior – to optimal conventional radiotherapy, and that it has fewer adverse effects in the long term. The cohort studies (with evidence level C) on which this is based can be accepted as conclusive evidence, as the main aim of the therapy is to reduce/prevent late side effects (see section 2 on the relevance of the aim of the therapy);
- these are rare tumours (with a low prevalence), which explains the lack of studies with a higher level of evidence

(such as RCTs);

- proton therapy has been used on such tumours for more than 20 years. International consensus exists that this can be the preferred treatment for selected tumours. The generation of scientific evidence of a higher level is therefore unlikely.

4.c. Outcome of assessment

CVZ's standpoint

In the previous two paragraphs, CVZ concluded that, for the indication field chordomas and chondrosarcomas, proton therapy is care normally provided by medical specialists and it complies with the 'established medical science and medical practice' criterion. This means that, for the indication field chordomas and chondrosarcomas, proton therapy can be regarded as a provision insured under the Zvw.

This does not detract from the fact that for each *individual* patient, one should determine whether proton therapy is indeed the most appropriate form of radiotherapy in comparison with other techniques, such as, for example, brachytherapy. We discuss this in more detail in paragraph 6.b.

5. Paediatric tumours

5.a. Assessment of 'normal practice'

'Normal practice'

Care that is part of 'normal practice' is – in brief – care that the professionals (in casu: the professional group of medical specialists) regard as being part of their accepted care arsenal. CVZ feels that this condition has been fulfilled for proton therapy. Though this care is not available in the Netherlands, in practice, Dutch doctors have been referring patients with the said indications, and for whom they have established that proton therapy is the most appropriate form of radiotherapy (in comparison with other forms of radiotherapy), to a foreign care-provider. In CVZ's opinion, this implies that the treatment is part of the accepted care arsenal for the professional group concerned. This leads to the conclusion that proton therapy 'is care that is normally provided by medical specialists.[10]

5.b. Assessment of 'established medical science and medical practice'

Working method

Initial comment on the working method

Among other things, CVZ used the above-mentioned report on Proton Radiation Therapy of the GR (1) to assess 'established medical science and medical practice', as well as a number of recent systematic reviews on proton therapy involving various indications (3-6). The conclusions of the reviews are not always identical, depending on – among other things – the inclusion criteria for the review. For this reason, each review of the indication concerned is discussed individually, although they do overlap in part (even with respect to the authors).

[10] CVZ also drew this conclusion when publishing their report, the Importance of the 'normal practice' criterion and its assessment. Diemen: CVZ, 2008. Publication number 268. www.cvz.nl.

Assessment

Chronic disease, secondary tumours and risk of development disorders

An important disadvantage of radiotherapy is that late damage can occur, even leading to symptoms after >10 years. Furthermore, secondary tumours can occur as a result of radiotherapy. In addition, for children there is also the problem that development (both growth [due to GH-deficiency] and cognitive development) can be disrupted as a result of radiotherapy on the central nervous system. Radiation of an extremity or of the face can lead to asymmetries due to growth deceleration in the body part involved. Long-term survival after cancer is increasing: the 5-year survival for children is currently 80 to 85% (7). As a result, the late consequences of radiotherapy are also of increasing importance. During recent years in particular, relevant data have been published from large cohort studies. Below is a short discussion of the most important publications in this field.

Epidemiological long-term data

The American Childhood Cancer Survivor Study (CCSS) followed the state of health of a large cohort (> 10,000 persons) who had undergone cancer-related treatment during childhood in the period between 1970 and 1986. The results were compared with those of healthy siblings. Detailed reports were published in 2006, 2007 and 2009 (8-13).
62% of the persons studied had to contend with a chronic disorder; whereby the disorder was severe or life-threatening for 27%. In comparison with siblings, the chance of problems involving posture and the locomotor apparatus, neurocognitive disorders, heart failure and cardiovascular disease is severely increased (RR 54 - 10). The relative risk of a (secondary) malignancy is 15.1. Five treatment combinations were identified with a relative risk >10 for a severe chronic disorder. Four of these combinations included radiotherapy.

A follow-up report analysed the occurrence of secondary malignancies separately. The cumulative incidence was 3.2% after 20 years and 9.3% after 30 years. This means that even after a long time the chance of a secondary malignancy continues to rise, and it actually rises more quickly after >20

years (see figure 1). Radiotherapy is one of the risk factors for the occurrence of secondary malignancies, and this risk is generally dose-dependent.
Fertility can also be affected by oncological treatment. Radiotherapy is a dose-dependent risk factor for both acute and later ovarian failure (12). The CCSS does not report over effects on testicular function. Radiotherapy also affects the success of subsequent pregnancies: the chance of both spontaneous abortion and of dysmaturity may increase.

The report on late mortality shows that late causes of death are, in particular, secondary malignancies and late damage to heart and lungs. Radiotherapy is an important risk factor for mortality resulting from a secondary malignancy and from cardiac damage (11).

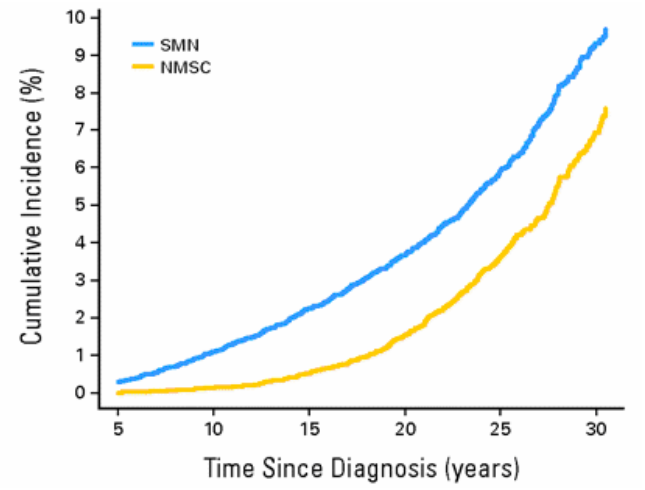

Figure 1: Cumulative incidence of second malignant neoplasms (SMNs) and nonmelanoma skin cancer (NMSC) in childhood cancer survivors. At the 30-year follow-up, the cumulative incidence of SMNs and NMSC continues to increase with time since 5 years after diagnosis of primary childhood cancer (13).

Dutch cohort Geenen et al. described the long-term data of a *Dutch* cohort

of more than 1300 persons who were treated for cancer during childhood (14). The median follow-up duration was 17 years, the average age at the end of the follow-up was 24.4 years. 75% of the persons had suffered one or more adverse events.[11] Numerous, and/or severe, adverse events were suffered by 55% of persons who had been treated with radiotherapy, 25% of those treated with surgery and 15% of those treated with chemotherapy.

Protons also less harmful as a result of state-of-the-art photon therapy

The above-described cohorts were treated with radiotherapy in the nineteen-eighties. Conventional (photon) radiotherapy has undergone further development, whereby the most recent modification is intensity-modulated radiotherapy. This makes it possible to reduce the radiation of surrounding tissues, thereby reducing the risk of late damage.
However, the integral dose has not been reduced, and may even have increased, so that the chance of secondary tumours is not expected to fall, but may actually rise even further (15). With the help of proton therapy, it is possible to reduce the integral dose considerably, so that the chance of secondary tumours is also expected to fall (15, 16).
For the rest, for the first time a retrospectively matched cohort study recently showed that, for adults, the risk of malignancies is lower after treatment with protons than after treatment with photons. In this study, in which 503 proton patients were matched with 1591 photon patients, after a median follow-up of 7.7 years, secondary tumours occurred in 6.4% of the proton patients and 12.8% of the photon patients (17). These data have as yet only been published in abstract form.

Systematic reviews

The systematic reviews of Lodge, Brada and Pijls (3-5) did not discuss paediatric tumours separately. Olsen et al. described six case series involving proton treatment for intracranial

[11] These side effects or adverse events were defined by the US National Cancer Institute: CTCAEv3.0, www.ctep.cancer.fov/formsCTCAEv3.pdf. A number of examples of adverse events that frequently occur are: psychosocial or cognitive problems, tissue hypoplasia, problems in the posture and locomotor apparatus (amputation, scoliosis), nephrological disorders, growth hormone deficiency and fertility disorders.

tumours in children (6). Comparison with conventional treatment did not take place. Local tumour control was good, though complications were reported such as neuropsychological damage, damage to the pituitary and cataract.
The duration of the follow-up is as yet too short to be able to make statements on the occurrence of secondary malignancies.

GR

The GR report (1) contains an elaborate discussion of the late effects of radiotherapeutic treatment in juveniles. According to the GR, a realistic approach would be to consider treatment with protons – assuming that this modality is available – for every child who is eligible for radiotherapy due to cancer. "An individual assessment, based on simulated treatment plans, can then reveal whether important advantages can be expected of proton radiation. Naturally, such an assessment should also involve the costs of treatment."
The GR report contains a review of the medical-scientific literature relating to paediatric tumours and proton radiotherapy.

CVZ's conclusion

From the literature available and the GR report, CVZ concludes that, for selected paediatric tumours, proton therapy is a form of care that complies with established medical science and medical practice. This is based on the following arguments:

- there are indications that proton therapy is at least equivalent to an optimal conventional radiotherapy with respect to local tumour control, whilst resulting in fewer adverse effects in the long term;
- In particular, the risk of secondary malignancies is reduced as a result of opting for proton therapy.
  This means that, in principle, even when efficacy is equivalent with respect to local tumour control, treatment with proton therapy is the preferred choice;
- With respect to intracranial tumours in juveniles, conventional radiotherapy can lead to disorders in neurocognitive development. For these patients in particular, treatment with proton therapy is, in principle,

the preferred choice, due to the more favourable dose distribution of proton therapy and the resulting reduced risk of neurocognitive damage;
- Proton therapy has been in use for paediatric tumours for some time. International consensus exists that this is the preferred treatment for selected tumours.

5.c. Outcome of assessment

Outcome

In the previous two paragraphs, CVZ concluded that, for the indication field paediatric tumours, proton therapy is care normally provided by medical specialists and it complies with the 'established medical science and medical practice' criterion. This means that, for the indication field paediatric tumours, proton therapy can be regarded as a provision insured under the Zvw.

This does not detract from the fact that for each *individual* patient, one should determine whether proton therapy is indeed the most appropriate form of radiotherapy in comparison with other techniques, such as, for example, brachytherapy. We discuss this in more detail in paragraph 6.b.

6. Points of attention/consequences

Conclusion: insured care

In the previous sections, CVZ has established that, for the indications intraocular tumours, chordomas/chondrosarcomas, and paediatric tumours, proton therapy belongs in the basic package. After all, it fulfils the current statutory conditions (it is care normally provided by medical specialists and it complies with the established medical science and medical practice criterion).

CVZ discusses four points in more detail below, namely:

- availability of the care and the consequences for the (amount of the) reimbursement of costs;
- general Zvw indication requirement;
- indication protocol
- WBMV authorisation.

6.a. Availability of proton therapy and (size of) the reimbursement

Care only available outside the Netherlands

Proton therapy is not (yet) available in the Netherlands. At the moment the care can only be obtained abroad and Dutch doctors refer patients who are eligible for the treatment to a foreign hospital. How many patients will be involved? In their report, published in December 2009 (1), the GR estimated the number of Dutch patients for whom proton radiotherapy can be regarded as 'standard treatment'. That number will be, at maximum, 252 patients per year. According to the GR, this is about 0.6% of the total number of patients eligible for radiotherapy.

The question that arises is: will an insured person who is indicated for proton therapy (see also paragraph 6.b) and who undergoes the treatment abroad actually receive that care or a reimbursement of the costs of the treatment? The reply to this question is 'Yes', although – depending on the individual situation – conditions and limits may apply.
This is described in brief below, starting with application of the Zvw, followed by application of the (EEC) Council Regulation.

Applying the Zvw

Applying the Zvw (appeal based on a policy)
Application of the Zvw is not limited to care within the borders of the Netherlands. In fact, the Zvw (and the individual insurance policies based upon it) provides world-wide cover. How does this apply in a case involving a benefit in-kind, and how does it differ when reimbursement is involved?

In-kind

Benefit in-kind
If an insurance policy interprets an insured provision as a benefit in-kind, then for that item the insured client has a *right to care*. A health insurer provides this by entering into contracts with care-providers. In principle – if care is to be covered –, insured clients are obliged to apply to a contracted care-provider. If an insured client applies to a non-contracted care-provider, then he will receive a reimbursement of the costs, but he may be confronted with a reduction in the costs reimbursed.

The right of health insurers to impose a deduction if an insured client applies to a non-contracted care-provider is based on article 13 of the Zvw. Health insurers determine the size of that reduction in their policies. This differs per health insurer.

Contracted care

On behalf of its clients, a health insurer can decide to purchase proton therapy from certain clinics abroad (by contracting them). Once an insured person applies to such a clinic, the health insurer pays the agreed tariff directly to the clinic concerned, without involving the insured client.

Non-contracted care

A health insurer may not have purchased any proton therapy, so that no such contracted care is available. In such a case, could an insured person be confronted with a reduction as mentioned in a policy? CVZ's reply to this must be in the negative, whereby they have deliberated as follows. A consequence of the in-kind system is that the insurer is under an obligation to deliver: the insurer is obliged to supply an insured client with the insured care within a reasonable period

of time. An insurer who is unable to do this either himself, or via a contracted care-provider, thereby forcing the insured client to apply to a non-contracted provider (whether or not in the Netherlands), has failed to fulfil his obligation. On the grounds of the Civil Code, the health insurer must reimburse damages thus inflicted upon the insured client. These damages amount to the full costs of the treatment received abroad (the full tariff of the other country).

Reimbursement

Reimbursement of a provision

An insured person who has a reimbursement policy has a *right to the reimbursement of the costs of care*. In this case, the insured person is not obliged to approach a care-provider who has been contracted by his/her health insurer[12].

The insured person has freedom of choice and is at liberty to apply to a foreign care-provider. Article 2.2, second paragraph, under b, of the Bzv is relevant to a reimbursement policy. This stipulates that the reimbursement of costs will be reduced if the costs are higher than what is reasonably regarded as appropriate according to the Dutch market. However, CVZ feels that an insurer cannot appeal to this stipulation in the case of proton therapy. Proton therapy is not available in the Netherlands, so there is no question of a tariff that conforms with the Dutch market. Nor is it possible, in this specific case, to harmonise with the DCB-tariff for a comparable treatment that is available in the Netherlands. After all, there is no comparable treatment for an insured client for whom, according to his/her Dutch doctor, proton therapy is the first-choice treatment and who therefore depends on that care. Therefore, in this specific case, there is no ground for reducing the reimbursement. A health insurer will be liable to reimburse the full costs of the care provided abroad – even in the case of a reimbursement policy.

Insured client's travelling expenses

Reimbursement of travelling expenses of the insured client and his/her escort(s) on the grounds of the policy

[12] For the rest: even with a reimbursement policy, a health insurer can stipulate that insured clients must apply to certain care-providers with whom the health insurer has taken out a contract.

Zvw policies (both in-kind and reimbursement forms), provide a right to the reimbursement of travelling expenses incurred by car or by public transport (lowest price class) over a maximum one-way distance of 200 kilometres, in as far as the insured client is undergoing oncological treatment with chemotherapy or radiotherapy. Proton therapy is a form of radiotherapy. Furthermore, the policy stipulates that if the health insurer grants an insured client permission to apply to a given person or institution, the 200-kilometre limit does not apply[13].

Travelling expenses of escort(s)

Furthermore, Zvw policies (both in-kind and reimbursement forms) stipulate that transport includes that of an escort, if accompaniment is required, or if the accompaniment of children younger than 16 years is involved. In addition, they also stipulate that in exceptional cases the health insurer can permit accompaniment by two persons.[14]

(EEC) Council Regulation

Application of (EEC) Council Regulation 1408/71

In as far as the care is provided within Europe, the EEA-countries[15] and Switzerland, the (EEG) Council Regulation 1408/71 (henceforth: the Regulation) also applies, in addition to the personal policy (health insurance). Relevant within this framework is that an insured person can appeal to article 22, paragraph 1, under c and under i, of the Regulation, and ask his/her health insurer for permission to go to another member state in order to undergo treatment that is appropriate for his/her state of health. In that case, the client has a right to medical treatment *according to the statutory regulation of the member state where the care is provided*.[16] According to the second paragraph of article 22, permission may not be refused if the treatment concerned is a provision covered under the statutory regulation of one's own member state (for the

[13] See article 2.14 of the Bzv.
[14] See article 2.15, para. 2, of the Bzv.
[15] EEA-countries are states that are party to the Agreement relating to the European Area. These are: Lichtenstein, Norway and Iceland.
[16] This means that a right only exists if proton therapy is a provision according to the national health insurance system of the country in which the insured client will undergo the treatment.

Netherlands this is a right based on a personal policy), and the treatment in question cannot be given to the insured client in the member state in which he/she lives within the space of time normally required for that treatment. The patient's current state of health must be taken into account and the expected course of the disease. In other words, if treatment is involved which is – in principle – covered by the Dutch policy, but which cannot be provided, or not in time (taking into account the patient's state of health, etc.), then the health insurer may not deny the requested permission to go to a non-contracted institution elsewhere in Europe (or an EEA-country or Switzerland).

Personal contribution

It is also important that, if a personal contribution applies abroad, the health insurer is obliged to reimburse the insured client with this, unless a (similar) personal contribution applies to the same provision in the Netherlands.[17]

Insured client's travelling expenses

Furthermore, the right to a reimbursement of the costs of travelling to a foreign country only exists if a similar right exists for treatment in a local hospital (article 49 EC convention) based on the statutory regulation in one's own member state (for the Netherlands, this is a right based on the individual policy). This is the case in the Netherlands. On the grounds of article 2.14 of the Bzv, transport by car or by public transport is an insured provision over a maximum (one-way) distance of 200 kilometres, in as far as the insured person is undergoing treatment with chemotherapy or radiotherapy. Proton therapy is a form of radiotherapy. Furthermore, it is stipulated that the 200-kilometre limit does not apply if the health insurer has given permission to apply to a given person or institution.

Travelling expenses of companion(s)

There is also a right to the reimbursement of the travelling expenses of the insured person's companion, although here also, this reimbursement is only available if – to put it briefly - the same right exists on the grounds of the Dutch statutory

[17] Vanbraekel ruling: RZA 2001, 117 Court of Justice EC, C-368/98 12-07-2001.

regulation. This is the case. Article 2.15, para. 2, of the Bzv covers transport, also for a companion, if such is needed, or, where it involves the accompaniment of children younger than sixteen years. Furthermore, it stipulates that in exceptional cases a health insurer can permit accompaniment by two persons.

New Regulations

An attention point is that new EC Council Regulations will apply as of 1st May 2010. As of that date, article 20 of Council Regulation (EC) No. 883/2004[18] and article 26 of Council Regulation (EC) No. 987/2009[19] will be relevant to this subject. The above-described permission regulations remain largely unaltered in the new situation. An explanation of the new Council Regulations will soon be placed on CVZ's website (www.cvz.nl).

Core message

The core message is that an appeal based on the Council Regulation can only be made if the proton therapy takes place in an EU country, an EEA country or Switzerland, and it is covered by the national health insurance system of the country concerned (the country in which the insured client receives the care). We understand that, as far as Europe is concerned, Dutch patients mainly go to Switzerland (Villingen), France (Paris/Orsay) and Germany (Munich and in the future, Heidelberg and Essen) for proton therapy. As far as CVZ has been able to ascertain, proton therapy is an insured right in the countries concerned. In individual cases, it will be up to health insurers to obtain more detailed information about this from the local authorities/the liaison office.[20]

We understand that patients are sometimes referred to the USA (Boston). The rules of the Zvw (and policies based thereupon) apply to such a care provision. See above, the passage on 'application of the Zvw (appeal based on one's

[18] Published in PB L 166 dated 30-04-2004 and recently altered in PB L 284 dated 30-10-2009.
[19] Published in PB L 284 dated 30-10-2009.
[20] Also important is that the clinics/hospitals concerned must be so-called 'state/public' hospitals. Health insurers can obtain information about this from the local authorities/the liaison organisation.

policy)'.

It is also important that insured clients are able to choose the most favourable option for them, the insurance policy (Zvw) or the Council Regulation.

6.b. Zvw Individual indication requirement

No automatic right to reimbursement/ treatment

As stated above, proton therapy is deemed a provision that is insured under the Zvw for the indications intraocular tumours, chordomas/chondrosarcomas and paediatric tumours. However, this does not mean that every insured client who has a disorder that is classified amongst these indications is automatically eligible for (reimbursement of the costs of) proton therapy. As indicated above, for each of the indications, it will be necessary to determine for each insured person whether proton therapy is the most appropriate form of radiotherapy in his/her case. For health insurance this is based on article 2.1, third para., of the Bzv. This article stipulates that an insured client only has a right to the reimbursement of the costs of care in as far as he/she can reasonably be said to depend upon that form and amount of care. Whether this is the case depends on the individual circumstances of the case, whereby a health insurer also has the possibility of weighing up the costs of the treatment against the added value of the specific treatment for the insured client in comparison with other treatments available.

Individual assessment

In practice, in many cases health insurers base their individual assessment (is the insured client reasonably dependent upon the care?) on the assessment and indication as determined by the doctor in charge. CVZ advises keeping to this procedure for proton therapy, as such an assessment requires specific expertise and procedures that need to be followed in medical practice. There should be a fixed procedure so that, for each individual patient for whom proton therapy is a possible option, the doctor in charge weighs up whether proton therapy presents the patient with a considerable advantage in comparison with other radiotherapy possibilities that are available. This assessment takes place based on simulated

treatment plans, which can be used to compare photon treatment and proton treatment with one another. In addition to simulated treatment plans, the doctor's assessment will also take into consideration the patient's capabilities (will his/her condition/personal circumstances permit the burdensome journey to another country?). In the opinion of CVZ, due to a lack of unambiguous data, the added costs of proton treatment above those of other radiotherapy possibilities should not, for the moment, be included in the assessment.

Recommendation

CVZ adds that they recommend that carers use standardised methods both for the individual assessment based upon simulated treatment plans and for the post-treatment follow-up, as this will facilitate meticulous record-keeping.

6.c. Indication protocol

Drawing up indication protocol

In the opinion of CVZ, the fact that the care is not available in the Netherlands (though for certain indications it is regarded as a provision insured under the Zvw), obliges the professional groups to draw up guidelines indicating how patient selection should take place. We understand that the professional group of radiotherapists (the NVRO) is currently drawing up plans to arrive at just such an indication protocol. CVZ applauds this and urges them to press on in this matter.

From the response of the Dutch Association for Paediatrics (NVK), within the framework of the consultative discussions on this matter (see section 7), CVZ understands that (inter)national protocols currently exist for the oncological treatment of children, within which agreements on determining the indication for proton therapy have already largely been established.

6.d. WBMV permit obligation

WBMV permit obligation

By virtue of the Decision for determining special medical procedures (based on the WBMV, the Special Medical Procedures Act), radiotherapy – including teletherapy and brachytherapy – may not be provided without a permit from

the Minister of VWS. This means that the treatment of patients by means of radiotherapy is reserved for hospitals with a permit. A new planning decision came into effect on 11th November 2009: the Radiotherapy Planning Decision 2009 [21]. This planning decision permits room for extending the number of radiotherapeutic centres. This meant abandoning the current maximum of 21 licensed centres that applied up until 1st January 2010.

Removal from the WBMV

The appendix to the new planning decision also refers to the Minister's decision to remove radiotherapy from article 2 of the WBMV as of 2012. This means the permit obligation would lapse as of 2012. According to the appendix to the planning decision, this will not apply to proton therapy. This is explained as follows:

"One aspect of radiotherapy is proton therapy. This is a promising technology, though it is still in an early phase of development. The treatment has a proven added value above conventional radiotherapy for only a few indications. I have concluded that there are still many research questions in the field of determining the indication, efficacy and cost-effectiveness. I therefore consider that it would be irresponsible to exclude proton therapy as of 2012. This form of radiotherapy will therefore remain an exceptional medical procedure under article 2 of the WBMV after 2012. In so doing I have heeded the advice of the GR."

Limiting the number of centres

In advice issued to the Minister of VWS on 18th December 2008, 'A horizon scanning report of radiotherapy. Looking ahead to 2015' (18), the *GR* also argued for limiting the use of proton therapy to a number of locations in the Netherlands. The GR referred to this again in their report on proton radiotherapy published in December 2009 (1). CVZ agrees with this, as indicated earlier in their proton therapy report dated

[21] State Newspaper dated 9 November 2009, no. 16811.

March 2009 (2).

There is currently no limit to the number of centres. The current standpoint adopted by the Ministry of VWS is that the permit currently granted to centres, or which will soon be granted on the grounds of the new planning decision, allows them to use proton therapy. In other words, according to the VWS, proton therapy falls under the current radiotherapy permits and those soon to be granted.
CVZ understands that in the Netherlands there are at the moment no centres that have definitely decided to set up a proton facility. There are three initiatives currently in the stages of recognition and preparation. In order to avoid proton therapy starting at more centres that is desirable, in CVZ's opinion, the Minister should – a soon as the plans start taking shape - limit the number of centres for proton therapy by making a formal amendment of the planning decision.

Uniform data registration

Furthermore, CVZ emphasises that the permit to use proton therapy that will be granted to a number of hospitals (based on an adjusted planning decision) should be subject to the condition that uniform data registration takes place within the centres.[22]

[22] In their response to the draft document, with reference to data registration the NVK refer to the SKION, the Dutch Paediatric Oncology Foundation, which provides a basic structure for registering such data, including their collaboration with the project group LATER (Registration of Long-term effects). According to the NVK, collaboration should be sought with this organisation on the matter of data registration.

7. Consultation over content

Consultation CVZ presented the draft report – in as far as it relates to the conclusions regarding established medical science and medical practice – to a number of professional associations of specialists. These include the professional associations for: Radiotherapy and Oncology, Medical Oncology, Paediatrics, Surgery, Ophthalmology and Neurology. The draft document was also sent to the *Order of Medical Specialists*.

Responses received The main outlines of the responses received are reproduced below, together with – where possible – our reply. A number of comments led us to add to or revise the text of the report.

NVK ***Response of the Dutch Paediatrics Association (NVK)***
The NVK indicated their endorsement of CVZ's conclusion that proton therapy is in accordance with 'established medical science and medical practice for selected paediatric tumours'. They added that children are currently also being referred abroad. Such referrals take place partly on the grounds of (inter)national protocols for surgical paediatric oncology treatment, in which agreements on the indication for proton therapy have largely been recorded. In their letter, the NVK drew attention to the enormous burden placed on children, parents and siblings when treatment takes place abroad and they also provided a summary of the conditions/specific requirements involved and which form the basis of paediatric oncology treatment. For the sake of brevity, CVZ refers to the letter from the NVK for these aspects. Lastly, the NVK indicated that they emphatically endorse the need for strict registration of diagnosis and treatment, particularly due to the late effects of this therapy. In relation to this, the NVK referred to the SKION, the Dutch Paediatric Oncology Foundation, which provides a basic structure for registering this type of data, including collaboration with the project group LATER (registration of long-term effects). The NVK emphatically advises collaboration with this existing organisation.

LWNO/NVN ***Response of the National Working Group on Neuro-***

oncology (LWNO) and the Dutch Neurological Association (NVN)

The response of the LWNO and the NVN relates to proton therapy in general and does not discuss the specific indications described in this report. They had two comments:
1) CVZ were probably overoptimistic in estimating the number of patients and the direct health benefits of proton radiotherapy. According to the LWNO/NVN, there is too little clinical evidence that proton therapy is better than conventional high-precision radiotherapy with photons and internal radiotherapy (brachytherapy).
2) On the other hand, according to the LWNO/NVN, CVZ paid little attention to the indirect benefits to medical-scientific research, technological innovation and economic spin-off. They point out that the Netherlands is ahead of the USA and neighbouring countries in oncology research, but that this head start is largely being negated due to technological inferiority in the Netherlands. The LWNO/NVN argue in favour of investing in proton radiotherapy, because it would result in a win-win situation: benefits for health care, benefits in the form of technological knowledge and benefits in economic spin-off, so that the Netherlands can continue to fulfil its role as pioneer in cancer research.

CVZ's response

With respect to the first point (too little clinical evidence), CVZ points out that in their report over proton therapy dated 9th March 2009 (2), they explained – in brief – that the outcomes of clinical comparative studies are not always necessary in order to be able to issue a statement on 'established medical science and medical practice', and that for some indications model studies (planning studies and NTCP models) can serve as a basis for decision-making.

This is in keeping with the approach described by the GZ in their report that was published in December of last year (1). Obviously, proper data registration and analysis is necessary in order to be able to examine in practice the effects calculated on the basis of models. CVZ mentioned this necessity in their March 2009 report and defend it again in this report.

Furthermore, CVZ comments that their conclusion in this report – i.e., that this form of care complies with 'established medical science and medical practice' for the 'standard indications' discussed – is mainly based on the fact (also mentioned by the GZ) that worldwide consensus exists among radiotherapists/oncologists that proton therapy is an accepted care form for the indications concerned, alongside other, more contemporary forms of radiation.

It is true that no attention was paid to the importance of introducing proton therapy into the Netherlands for medical-scientific research, technological innovation and economic spin-off. This is understandable in view of the subject of this report. The above-mentioned report on proton therapy (2), dated 9th March 2009, does refer to the importance that CVZ attaches to the dynamic introduction of promising medical innovations. This is evidenced by the approach described in that report (how does CVZ examine for which indications proton therapy is care that complies with 'established medical science and medical practice'?), thereby creating an opportunity to arrive at a positive assessment of 'established medical science and medical practice' based on model studies.

NVRO

Dutch Association for Radiotherapy and Oncology (NVRO)
The NVRO announced that they endorse the draft standpoint. However, the NVRO does have a few comments (relating to medical content):
1) The analysis lumps all paediatric tumours together, which – in the eyes of the NVRO – ignores the diversity of locality, behaviour and treatment and thereby also the positive and negative consequences these may have.
2) Ref. 17 refers to an abstract. A satisfactory assessment of the results will first have to await the full publication.
3) Expectations are that the choice of apparatus will make it possible to reduce neutron radiation to a low level. According to the NVRO, for the moment, measurements will remain necessary in order to verify this.
4) The localisation of chordomas and chondrosarcomas referred to in the draft text is not entirely correct.

5) Furthermore, what remains important is the individual – per patient – assessment as to whether radiotherapy with protons has added value above radiotherapy with photons.

CVZ's response

CVZ's response to these comments is as follows.
1) Proton therapy is a treatment option that should be considered for all tumours in juveniles that are eligible for radiotherapy. CVZ has chosen for this approach on the basis of the literature available. This approach is also in keeping with the GR's opinion. For each individual patient it is important to determine whether proton therapy is the most appropriate form of radiotherapy in his/her case. CVZ addresses this in section 6.b.
2) We have adjusted the text in response to this comment.
3) CVZ has taken note of this comment.
4) The data in the text were obtained from the literature. For this reason, this text will remain unaltered.
5) CVZ agrees with this comment and points out that section 6.b. of the report discusses the individual assessment requirement.

8. Approval of assessments

Outcome of assessment The outcomes of assessments mentioned in sections 3.c., 4.c. and 5.c. of this report were approved on 23rd March 2010.

College voor zorgverzekeringen

Member of the Executive Board

Dr. A. Boer

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