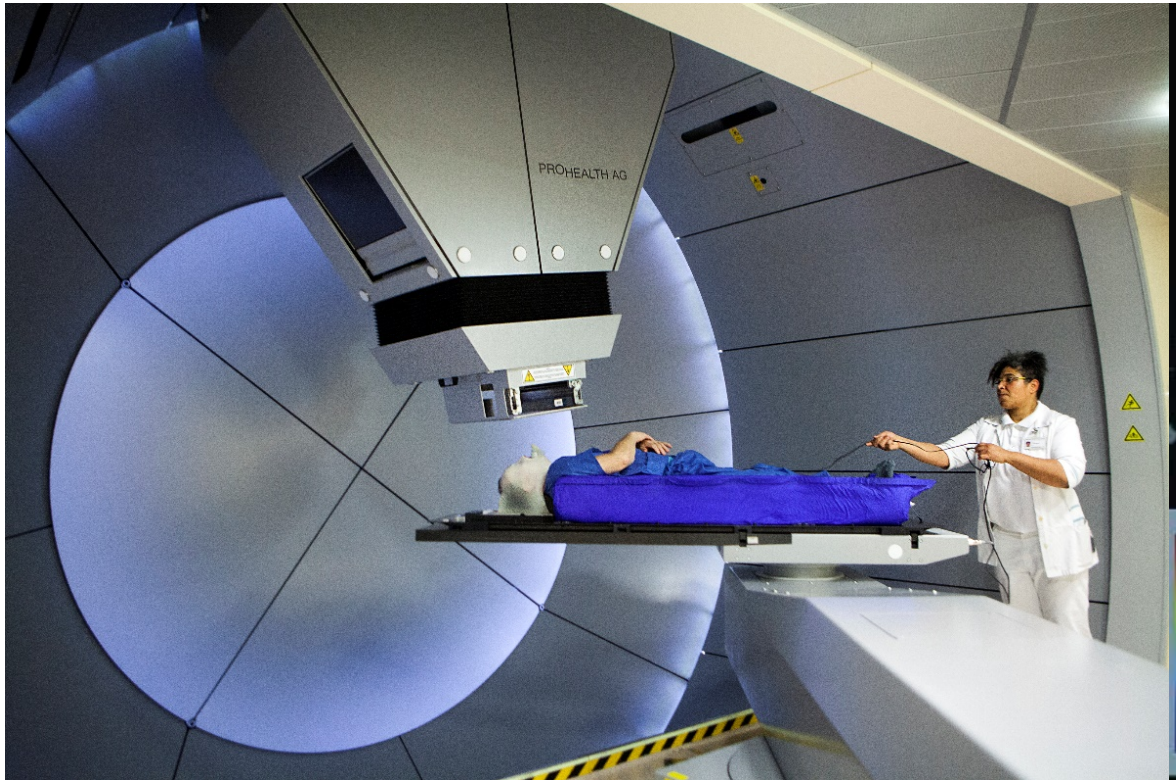
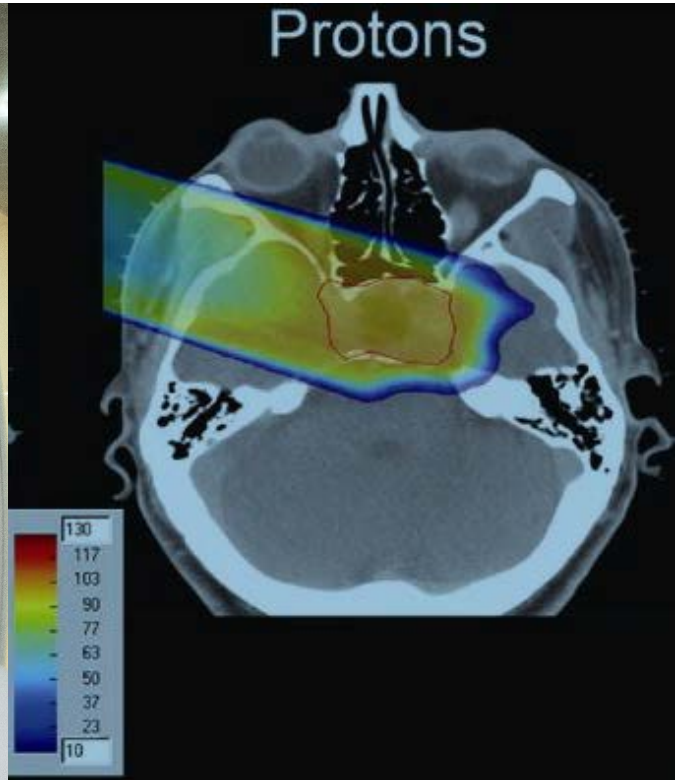
KCE REPORT 307

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

PROTON BEAM THERAPY IN ADULTS – A SYSTEMATIC REVIEW





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HEALTH TECHNOLOGY ASSESSMENT

Federaal Kenniscentrum voor de Gezondheidszorg
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PROTON BEAM THERAPY IN ADULTS – A SYSTEMATIC REVIEW

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
3D-CRT	Three-dimensional conformal radiation therapy
95%CI	95% confidence interval
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ANZCTR	Australian New Zealand Clinical Trials Registry
CADTH	Canadian Agency for drugs and Technologies in Health
CENTRAL	Cochrane Controlled Register of Trials
CIRT	Carbon ion beam radiotherapy
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
EUnetHTA POP	EUnetHTA Planned and Ongoing Projects database
EMBASE	Excerpta Medica database
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray
GyE	Gray Equivalents
HART	Hyperfractionated acceleration radiotherapy
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HTA	Health technology assessment
ICER	Institute for Clinical and Economic Review
IMRT	Intensity-modulated radiation therapy

INAHTA	International Network of Agencies for Health Technology Assessment
INESSS	Institut national d'excellence en santé et services sociaux
ISRCTN	International standard randomised controlled trial number
KCE	Belgian Healthcare Knowledge Centre
LGG	Low-grade glioma
MeV	Megaelectron volt
NSCLC	Non-small-cell lung cancer
NTR	Netherlands Trial Registry
QUERI	Quality Enhancement Research Initiative
RCT	Randomized controlled trial
RIHTA	Rete Italiana HTA
RIZIV/INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut National d'Assurance Maladie-Invalidité
RR	Relative risk
RTOG	Radiation Therapy Oncology Group
S-1	Tegafur/gimeracil/oteracil
SR	Systematic review
TACE	Transarterial chemoembolization
WHO	World Health Organization

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

Proton beam therapy (PBT) is a radiation technique which delivers proton particles, instead of the X-rays used in conventional photon radiotherapy. The main advantage of PBT is its precision, which results in almost no radiation of the normal (healthy) tissue surrounding the tumour. This is in contrast with X-rays, which continue to deposit diminishing radiation doses as they exit the patient's body.

Modelling suggests that this lower overall radiation doses to the healthy tissue could results in a reduction of side effects and risks of radiotherapy induced second malignancies. Such considerations make it particularly interesting for delivering radiotherapy to children and young adults. (For detailed background information on PBT see section 1.2 of KCE report 235 on Hadron therapy for children).[1]

This report aims at reviewing the existing clinical data to support the use of proton beam therapy in specific indications.

1.2 Belgian context

Two KCE reports have been published on hadron therapy up to date. The first one, published in 2007,[2] offered an overview of all literature available at that time and did not focus on specific indications. A more recent report[1] focused entirely on the use of hadron therapy in children.

In the meantime, a procedure has been developed at RIZIV/INAMI to reimburse this treatment, if delivered in a specialized center for hadron therapy, for patients who meet certain conditions. Table 1 summarises the adult indications for hadron therapy currently reimbursed in Belgium. More detailed information on the specific conditions needed to be fulfilled (other than clinical indications) are available on the RIZIV/INAMI website[a].

a https://www.inami.fgov.be/fr/professionnels/etablissements-services/hopitaux/soins/Pages/Hadron-english.aspx

Table 1 – Reimbursed adult indications for Proton Beam Therapy and Carbon Ion Therapy in Belgium

Proton Beam Therapy	Carbon Ion Therapy
Ocular melanoma, where brachytherapy is not possible	Malignant mucosal melanoma
Paraspinal or sacral, skull base chordoma	Paraspinal or sacral, skull base chordoma
Paraspinal or sacral, skull base chondrosarcoma/sarcoma	Paraspinal or sacral, skull base chondrosarcoma/sarcoma
Meningioma, for which no other medical treatment (surgery, chemotherapy, photon therapy etc.) is possible	Non-resectable or insufficiently resected adenoid cystic carcinoma
Cerebral arteriovenous malformations (AVM), for which surgery, embolisation and (stereotactic) photon radiotherapy are all impossible or have already been delivered without success.	Non-resectable or insufficiently resected salivary gland carcinoma (except for squamous cell carcinoma)
Medulloblastoma	

At present, patients have to be sent abroad for treatment, but the first proton therapy centre in Belgium is currently under construction and it is envisaged that in 2019 this therapy will be available at the University Hospital of Leuven. However, carbon ion therapy will still require patients to be sent abroad.

Based on the current procedure, the number of patients submitting an application for being treated (and reimbursed) with hadron therapy in Belgium in the last four years appears to be rather stable, below 50 patients per year (source: RIZIV internal data). However, although at present, the target population for hadron therapy remains a minority of oncological patients, focusing primarily on children, this could potentially increase considerably with new indications which have recently been (and are still being) studied.

The cost per treatment is high, and thus, hadron therapy must offer sufficient clinical added value to justify its potential budget impact. Therefore, it is crucial to gather as much evidence as possible to carefully select the most appropriate indications for its use.

1.3 Project scope

This report complements the health technology assessment (HTA) in paediatric indications published in 2015,[1] by pursuing a systematic review of the clinical literature in adults (aged 18+).

The original aim of this review was to answer two key questions:

1. For the already reimbursed indications in Belgium: Is carbon ion therapy more effective and appropriate for use than proton therapy in certain indications/patients?

   Given that only proton beam therapy treatment will be available in Belgium and any patients likely to benefit more from carbon ion therapy should still be sent abroad, a clear understanding of the indications/cases in which carbon ion offers greater efficacy/tolerability would be very informative.

2. For indications not yet reimbursed in Belgium: Would proton beam therapy or carbon ion therapy be clinically effective? Would they offer greater efficacy or less, or less severe short and long term adverse events (AE), when compared to conventional radiotherapy methods (combined or not with other therapies)?

A preliminary list of relevant non-reimbursed indications was provided by the RIZIV/INAMI and was afterwards discussed and refined with experts. Following these discussions, two indications which were originally in the list, were excluded. These were prostate cancer and lung cancer.

On the one hand, prostate cancer was not considered to be appropriate for treatment with hadron therapy, following the negative recommendations by the American Society for Radiation Oncology (ASTRO)[b] for the primary treatment of prostate cancer, outside of a prospective clinical trial or registry. These recommendations were based largely on the strength of evidence about effectiveness for treatment with PBT.[3]

On the other hand, a review of the evidence on lung cancer was considered premature given the fact that there are a number or ongoing studies in this indication. These include three randomized controlled trials (RCT)[c], comparing proton versus photon radiation in non-small-cell lung cancer (NSCLC). The largest of these has a sample size of 330 patients and is aimed at assessing overall survival as a primary outcome, while the other two are focused on treatment-related adverse events and recurrences. The experts consulted, agreed that a review focusing specifically on lung cancer, would be more informative once the results from these ongoing studies become available.

Finally, the list of indications not yet reimbursed in Belgium to be considered in this review included:

1. Low grade glioma (LGG)
2. Primary sinonasal tumours and recurrences of head & neck tumours
3. Breast cancer in women
4. Pancreatic cancer
5. Hepatocellular cancer (HCC)
6. Locally recurrent rectal cancer.

Prior to the start of the project, a scoping exercise was completed by the KCE research team in order to identify any similar ongoing research or any recently completed assessments performed by other HTA agencies. This is a crucial step pursued for all KCE projects to avoid any duplication of efforts and identify potential collaborations with other research agencies.

A consultation of the EUnetHTA POP database,[d] listing ongoing, completed or planned HTAs by European agencies was performed. In addition to this, the web pages of other, non-European, HTA agencies, members of INAHTA[e] were consulted.

This exercise resulted in the identification of a very recent HTA carried out by the Ludwig Bolzmann Institute for Health Technology Assessment, on carbon ion beam radiotherapy for cancer treatment.[4] The report offered a broad scope (54 indications in 12 different locations included), and used a robust methodology. The authors concluded that "*As a treatment modality, carbon ion beam radiotherapy (CIRT) can be described as a potentially less invasive cancer treatment due to its physical properties. Due to the lack of*

b https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf

c Further information available at https://clinicaltrials.gov/ct2/home. Trial numbers: NCT01993810; NCT00915005; NCT02731001.

d https://eunethta.dimdi.de/PopDB/faces/SearchPage.xhtml

e http://www.inahta.org/members/

controlled trials, no conclusions may be drawn on the comparative effectiveness of CIRT when compared to conventional photon therapy. As of today, CIRT must be considered as experimental treatment".

This review on carbon ion was thought to fully answer research question 1 and part of research question 2, and thus a decision was taken to exclude carbon ion from the present report. Therefore, this systematic review focusses only on indications for proton beam therapy not yet reimbursed in Belgium.

1.4 Incidence and prognosis

These above mentioned indications present higher incidence rates than the already reimbursed indications, and consequently higher patient volumes. Most of these indications also have a relatively poor prognosis, with the exception of breast cancer for which survival has greatly improved in the last years. Data from the Belgian Cancer Registry on this regard is presented in Table 2, covering both incidence rates and survival data. Figures presented for both head and neck tumours and rectal cancer offer a global estimate and are not limited to local recurrences, since information on recurrences was not available.

The higher patient volumes and generally poor prognoses make them of great interest to decision makers.

1.5 Aim of the study

The final goal of this research is to ensure proton beam therapy is used as objectively and as effectively as possible, saving it for those patients likely to benefit the most.

Table 2 – Incidence (2016) and survival (2012-2016) of selected non-reimbursed indications for Proton Beam Therapy in Belgium

Type of Cancer	Number of new cases 2016	Crude rate** 2016 (M/F)	Age standardised rate*** 2016 (M/F)	Five year survival 2012 2016 (%) (M/F)
Low grade glioma*	162	2.3/1.4	2.3/1.5	81.5/83.4
Sinonasal tumours (C30-C31)	119	2.2/0.5	1.9/0.3	58.8/50.1
Head and neck (C00-C14, C30-C32)	2689	45.8/14.9	39.3/11.8	51.3/59.4
Breast cancer women (C50)	10,735	232.7	195.8	90.5
Pancreas (C25)	1,778	20.3/19.3	15.8/13.5	12.4/12.6
Liver (C22)	932	15.2/5.8	12.3/4.1	22.5/21.7
Rectal cancer (C20)	2,406	34.1/19.9	27.1/14.1	70.3/69.5

Data from the Belgian Cancer Registry. Cancer in Belgium 2016. (https://kankerregister.org).
Rates separated by gender: M: male; F: female.
** Selection of CNS tumours WHO grade I and II as defined in the WHO classification of Tumours of the Central Nervous System, revised 4th edition. Includes a selection of non-malignant brain tumours. ICDO code: (9383;9384;9394;9421;9431;9444)/1 and (9391;9393;9396;9400;9411;9424;9425;9450)/3.*
*** Crude rate (N/ 100,000 person-years).*
**** Age-standardised rate, using European Standard Population (N/ 100,000 person-years).*

2 METHODOLOGY

This report was developed based on a systematic review of the medical literature. Further details about the KCE methods are available at https://kce.fgov.be/content/kce-processes.

2.1 Clinical research question

The aim of this report is to provide the evidence for the clinical effectiveness and safety of proton beam therapy for selected indications in adults. The clinical research question was formulated using the PICOS (Participants-Interventions-Comparator-Outcomes-Study Design) framework (Table 3).

Table 3 – Clinical research question

PICOS item	Description
Population	Adults (i.e. 18+) with: • Low grade glioma • Primary sinonasal tumours and recurrences of head & neck tumours • Breast cancer in women • Pancreatic cancer • Hepatocellular cancer • Locally recurrent rectal cancer
Intervention	Proton beam therapy (whether or not in combination with chemotherapy and/or surgery)
Comparator	Photon therapy (whether or not in combination with chemotherapy and/or surgery)
Outcomes	Clinical effectiveness: overall survival (or mortality), recurrence- or progression-free survival, quality of life, local tumour or cancer control Complications Side effects Secondary tumours
Study design	HTA reports and systematic reviews Randomized controlled trials (RCTs) Comparative studies Case series included only if reporting on the following outcomes: complications, side effects and/or secondary tumour rates

2.2 Literature search and selection

The following electronic databases were searched:

- Medline (systematic reviews and primary studies)
- EMBASE (systematic reviews and primary studies)
- Cochrane Library:
  - Cochrane Database of Systematic Reviews (systematic reviews)
  - HTA database and DARE (systematic reviews)
  - CENTRAL (primary studies)

The search strategies are documented in the appendix.

In addition, HTA reports were looked for in the HTA database as well as at agencies' sites. Reference lists of any relevant articles were checked to identify additional relevant studies/reports.

To be eligible, a systematic review or HTA report had to be based on a search in Medline and at least one additional electronic database. Above this, systematic reviews or HTA reports had to report on the quality of the included studies. To be eligible, a primary study had to compare proton beam therapy (whether or not in combination with chemotherapy and/or surgery) with photon radiotherapy (combined or not with chemotherapy and/or surgery). Case series were included only if they had a sample size of at least 50 patients (for feasibility reasons) and if reporting on the following outcomes: complications, side effects and/or secondary tumour rates. Only full articles published in English, German, Dutch and French were included. Letters, editorials, commentaries, abstracts and narrative reviews were excluded. Studies or reports based on models (e.g. for the prediction of side effects or secondary tumours) were excluded, as were

studies solely focusing on dosimetry and/or treatment planning. No date limit was used for the search, which was done in July 2018.

Finally, a search for ongoing RCTs was done in the available trial registers: ClinicalTrials.gov, Netherlands Trial Registry (NTR), EU Clinical Trials Register, WHO, ISRCTN, Deutsches Register Klinischer Studien, and ANZCTR.

Studies were screened by one researcher on title and abstract using the PICOS in- and exclusion criteria. Irrelevant studies were eliminated with explicit reason. In a second step, the remaining papers were screened by reading the full-text. If the full-text was not accessible by any means, the study was excluded.

2.3 Quality appraisal and data extraction

2.3.1 Quality appraisal

Quality appraisal of the included studies was done by two reviewers independently using the AMSTAR checklist for systematic reviews and the "Cochrane Collaboration's tool for assessing risk of bias" for RCTs.

For the quality appraisal of comparative observational studies the "Cochrane Collaboration's tool for assessing risk of bias" was used, but with the addition of two extra items that apply to potential bias due to the selection of participants: "Concurrency of the intervention and comparator group" and "Comparability of the intervention and comparator group". For the first item low risk of bias was assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel). For the second item low risk of bias was assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis (e.g. age, tumour type, stage, performance status).

In the absence of a widely accepted appraisal instrument for uncontrolled studies (incl. case series), the following criteria were used: adequate definition of the disease, clear description of baseline characteristics, inclusion of a representative cohort, adequate diagnosis of the disease using a valid method, standardised collection of the outcome data, and objective measurement of the outcomes.

Discordant scores were resolved by discussion. In case of disagreement, the third reviewer was decisive.

2.3.2 Data extraction

From each systematic review and HTA report the following data were extracted, using the standard KCE templates: title and reference, funding sources, search date, databases being searched, number and types of included studies (RCT, comparative cohort study or other study type), details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics, details of the intervention and comparator groups that have been addressed in the review, results for the outcomes as defined in the PICO question, and limitations and other comments regarding the review.

From each primary study the following data were extracted, again using the standard KCE templates: title, reference, type of study (RCT, comparative cohort study or other study type), source of funding, country and setting, sample size, duration and follow-up, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics (including baseline comparability), details of the intervention and comparator (e.g. type, dose, duration, route of administration), and limitations and other comments regarding the study. For observational studies the results that were adjusted for confounders were reported in preference, if presented in the original study.

Data extraction was done by one reviewer and checked by a second reviewer.

2.4 Statistical analysis

In the study protocol, it was foreseen to perform separate meta-analyses for each population and comparison (proton vs. photon), if data were available. However, for none of the populations of interest more than one comparative study was available. For the selected comparative studies, data for the

outcomes of interest (as reported in Table 3) were anyhow entered in the Review Manager Software (Review Manager version 5.3.5), but only to allow an interpretation of the precision of the estimate during the GRADE evaluation. For completeness reasons, these forest plots are reported in the appendix, when appropriate (see appendix 6).

Calculations of the appropriate sample size per estimate were done using an online calculator (https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). This optimal information size (OIS) was used for the evaluation of the imprecision criterion in GRADE (see below).

2.5 GRADE

For each outcome, GRADE was used to grade the quality of the supporting evidence. For this report, GRADE for systematic reviews was used. For systematic reviews, quality of evidence refers to one's confidence in the estimates of effect. In systematic reviews each outcome is considered separately, in contrast to guidelines, where the evidence is assessed across all outcomes and studies for a particular recommendation.

According to GRADE, the quality of evidence was classified into four categories: high, moderate, low, and very low. Quality rating for RCTs was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 steps, respectively. Observational studies were considered low level of evidence by default. However, the level of evidence of observational studies with no threats to validity could be upgraded for a number of reasons.

Reasons for (not) downgrading were summarized in GRADE profiles (see appendix 5).

As a note, within the GRADE philosophy it is common practice to report the results compiled by indication and by outcome. The latter (by outcome) was deliberately not done because of the diversity of outcomes.

3 RESULTS

3.1 Overview of selected studies

In total, 11 systematic reviews / HTA reports were included (Table 4). Six studies compared proton beam therapy with photon therapy (Table 5), while two studies had the wrong comparator but sufficient patients in the proton beam therapy group (and thus were included as a single-arm study) (Table 6). Finally, 22 single-arm studies included at least 50 patients and reported on the relevant outcomes (Table 6).

Table 4 – Overview of included HTA reports and SR [#]

Organisation / author	Indication(s) of interest for this report	Search date	N studies	General conclusions as reported by the authors
Olsen DR 2007 [7]	Hepatocellular carcinoma	March 2006	1	The evidence on clinical efficacy of proton therapy relies to a large extent on non-controlled studies, and thus is associated with low level of evidence according to standard health technology assessment and evidence based medicine criteria.
Lodge M 2007 [6]	Head and neck cancer Hepatocellular carcinoma Pancreatic cancer	January 2007	137	The current literature shows that the introduction, or significant extension, of hadron therapy as a major treatment modality – except on a minor scale for certain rare tumours (ocular, chordomas, etc.) – into standard clinical patient care cannot be supported by the evidence base currently available. There are little reliable evidence-based data available concerning the relative cost-effectiveness of hadron therapy interventions when compared with each other, with photon therapy, or with other cancer treatments. This also represents an important area for future research.
KCE 2007 [2]	Head and neck cancer Hepatocellular carcinoma	March 2007	45	Our research was not able to show any evidence in favour of hadrontherapy. … There were no comparative studies with regard to the toxicity of hadrontherapy. There were no reports of patients with toxicity Grade ≥ 4 severity. …
RIHTA [14*]	Head and neck cancer Hepatocellular carcinoma Pancreatic cancer	October 2011	33	All the secondary studies included in this report state that the paucity of well conducted clinical studies (RCTs, prospective cohort studies, comparative studies) makes it impossible to draw firm conclusions about the effects of hadrontherapy for cancer treatment. … Because of the lack of evidence regarding hadrontherapy, hadrontherapy facilities operating in Italy in the next years should produce high quality evidence, setting up comparative studies adequate in design and methods. It is important that high quality evidence be sought prior to planning the diffusion of this technology.
Dionisi F 2014 [5]	Hepatocellular carcinoma	December 2012	16	The low quality of the retrieved studies reduces without eliminating the interest toward the impressive clinical results that have been registered in several stages of HCC. The cost-benefit of proton versus other treatment options is worth of study given the high cost of protons. A number of proton therapy centers are currently recruiting patients in various prospective trials and are testing proton therapy alone, comparing proton therapy vs TACE, or evaluating the role of proton therapy in advanced disease. A positive outcome of such trials would suggest the role of proton therapy as an effective option in the local treatment of unresectable HCC. Active-scanning based proton therapy

				treatment for HCC is under development, and it should be considered one of the ''modern approaches'' to be tested in the next future.
ICER 2014 [11]	Breast cancer Low-grade glioma Head and neck cancer Hepatocellular carcinoma Pancreatic cancer	February 2014	321	… Evidence of proton beam therapy's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. … Patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of proton beam therapy is highly problematic. We rated the net health benefit of proton beam therapy relative to alternative treatments to be … "Incremental" (small net health benefit) in adult brain/spinal cancers …. We judged the net health benefit to be "Comparable" (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, …. It should be noted, however, that we made judgments of comparability based on a limited evidence base that provides relatively low certainty that proton beam therapy is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that proton beam therapy is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. … For relatively common cancers, the ideal evidence of proton beam therapy's clinical impact would come from randomized clinical trials such as those currently ongoing in liver, lung, and prostate cancer. To allay concerns regarding the expense and duration of trials designed to detect survival differences, new RCTs can focus on validated intermediate endpoints such as tumour progression or recurrence, biochemical evidence of disease, development of metastases, and near-term side effects or toxicities. In any event, overall and disease-free survival should be included as secondary measures of interest. …
Patel SH 2014 [8]	Paranasal sinus and nasal cavity cancer	April 2014	41	Compared with photon therapy, charged particle therapy could be associated with better outcomes for patients with malignant diseases of the nasal cavity and paranasal sinuses. Prospective studies emphasising collection of patient-reported and functional outcomes are strongly encouraged.
Qi WX 2015 [9]	Hepatocellular carcinoma	August 2014	70	Survival rates for charged particle therapy are higher than those for conventional radiotherapy, but similar to stereotactic body radiotherapy in patients with hepatocellular carcinoma. Toxicity tends to be lower for charged particle therapy compared to photon radiotherapy.
QUERI 2015 [13]	Breast cancer Low-grade glioma	December 2014	31	Despite the common claim that the advantage of proton beam therapy is self-evident, comparative studies have not demonstrated any common clinical

				situations in which proton beam therapy has an important clinical advantage over photon radiotherapy modalities on meaningful long-term health outcomes, but have uncovered low-strength evidence of the potential for increased late toxicity compared with IMRT and 3D-CRT for breast, … and spinal cord glioma cancers. Existing comparative studies have numerous methodological deficiencies that limited our confidence in their findings … Although numerous randomized controlled trials are underway that carry the promise of improved toxicity measurement, it is unclear whether they will fully address gaps in evidence on other important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies. Because this is still a rapidly evolving field, with ongoing efforts to improve techniques and reduce costs, this review may need frequent updating to keep up-to-date with emerging research.
INESSS 2017 [12] *	Breast cancer Head and neck cancer Hepatocellular carcinoma	July 2016	7	… Since the quality of the existing data is inadequate, it is presently not relevant to propose treatment with proton therapy for … hepatocellular carcinoma, … breast cancer, re-irradiation cases.
CADTH 2017 [10] *	Breast cancer Low-grade glioma Head and neck cancer Hepatocellular carcinoma	March 2017	9	The overall evidence from the assessment of the clinical effectiveness suggests that proton beam therapy, alone or in combination with photon radiotherapy, is comparable to other types of radiotherapy in most types of cancer, and safety varies by type of cancer.

** Overview of reviews.*

[#] *Only extracts of the conclusions are included here, focusing on the indications of interest of this report. More complete conclusions can be found in the evidence tables.*

Table 5 – Overview of included comparative studies

Author	Indication(s)	N patients	Comparison	Reported outcomes
Galland-Girodet S 2014 [15]	Breast cancer	98	Proton therapy (N=19) Photon radiotherapy (N=79; 60 patients also received electron radiotherapy)	Toxicity Cancer control
Maemura K 2017 [16]	Locally-advanced pancreatic cancer	25	Proton therapy (N=10) Hyper-fractionated acceleration radiotherapy + concomitant S-1 chemotherapy (N=15)	Overall survival Tumour response Toxicity
Otsuka M 2003 [17]	Hepatocellular carcinoma (recurrent)	8	Proton therapy (N=5) Photon radiotherapy (N=3)	Cancer control Toxicity Overall survival
Acharya S 2018 [18]	Low-grade glioma	160	Proton therapy (N=37) Photon radiotherapy (N=123)	Radiation necrosis
Bronk JK 2018 [19]	Low-grade glioma	99	Proton therapy (N=34) Photon radiotherapy (N=65)	Pseudoprogression Progression-free survival Overall survival
Kahn J 2011 [20]	Low-grade glioma	26	Proton therapy (N=6) IMRT (N=20)	Cancer control Progression-free survival Overall survival Toxicity

Table 6 – Overview of included single-arm studies (reported outcomes are toxicity and/or secondary tumours)

Author	Indication(s)	N	Proton therapy
Bush DA 2014 [21]	Breast cancer	100	Postoperative partial breast irradiation, followed by systemic therapy
Verma V 2017 [22]	Breast cancer	91	Adjuvant proton beam radiotherapy
Bush DA 2011 [23]	Hepatocellular carcinoma	76	Proton beam radiotherapy
Chiba T 2005 [24]	Hepatocellular carcinoma	162	Proton beam radiotherapy +/- TACE +/- percutaneous ethanol injection
Fukuda K 2017 [25]	Hepatocellular carcinoma	129	Primary proton therapy
Fukumitsu N 2009 [26]	Hepatocellular carcinoma	51	Hypofractionated proton beam radiotherapy
Kawashima M 2011 [27]	Hepatocellular carcinoma	60	Primary proton therapy
Kim TH 2018 [28]	Hepatocellular carcinoma	71	Hypofractionated proton beam radiotherapy
Komatsu S 2011 [29]	Hepatocellular carcinoma	242	Proton beam radiotherapy
Matsuzaki Y 1998 [30]	Hepatocellular carcinoma	62	Primary proton therapy
Mizumoto M 2008 [31]	Hepatocellular carcinoma	53	Proton beam radiotherapy
Mizumoto M 2011 [32]	Hepatocellular carcinoma	266	Proton beam radiotherapy
Mizumoto M 2012 [33]	Hepatocellular carcinoma	259	Proton beam radiotherapy
Nakayama H 2009 [34]	Hepatocellular carcinoma	318	Proton beam radiotherapy
Oshiro Y 2017 [35]	Hepatocellular carcinoma	83	Proton beam radiotherapy
Yu JI 2018 [36]	Hepatocellular carcinoma	101	Proton beam radiotherapy
McDonald MW 2016 [37]	Recurrent or second primary head and neck cancer	61	Proton beam radiotherapy
Phan J 2016 [38]	Recurrent or second primary head and neck cancer	60	Proton beam radiotherapy
Romesser PB 2016 [39]	Recurrent or second primary head and neck cancer	92	Proton beam radiotherapy
Takatori K 2014 [40]	Inoperable pancreatic cancer	91	Proton beam radiotherapy + gemcitabine
Terashima K 2012 [41]	Localy-advanced pancreatic cancer	50	Proton beam radiotherapy + gemcitabine
Dagan R 2016 [42]	Sinonasal cancer	84	Primary or adjuvant proton therapy
Russo AL 2016 [43]	Sinonasal cancer	54	Primary or postoperative proton beam radiotherapy
Zenda S 2015 [44]	Sinonasal cancer	90	Primary or postoperative proton beam radiotherapy

3.2 Systematic reviews and HTA reports

In total, 11 systematic reviews / HTA reports were included (Table 4). Three systematic reviews focused on one cancer type, i.e. two reviews on hepatocellular cancer [5, 9] and one review on sinonasal cancer.[8] All other systematic reviews and all HTA reports had no limitations in scope regarding the clinical indications. Three HTA reports were (mainly) an overview of reviews.[10, 12, 14] Unfortunately, these were also the most recent HTA reports. As a result, recently published primary studies were not captured by these reviews and HTAs.

The most recent HTA report was published by CADTH.[10] The literature search was of good quality and was run in June 2017. The report focused on systematic reviews, results were presented narratively. In general, the authors concluded that in most cancer types the clinical effectiveness of proton treatment, alone or in combination with photon radiotherapy, is comparable to other types of radiotherapy. INESSS also published a HTA report that mainly focused on secondary literature.[12] Their search was run in October 2016, and was of moderate quality (English and French literature only, unclear selection and data extraction process). In general, the authors concluded that the evidence was inadequate to recommend proton treatment for the studied indications (non-small-cell lung cancer, hepatocellular cancer, prostate cancer, oesophageal cancer, breast cancer, re-irradiation cases). RIHTA published a HTA report that was based on a literature search between 2007 and November 2011.[14] The search was of moderate quality (poor description of included studies) and mainly focused on secondary literature. The authors concluded that the evidence was inadequate and stressed the need for high-quality comparative studies.

QUERI published a HTA report, based on a review of moderate quality (English literature only).[13] The search was run in December 2014 and focused on systematic reviews and comparative studies. In general, the authors concluded that the evidence was inadequate.

ICER published a HTA report, based on a literature search of moderate quality (English literature only, unclear selection and data extraction process) run in February 2014.[11] The search was focused on RCTs or comparative cohort studies. The authors stressed the paucity of evidence for most indications, and the lack of data on the cost-effectiveness of proton treatment.

Dionisi et al. focused their search on hepatocellular cancer.[5] The search was run in December 2012, and was of low to moderate quality (limited databases, limited quality appraisal, English literature only, unclear data extraction process). Based on five clinical studies, the authors stressed the low quality of the available evidence and the experimental character of the treatment at that time. Qi et al. also focused their search on hepatocellular cancer.[9] The search was run in August 2014, and was of good quality. The authors performed a meta-analysis, that was done using correct methods when looking at the individual treatments. However, when comparing the different types of radiotherapy, baseline risk was not taken into account. For the meta-analysis a total of 70 non-comparative observational studies (73 cohorts) was used, including 53 cohorts treated with photon therapy and 20 cohorts that received charged particle therapy. Separate results for proton therapy were not provided.

Patel et al. focused their search on sinonasal cancer.[8] The search was run in April 2014, and was of good quality. The authors performed a meta-analysis, that was done using correct methods when looking at the individual treatments. However, when comparing the different types of radiotherapy, baseline risk was taken into account by adjusting for tumour stage only. For the meta-analysis a total of 41 non-comparative observational studies (43 cohorts) was used, including 30 cohorts treated with photon therapy and 10 cohorts treated with proton treatment (also other types of charged particle therapy were included, and some cohorts received combinations of treatment). Overall survival at the longest follow-up did not differ significantly between proton treatment and IMRT (RR = 1.02; 95%CI 0.77-1.35, p = 0.89), nor did the five-year overall survival (RR = 1.39; 95%CI 0.99-1.94, p = 0.057). In addition, disease-free survival at the longest follow-up did not differ significantly between proton treatment and IMRT (RR = 0.98; 95%CI 0.40-2.42, p = 0.97). However, the five-year disease-free survival was significantly better in the proton group (RR = 1.93; 95%CI 1.36-2.75, p = 0.0003). Also locoregional control at the longest follow-up was significantly better in the proton group (RR = 1.18; 95%CI 1.01-1.37, p = 0.031), but the

five-year locoregional control did not differ significantly (RR = 1.06; 95%CI 0.68-1.67, p = 0.79).

The earlier reports and/or reviews published by KCE,[2] Lodge et al.[6] and Olsen et al.[7] all dated from 2007, and did not add new information to the above.

3.3 Effectiveness by indication

3.3.1 Low-grade glioma

Three studies were identified that compared proton therapy with photon therapy in patients with low-grade glioma. However, none of these studies were randomized. Furthermore, only one study provided some comparison for effectiveness outcomes between proton and photon radiotherapy.[20] The two other studies[18,19] are discussed in the chapter on safety (see chapter 3.3).

Kahn et al. retrospectively included 32 patients with primary intramedullary spinal cord gliomas.[20] Twenty-six patients had a low-grade tumour. The median age at time of diagnosis was 34 years, with a range of ages from 2 to 84 years and 10 patients with an age below 25 years. Patients were treated by photon intensity-modulated radiotherapy (IMRT) (N=22, of which 20 with a low-grade glioma) or conformal proton radiotherapy (N=10, of which 6 with a low-grade glioma). No separate detailed description of the proton treatment was reported. In all, 26 patients received total doses ranging from 50 to 55 Gy, and 6 patients received between 45 and 50 Gy. The fraction sizes ranged from 1.0 to 2.0 Gy. Patients and clinicians were not blinded for treatment assignment. In view of the long recruitment period (1991 – 2005), concurrency of the treatment groups was considered to be highly unlikely. The median follow-up was 24 months. Five-year overall survival for the entire cohort was 65% (95%CI 42-82%). Patients treated with proton radiotherapy were more likely to die (from any reason) than patients treated with photon radiotherapy, even after adjustment for age and pathology (HR = 40, p = 0.02). Five-year progression-free survival for the entire cohort was 61% (95%CI 39-77%). Tumour recurrence or progression was found in 41% of all patients. Local recurrence was found in 20% of proton-treated patients vs. 23% of photon-treated patients. Brain metastasis recurrence (i.e. recurrence in the brain) was found in 10% of proton-treated patients vs. 5% of photon-treated patients. None of these results were reported separately for low-grade tumours.

3.3.2 Primary sinonasal tumours and recurrences of head & neck tumours

No comparative studies were found for primary sinonasal tumours and recurrences of head & neck tumours.

3.3.3 Breast cancer

One phase 1/2 study was identified that compared proton therapy with photon therapy in women with breast cancer. Galland-Girodet et al. prospectively included 98 women with pT1N0M0 invasive breast cancer.[15] All patients received accelerated partial-breast irradiation (32 Gy in 8 fractions given twice daily). Of these, 19 received proton therapy and 79 received photon radiotherapy (60 with mixed photons and electrons, 19 with photons only). Arrangements of the proton radiotherapy were left to the discretion of the treating physician. One to three fields were treated using the passive scattered technique. Only 1 field was treated per fraction for those patients treated with 2 to 3 fields, owing to the availability of the proton machine. Blinding was not reported (but unlikely), no matched design or risk adjustment was used. The 7-year cumulative incidence of local failure in the entire population was 6%. The 7-year local failure rate did not differ statistically significantly between proton and photon therapy (11% vs. 4%, p = 0.22). At 60 months, overall cosmesis as rated by physicians was good or excellent in 62% of patients treated with proton therapy vs. 94% of patients treated with photon therapy (p = 0.03). Also at 60 months, overall cosmesis as rated by patients was good or excellent in 88% of patients treated with proton therapy vs. 93% of patients treated with photon therapy (p = 0.69).

3.3.4 Pancreatic cancer

One study was identified that compared proton therapy with photon therapy in patients with pancreatic cancer. Maemura et al. prospectively included 25 patients with locally-advanced and unresectable pancreatic cancer.[16] All patients received induction chemotherapy (gemcitabine and S-1) and post-radiotherapy chemotherapy (S-1). Ten patients received proton therapy, while 15 patients received hyperfractionated acceleration radiotherapy with concomitant S-1. Patients treated with proton radiotherapy received either a standard dose of 50 GyE in 25 fractions via conventional 3-dimensional conformal irradiation, or an escalated dose of 67.5 GyE via a field-in-field technique if the dose-planning simulations suggested the patient would benefit from dose escalation. Blinding was not reported (but unlikely), no matched design or risk adjustment was used. Median overall survival was 22.3 months in the proton group vs. 23.4 months in the photon group (p-value not reported). One-, two-, and three-year overall survival rates in the proton group were 80%, 45%, and 22.5%, respectively, and the corresponding survival rates in the photon group were 86.7%, 33.3%, and 26.6%, respectively. The incidence of local progression in the photon group was higher than that in the proton group (60% vs. 40%, p-value not reported). Median time-to-progression was 15.4 months for both groups. Disease control rates (partial response or stable disease, four weeks after radiotherapy completion) were 93% in the photon group vs. 80% in the proton group ($p > 0.05$).

3.3.5 Hepatocellular cancer

One small retrospective study was identified that compared proton therapy with photon therapy in patients with hepatocellular cancer. Otsuka et al. included 8 patients with recurrent hepatocellular carcinoma.[17] Five patients were treated with proton therapy (250MeV protons, 3.0-4.5Gy/fraction), while three patients received photon-based radiotherapy. Apart from the very small sample size, no matched design or risk adjustment was used. Furthermore, no statistical comparison was made. In two patients treated with proton therapy, the tumour reappeared in the radiation field, versus none in the photon group. The overall local control rate was thus 78%. Seven patients died 9 months to 4 years after radiotherapy, one patient treated with photon-based radiotherapy was still alive 104 months after the first radiotherapy for recurrence.

No comparative studies on primary hepatocellular cancer were included.

3.3.6 Locally recurrent rectal cancer

No comparative studies were found for locally recurrent rectal cancer.

3.3.7 Key points

- **The available evidence on the effectiveness of proton treatment for the selected indications is limited to non-randomized comparative studies with methodological limitations and/or small sample sizes. The conclusions below therefore have a high degree of uncertainty.**
  - **There is evidence of very low level (1 study, 32 patients) that proton treatment is associated with a worse survival than photon radiotherapy in patients with primary intramedullary spinal cord gliomas. The data on recurrence are too imprecise to draw a firm conclusion.**
  - **There is evidence of very low level (1 study, 98 patients) that proton treatment is associated with worse physician-rated cosmetic results at 5 years than photon radiotherapy in patients with stage I breast cancer. No significant difference was found for patient-rated cosmetic results. The data on local failure rate are too imprecise to draw a firm conclusion.**
  - **There is evidence of very low level (1 study, 25 patients) that proton treatment and hyperfractionated acceleration radiotherapy with concomitant S-1 do not differ significantly in their effect on survival and disease control in patients with locally advanced and unresectable pancreatic cancer,**

although the estimates are imprecise. The data on local progression are too imprecise to draw a firm conclusion.

- **The data on the effect of proton treatment vs. photon radiotherapy on local recurrence rate in patients with recurrent hepatocellular cancer are too imprecise to draw a firm conclusion.**

- **In the absence of clinical studies comparing proton treatment with photon-based radiotherapy, no conclusions can be drawn on the effectiveness of proton treatment for primary sinonasal cancer, recurrent head and neck cancer, and locally recurrent rectal cancer.**

3.4 Safety

3.4.1 Low-grade glioma

3.4.1.1 Comparative studies

As mentioned above, three studies were identified that compared proton therapy with photon therapy in patients with low-grade glioma.

Acharya et al. retrospectively included 160 adults with newly diagnosed WHO grade 2 or 3 cranial oligodendrogliomas or astrocytomas.[18] Brainstem gliomas were excluded. Thirty-seven patients received proton therapy, while 123 patients were treated with IMRT. Patients and clinicians were probably not blinded, but evaluation of cases was done by a board. The primary outcome was clinically significant radiation necrosis, defined as a radiologic abnormality that was associated with new neurologic symptoms unrelated to tumour progression or other causes (symptomatic radiation necrosis) or that resulted in surgery or bevacizumab administration in the absence of symptoms (asymptomatic radiation necrosis). After a median follow-up of 28.5 months, the incidence of radiation necrosis was 6 patients in the proton group vs. 12 patients in the IMRT group. The two-year cumulative incidence was 18.7% (95%CI 7.5-33.8%) vs. 9.7% (95%CI 5.1-16%) (p = 0.16). Other complications or side effects were not reported.

Bronk et al. retrospectively included 99 adults with histologically confirmed grade II or III oligodendroglioma (N=67) or astrocytoma (N=32).[19] Thirty-four patients were treated with proton therapy, while 65 patients were treated with IMRT. The patients were not blinded for treatment assignment, but the radiologists evaluating pseudoprogression were. In view of the long recruitment period (2004 – 2015), concurrency of the treatment groups was considered to be highly unlikely. Pseudoprogression was diagnosed in 14.7% of the proton-treated patients vs. 13.8% in the IMRT group (p = 1.00). Other complications or side effects were not reported.

Kahn et al. retrospectively included 32 patients with primary intramedullary spinal cord gliomas.[20] Twenty-six patients had a low-grade tumour. The median age at time of diagnosis was 34 years, with a range of ages from 2 to 84 years and 10 patients with an age below 25 years. Patients were treated by photon IMRT (N=22, of which 20 with a low-grade glioma) or conformal proton radiotherapy (N=10, of which 6 with a low-grade glioma). Patients and clinicians were not blinded for treatment assignment. In view of the long recruitment period (1991 – 2005), concurrency of the treatment groups was considered to be highly unlikely. The median follow-up was 24 months. For complications or side effects no statistical comparison was made between the two treatment groups. Long-term toxicity was evaluated with the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme. However, no clear definition was provided. None of the patients had significant long-term toxicity or myelopathy. The most common side effects were: fatigue (41%), erythema (16%), nausea and vomiting (28%), skin irritation (25%), back pain (13%), arm pain (13%), leg pain (6%), dysphagia and odynophagia (9%).

3.4.1.2 Single-arm studies

No additional single-arm studies with at least 50 patients were included.

3.4.2 Primary sinonasal tumours and recurrences of head & neck tumours

3.4.2.1 Comparative studies

No comparative studies were found for primary sinonasal tumours and recurrences of head & neck tumours.

3.4.2.2 Single-arm studies

Three studies reported on complications or side effects of proton therapy in patients with recurrent or second primary head and neck cancer.

McDonald et al. retrospectively included 61 adults with recurrent or second primary head and neck cancer (squamous cell carcinoma 52%) after previous radiation therapy, who were treated with proton therapy.[37] The study was flawed by potential selection bias. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Acute toxicities were considered those occurring during therapy and within the first 90 days after completion of reirradiation, and late toxicities were those persistent or occurring >90 days after reirradiation. Acute toxicity with a maximum of grade 3 occurred in 13.1% of the patients (3 cases of dermatitis, 2 cases of mucositis, 3 cases of soft tissue / bone toxicity), and grade 5 in 1.6% of the patients (i.e. one treatment-related death due to subdural haematoma with brainstem oedema). Of the 53 patients surviving >3 months after reirradiation, late toxicity of maximum grade 3 occurred in 15.1% (8 cases of soft tissue / bone toxicity, 1 case of central nervous system toxicity), grade 4 in 5.7% (1 case of soft tissue necrosis, 2 cases of anticipated vision loss), and grade 5 in 3.8% of the patients (i.e. two treatment-related deaths, one because of clival osteoradionecrosis and one because of cerebrospinal fluid leak with meningitis).

Phan et al. retrospectively included 60 adults who underwent proton reirradiation for recurrent or second primary head and neck cancer (squamous cell carcinoma 67%) after previous radiation therapy.[38] Toxicity was scored according to the CTCAE, version 4. Acute toxicity was determined by weekly examinations during treatment. Late toxicity was defined as events occurring or persisting ≥2 months after the completion of radiotherapy. All grade 3 through 5 toxicities were verified independently by 2 physicians. Eighteen patients (30%) experienced acute grade 3 toxicity, with a total of 27 reporting adverse events: dermatitis (N=8), mucositis (N=6), odynophagia (N=6), dysphagia (N=3), xerostomia (N=2), and weight loss (N=2). Thirteen patients (22%) required a feeding tube. One patient did not complete the proton treatment because of worsening of several medical comorbidities. One patient died because of multisite organ failure and acute cerebral infarction. Twelve (20%) patients experienced late grade 3 toxicity: dysphagia (N=1), xerostomia (N=1), feeding tube (N=6), neurotoxicity (N=2), and tracheostomy (N=2). Two patients had potentially treatment-related grade 5 toxicity (osteoradionecrosis).

Romesser et al. retrospectively included 92 consecutive patients with locally recurrent head and neck cancer (squamous cell carcinoma 57%) with a history of at least one prior course of definitive intent external beam radiotherapy.[39] All patients were reirradiated with curative intent proton radiotherapy. Acute and late toxicities were assessed by the CTCAE, version 4.0, and by the RTOG late radiation morbidity scoring system, respectively. Late toxicity was assessed beginning at 90 days after completion of proton radiotherapy. Grade 3 or greater acute toxicities included mucositis (9.9%), dysphagia (9.1%), oesophagitis (9.1%), and dermatitis (3.3%). Five patients (5.4%) did not complete proton treatment (4 due to tumour progression and 1 due to severe nausea). Grade 3 or greater late toxicities included skin toxicity (8.6%), dysphagia (7.1%), and bleeding (2.9%). There were two patients with grade 5 toxicity secondary to treatment-related nasopharyngeal or parapharyngeal bleeding / carotid rupture.

Three studies reported on complications or side effects of proton therapy in patients with sinonasal cancer.

Dagan et al. retrospectively included 84 adult patients with sinonasal cancer who received curative treatment including primary or postoperative proton therapy, and who had a minimum follow-up of 6 months from radiotherapy completion.[42] Toxicities were graded according to the CTCAE, version 4. No

clear separation was made between acute and late toxicity. Toxicity data were narratively reported, with a mixed use of absolute numbers and percentages. The study also suffered from potential selection bias. Twenty-four percent of patients had a significant (i.e. grade 3-5) toxicity. Toxicities that were mentioned included: unilateral vision loss (N=2), bone or soft-tissue necrosis (N=7), prolonged use of feeding tubes (N=4), central nervous system necrosis requiring steroids (11%), infection and cerebrospinal fluid leak. In 3 patients death was attributed at least in part to therapy.

Russo et al. retrospectively included 54 patients newly diagnosed stage III or IV squamous cell carcinoma of the nasal cavity and paranasal sinus, for whom protons could potentially result in improved dosimetric and clinical outcomes when compared with photon therapy.[43] Toxicity was scored using the CTCAE, version 4. Toxicity was considered late if occurrence was >90 days from radiotherapy completion. The study suffered from potential selection bias. Nine patients experienced grade 3 toxicity, 6 patients had grade 4 toxicity. There was no grade 5 toxicity. The most common late toxicities of at least grade 2 were ocular and visual toxicity (N=14), auditory toxicity (N=10), wound and soft tissue toxicity (N=9), neurologic toxicity (N=8), nasal stenosis (N=7), and bone toxicity (N=5).

Zenda et al. retrospectively included 90 patients with malignancies of the nasal cavity, paranasal sinuses, or involving the skull base, who were treated with proton therapy.[44] The primary site involved the maxillary sinus in 12 patients, the ethmoid sinus in 8 patients, the sphenoid sinus in 5 patients, and the nasal cavity in 62 patients (not reported for 3 patients). Toxicity was graded according to the CTCAE, version 4. A clear definition of late toxicity was not provided. Grade 3 late toxicities occurred in 17 patients (19%) with 19 events. The most common toxicities were cataract (N=5), hearing loss (N=2) and bone necrosis (N=2). Grade 4 late toxicities occurred in 6 patients (7%) with 6 events (encephalomyelitis infection in 2 patients, optic nerve disorder in 4 patients). Median time to onset of grade 2 or greater late toxicity (with the exception of cataract) was 39.2 months.

3.4.3 Breast cancer

3.4.3.1 Comparative studies

As mentioned above, one phase 1/2 study was identified that compared proton therapy with photon therapy in women with breast cancer. Galland-Girodet et al. prospectively included 98 women with pT1N0M0 invasive breast cancer.[15] All patients received accelerated partial-breast irradiation (32 Gy in 8 fractions given twice daily). Of these, 19 received proton therapy and 79 received photon radiotherapy (60 with mixed photons and electrons, 19 with photons only). Blinding was not reported (but unlikely), no matched design or risk adjustment was used. Late toxicity was graded by the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. However, no clear definition of late toxicity was provided.

At 5 years significant differences were found in skin colour changes between patients treated with proton therapy (44% with moderate skin colour change) versus photon-based therapy (2%) ($p \leq 0.0001$). No significant differences were found in rates of erythema or dry or moist desquamation. Fifty percent of proton patients developed patchy atrophy in the irradiation portal, compared with 5% of photon patients ($p \leq 0.0001$). At 7 years, skin colour change ($p = 0.02$) and late skin toxicity ($p = 0.029$) were significantly worse in the proton group. Telangiectasia >4 cm^2 was observed for 38.5% of the proton group as compared with 4% of the photon-based group ($p = 0.0013$). There was no difference between the treatment groups in non-cutaneous toxicities, including breast pain, breast oedema, and rib tenderness, at either 5 or 7 years. Four cases of rib fracture were observed after 60 months of follow-up: 1 in the proton group and 3 in the photon-based group ($p = 0.072$). Twelve patients developed fat necrosis: 2 from the proton group and 10 from the photon-based group ($p = 0.47$).

3.4.3.2 Single-arm studies

Two single-arm studies reported on complications or side effects of proton therapy in patients with breast cancer.

In a phase 2 study, Bush et al. included 100 adult women with invasive nonlobular breast cancer with a maximal dimension of 3 cm.[21] All women underwent partial mastectomy with negative margins and pathologically negative lymph nodes, and were treated with postoperative proton beam radiation therapy to the surgical bed. Acute toxicities (within 3 months following treatment completion) were rated according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The study suffered from potential selection bias. Acute skin toxicity included mild to moderate radiation dermatitis in 62% of the patients (graded as 1 or 2). There were no cases of grade 3 or higher skin toxicity, nor were other acute toxicities encountered. Late skin reactions included primarily development of grade 1 telangiectasias in 7% of the population. There was one case of clinical fat necrosis at 1 year after treatment that required drainage. There were no reported cases of rib fractures, clinical pneumonitis, or cardiac events.

Verma et al. retrospectively included 91 women with locally-advanced breast cancer, who received primary adjuvant PBT to either the intact breast or chest wall plus the comprehensive regional lymphatics.[22] Toxicities were recorded according to the CTCAE, version 4. A clear definition of acute and late toxicity was not provided. Acute dermatitis of grades 1, 2, and 3 occurred in 23%, 72%, and 5% of cases, respectively. Nineteen patients (21%) required opioids for pain associated with acute skin toxicity, and 7 (8%) required a treatment break. In all patients this was due to skin toxicity; six of the seven patients had grade 2 dermatitis, and the seventh had grade 1 dermatitis. All but two patients completed the prescribed treatment; one electively discontinued due to grade 2 dermatitis, and the other declined a boost. Seven patients developed skin infection requiring a course of antibiotics. One patient had a non-healing wound requiring closure via a latissimus flap, and one patient developed nonlethal sepsis secondary to the skin infection. There was no grade 3 oesophageal toxicity; 33% and 31% developed grade 2 and 1 esophagitis, respectively. Two patients (2%) experienced uncomplicated rib fracture. At last follow-up, three (3%) patients had clinically evident lymphedema for which compression sleeves and/or pumps were used.

3.4.4 Pancreatic cancer

3.4.4.1 Comparative studies

As mentioned above, one study was identified that compared proton therapy with photon therapy in patients with pancreatic cancer. Maemura et al. prospectively included 25 patients with locally-advanced and unresectable pancreatic cancer.[16] All patients received induction chemotherapy (gemcitabine and S-1) and post-radiotherapy chemotherapy (S-1). Ten patients received proton therapy, while 15 patients received hyperfractionated acceleration radiotherapy (HART) with concomitant S-1. Blinding was not reported (but unlikely), no matched design or risk adjustment was used. Toxicities were recorded according to the CTCAE, version 4. No clear definition of acute and late toxicity was provided. All patients in both groups, received the scheduled radiotherapy doses. Although the incidence of haematological toxicities was higher in the HART group, no grade 4 toxicities were observed in either group. However, three patients in the HART group developed grade 3 leukopenia and thrombocytopenia. No patients developed febrile neutropenia. Regarding gastrointestinal effects, patients in the HART group reported nausea and anorexia, and two patients in the proton group developed a grade 2 or 3 gastric ulcer.

3.4.4.2 Single-arm studies

Two single-arm studies reported on complications or side effects of proton therapy in patients with pancreatic cancer.

Takatori et al. prospectively included 91 patients with either locally unresectable or clinically inoperable pancreatic cancer.[40] Patients with metastatic disease were included if their distant disease was of low volume and if their prognosis was favourable with control of the primary tumour. Patients with resectable pancreatic tumours were included if they had several reasons for a diagnosis of clinically inoperable, such as high age, severe comorbidities, and patient will. All patients were treated with gemcitabine-concurrent proton radiotherapy. Acute gastrointestinal complications were evaluated using small-bowel endoscopy. Toxicities were assessed using the CTCAE, version 3. Post-treatment endoscopic examinations showed that 49.4% of the patients had a total of 51 radiation-induced ulcers in the stomach and duodenum. No mucosal lesion with spontaneous or active bleeding, and no cases of gastrointestinal perforation were found. During the 10-month follow-up period after treatment completion, 2 patients (2.2%) exhibited grade 4 and grade 5 bleeding gastric ulcers at 3 and 10 months, respectively. In addition, 1 patient (1.1%) with pancreatic head cancer with a metallic biliary stent exhibited a grade 5 duodenal perforation at 5 months after treatment completion.

In a phase 1/2 study, Terashima et al. included 50 patients with locally advanced pancreatic cancer, borderline resectable cancer or unresectable cancer without distant metastases.[41] All patients were treated with gemcitabine-concurrent proton radiotherapy, three different proton schedules were used. The study suffered from potential selection bias. Toxicities were assessed using the CTCAE, version 3. No clear definition of acute and late toxicity was provided. Five patients were treated with 50 GyE in 25 fractions, while five patients received 70.2 GyE in 26 fractions. In the latter group, one patient could not complete proton therapy at 62.1 GyE in 23 fractions due to gastric bleeding caused by acute radiation mucositis. Forty patients were treated with 67.5 GyE in 25 fractions. Of these, five patients could not receive the third gemcitabine administration because of acute haematologic and gastrointestinal toxicities. One patient had acute grade 4 leukopenia, while 2 patients had grade 4 neutropenia. One patient died of gastric haemorrhage six months after treatment completion. Overall (for the entire population), the most common acute adverse events of at least grade 3 were: leukopenia (N=20), neutropenia (N=14), and anorexia (N=5). Late adverse events of at least grade 3 included gastric ulcer (N=5), anorexia (N=1) and fatigue (N=1).

3.4.5 Hepatocellular cancer

3.4.5.1 Comparative studies

As mentioned above, one small retrospective study was identified that compared proton therapy with photon therapy in patients with hepatocellular cancer. Otsuka et al. included 8 patients with recurrent hepatocellular carcinoma.[17] Five patients were treated with proton therapy, while three patients received photon-based radiotherapy. Apart from the very small sample size, no matched design or risk adjustment was used. Furthermore, no statistical comparison was made. It is unclear how toxicity was assessed. No definition for acute and late toxicity was provided. Bone marrow depression or gastrointestinal complications were not observed during or after radiotherapy.

3.4.5.2 Single-arm studies

Fourteen single-arm studies reported on complications or side effects of proton therapy in patients with hepatocellular cancer. Of these, 9 studies were run in the Tsukuba proton centre in Japan (Table 7). Based on the study periods, number of patients, inclusion criteria and treatment schedules it can be assumed that several studies had an important overlap in population. The studies of Mizumoto et al. from 2011[32] and 2012[33] refer to the same population, but also show a big overlap with the study population of Nakayama et al.[34]. Furthermore, they seem to include the populations of Fukumitsu et al.[26] and Mizumoto et al. (2008)[31]. In addition, the studies of Chiba et al.[24] and Matsuzaki et al.[30] show at least some overlap. If possible, these overlapping studies will be discussed together to avoid double counting.

Table 7 – Overview of included single-arm studies on hepatocellular cancer run in the Tsukuba proton centre

Author	Study period	N	Inclusion criteria
Chiba T 2005 [24]	November 1985 – July 1998	162	Unresectable, 3 or fewer tumours
Fukuda K 2017 [25]	2002 - 2009	129	Previously untreated
Fukumitsu N 2009 [26]	September 2001 – August 2004	51	>2 cm away from the porta hepatis or gastrointestinal tract
Matsuzaki Y 1998 [30]	March 1995 – January 1998	62	Unresectable (or refused surgery), single or multinodular tumours
Mizumoto M 2008 [31]	September 2001 – December 2004	53	<2 cm from the porta hepatis
Mizumoto M 2011 [32]	January 2001 – December 2007	266	>2 cm away from the porta hepatis or gastrointestinal tract <2 cm from the porta hepatis <2 cm from the gastrointestinal tract
Mizumoto M 2012 [33]	January 2001 – December 2007	259	>2 cm away from the porta hepatis or gastrointestinal tract <2 cm from the porta hepatis <2 cm from the gastrointestinal tract
Nakayama H 2009 [34]	November 2001 – December 2007	318	>2 cm away from the porta hepatis or gastrointestinal tract <2 cm from the porta hepatis <2 cm from the gastrointestinal tract
Oshiro Y 2017 [35]	2002 - 2010	83	Repeated proton beam radiotherapy

The largest series was published by Nakayama et al.[34] As explained above, this series shows an important overlap with the studies of Mizumoto et al. from 2011[32] and 2012[33], and also seems to include the populations of Fukumitsu et al.[26] and Mizumoto et al. (2008)[31]. Nakayama et al. retrospectively included 318 patients with hepatocellular cancer (solitary or multiple tumour foci totalling <3 in number or any number of lesions provided all could be covered in the same irradiation field), that was considered not suitable for surgery or considered difficult to control with nonsurgical treatments (or patient's refusal of surgery and/or other nonsurgical treatments). Most patients (N=255) were treated with schedules from protocol studies depending on tumour location: a total dose of 77.0 GyE in 35 fractions was used for tumours within 2 cm of the digestive organ (N=66), 72.6 GyE in 22 fractions was used for tumours within 2 cm of the porta hepatis (N=85), and 66.0 GyE in 10 fractions was delivered to peripheral tumours >2 cm from both the gastrointestinal tract and the porta hepatis (N=104). The remaining patients were treated with modified schedules of the protocol studies. Toxicities were graded according to the CTCAE (version 3). No clear definition of acute and late toxicity was provided. According to the authors, treatment-related toxicity was minimal, with no treatment-related death and no treatment discontinuation because of liver toxicity. Four patients developed radiation-related gastrointestinal toxicity. Of these, 3 had grade 2 gastrointestinal ulcers, which were successfully treated by medication. The remaining patient suffered from grade 3 haemorrhage of the colon, which was successfully removed by surgery. Three patients had symptomatic rib fractures, which cured without medication. Haematologic toxicities of grade 3 or higher occurred in 6

patients. Mizumoto et al. (2011) additionally reported acute grade 3 radiation dermatitis in 2 patients and late grade 3 dermatitis in 1 patient. Mizumoto et al. (2012) reported on the effects of proton treatment on liver function. On the final day of treatment, 0.4% of patients had an increase in Child-Pugh score of 2. At 6, 12 and 24 months after treatment, 9%, 11% and 22%, respectively, had an increase in Child-Pugh score of at least 2.

Chiba et al. retrospectively included 162 patients with hepatocellular carcinoma, considered unsuitable for surgery for various reasons.[24] All patients were treated with proton treatment with or without transarterial embolization and percutaneous ethanol injection. Late toxicity was graded according to the late radiation morbidity scoring scheme of the RTOG/European Organization for Research and Treatment of Cancer. No clear definition of acute and late toxicity was provided. The study also suffered from potential selection bias. The authors reported no treatment discontinuation because of acute reactions. Acute and subacute treatment sequelae included elevation of bilirubin (2.1%), anemia (1.1%), leukocytopenia (0.5%), thrombocytopenia (3.2%), and elevation of the transaminase level (9.7%). Late treatment sequelae, all grade 2 or higher, included biloma with infection (1.1%), common bile duct stenosis (0.5%), and gastrointestinal tract bleeding (1.1%).

As explained above, the study of Matsuzaki et al.[30] probably has some overlap with the study of Chiba et al.[24] They compared proton radiotherapy (N=62) with Lipiodol-targeted chemotherapy (N=42) in patients with hepatocellular carcinoma with single or multinodular tumours who had refused surgery or had unresectable hepatocellular carcinoma. Because of the wrong comparator only the proton-treated patients will be discussed here. It is unclear how toxicity was evaluated, and no clear definition of acute and late toxicity was provided. The study also suffered from potential selection bias. No patients experienced any serious adverse reactions, no clinical symptoms, such as general fatigue, appetite loss, or nausea, were seen. The most common side effects were leukocytopenia (N=24), thrombocytopenia (N=19), elevation of transaminase (N=14) and elevation of bilirubin (N=7).

Fukuda et al. included 129 patients with hepatocellular carcinoma that was previously untreated.[25] All patients received proton treatment (66.0-77.0 GyE in 10-35 fractions). Toxicities were graded according to the CTCAE (version 2). No clear definition of acute and late toxicity was provided. The study also suffered from potential selection bias due to heterogeneous referral. Toxicity data were mainly reported narratively. No patients had severe complications due to proton treatment or adverse events higher than grade 2, except for haematologic abnormalities. For haematologic toxicities the relation to proton treatment was difficult to assess, because cirrhotic patients usually have pancytopenia due to splenomegaly. No patient required a blood transfusion during treatment or treatment cessation. Radiation dermatitis was common, but no patient had grade 3 or higher dermatitis.

Oshiro et al. retrospectively included 83 patients with hepatocellular carcinoma who received multiple courses of definitive proton beam therapy.[35] Few details on the actual inclusion criteria were reported. Acute and late toxicities associated with treatment were evaluated using the CTCAE (version 4). No clear definition of acute and late toxicity was provided. There was no grade 3 or higher acute toxicity. One patient had intestinal bleeding and underwent hemicolectomy 8 months after the first treatment. Eight patients (9.6%) died of hepatic failure, but there was no radiation-induced liver dysfunction, clinical syndrome of anicteric hepatomegaly, ascites, or elevated liver enzymes between 2 weeks and 4 months after radiotherapy. Four of the eight deaths occurred more than 1 year after the last treatment, and proton treatment was not the direct cause of liver failure.

Five included single-arm studies were run outside the Tsukuba centre.

In a phase 2 study (NCT00614172), Bush et al. prospectively included 76 patients with hepatocellular cancer and cirrhosis.[23] All patients were treated with proton therapy (63 Gy in 15 fractions of 4.2 Gy). Treatment toxicity was evaluated according to the CTCAE, version 2. No clear definition of acute and late toxicity was provided. The study suffered from potential selection bias. Acute toxicity during proton therapy was minimal and included mild fatigue and skin reactions consisting of erythema (grade 1). No acute

toxicities required the 3-week treatment course to be interrupted or discontinued. Five patients experienced gastrointestinal adverse effects after treatment (gastrointestinal bleeding, significant inflammation or ulceration within the gastrointestinal tract at or near the area of radiation treatment; all grade 2). All gastrointestinal toxicity was observed in the first 30 patients enrolled in the trial. Afterward, greater care was taken to reduce field margins when tumours occurred adjacent to the bowel, and subsequent patients did not demonstrate evidence of bowel injuries. Overall, no statistically significant change was observed in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, or albumin levels or prothrombin time.

Kawashima et al. retrospectively included 60 consecutive patients with unresectable hepatocellular cancer that underwent proton treatment.[27] The severity of adverse events was assessed using the CTCAE, version 3. No clear definition of acute and late toxicity was provided. The authors reported no treatment discontinuation because of acute reactions, one patient's treatment was extended because of fever associated with grade 3 elevation of total bilirubin. Adverse events during proton treatment included transient grade 3 leukopenia and/or thrombocytopenia (N=14) and grade 3 elevation of transaminases (N=8). Proton-induced hepatic insufficiency occurred in 11 patients (all treated with 76 GyE) at 1 to 6 months after completion of proton treatment. Of these, 6 patients died. Three patients experienced a gastrointestinal toxicity grade of ≥2. There were no other adverse events of ≥3 grade.

Kim et al. retrospectively included 71 patients with inoperable or recurrent hepatocellular carcinoma ≥2 cm from gastrointestinal structures.[28] All patients received hypofractionated proton therapy (66 GyE in 10 fractions). It is unclear how toxicity was evaluated. Furthermore, the study suffered from potential selection bias. No patient experienced grade ≥3 toxicity. Acute toxicities (within 3 months after proton treatment) were transient, easily manageable, and caused no interruption in the treatment course. Three (4.2%) patients experienced grade 1 elevated ALT without evidence of tumour progression, and six (8.5%) patients experienced grade 1 leukopenia and thrombocytopenia. No late gastrointestinal toxicities (gastric or duodenal ulcers within the radiotherapy field), late hepatic failure induced by radiation-induced liver disease or treatment-related death was observed.

Komatsu et al. retrospectively included 242 consecutive patients with hepatocellular carcinoma that were treated with proton therapy.[45] Acute and late toxicities were graded according to the CTCAE (version 2). However, a clear definition of acute and late toxicity was not provided. All acute toxicities that occurred during treatment were transient, easily manageable and acceptable. However, grade ≥3 late toxicities were observed in 8 patients on proton therapy. These included dermatitis (N=5), elevation of transaminase level (N=1), upper gastrointestinal ulcer (N=1), and biloma (N=1). No patient died of treatment-related toxicity.

Finally, Yu et al. prospectively included 101 patients with hepatocellular carcinoma who were not indicated for standard curative local modalities and who were treated with proton therapy.[36] Toxicity was scored using the CTCAE, version 4. At 3-month follow-up after proton treatment, 22 acute toxicities of ≥3 grade were recorded, including thrombocytopenia (9.9%), hyperbilirubinemia (5%), leukopenia (3%), anemia (2%), AST elevation (1%), and ALT elevation (1%). Among these, there was one case of grade 4 hyperbilirubinemia. During the follow-up period after completion of proton therapy, two cases (2.0%) of newly developed gastroduodenal ulcers were detected. In three other cases, gastroduodenal changes including erosion and/or inflammation were found within the irradiation field.

3.4.6 Locally recurrent rectal cancer

No comparative studies or single-arm studies with at least 50 patients were included.

3.4.7 Key points

- **The available evidence on the safety of proton treatment for the selected indications is limited to non-randomized comparative studies with methodological limitations and/or small sample size, and single-arm studies. The conclusions below therefore have a high degree of uncertainty.**
- **Toxicity is heterogeneously and often selectively reported. Furthermore, definitions of acute and late toxicity differ across studies, making comparison and conclusions difficult.**
- **Toxicity data per indication reflect that the types of adverse events are highly dependent on the dose delivered to a certain volume of an organ at risk.**
- **The incidence of fatal toxicity and treatment cessation because of toxicity seem to be comparable to that of conventional radiotherapy.**
- **Based on the comparative studies the following additional conclusions can be drawn:**
  - **The data on the effect of proton treatment vs. photon radiotherapy on radiation necrosis and pseudoprogression in patients with primary intramedullary spinal cord gliomas are too imprecise to draw a firm conclusion.**
  - **There is evidence of very low level (1 study, 98 patients) that proton treatment is associated with more dermatologic toxicity (skin colour changes, patchy atrophy, telangiectasia) than photon radiotherapy in patients with stage I breast cancer. The data on rib fractures and fat necrosis are too imprecise to draw a firm conclusion.**
  - **The data on the effect of proton treatment vs. hyperfractionated acceleration radiotherapy with concomitant S-1 on acute grade 3 leukopenia, thrombocytopenia and ulcer in patients with locally advanced and unresectable pancreatic cancer are too imprecise to draw a firm conclusion.**
  - **The data on the effect of proton treatment vs. photon radiotherapy on toxicity in patients with recurrent hepatocellular cancer are too scarce to draw a firm conclusion.**

3.5 Secondary tumours

Only two single-arm studies explicitly reported on the incidence of secondary tumours after proton treatment, both in patients with sinonasal cancer. Dagan et al. reported one secondary malignancy (on a total of 84 patients) presenting as an out-of-field unknown primary adenocarcinoma involving the liver less than 5 years after treatment of a squamous cell carcinoma of the maxillary sinus (a time period in which a secondary malignancy is not attributed to prior radiation).[42] Russo et al. also reported one secondary malignancy (on a total of 54 patients) presenting as a spindle cell sarcomatoid carcinoma in the maxillary sinus 9 years after the completion of radiation.[43]

3.6 Ongoing trials

Three relevant ongoing RCTs were identified comparing proton treatment with photon-based radiotherapy (Table 8). One large trial is actively recruiting women with non-metastatic breast cancer, aiming at a total of 1720 participants. Study completion is not expected before November 2030. One trial is recruiting patients with unresectable or locally recurrent hepatocellular carcinoma, while another trial is recruiting patients with grade II or III glioma. For both studies, completion is not expected before August 2027.

In addition to the trials listed in Table 8, a very large prospective observational study is actively recruiting a total of 20000 participants with solid tumours eligible for radiation therapy (NCT01255748). Various forms of radiation therapy will be compared, such as proton therapy, photon therapy, brachytherapy and stereotactic radiosurgery. Results are expected by June 2029.

Table 8 – Overview of ongoing trials on proton treatment for the indications of interest

Trial ID	Indication	N	Proton treatment	Comparator	Anticipated end date
NCT02603341	Non-metastatic breast cancer	1720	Proton therapy: once a day, 5 days a week, for 5 to 7 weeks	Photon therapy: once a day, 5 days a week, for 5 to 7 weeks	November 2030
NCT03186898	Unresectable or locally recurrent hepatocellular carcinoma	186	Proton therapy over 15-24 days for 5 or 15 fractions	Photon therapy over 15-24 days for 5 or 15 fractions	August 2027
NCT03180502	Grade II or III glioma	120	Proton therapy, 5 days a week for 6 weeks for a total of 30 fractions	Photon-based IMRT, 5 days a week for 6 weeks for a total of 30 fractions	August 2027

4 DISCUSSION

4.1 Scarce and flawed evidence on the effectiveness of proton treatment

When evaluating the effectiveness of an intervention, comparison with a standard treatment is a necessity. Randomized studies are the preferred design, because – in most circumstances – it is least likely to be biased. Randomization is the only way to prevent systematic differences between baseline characteristics of participants in different intervention groups in terms of both known and unknown (or unmeasured) confounders.[46] According to the Non-Randomized Studies Methods Group of the Cochrane Collaboration, there are three main reasons that justify the inclusion of non-randomized studies in a systematic review: a) to examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available non-randomized studies and/or to inform the design of a subsequent randomized trial, e.g. through the identification of relevant subgroups; b) to provide evidence of the effects (benefit or harm) of interventions that cannot be randomized, or which are extremely unlikely to be studied in randomized trials; c) to provide evidence of effects (benefit or harm) that cannot be adequately studied in randomized trials, such as long-term and rare outcomes (e.g. secondary cancers), or outcomes that were not known to be important when existing, major randomized trials were conducted. None of these reasons apply to the current systematic review, and thus the absence of randomized trials should be considered a major conclusion.

For four of the studied indications a single comparative observational study was available that reported on effectiveness outcomes. None of these studies was free from methodological flaws, and only one study adjusted for age and pathology. Therefore, in all cases downgrading to a very low level of evidence was necessary, and thus conclusions must be interpreted with caution.

Only two studies reported on *survival*. One retrospective study found that patients with primary intramedullary spinal cord gliomas treated with proton radiotherapy were more likely to die than patients treated with photon radiotherapy, even after adjustment for age and pathology.[20] However, no confidence intervals were reported, making it difficult to evaluate the precision of the estimate. Furthermore, some patients had a grade 3 glioma, which was outside the scope of this report. A second prospective study found no apparent difference in survival in patients with locally-advanced and unresectable pancreatic cancer treated with proton therapy or hyperfractionated acceleration radiotherapy with concomitant S-1.[16] However, p-values were not reported. Three studies reported on the *local failure (or recurrence) rate*,[15, 17, 20] while one study reported on *local progression*.[16] In all these studies, the data were too imprecise to draw firm conclusions. Finally, one study reported on *cosmetic outcomes* in patients with stage I breast cancer.[15] Cosmesis was considered as an outcome related to well-being and quality of life, and therefore considered as an effectiveness rather than a safety outcome. Physician-rated cosmesis was significantly better in patients treated with photon radiotherapy, while no significant difference was found for the patient-rated cosmesis.

No comparative studies were found for primary sinonasal cancer, recurrent head and neck cancer, and locally recurrent rectal cancer. The effectiveness of proton treatment for these indications is therefore currently unknown.

In conclusion, high-quality evidence on the effectiveness of proton treatment is lacking for the studied indications. With the available evidence, it is impossible to conclude that proton treatment is better or worse than photon-based radiotherapy. However, there are some concerns in patients with primary intramedullary spinal cord gliomas (survival) and stage I breast cancer (cosmesis).

4.2 Uncertainty about the safety of proton treatment

As stated above, randomized studies are the preferred design when evaluating the effectiveness of an intervention. However, rare and/or long-term adverse events are unlikely to be observed in randomized trials, and a thorough investigation of the safety of the intervention may require the inclusion of cohort studies, case-control studies and even case series or case reports. For this report, single-arm studies were also searched for this reason (although limited to a sample size of at least 50 patients).

Most studies used the Common Terminology Criteria for Adverse Events to evaluate acute toxicity, but the results were heterogeneously and often selectively reported, making it difficult to provide a general overview or a compiled table summarizing toxicity. Definitions of acute and late toxicity were often lacking or differed across studies, making comparison and conclusions difficult. In general, and not surprisingly, toxicity highly depended on the radiation field.

Most studies were found for hepatocellular cancer. Acute and late toxicity appeared to be acceptable, with no treatment cessations because of toxicity and no acute grade 5 toxicity. Late grade 5 toxicity was also exceptional, although some fatal cases of proton-induced hepatic insufficiency were reported.[27]

For the other indications, acute grade 5 toxicity varied between 0% and 3.6% when reported, while late grade 5 toxicity varied between 2% and 3.8%. Treatment cessation occurred in 1.1% to 5.4% of patients, when reported.

For breast cancer in particular, one comparative study reported significantly more dermatologic toxicity (patchy atrophy in the irradiation portal, skin colour change, late skin toxicity, telangiectasia >4 cm^2) in stage I breast cancer patients treated with proton therapy compared to photon radiotherapy.[15]

For low-grade glioma in particular, the three included studies limited their evaluation to radiation necrosis[18] or pseudoprogression,[19] or did not provide separate results for proton treatment.[20] Conclusions on safety are therefore difficult for this indication. The incidence of radiation necrosis seemed to be higher in the proton group, but the difference was not statistically significant.[18] Brainstem necrosis (sometimes fatal) is a particular concern in paediatric patients, that resulted in lower dose constraints to the brainstem for proton treatment.[47] As a result, for those tumours that need higher doses or that show better results with higher doses (e.g. ependymoma), there are concerns that these lower doses would lead to worse long-term outcomes. However, the available evidence in adults does not allow to confirm these observations and concerns.

Finally, no studies with a minimal sample size of 50 patients were found for locally recurrent rectal cancer.

In conclusion, acute and late toxicity of proton treatment for the studied indications appear to be comparable to those of conventional radiotherapy, although there are some concerns in patients with stage I breast cancer (skin toxicity).

4.3 Few data on secondary tumours

Only two single-arm studies explicitly reported on the incidence of secondary tumours after proton treatment, both reporting one secondary malignancy in a population of patients with sinonasal cancer. Because of the potential underreporting, no conclusions can be drawn.

Interestingly, in 2013, Chung et al. examined the incidence of second malignancies in a large cohort of 558 patients treated with proton therapy and matched with 558 patients treated with photon radiotherapy.[48] As primary tumour, most patients had genitourinary cancer (33%), central nervous system tumours (32%), or head and neck tumours (24%). Overall, 44 proton patients and 44 photon patients were defined as paediatric patients because they received treatment when aged younger than 18 years. Second malignancies occurred in 29 proton patients (5.2%) and 42 photon patients (7.5%). After adjustment for sex, age at treatment, primary site, and year of diagnosis, proton therapy was not associated with an increased risk of second malignancy (adjusted hazard ratio = 0.52, in favour of proton therapy; 95%CI 0.32-0.85; p = 0.009). Primary tumour site was not significantly associated with the risk of secondary tumours. Importantly, follow-up was too short (median of 6.7 years for proton group) to allow a thorough evaluation of secondary malignancies. A large part of the excess

of secondary malignancies in the photon group (57%) occurred in the first 5 years following radiation treatment, a time period in which a secondary malignancy is not attributed to prior radiation. After that period, the secondary malignancy incidence rates were very similar between both groups. Furthermore, the patient enrolment period was very long (1973-2001). Therefore, conformal x-ray techniques (e.g. IMRT) were only applied in the patients enrolled at the end of this period.

4.4 Some RCTs underway, but not in the very near future

Only three ongoing RCTs were identified comparing proton treatment with photon-based radiotherapy, one for breast cancer, one for hepatocellular cancer and one for glioma, respectively. Results are not expected before 2027. In addition, one large observational study is recruiting 20000 patients with solid tumours, results are expected by June 2029. As a result, the conclusions of this report are not very likely to change within the next 10 years. In addition, no ongoing trials were identified for pancreatic cancer, primary sinonasal cancer, recurrent head and neck cancer and locally recurrent rectal cancer. Unless additional RCTs are planned, the evidence for these indications will remain observational.

4.5 Limitations of this report

The present report describes a systematic review of the effectiveness and safety of proton beam therapy for a selection of indications. A systematic review is no guarantee for the identification of all available evidence, which is certainly true for observational studies. A language restriction was used, which may have caused a limited bias. Authors of included studies were also not contacted, which probably caused an incompleteness in the presented data.

To allow a recommendation for or against the reimbursement of proton therapy for these indications, more information is needed in addition to this systematic review. Cost-effectiveness, organisational and ethical issues, which are part of a classical HTA approach, should ideally be put in the balance as well. However, in the absence of reliable data on the effectiveness of a treatment, which is the case for proton treatment for the selection of indications in this report, a cost-effectiveness analysis is not adequate. In addition, one may consider it unethical to treat patients with an experimental treatment just based on assumptions of its advantages.

Some experts advocate a model-based approach to evaluate the added value of proton treatment to prevent side effects, an approach that is currently being implemented in the Netherlands. The argument is that both effectiveness and toxicity are inherently linked to the dose delivered to the tumour or the respective organ at risk. However, this approach - which remains theoretical and to be evaluated - is outside the scope of the present report.

Finally, as technologies evolve and long-term toxicity takes a long time, results from historical series no longer reflect the clinical reality. This is further complicated by the fact that the reporting and details on the specific type of proton technology used was not always available in the included studies.

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