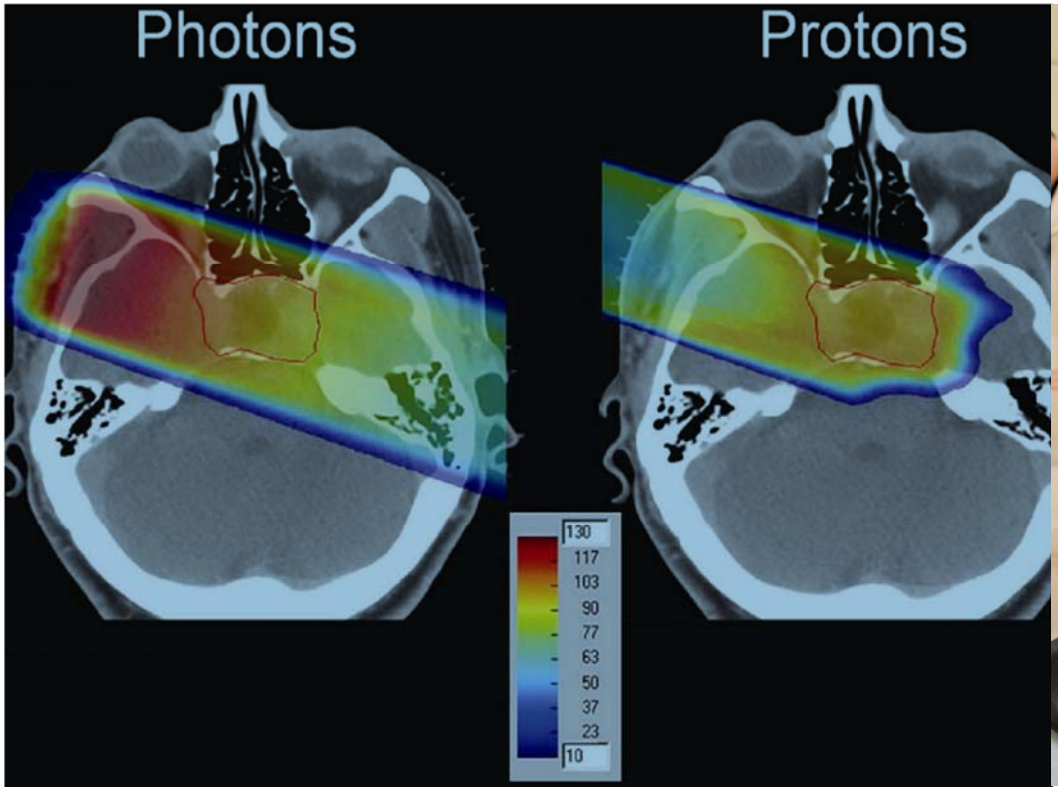
KCE REPORT 235

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

HADRON THERAPY IN CHILDREN

AN UPDATE OF THE SCIENTIFIC EVIDENCE FOR 15 PAEDIATRIC CANCERS



KCE REPORT 235
HEALTH TECHNOLOGY ASSESSMENT

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LIST OF ABBREVIATIONS & ACRONYMS

ABBREVIATION	DEFINITION
2D-EBRT	Two-dimensional external beam radiotherapy
3D-CPT	Three-dimensional conformal proton therapy
ALARA	As low as reasonably achievable
ARMS	Alveolar rhabdomyosarcoma
BCR	Belgian Cancer Registry
BRIEF	Behaviour Rating Inventory of Executive Function
cCR	Clinically assessed complete response
CEBAM	Belgian Centre for Evidence-Based Medicine
CE-PET/CT	Contrast enhanced positron emission tomography - computed tomography
CFFS	Cystic failure-free survival
CGE	Cobalt gray equivalent
CH	Chordoma
CI	Confidence interval
CIn	Cumulative incidence
CIRT	Carbon ion radiotherapy
CND	Comprehensive neck dissection
CNS	Central Nervous System
CoR	Complete remission
CRT	Chemoradiotherapy
CS	Chondrosarcoma
CSI	Craniospinal irradiation
CT	Computed tomography
CTC or CTC AE	Common terminology for adverse events
CTV	Clinical target volume
DFS	Disease free survival
DNA	Deoxyribonucleic acid
DR	Distal recurrence rate

DSS	Disease specific survival
EBRT	External beam radiotherapy
EFS	Event free survival
ENB	Esthesioneuroblastoma
ERMS	Embryonal rhabdomyosarcoma
ESMO	European Society for Medical Oncology
FDG-PET/CT	Fluorodeoxyglucose Positron emission tomography - computed tomography
FFS	Failure free survival
FU	Follow-up
GBM	Glioblastoma multiforme
GCT	Germ cell tumour
GH	Growth hormones
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSI	Gesellschaft für Schwerionenforschung
GTR	Gross total resection
GTV	Gross tumour volume
Gy	Gray, International System of Units (SI) unit of absorbed radiation
GyE	Gray equivalent
HIT	Heavy ion therapy
HIT	Heidelberg Ion Therapy Center
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICCC	International Classification of Childhood Cancers
IGF-I	Insulin-like growth factor 1
IMPT	Intensity modulated proton beam therapy
IMRT	Intensity modulated radiotherapy
Incl.	Including

IORT	Intraoperative radiotherapy
IQ	Intelligence Quotient
KCE	Belgian Health Care Knowledge Centre
KPS	Karnofsky Performance Scale
LCR	Local control rate
LET	Linear energy transfer
LR	Local recurrence rate
MDI	Mental development index (inventory)
MRI	Magnetic resonance imaging
NFFS	Nodular failure-free survival
NGGCT	Nongerminomatous germ cell tumour
NIRS	National Institute for Radiation Science
NR	Not reported
OAR	Organs at risk
OER	Oxygen enhancement ratio
OR	Odds ratio
OS	Overall survival
PB	Pineoblastoma
PBT	Proton beam therapy
PC	Pineocytoma
PET	Positron emission tomography
PET-CT	Positron emission tomography - computed tomography
PICO	Participants–Interventions–Comparator–Outcomes
PFS	Progression-free survival
PNET	Primitive neuroectodermal tumours
PP	Pseudo progression
PPT	Pineal parenchymal tumours
PPTID	PPT with intermediate differentiation

PR	Partial remission
PSI	Paul Scherrer Institute
PTV	Planning target volume
QoL	Quality of life
RANO	Response assessment in neuro-oncology
RBE	Relative biological effectiveness
RcR	Recurrence rate
RCT	Randomised controlled trial
RIZIV-INAMI	National Institute for Health and Disability Insurance (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering - Institut National d'Assurance Maladie-Invalidité)
RMS	Rhabdomyosarcoma
RpR	Response rate
RR	Risk ratio/ relative risk
RT	Radiotherapy
RT-ind	Radiotherapy induced
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology and End Results (database)
SIB-R	Scales of Independent Behaviour-Revised
SM	Secondary malignancy
SOBP	Spread Out Bragg Peak
SRT	Stereotactic radiotherapy
SSF	Special solidarity fund
StD	Stable disease
STS	Soft tissue sarcomas
TNM Classification (of Malignant Tumours	T describes the size of the primary tumour and whether it has invaded nearby tissue; N describes nearby (regional) lymph nodes that are involved; M describes distant metastasis
WHO	World Health Organisation
WVRT	Whole ventricular radiation therapy

SCIENTIFIC REPORT

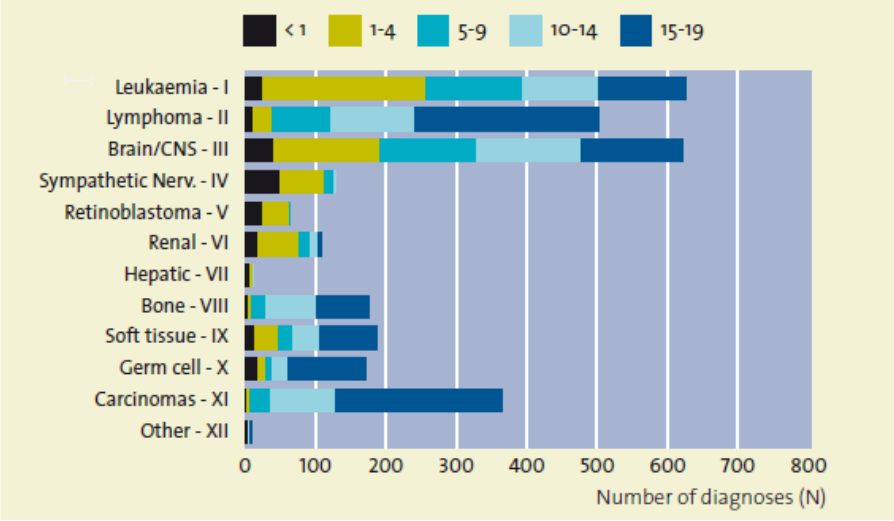
1 INTRODUCTION

1.1 Cancer in children and adolescents

1.1.1 The burden of cancer in children and adolescents

In Belgium, childhood cancer comprises less than 1% of the total cancer burden. Every year, about 320 children (0-14 years) and 175 adolescents (15-19 years) are diagnosed with cancer[1]. Leukaemias, brain tumours, lymphomas and carcinomas are the most frequent malignancies in children and adolescents (Figure 1). Yet, the proportion of each tumour type varies by age group. In the age category 0-4 years, leukaemias comprise 31% of all tumour diagnoses; after that age, the incidence decreases. In adolescents, lymphomas (25%) and carcinomas (22%) are the most common tumour types; they are less common at younger age (4% and 1% respectively in the age group 0-4 years)[1](Figure 2).

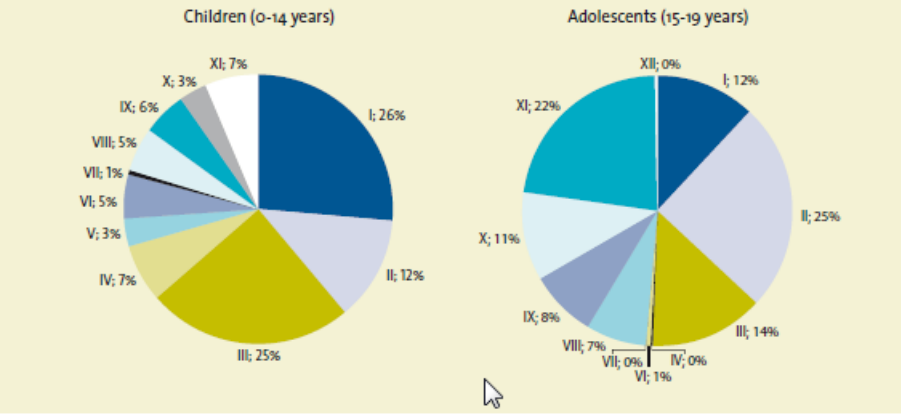
Figure 1 – Cancer in children and adolescents: new diagnoses by tumour type and age group, Belgium 2004-2009



[Figure – Source: BCR report "Cancer Incidence in Belgium. Special Issue: Cancer in children and adolescents. 2013" p14[1]]

The highest incidence rates for neuroblastomas and other peripheral nerve cell tumours (IV), retinoblastomas (V), renal tumours (VI) and hepatic tumours (VII) are observed in infants (i.e. age <1 y.o.). Germ cell tumours (X) and soft tissue sarcomas (IX) are frequently diagnosed in very young children and in adolescents; they are less frequently occurring in children aged 5-15 years. Bone tumours (VIII) are less frequent under the age of 10 years; their incidence rates are highest in the age categories 10 to 19 years.[1]

Figure 2 – Cancer in children and adolescents by tumour type, Belgium 2004-2009



Legend: I: leukaemia, II: lymphoma, III: brain/CNS tumour, IV: sympathetic nerve tumour, V: retinoblastoma, VI: renal tumour, VII: hepatic tumour, VIII: bone tumour, IX: soft tissue tumour, X: germ cell tumour, XI: carcinoma, XII: other.
[Figure – Source: BCR report "Cancer Incidence in Belgium. Special Issue: Cancer in children and adolescents. 2013" p14[1]]

Up-to-date Belgian incidence data for all cancer types under study in this report were provided by the Belgian Cancer Registry (BCR); they are presented in Table 7.

1.1.2 Prognosis

Roughly, the prognosis for paediatric tumours has improved the last decades.[2] The analysis of survival data for 157 499 children (age 0–14 years; diagnosed between 1 January 1978 and 31 December 2007), collected in 74 population-based cancer registries in 29 European countries (including Belgium), revealed that the 5-year overall survival for all cancers combined rose from 76.1% (95% CI: 74.4–77.7) in 1999–2001 to 79.1% (77.3–80.7) in 2005–07. Yet, for several cancers overall survival did not improve in Europe; this was the case for Hodgkin's lymphoma, CNS cancers, neuroblastoma, nephroblastoma, Ewing sarcoma, and osteosarcoma.[2]

For most haematological cancers the 5-year overall survival for cases diagnosed between 2000 and 2007 was high (ranging from 84% to 95%, except for acute myeloid leukaemia with a 5-year OS of 62.7% (95% CI: 60.5–64.9)); this was also the case for e.g. retinoblastoma (96.4% (95% CI: 94·6–97·6)). In the meantime, the 5-year overall survival rates for osteosarcoma (69.3 (95% CI: 66.2–72.3), Ewing sarcoma (67.9 (95% CI: 64.2–71.2), rhabdomyosarcoma (67.7 (95% CI: 64.7–70.6) and CNS cancers were rather modest (57.5%, 95% CI: 56.1–58.8) (Table 1).[2]

Table 1 – Country-weighted 5-year overall survival (95% CI) by ICCC diagnostic category, sex and age, for cases diagnosed between 2000 and 2007

	N	All children	Girls	Boys	Age < 1 year	Age 1-4 years	Age 5-9 years	Age 10-14 years
All cancers	57956	77.9 (77.4-78.3)	78.3 (77.6-79.0)	77.5 (76.9-78.2)	77.9 (76.4-79.4)	79.3 (78.4-80.0)	77.6 (76.6-78.5)	76.6 (75.7-77.5)
Ia: acute lymphoid leukaemia	15860	86.3 (85.5-87.1)	87.6 (86.4-88.6)	85.3 (84.1-86.4)	61.8 (56.0-67.1)	90.6 (89.5-91.7)	88.1 (86.8-89.3)	77.7 (75.5-79.7)
Ib: acute myeloid leukaemia	3094	62.7 (60.5-64.9)	62.6 (59.3-65.7)	62.6 (59.4-65.6)	53.5 (47.0-59.6)	65.1 (61.4-68.5)	67.9 (63.5-71.9)	59.5 (55.1-63.5)
IIa: Hodgkin's lymphoma	3142	95.4 (94.1-96.5)	94.3 (92.0-96.0)	96.6 (95.5-97.4)	-	95.5 (91.1-97.8)	94.1 (89.9-96.6)	95.8 (94.5-96.8)
IIb: non-Hodgkin lymphoma (except Burkitt's lymphoma)	2544	84.0 (82.0-85.8)	84.0 (80.7-86.7)	84.0 (81.5-86.2)	63.3 (49.8-74.0)	78.1 (72.7-82.5)	87.0 (83.8-89.6)	85.4 (82.7-87.8)
IIc: Burkitt's lymphoma	1443	90.2 (88.5-91.7)	85.4 (80.0-89.4)	90.7 (88.8-92.3)	40.1 (40.1-40.1)	89.3 (85.3-92.3)	91.1 (88.8-93.0)	87.2 (84.0-89.8)
III: CNS and miscellaneous intracranial and intraspinal neoplasms	9277	57.5 (56.1-58.8)	56.8 (54.7-58.9)	58.0 (56.2-59.7)	48.3 (43.8-52.7)	57.4 (55.0-59.8)	57.0 (54.6-59.3)	60.3 (57.8-62.7)
IIIa: ependymomas and choroid plexus tumour	1233	62.8 (58.4-66.8)	61.6 (55.1-67.4)	62.5 (56.5-67.9)	42.4 (30.0-54.3)	55.3 (50.6-59.8)	74.7 (66.5-81.1)	76.2 (68.6-82.2)
IIIb: astrocytomas	2714	61.5 (59.0-63.9)	62.1 (58.7-65.3)	60.7 (57.1-64.1)	64.1 (56.3-70.9)	79.4 (75.6-82.7)	55.6 (51.1-60.0)	49.3 (45.0-53.5)
IIIc: intracranial and intraspinal embryonal tumors	3119	57.1 (54.6-59.6)	57.1 (53.0-60.9)	57.1 (53.9-60.2)	33.3 (26.6-40.2)	46.5 (42.3-50.5)	67.3 (63.3-71.0)	67.3 (62.2-71.9)
IVa: neuroblastoma and ganglioneuroblastoma	4588	70.6 (68.4-72.6)	71.7 (68.3-74.8)	69.5 (66.7-72.1)	91.1 (89.6-92.5)	58.7 (54.8-62.5)	52.1 (45.8-58.0)	55.7 (45.5-64.6)
V: retinoblastoma	1627	96.4 (94.6-97.6)	96.1 (93.3-97.8)	97.2 (95.5-98.2)	98.3 (96.6-99.1)	94.6 (89.9-97.2)	96.4 (79.9-99.4)	-
VIa: nephroblastoma and other nonepithelial renal tumours	3554	89.4 (88.0-90.7)	89.7 (87.7-91.3)	89.2 (87.0-91.0)	84.3 (80.2-87.6)	91.4 (89.7-92.9)	88.2 (85.4-90.4)	76.7 (66.0-84.5)
VIIIa: osteosarcomas	1500	69.3 (66.2-72.3)	72.8 (68.3-76.8)	66.4 (62.1-70.4)	-	59.8 (47.6-70.1)	72.1 (66.7-76.8)	68.5 (64.9-71.9)
VIIIc: Ewing's sarcoma and related sarcomas of bone	1397	67.9 (64.2-71.2)	66.7 (61.4-71.4)	68.7 (63.7-73.1)	70.6 (58.8-79.6)	73.7 (64.6-80.7)	76.3 (71.5-80.4)	62.1 (57.1-66.6)
IX: rhabdomyosarcomas	2197	67.7 (64.7-70.6)	64.7 (59.4-69.4)	69.7 (66.1-73.0)	61.0 (49.7-70.5)	71.2 (66.2-75.5)	70.6 (65.5-75.2)	62.3 (56.6-67.5)

ICCC=International Classification of Childhood Cancers
[Table – Source: Gatta et al., 2014, p39[2]]

1.1.3 Sequelae of cancer (therapy) in paediatric cancer survivors

Thanks to the substantial improvements in treatment outcomes, the number of survivors after cancer in childhood and adolescence is substantial. According to Olsen et al. (2009) one person in 1000 in the general population in high-income countries is a survivor of childhood cancer.[3] Hence, the greatest challenge is now to maintain a sound balance between cure and long-term morbidity in those who survive.

In fact, in childhood cancer survivors the burden of chronic health problems is huge: 30 years after cancer diagnosis the cumulative incidence of chronic health conditions reached 73.4% (95% CI: 69.0 to 77.9), with a cumulative incidence of 42.4% (95% CI, 33.7 to 51.2) for severe, disabling, or life-threatening conditions or death due to a chronic condition.[4] Survivors face major health risks, as much due to sequelae of their treatment as due to the risk of recurrence of the original tumour[5]. These risks include a continuing excess risk of mortality, second primary neoplasms, neurocognitive defects, cardiovascular disease, other organ dysfunction, endocrine disturbances, growth retardation and disturbance, social and mental impairments and the psychosocial effects of their disease and treatment on the patients as well as their families.[4-6]

1.1.3.1 Impact of radiotherapy

Radiation therapy is an inherent component of the curative treatment of many childhood tumours. Sadly, radiation exposure entails a major risk of late morbidity in long-term cancer survivors. Children are particularly susceptible to the late effects of radiation, even at low doses, as demonstrated in epidemiologic studies of exposed populations.[7,8] The reasons for this high susceptibility include the sensitivity of developing and growing tissues, more proliferating cells in young patients, the longer life expectancy resulting in a larger window of opportunity for expressing radiation damage, and the large number of long-term survivors[8-10]. In addition, younger patients face dosimetric disadvantages as they tend to receive on average higher secondary organ doses than adults due to geometrical factors.[10]

In particular, radiation to the brain has been associated with neurocognitive deficits, neuroendocrine dysfunction, and hearing loss, with children younger than 7 years old being the most profoundly affected.[8, 11] However, these side effects may also be caused by other factors, including the brain tumour itself, hydrocephalus, chemotherapy, surgical morbidity and peri-operative complications.[8, 11] Craniospinal irradiation, e.g. used as part of medulloblastoma treatment, can further lead to primary thyroid dysfunction, spinal growth impairment and damage to the lung, heart and intestinal tract.[11, 12] The effect of radiation on spinal growth and development is a complex problem and depends not only on the age and sex of the patient and the radiation dose. Also, not all spinal vertebrae respond equally to radiation.[12, 13] The age of the paediatric patient plays a major role in the design of the treatment plan. New developments aim at avoiding and/or postponing radiotherapy in children, e.g. by altering the chemotherapy regimen.

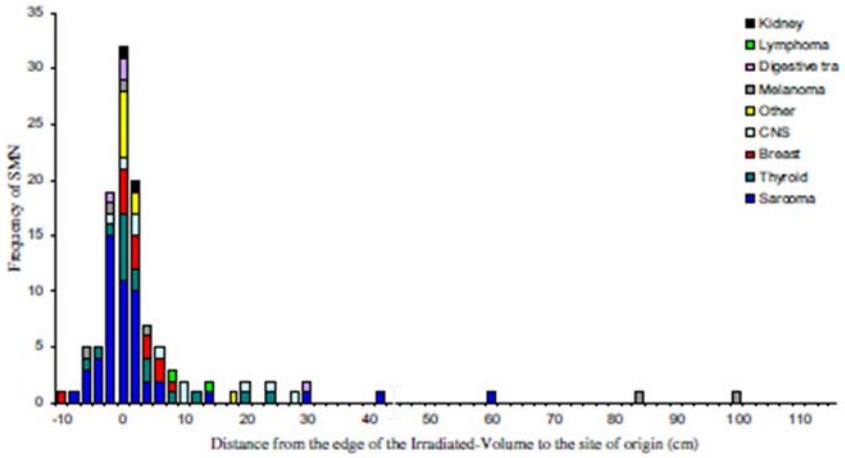
1.1.3.2 Secondary malignancies

Among childhood cancer survivors, subsequent malignancies are the leading cause of non-relapse mortality.[14, 15] The Childhood Cancer Survivor Study reported a 30-year cumulative incidence of 7.9% (95% CI: 7.2-8.5) for second malignant neoplasms (excluding non-melanoma skin cancer).[16] This represents a 6-fold increased risk of subsequent malignancies (occurring at least 5 years after treatment) relative to the general population.[15] Childhood cancer survivors are likely to experience more cancers as adults than are individuals of similar age in the general population as a result of host-related factors (e.g. deletion of the RB1 gene, which causes heritable retinoblastoma) and/or as a result of certain aspects of the anticancer therapy they received.[17]

In radiotherapy patients, the induced tumours include carcinomas, which may arise in sites adjacent to or remote from the treated area.[9] Their number is relatively large, but the relative risk is small. Sarcomas may appear in heavily irradiated tissues, either within or close to the treatment field. The absolute number of sarcomas is small, but their relative risk after radiation large.[9]

Further, second cancers are more likely to arise in the intermediate than in the high-dose area, suggesting a bell-shaped dose-response curve or a levelling off at increasing dose due to the competing factors of cell kill and cell mutation.[18, 19] In a study analysing 115 cases of secondary cancers after radiation therapy in childhood, Diallo et al. (2009) observed that 66% of secondary tumours had occurred in the beam-bordering region (i.e., the area surrounding the planning target volume), 22% in regions located more than 5 cm from the irradiated volume and 12% in the central area of the irradiated volume (which corresponds to the planning target volume)(Figure 3). Of interest, the peak frequency (36/115 cases, 31%) was observed for volumes that had received a dose of <2.5 Gy.[20]

Figure 3 – Frequency distribution of the distances from the edge of the irradiated volume to the site where solid second neoplasms developed among 115 patients.



The geometric limit of the closest beam path is considered to represent the limit of the irradiated volume. On the x-axis, the origin (0) is the edge of the beam path. The distances are negative from the beam edge inward and positive from the beam edge outward. CNS: brain and other nervous system tumours.

[Figure – Source: Diallo et al., 2009, p880[20]]

Radiation-related solid malignancies develop a minimum of at least 5 to 10 years after treatment.[15] Hence, solid cancer events within 5 years after therapeutic radiation are not plausibly attributed to radiotherapy.[15] Using current technology, it is very well possible to calculate for each part of the body/organ the dose (incl. secondary neutrons) received.

The knowledge on secondary malignancies in cancer survivors is constrained by the (limited) follow-up period (25 to 30 years) of the existing survivor cohorts.[17] Also, most studies have a too short follow-up to permit sound conclusions. However, the Childhood Cancer Survivor Study (which follows over 14 000 children with a sibling control group) demonstrated that second tumour risk continues to increase with time with no sign of plateau even 30 years post-treatment.[19] Second, in most cases assessment of the risk of second cancers in radiotherapy patients is difficult because no appropriate control group exists; that is, a group of individuals who have the same initial malignancy but did not receive radiotherapy.[9] Exceptions are prostate cancer and cancer of the cervix, in which surgery is an alternative to radiotherapy.[9] Another example is Hodgkin's lymphoma, where the risk of secondary tumours after radiation therapy cannot be missed: a Finnish study for instance, which reviewed the medical records of 202 consecutive patients who survived at least for 5 years after radiotherapy for Hodgkin's disease, revealed a cumulative risk for a second cancer of 17% (95% CI: 10.4 - 23.1 %) at 20 years after the diagnosis.[21] Also, evaluation of the toxicity of radiotherapy is complicated when radiotherapy is combined with surgery and/or chemotherapy.

Several approaches have been suggested for estimating the risk of secondary cancer induction via different models with dose-responses relating to either linear, linear-exponential or linear-quadratic behaviour.[22] However, depending on the site and cancer type, the predictive power of current risk models is not clear.[19]

1.1.3.3 Conclusion

In paediatric radiation oncology, the ultimate goal is to treat the disease while reducing the (late) effects of radiation on growth and development, cognition, neuroendocrine function and the induction of secondary tumours. Reducing the exposure of normal tissues to therapeutic radiation would presumably decrease the risk of subsequent malignancies.[15] Here, the option of hadron therapy, particularly proton beam therapy, comes in. Based on the comparison of treatment plans, it was demonstrated that the use of scanned protons could lead to a reduction of the integral dose by a factor two to three and to a reduction of the mean and mid-to-low doses to critical structures when compared to intensity modulated photon plans and conventional photon techniques.[23] These and other aspects of hadron therapy are further explored in the following paragraphs.

1.2 Hadron therapy

1.2.1 Radiotherapy and radiation effects

Among the treatment options for cancer, radiation therapy is widely used. Based upon indications for radiotherapy stated in evidence-based guidelines, it was estimated that 52% of cancer patients should receive radiotherapy at some point during the treatment course.[24] Radiotherapy uses high-energy radiation to kill cancer cells. Radiation therapy kills cancer cells mostly by damaging their DNA; this damage is either direct or indirect[a] ionization of the atoms which make up the DNA chain. Cancer cells whose DNA is damaged beyond repair, stop dividing and die. When the doomed cells die, they are broken down and eliminated by the body's natural processes.[25] Radiation oncology is confronted with a dichotomy: on the one hand the tumour's location and extent has to be defined precisely and the radiation dose conformed to it so that the probability of local tumour control (or palliation) can be maximised while on the other hand ill effects of radiation should be avoided by minimising the dose to uninvolved healthy tissues.[26]

For cancer treatment X-rays (photon therapy, conventional radiotherapy), gamma rays, and charged particles are used. Charged particle radiation therapy or hadron therapy uses beams of protons or other charged particles, such as carbon, helium, neon, or silicon. At present only protons and carbon ions are in clinical use.[27]

1.2.2 History of hadron therapy

In 1954 the very first human patient was treated with proton beam therapy at Berkeley Radiation Laboratory (California),[28] in Europe the first patient was treated in Uppsala (Sweden) in 1957. Hadron therapy developed at scientific accelerator laboratories and was initially established as a niche within radiation oncology by pioneering clinicians and scientists working in partnership with accelerator physicists.[29] In Massachusetts General Hospital (Boston, US) for instance, the first patient was treated with proton beam therapy in 1961 at Harvard University's physics laboratory; it lasted another 40 years before patients could be treated in a clinical setting.[30] In most facilities the technical equipment was limited, either regarding the usable energy (with low energy only superficially located tumours as tumours of the eye could be treated) or regarding the mobility of the therapy nozzle, as most of the centres had fixed beam lines only (allowing treatment for eye and base of skull site or prostate). Therefore, the longest and most extensive experience was made with eye or base of skull tumours as well as with prostate cancer.[6] Nowadays, proton centres implement rotating beam application systems (gantries) to further enlarge the freedom of beam arrangements and thus enlarge the list of possible indications.[6]
Worldwide, more than 120 000 patients have been treated with particle therapy: more than 13 000 with carbon ions and more than 105 000 with proton therapy.[27]

It is important to underscore that hadron therapy did not enter clinical practice through an incremental series of carefully designed hypothesis-driven clinical trials,[29] as opposed to e.g. medicinal products which cannot enter the market (and thus clinical practice) without clinical trials.

[a] Indirect ionization happens as a result of the ionization of water, forming free radicals within the cells that can in turn damage the DNA.

1.2.3 Photon versus hadron (charged particle) therapy

1.2.3.1 Physical properties

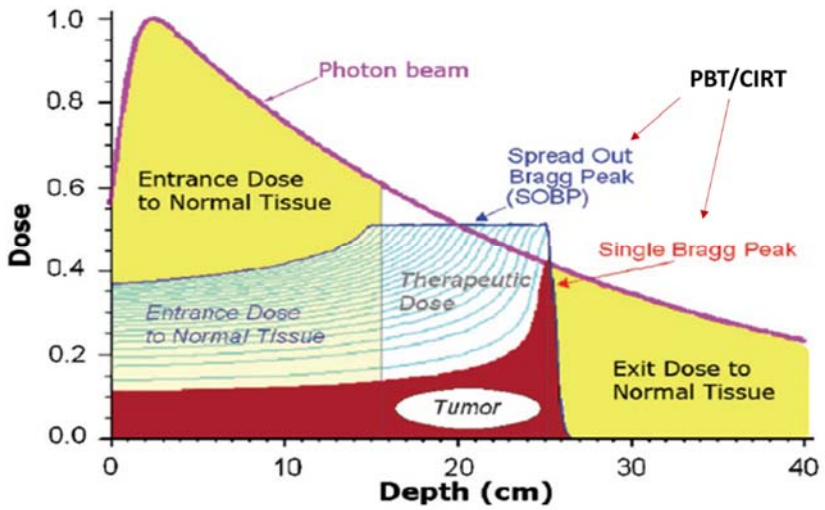
Photon radiation consists of high-energy electromagnetic waves. It deposits most of its energy below the skin surface and in normal tissue going in ('proximal dose'), hits the target site (the tumour) and still deposits energy and thus affects normal tissues when coming out past the target ('distal dose') (Figure 4). Radiation oncologists try to minimize the effects on healthy tissues as much as possible by varying the delivery paths, shaping the beam and/or modulating the beam intensity (e.g. IMRT).

In contrast, charged particles deposit a low dose near the surface and a large fraction of their energy at or around the target, at the end of the range[b] of beam penetration. Tissues beyond the tumour location receive very little of the dose. This peak energy delivery is known as the Bragg Peak (Figure 4).[32] The absence of radiation distal to the target is one of the major advantages of proton radiotherapy, allowing for substantial tissue sparing, which is of utmost importance in nearly all anatomic sites (e.g. head and neck, chest, spinal cord, pelvis, central nervous system).

The initial energy of the charged particles determines how deep in the body the Bragg Peak will form. The intensity of the beam—that is, how many particles traverse a particular area in unit time—determines the dose that will be deposited to the tissues. By adjusting the energy of the charged particles and the intensity of the beam, one can deliver pre-specified doses anywhere in the body with high precision.[33] In this way the proton beam can be adjusted to match the depth and extent of the target volume and excellent conformity can be achieved. Because the Bragg Peak of a mono-energetic proton beam is narrow, several beams with closely spaced penetration depths are used to treat the entirety of the tumour. This area of uniform dose over the entirety of the tumour is termed a Spread Out Bragg Peak (SOBP)(Figure 4). While the SOBP does increase dose deposition proximal to the tumour, the entrance dose usually remains substantially lower than that of photon radiotherapy.[11]

An additional advantage is that the lateral penumbra[c] is generally smaller for proton than for photon beams, resulting in higher conformity of the former.[34] There remains however some uncertainty about the exact extent of the lateral penumbra.[35] This aspect and some other issues of concern will be further explored in paragraph 1.2.6.3.

Figure 4 – Radiation dose profiles: photons vs. protons



[Figure – Source: Cotter et al., 2012 p269[11]]

[b] In passing through matter, charged particles ionize and thus lose energy in many steps, until their energy is (almost) zero. The distance to this point is called the range of the particle. The range depends on the type of particle, on its initial energy and on the material through which it passes. The range of a heavy charged particle is approximately proportional to the mass of the particle and the inverse of the density of the medium, and is a function of the initial velocity of the particle[31].

[c] The penumbra is the space in the periphery of the main target of radiation therapy; it is the volume that receives between 80% and 20% of the isodose.

1.2.3.2 *Radiobiological effect*

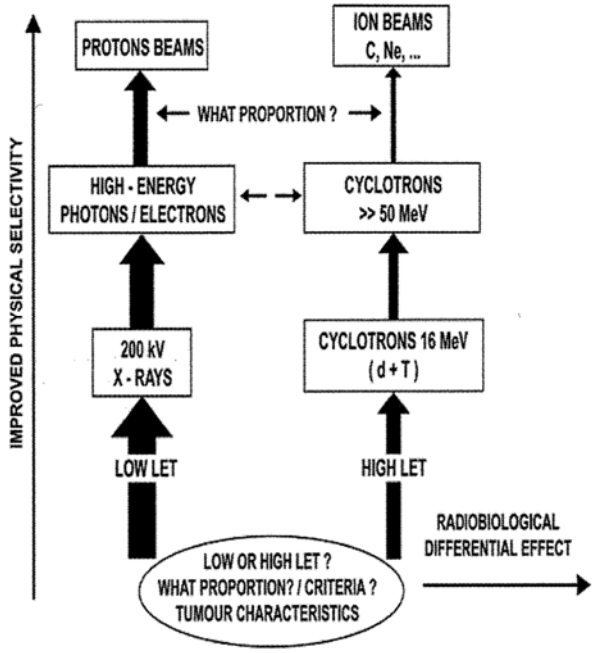
Because charged particles damage cell DNA in qualitatively different ways than photons, the same amount of physical radiation can have much more pronounced biological effects, resulting in larger cellular damage.[33] The concept of relative biological effectiveness (RBE) has been introduced to account for this increased efficiency of cell killing. RBE is defined as the ratio of a dose of photons to a dose of any particle to produce the same biological effect. The RBE of protons is approximately 1.1, indicating that protons result in approximately 10% more biological damage per unit dose than photons.[33] As such, a proton dose is described as a cobalt Gray equivalent (CGE), which translates to an equivalent photon dose measured in Gray (Gy).[11] For example, a proton dose of 50.4 CGE represents an energy deposit equivalent to 45.8 Gy of photon radiation but has an *in vivo* effect of 50.4 Gy, attributable to the increased RBE. Carbon ions have a similar RBE to protons along the particle path but have a markedly increased RBE (estimated at 3-4) at their maximum depth of penetration. As a result, the deleterious effects on normal tissues proximal to the tumour are expected to be similar to proton radiotherapy, while tumour killing is enhanced at maximum depth.[11]

Charged particles have a more pronounced biological effectiveness than x-rays because they have a high rate of energy deposition (high linear energy transfer (LET)) over a portion of the particle track which is targeted to the tumour volume. Roughly, the higher the linear energy transfer of the radiation, the greater the relative ability to damage cellular DNA.[26, 33] Protons have a higher linear energy transfer (LET) than photons, but their radiobiological properties do not differ substantially.[36] The LET of carbon ion beams increases steadily with increasing the depth to reach the maximum in the peak region.[37]

An additional advantage of high linear energy transfer radiation is that it can affect hypoxic cells within a tumour, which are generally more resistant to low linear energy transfer radiation, such as photons and electrons.[33]

When comparing the relative merits of different types of radiations used in therapy, two factors have to be considered: the physical selectivity and the radiation quality (i.e. high-LET versus low-LET) (Figure 5).[38] Improving the physical selectivity (on the ordinate) should be per se always an advantage. Selection between low- and high-LET radiation (in abscissa) depends on the tumour characteristics, i.e. histology, grade, doubling time, etc. This is thus a pure radiobiological and medical issue (not technique or machine dependent).[38]

Figure 5 – Physical effectivity and radiobiological differential effect of different RT types



[Figure – Source: Wambersie et al., 2004[38]]

1.2.4 Radioprotection[d]

Any practitioner treating a child with hadron therapy should be aware that it should be done in the most optimal way, as it should for any therapy. This is especially the case for children: they are growing and their tissues are in full development, therefore making them more sensitive to ionizing radiation than adults. They also have a longer life expectancy and thus more time to develop long-term radiation-induced health effects like cancer.

The three fundamental principles of radioprotection should always be kept in mind: justification, optimization and dose limitation.[39] The first principle, **justification**, refers to the fact that the use of ionizing radiation and, more specifically, of this kind of therapy should be justified, i.e. the benefits of treating a patient with ionizing radiation should outweigh the risks associated with the use of ionizing radiation. Justification is needed on the generic level as well as on the individual patient level.[40]

The second principle, **optimization**, refers to the fact that the dose of radiation should be kept as low as reasonably achievable (ALARA principle). In this case, we should understand that the dose of radiation to healthy, non-targeted tissues should be kept as low as reasonably achievable, the dose to the target – besides being as homogenous as possible – remaining of course therapeutic.[41]

The process of optimization of medical exposure also includes – among others – choice of equipment, quality assurance including quality control, evaluation of doses or activities administered to the patient.[42] Concerning equipment choice, taking the example of delivery system, the pencil beam (cf. infra) is in most cases to be preferred to the double scattering beam (cf. infra) because of the sparing of normal surrounding tissues in the first case.[43] More specifically in this kind of treatment, justification and optimization also imply selecting the most optimal treatment planning.

The principle of **dose limitation** is applicable to exposed workers and the public, but not to patients, should it be for diagnostic procedures or therapeutic procedures.[39] However, deterministic effects will appear in patients treated by hadron therapy if a certain limit is exceeded and the probability of stochastic effects increases with radiation dose to healthy tissues.

When considering available options for disease management, the practitioner takes his/her decision in a multidisciplinary team, taking several factors in consideration like the age of the child, the type of tumour, in order to offer the best treatment to his/her paediatric patient. When opting for hadron therapy, as for any other therapy using ionizing radiation, the practitioner should keep radioprotection in mind.

1.2.5 Carbon ion therapy

Heavy ions (e.g. carbon ions) differ from protons in their radiobiological properties; the enhanced RBE is a result of the much higher ionization density (high LET). These differences constitute a two-edged sword: some may be advantageous while other may be disadvantageous.[44] For instance, carbon ion beams are attributed an enhanced oxygen enhancement ratio (OER)[e].[44] Tumours with low radioresponsiveness against low-LET radiations are assumed to have a high proportion of hypoxic cells, poor reoxygenation pattern and high intrinsic repair capacity. It is assumed that such tumours could benefit from high-LET radiations because the reduction in the OER is achieved with increasing LET.[37] If reduced OER is aimed at, neon ions perform better than carbon ions.[44] Heavy ions also exhibit a lesser dependence of radiosensitivity on the position in the cell cycle. This is one of the rationales for introducing high-LET carbon ions in cancer therapy.[37] However, this may also be disadvantageous, as normal cells tend to spend less time in the X-radiosensitive phases of the cell-cycle than malignant cells, which may result in less healthy cell protection with carbon ions than with photons.[44]

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[d] Paragraph written by S Carbonnelle, Federal Agency for Nuclear Control

[e] The oxygen enhancement ratio (OER) is the ratio of radiation dose needed to inactivate severely hypoxic or anoxic tumour cells relative to the dose needed to inactivate well-oxygenated tumour cells. It has a value of approximately 3 for low-LET photons, electrons, or protons, but is diminished with the use of high-LET irradiations to approximately 1.6 to 1.7 at LET values of about 100 keV/µm. The degree to which the OER is reduced is an indication of high-LET biologic effectiveness (http://www.expertconsultbook.com/).

It may be argued that the lack of repair of normal tissues when exposed to high LET radiation is not relevant, because the high LET region is confined to the tumour and the normal tissues, lying outside the tumour, are only exposed to low LET radiation.[44] In reality, however, this is not the case: (1) the treated volume always extends the gross tumour volume, (2) tumours can be intertwined or embedded in a substrate of normal tissue and (3) recent analyses suggested that the LET in a treatment with carbon ions was quite high even well outside the target volume.[45] Hence, the risk of normal tissue damage with carbon ions may be a larger problem than anticipated in many cases.[44]

Lastly, when comparing dose distributions between carbon ion and proton beams, the lateral fall-off around the target volume is more rapid in carbon ion beams than proton beams. However, in the region beyond the distal end of the peak, almost no dose is deposited in protons while a certain dose is deposited in carbon ions. This distal dose is caused as the primary carbon ions undergo nuclear interactions and fragment into particles with lower atomic number, which produces a fragmentation tail beyond the peak.[37] The distal tail and the associated potentially increased toxicity to organs close to the tail of high LET particles is a major concern about its use in children.[46]

The largest experience in carbon ion beam therapy comes from the National Institute for Radiation Science (NIRS) in Chiba, Japan, where since 1994 more than 8000 patients with different tumour types have been treated with carbon ion beams.[27, 47] In neither of the two references, special attention is given to carbon ion radiotherapy in children. Only a retrospective case series on carbon ion therapy in non-resectable osteosarcoma treated at NIRS in Chiba[48] with a patient population comprising a mixture of children and adults, was published. To the best of our knowledge, the paediatric experience with carbon therapy is extremely limited and includes 17 patients (age range 5-21) treated for skull base tumours (chordoma or low-grade chondrosarcoma) at Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany.[11, 49]

For the present report, the majority of research questions concerned the use of proton beam therapy, with one exception, the use of carbon ion therapy in children with non-resectable or incompletely resected high-grade osteosarcoma with or without metastases. The rationale for this question is the OSCAR trial (OSteosarcoma – CArbon Ion Radiotherapy Trial to determine the safety and efficacy of heavy ion radiotherapy in patients with osteosarcoma) that is presently running at the Heidelberg Ion Therapy Center (HIT)). Enrolment is scheduled until 15 July 2015, but this may be altered[f].

1.2.6 Proton beam therapy

1.2.6.1 Types of proton therapy

The protons emerging from a cyclotron[g] or synchrotron[h] form a narrow pencil beam; in order to cover a treatment field of the size of a tumour and hence produce a Spread Out Bragg Peak, the pencil beam must be either scattered by a foil or scanned. Currently, both passive and active scanning beam delivery systems are in use, though in the majority of centres the passive scattering system is used.

Passive scattering technique (or scatter foil technique)

Passive scattering is the simplest technique: a proton beam hits the scatter foil and is spread laterally (Figure 6). The beam is further shaped via brass apertures that are placed in the gantry head. Beam depth is manipulated via a modulation wheel, which produces the varying energies needed to treat the entire target under the SOBP. The beams are further shaped to conform

f http://www.klinikum.uni-heidelberg.de/OSCAR.129200.0.html?&L=1

g A cyclotron is a type of particle accelerator in which charged particles accelerate outwards from the centre along a spiral path. The particles are held to a spiral trajectory by a static magnetic field and accelerated by a rapidly varying (radio frequency) electric field.[31]

h A synchrotron is a particular type of cyclic particle accelerator, descended from the cyclotron, in which the guiding magnetic field (bending the particles into a closed path) is time-dependent, being synchronized to a particle beam of increasing kinetic energy. The synchrotron is one of the first accelerator concepts to enable the construction of large-scale facilities, since bending, beam focusing and acceleration can be separated into different components.[31]

to the distal edge of the tumour with Lucite compensators that account for both tissue inhomogeneity and tumour shape.[11] This technique has been in use since the 1950ies and is currently the most common proton beam technique employed.[6, 11]

There are several disadvantages associated with the passive scattering technique: (1) for each beam individual hardware (compensators and collimators) is required; (2) there is little control of the proximal edge of the beam and hence conformity is often less than with IMRT and, last but not least, (3) as the proton beam is always larger than the patient-specific aperture shaped to match the target, the protons will bombard the brass collimator and produce secondary neutrons.[6, 50, 51] During passive scattered proton therapy neutrons are generated both in the treatment head (external neutrons) and inside the patient (internal neutrons) through proton-nuclear interactions.[10] It is estimated that these external neutrons deliver a total-body equivalent dose that is even larger than the leakage radiation from conventional linear accelerators.[9] Upon Hall's 2006 publication,[9] animated discussions on the extent and impact of the secondary neutrons have been held in the literature.[52-54] As this issue is so important, it will be further discussed in paragraph 1.2.6.3. Yet, the passive scattering technique may be indicated in those cases where the target has a regular, not too complex shape (G Goitein, personal communication).

Active scanning technique

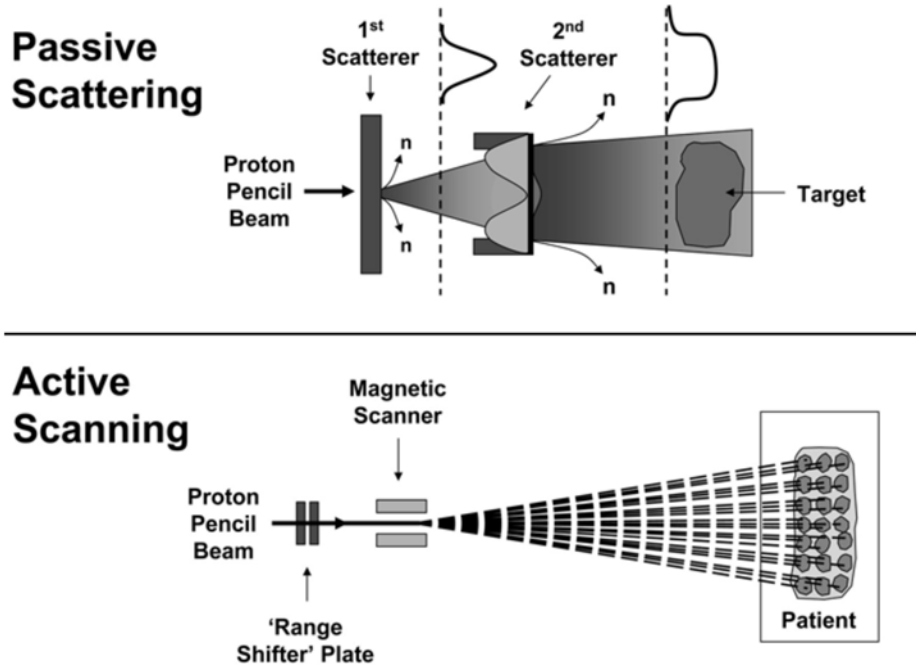
There are two categories of active scanning systems: spot-scanning or pencil beam scanning on the one hand and uniform beam scanning on the other.

Spot-scanning or pencil beam scanning

This technique was first introduced at the Paul Scherrer Institute in Switzerland. At present it is employed in only a couple of centres worldwide. In this technique, magnets steer a small pencil beam of protons to specific positions within a tumour target without the need for brass apertures or compensators (Figure 6).[11] Hence, by magnetic control, directing of range shifter plates into the beam and table movements during treatment, the proton beam gets adjusted to the target volume.[6, 55] The depth of the beam is varied in the accelerator itself; this process is called active modulation.[11]

The pencil beam technology has two main advantages over the passive scattering technique. First, it allows for shaping of both the proximal and distal edges of the treatment field: decreasing the entry dose while maintaining a lack of exit dose. Second, the neutron scatter, which is of concern regarding secondary cancer induction, is reduced significantly thanks to the lack of shielding and blocks in the gantry head, an advantage that will be particularly important for the paediatric patient.[6, 11] On top of that, pencil beam scanning offers the possibility of intensity modulated proton beam therapy (IMPT).

Figure 6 – Passive scattering vs. pencil beam (active) scanning



[Figure – Source: Hall 2006 p6[9]]

Intensity modulated proton beam therapy enhances the ability of the pencil beam to treat the tumour from multiple angles, at various depths and degrees of intensity. While each treatment field generated in pencil beam covers the entire area of the tumour, true IMPT patches together fields that treat one portion of the target area at a time until the entire tumour is treated. This distinction allows for more precise dose distribution in which very specific amounts of radiation can be given across the peaks and valleys of the tumour. It's especially well-suited for patients with complicated tumour shapes nestled in the head and neck region where you want to retain key functions such as vision, speech, swallowing and taste (http://www.mdanderson.org/patient-and-cancer-information/proton-therapy-center/for-patients/videos-articles-and-podcasts/impt-background.pdf).

Yet, pencil beam is more sensitive to any misalignment or density change.

Uniform beam scanning

In the uniform scanning technique, the system uses a range modulator, patient collimator and range compensator similar to the passive scattering technique, but it utilizes magnets instead of scattering foils to spread the beam laterally.[56] With this system, the beams are scanned in a fixed pattern with a uniform intensity for each layer, while in the pencil beam scanning system, beams are scanned with variable intensity and pattern.[57] Overall, the uniform scanning system uses less material in the beam path compared to the passive delivery system and therefore is supposed to produce fewer neutrons.[56]

1.2.6.2 Proton beam therapy – the holy grail in paediatric radiation oncology?

As was explained above, the principal motivation for using proton beams instead of photons is the avoidance of high local doses to sensitive tissues ("organs at risk", OAR), in order to reduce acute and late effects (e.g. secondary malignancies, growth disturbances, neurocognitive deficits, neuroendocrine dysfunction, hearing loss). This is especially the case in children. Brain tumours, metastases in the spinal cord or tumours in the pelvic region may be extremely difficult to treat with surgical interventions, and radiation therapy (e.g. in case of incomplete resection) may have a tremendous acute and/or late impact (see higher).

Based on (*in silico*) planning comparative studies, it has been concluded that proton beams have the potential for a similar or even improved coverage of the planning target volume while keeping the dose at the organs at risk significantly lower.[23,58] It has been suggested that in the near future a large fraction of definitive radiation treatment would be based on particle beams and 4D image guiding.[59]

An additional advantage of proton beam therapy is that it leaves its "signature" in the body for some time as irradiated tissue emits gamma rays; different isotopes (of carbon, nitrogen, or oxygen) have different half-lives, on the order of minutes.[60] Real-time positron emission tomographic (PET) scans are therefore possible: the radiation dose delivered to the tissue can be assessed and compared with the planned dose. In this way, subsequent doses and areas can be planned.[60]

Another method to verify the position of the end-of-range of the proton beam is prompt gamma imaging. While primary protons normally stop inside the patient, protons produce secondary prompt and delayed radiation that may be used for in vivo range verification.[61] Prompt gamma-rays are emitted almost instantaneously during the decay of the excited nuclear reaction products to their ground state. Therefore, they can be used for an immediate and more accurate proton range verification than PET scanners. A number of prompt gamma-ray measurements along the path of proton (and carbon ion) pencil-beams have been reported; several detectors are under development by different groups.[61]

Some experts are less enthusiastic about proton beam therapy and have expressed major concerns. Tepper (2008) notified that radiation dose distributions are a model for clinical reality, but they are not clinical reality.[62] Models usually predict outcomes effectively when they are used to predict situations within the realm from which the models were derived (i.e. interpolated from the data), but the use of those models to predict outcomes extrapolated beyond the range of the initial data, produces answers that are much more suspect.[62]

Merchant (2013) argued that the differences in radiobiological effect when comparing photons with protons imply that we are comparing a known entity with an unknown entity: the dose-volume histogram for proton therapy might mean something substantially different from the dose-volume histogram for photon therapy.[12] He underscores that the multifaceted difference between

the 2 modalities supports the argument for careful evaluation, follow-up, and clinical trials with adverse event monitoring when using proton therapy in children.[12]

With regard to the production of secondary neutrons as a result of the passive scattering technique (see higher), Hall & Brenner underline how uncertain current knowledge on the cancer risks from low doses of neutrons really is.[63]

Also, compared with photon-based radiotherapy, there is more impact of a change in tissue type through which the proton beam is travelling, and planning may have to be adjusted more frequently in order to keep the Bragg Peak conform to the tumour. This is for example the case when the beam passes the maxillary sinus, which can be filled or not.[64]

On top of that, in the previous KCE study on Hadron therapy (2007[65]) as well as in several systematic reviews on the clinical effectiveness of proton beam therapy it is clearly stated that for most clinical indications, it still cannot be concluded that proton beams are clinically truly superior to X-rays.[65-69] It remains unproven in the clinic whether protons are more suitable when OAR dose constraints limit the delivery of the most appropriate tumour X-ray radiotherapy doses.[69] Nor is it known whether hadron therapy allows radiation dose escalation without increasing side effects – leading to improved local tumour control and survival.[69] What's more, the clinical application of proton beams still suffers from several technical limitations and disadvantages, which are discussed in the next paragraphs.

1.2.6.3 Limitations and disadvantages of proton beam therapy

Secondary neutron exposure and secondary cancer risk

As mentioned above, secondary neutrons are generated in the passive scattering technique when the proton beam hits the scatter foil, the compensators and collimators (Figure 6). Generally, the largest source of these neutrons is the final collimator, which is located close to the patient; this collimator is fabricated out of brass with a patient-specific aperture shaped to match the target.[50] The exact neutron dose to which a patient is exposed is highly facility dependent and is subject to various factors, such as the initial beam, field-shaping devices, aperture, and treatment volume.[34] Therefore, and also because different measurement techniques may be used, measured neutron doses vary greatly among clinical proton facilities.[50]

Brenner & Hall further elucidate that it is extremely difficult to make neutron measurements in a realistic anthropomorphic phantom, which is what is needed to estimate organ doses and thus risks.[50] Also, very different assumptions were made about the relative biological effectiveness for the carcinogenic potential of low doses of high-energy neutrons, which may further explain the variability in estimates of the secondary cancer risks associated with secondary neutron exposure.[50]

It was estimated that the overall lifetime cancer risk attributable to secondary neutrons in proton radiotherapy, for a 15 year old is in the order of 5% for a male and 10% for a female; this estimation would be higher for a younger patient and smaller for an older patient.[50] On the contrary, Newhauser and colleagues calculated that the total lifetime risk of secondary cancer due exclusively to stray radiation was 1.5% for the passively scattered technique versus 0.8% for the scanned proton beam treatment.[70] They further conclude that the risk of secondary cancer induction from intensity-modulated radiation therapy and conventional photon treatments were 7 and 12 times higher than the risk associated with pencil beam proton therapy, respectively, and 6 and 11 times higher than with passively scattered proton therapy, respectively.[70]

Yet, despite these divergent estimates of actual secondary cancer risk, it has been very well established that low neutron doses have a high potential for carcinogenesis.[71] Therefore, it is extremely important to quantify the secondary neutron exposure related secondary cancer risk, in particular because the reduction of secondary cancer risk is in fact one of the principal reasons for the move from photons towards proton beam therapy in children. In addition, as worldwide the majority of proton beam facilities is using the passive scattering technique, research on the impact of the modification of (pre-)collimator design in terms of geometry and material, will be very important.[72]

For the sake of completeness we add here the results of a matched retrospective cohort study comparing the incidence of secondary tumours in 558 proton patients with the incidence in 558 photon patients from the Surveillance, Epidemiology and End Results (SEER) registry.[73] The participants had a variety of cancers, had a median age of 59 y.o. at treatment and were followed for a median of 6.7 years. Second malignancies occurred in 29 proton patients (5.2%) and 42 photon patients (7.5%). After

adjustment for sex, age at treatment, primary tumour site and year of diagnosis, PBT was associated with a risk of secondary malignancy approximately one-half that of photon therapy (HR: 0.52; 95% CI: 0.32-0.85; p=0.009).[73] These results should be interpreted with caution, though. First of all, the greater part of the excess of second cancers in the photon group occurred in the 5 years following radiation treatment, a time period in which a second cancer event is not attributed to prior radiation.[15] After that period, the second cancer incidence rates were very similar between groups. Second, patient enrolment period was very long (1973-2001); hence conformal x-ray techniques (e.g. IMRT) were only applied in the patients enrolled at the end of this period. Third, with regard to the particular scope of this report: none of the paediatric proton or photon patients developed a second cancer during follow-up.[73]

Sharpness of the lateral penumbra

Although the sharpness of the penumbra in proton beams decreases with the depth of penetration, in general, the penumbra is supposed to be smaller for proton than for photon beams (up to approximately 17 cm) resulting in higher conformity of the former.[34] However, in clinical practice, the penumbra is often larger.[35, 44] The double-scattering technique leads to a large virtual source and hence to penumbra.[44] Flanz & Bortfeld (2013) reported that the 80%-20% lateral penumbra width in the passive scattering facility at the Massachusetts General Hospital (Boston) was 6mm at a range of 15 cm, or almost twice as large as the physical ideal; they attributed this to the multiple Coulomb scattering.[35] There is also room for improvement in the pencil beam technique in order to keep the pencil beams narrow.[44]

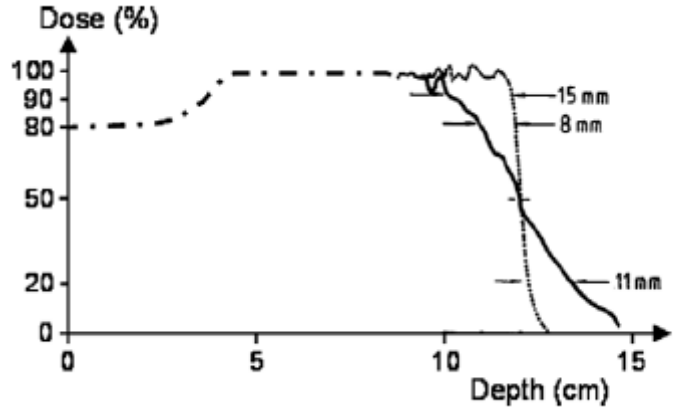
Distal edge degradation

When protons traverse complex density inhomogeneities, such as in the base of skull, their penetration is affected[44]. Not only is the average range affected, but the steepness of the distal dose fall-off can be compromised[74] leading to the need for generous safety margins in depth (having said which, the proton dose distribution, although degraded, is still superior to that of X-rays). Figure 7 shows a measurement in a proton beam demonstrating a rather extreme case of distal edge degradation. Distal edge degradation is a reality of physics about which little can be done except to try to use beam directions which avoid complex inhomogeneities and to ‘‘patch up” the distal dose with beams coming from other directions. The problem lies in the inadequacy of current treatment planning tools to both evaluate the extent of distal edge degradation in a given instance, and implement strategies to minimize its effects. The consequence is that relatively generous safety margins in depth are necessary.[44]

Range accuracy

Nowadays, significant range uncertainties in proton beam therapy still require improvements.[35] They are essentially due to uncertainties in the computed tomography (CT) imaging (such as imaging artifacts, image calibration issues, conversion of image intensity (Hounsfield numbers) to proton stopping power), as well as to dose calculation uncertainties and biological uncertainties in the relative biological effectiveness.[19, 35]

Figure 7 – Measured depth–dose curves of an approximately 130 MeV proton beam



Legend: Dotted line: depth–dose in water; solid line: depth–dose in water after traversing the petrous ridge of a human skull (data from Urie et al.[74]). The dot-dash line at shallower depths is schematic and not a measurement.

[Figure – Source: Goitein 2010, p25[44]]

OAR & tumour location uncertainties

The patient-position-related uncertainties should also be reduced; these include: setup errors, motion during the treatment, changes during the course of fractionation, contouring of the tumour target volume and critical structures.[35] Organ motion can result in quite large dose fluctuations ('interplay' effects) because cells can avoid being irradiated by moving away from the pencil beam intended to irradiate them, or can receive extra dose by remaining within a pencil beam as it is scanned.[44, 75] The current solution is a combination of (a) restricting motion where feasible (e.g. by respiratory gating); and (b) averaging out the dose fluctuations by applying the same beam multiple times ("repainting"). Unfortunately, in the commercial implementations, technical difficulties have resulted in inadequate repainting schemes, particularly in the depth direction, because this requires rapid changes in beam energy.[44] When treating superficially located tumours with proton beam therapy, it has to be taken into account that the skin is exposed to high doses.

Uncertainty analysis

Usually uncertainty analyses are performed in radiotherapy: a safety margin around the periphery of the field is used to allow for patient and organ motion, and for uncertainties in tumour delineation. An uncertainty analysis is even more necessary in planning charged particle therapy since there are additional uncertainties in particle penetration and, in general, in the way the dose distribution is affected by inhomogeneities, by organ motion, and by beam misregistration.[44] Goitein's greatest concern is not that these uncertainties cannot be managed, but that the need for such analyses may not be appreciated and that uncertainties may not be adequately allowed for.[44]

Operational aspects

Proton beam therapy is currently very time-consuming and labour-intensive: patient preparation is often very lengthy, radiographic localization requires much manual input and is often slow, and equipment motions are in some cases inefficient (requiring, for example, several actions to be taken when one would be enough).[44] As a result, complex multi-field treatments can easily take half-an-hour or more, even though the beam-on time per field may be of the order of a minute or less.[44] The treatment of children is even more time-consuming and labour-intensive. They often require anaesthesia and hence, it can take up to six times as long to treat a child with proton beams than a prostate cancer patient.[76] Older proton facilities which are not hospital-based may not be able to accommodate children who require anaesthesia and/or extra transportation may be indicated when patients need concomitant chemotherapy. Usually proton beam therapy is considered in complex tumour cases; yet, high quality can only be delivered if the operators have sufficient time. Economic pressure to increase the throughput of the machine should never prevail.

Cost effectiveness

With regard to cost-effectiveness, Pijls-Johannesma et al. (2008) reported in 2008 that the scientific literature on the cost-effectiveness of proton beam therapy was scarce, non-comparable and largely not performed according to standard HTA criteria.[77] Later on, De Ruysscher et al. (2012) stated that it had not been demonstrated that charged particle radiotherapy was more cost-effective than the most advanced photon techniques (e.g. IMRT, stereotactic body radiotherapy).[69] Just recently, Ollendorf et al. (2014) concluded 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 conditions.[78]

1.2.7 Conclusions

Essentially, there are two ways for which proton beam therapy can be used: (1) the dose to organs at risk can be reduced and/ or the risk for second malignancies can be lowered and (2) the dose to the tumour can be increased without putting the organs at risk to a higher dose. Despite the thorough physical underpinning of proton beam therapy, this has not been confirmed yet in clinical studies. In addition, there are still some technical limitations to be tackled.

Therapeutic interventions using radiation therapy differ in many ways from other treatments including drug treatments in oncology. Whereas personalised molecular modelling of the effects of specific drugs is still experimental, sophisticated *in silico* models of the biological effects following radiotherapy are standard of care. Some radiation oncologists are so confident in the clinical outcome that they do not see the need to run proper

clinical trials to confirm the assumed clinical efficacy and safety. This is not only the case for hadron therapy, but e.g. also for Intensity Modulated Radiotherapy (IMRT).[79]

Conducting randomized trials for proton radiotherapy in paediatric oncology is highly complex and probably not achievable. Incidences are low, few are eligible for proton therapy and they should then be further divided by tumour histologic type, stage, and location in the body. Even if there was international cooperation in doing a randomized clinical trial and even if there was an international quality assurance mechanism for assuring the compatibility of different treatment machines, it would be impossible to do a randomized prospective trial because the end point of the trial for most situations comparing protons to photons is reduced toxicity, not increased local control or better survival (EC Halperin, personal communication). Follow-up of patients over long periods in such studies is difficult and costly.

In addition, it is not sufficient to compare the use of proton therapy to external beam photon therapy. For example, in certain childhood intraocular tumours the best way to give localized therapy and minimize the dose to normal tissue is brachytherapy (typically by the placement of an iridium, iodine, or ruthenium scleral plaque). Plaque therapy would be expected to have an even lower risk of second malignant neoplasms than proton external beam therapy. Similarly, in certain clinical situations either brachytherapy or intraoperative radiotherapy (with either intraoperative electron beam therapy or intraoperative high dose rate brachytherapy) are the appropriate modalities to include in the comparison to proton therapy rather than compare it only to external beam photon therapy (EC Halperin, personal communication).

Furthermore, the device industry does not feel the need to finance and conduct clinical effectiveness studies as such data are not required to market a new radiotherapy device.

Nevertheless, it may be wise to first verify the assumed clinical superiority of a new technique before investing public health money. This is what this report is all about. Proton radiotherapy is a new technique and clearly more expensive. Its claimed clinical superiority compared to existing radiotherapy modalities is, in many indications, merely based on *in silico* data. Many questions remain. How does this translate into hard clinical endpoints in clinical trials and clinical practice? Where are we today, what should be done to answer these questions?

1.3 Conclusions of the 2007 KCE report on hadron therapy

In the previous KCE report on hadron therapy, the authors concluded that there was no evidence for a superior efficacy of hadron therapy (i.e. proton beam therapy, carbon ion therapy) compared to current therapy in terms of e.g. improving local control, disease free survival and/or overall survival. In addition, there were no comparative studies with regard to the toxicity of hadron therapy, hence it could not be evaluated if patients treated with hadron therapy suffer from less (severe) side effects.[65]

The authors further state that “proton beam therapy can represent an indication for rare and specific tumours in selected groups of patients where conventional therapy presents a significant risk for fragile structures in the vicinity. The quality of actual evidence is nevertheless poor. Carbon ion therapy is an appealing but still experimental approach.”[65]

With regard to hadron therapy in children, the following conclusions were drawn: “Proton radiation therapy seems to be safe and well tolerated by children suffering from CNS tumours (no RCTs available, sparse retrospective evidence). There is currently no evidence to support the use of proton therapy as first line treatment in CNS tumours in children.”[65] However, it is important to mention that re-irradiation of the same region with proton therapy after conventional radiotherapy has its limitations; especially the outside-target-dose given with photons and the added, unavoidable entrance dose of proton beams are of concern and can make re-irradiation unacceptable. (G Goitein, personal communication)

1.4 Hadron therapy in Belgium

Anno 2014 there are no hadron facilities in Belgium. Recently, it was announced that a first proton centre will be built in Leuven (http://www.uzleuven.be/radiotherapie-oncologie/news/14/02/20/nieuw-centrum-voor-protontherapie-in-strijd-tegen-kanker). A second centre is being planned in Charleroi (http://www.wallonie.be/fr/actualites/futur-centre-de-protontherapie).

Belgian citizens eligible for hadron therapy are sent abroad. The recent improvement of cross-border healthcare in Europe has facilitated the management of these patients. A list of proton centres where Belgian patients can be referred to is available on the website of the National Institute for Health and Disability Insurance (RIZIV – INAMI)[i]. The costs of transport and accommodation used to be paid by the RIZIV - INAMI through the Special Solidarity Fund (SSF) and the treatment costs could (potentially) be reimbursed through the E112/S2-procedure.

From September 2014 on (and until the end of September 2017), the costs related to hadron therapy (i.e. the treatment, transport and accommodation) are reimbursed through a specially designated budget of € 3.6 million per year (an amount that is index-linked). An “agreement council” (akkoordraad/ conseil d'accord) evaluates every application and decides whether the treatment is reimbursed. The procedure that has to be followed and the indications (for children and adults) are described on the RIZIV - INAMI website[i]. The list of indications was based on the Feasibility study of a Hadron Therapy Centre in Belgium (2013).[80]

1.5 Objective of this study

The objective of this study was to evaluate the clinical effectiveness of proton beam (or carbon ion) therapy in the 16 indications in children currently reimbursed by the RIZIV – INAMI special hadron therapy budget. It concerns the following indications:

Table 2 – Indications under study

	Pathology	Type of hadron therapy
1	Skull base & (para)spinal chordoma	Proton
2	Skull base chondrosarcoma	Proton
3	Spinal & paraspinal "adult" soft tissue sarcoma	Proton
4	Pelvic sarcoma	Proton
5	Rhabdomyosarcoma	Proton
6	Ewing's sarcoma	Proton
7	Retinoblastoma	Proton
8	Low-grade glioma (incl. optic pathway glioma)	Proton
9	Ependymoma	Proton
10	Craniopharyngioma	Proton
11	Pineal parenchymal tumours (“not pineoblastoma”)	Proton
12	Esthesioneuroblastoma	Proton
13	Medulloblastoma / primitive neuroectodermal tumours (PNET)	Proton
14	CNS germinoma	Proton
15	Unresectable osteosarcoma	Proton
16	Non-resectable or incompletely resected high-grade osteosarcoma with or without metastases	Carbon ion

i http://www.riziv.fgov.be/nl/professionals/verzorgingsinstellingen/ziekenhuizen/zorg/Paginas/Hadron-english.aspx; for osteosarcoma PBT & CIRT are considered, leading to 16 indications in 15 cancers.

2 METHODS

2.1 Literature search

A systematic search for relevant publications was carried out with the consultation of the **electronic reference databases** Medline (through OVID), EMBASE, and the Cochrane Library. Reviews and primary studies on proton beam therapy and/or carbon ion therapy published between 2007 (i.e. search strategy of previous KCE Hadron HTA[65]) up to March 2014 were searched; no filters on study design were used. Due to the expected paucity of reports, no minimal follow-up was added to the inclusion criteria. In addition, the medical indications (Table 2) were not adopted in the search as the searches for all indications under study were done simultaneously. An overview of the inclusion and exclusion criteria is presented in Table 3; the search strategy is given in Appendix 1.1.

A final update of the search (restricted to Medline through OVID) was performed on 11 September 2014.

Table 3 – PICO table and selection criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Cancer as defined in Table 2	Pathologies not listed in Table 2
Intervention	Proton beam therapy and/or carbon ion therapy	Photon therapy
Comparator	Photon therapy, surgery, chemotherapy	
Outcomes	Clinical effectiveness, complications, side effects, secondary tumours	Cost effectiveness
Study design	Systematic review, review, randomized controlled trial, comparative studies, case series	Case reports, simulation studies, animal studies, letters, editorials, notes, congress abstracts
Language	English, Dutch, French, German	All other languages

The references from the three electronic databases were merged into a unique EndNote file; duplicates were removed. We then screened titles and abstracts to identify and exclude articles that did not fulfil the inclusion criteria. As it was anticipated that the volume of scientific evidence for hadron therapy in (some of) the indications under study was small, the selection was deliberately performed in a "generous" way, in order to include also publications which reference list could serve as an additional source of references to primary studies. In a second phase the selected hits were classified according to the indications under study; in this phase an additional exclusion process was performed.

The websites of **all members of INAHTA and related websites** were also consulted for publications on proton beam therapy and/or carbon ion therapy. The search terms, in- and exclusion criteria, consulted websites and retrieved documents are documented in Appendix 1.2.

Finally, we searched the **International Clinical Trials Registry Platform** (http://www.clinicaltrials.gov/), which covers major clinical trials registry worldwide, to trace on-going trials.

The remaining papers were retrieved and read in full for a final selection of studies to include in the review. The flow chart of the selection process is presented in Appendix 1.4.

2.2 Quality appraisal

The quality appraisal was performed by at least one researcher:

- comparative observational studies were assessed with the Cochrane Collaboration's tool for assessing risk of bias.

The tools for and the results of the quality appraisal are available in Appendix 2.

2.3 Data extraction

For primary studies, the following data were extracted: publication year, study population, study intervention, and outcomes. Data extraction was performed by at least one researcher and entered in evidence tables using standard KCE templates. All evidence tables are reported in Appendix 2.3.

2.4 Statistical analysis

As no RCTs were retrieved and hardly any comparative studies, no statistical analyses were performed.

2.5 Grading evidence

For each indication, we provided the quality of the supporting evidence. According to GRADE,[81] we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 5). The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating is initially considered to be of high level (Table 4). The rating is 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 points respectively. Judgement of the overall confidence in the effect estimate is also taken into account.

Observational studies are by default considered low level of evidence (Table 4 and Table 5). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used to downgrade the quality rating are summarized in Table 6. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[81].

Table 4 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 5 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 6 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

2.6 Validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. The validation comprised a content as well as a methodological evaluation and validation. The names of the 3 validators are adopted in the colophon. The validation meeting took place on 13 November 2014.

3 RESULTS

3.1 Number of (potential) patients per indication under study[j]

Between 2004 and 2011 928 paediatric patients (0-14 y.o.) were diagnosed with a tumour (type under study in this report) in Belgium; thus on average 116 patients per year Table 7). For 79% of these patients (n=735), the Belgian Cancer Registry also holds the treatment plan details for newly diagnosed cancers: for 238 children (i.e. 32%) radiotherapy was adopted in the treatment plan. When this proportion is extrapolated to all affected children (n=928), it can be estimated that yearly 37 children may be eligible for RT/PBT (first treatment plan at diagnosis). As some indications under study in this report also occur in the adolescence period, incidence data for this age group were also examined. In the same time span (2004-2011) 309 adolescents (15-19 y.o.) were diagnosed with a tumour (type under study in this report) in Belgium; thus on average 39 patients per year. For 72% of these patients (n=223), the Belgian Cancer Registry also holds the treatment plan details: 78 adolescents (i.e. 35%) were considered eligible for radiotherapy. When this proportion is applied to the total number of adolescents (n=309), the estimated number of adolescents potentially eligible for RT/PBT is 14 per year.

Three important remarks have to be made when interpreting the data. For some tumour types the indications under study were slightly redefined. For instance, “skull base & (para)spinal chordoma” was redefined as “chordoma”, “spinal & paraspinal adult soft tissue sarcoma” was redefined as “sarcoma located at the central axis”. Second, some selection criteria were overlapping, resulting in double recordings of some patients. For instance some “ependymomas” are also included in the 376 cases with “low grade glioma (including optic pathway)”, but not all as e.g. anaplastic ependymomas are considered high grade. Some “pelvic sarcomas” are also included in the “Ewing sarcomas” and the “rhabdomyosarcomas”. This leads to a lower ‘actual’ total number of affected children, as compared to the sum made on the basis of all the generated results. Third, the variable ‘radiotherapy’ (RT) is based on the information available at the Belgian Cancer Registry, i.e. the report of the multidisciplinary oncological consultation where the treatment plan is discussed and decided upon (MOC/COM report). However, it is very well possible that a few children who were eligible for radiotherapy did not receive RT and that some children who were considered not eligible finally did receive RT. Taken together, earlier evaluations indicated that the MOC/COM reports seem to give a fairly reliable idea of the treatments effectively offered.

In addition, it must be mentioned that for certain forms of childhood cancer, that are relatively common indications for paediatric radiotherapy, there is either no conceivable indication for proton therapy or the value of proton therapy is remote. They include infiltrative pontine glioma, high grade supratentorial malignant glioma (glioblastoma multiforme, anaplastic astroycytoma), total body irradiation or C2 whole brain irradiation or testicular irradiation for acute lymphoblastic leukaemia or acute myelocytic leukaemia, total body irradiation for neuroblastoma, flank irradiation for Wilms tumour, palliative radiotherapy of e.g. bone metastases, Langerhans cell histiocytosis. (EC Halperin, personal communication) The treatment of these types of childhood cancer with proton beam therapy are at present not reimbursed by the RIZIV - INAMI and as a consequence not evaluated in this report.

[j] Data provided and paragraph written by Kris Henau, Nancy Van Damme and Liesbet Van Eycken, Belgian Cancer Registry

Table 7 – Number of (potential) patients per indication under study

	0-14 year				15-19 year			
Tumour type	**N**	**N with known treatment plan**	**N with RT in treatment plan**	**% with RT in treatment plan**	**N**	**N with known treatment plan**	**N with RT in treatment plan**	**% with RT in treatment plan**
Chondrosarcoma	4	3	0	0%	9	5	0	0%
Chordoma	2	0	0	NA	1	1	0	0%
Craniopharyngioma	27	21	7	33%	5	4	0	0%
Ependymoma	46	38	24	63%	16	10	4	40%
Esthesioneuroblastoma	1	1	1	100%	0	0	0	NA
Ewing sarcoma	65	59	20	34%	40	36	18	50%
CNS germ cell tumours	19	15	11	73%	13	11	11	100%
Low grade glioma (including optic pathway)	376	278	56	20%	104	62	18	29%
Medulloblastoma / primitive neuroectodermal tumours (PNET)	97	88	64	73%	13	10	7	70%
Osteosarcoma	70	61	4	7%	56	45	3	7%
Pineal parenchymal tumours (not pineoblastoma)	1	1	0	0%	1	1	0	0%
Retinoblastoma	98	68	8	12%	0	0	0	NA
Rhabdomyosarcoma	74	64	31	48%	17	14	3	21%
Sarcoma located at the central axis	4	1	1	100%	7	5	3	60%
Pelvic sarcoma	44	37	11	30%	27	19	11	58%
TOTAL*	**928**	**735**	**238**	**32%**	**309**	**223**	**78**	**35%**

*The number of children and adolescents per indication is based on the data of registered cases during the period 2004-2011. Histology codes and the ICD-O3 topography codes were used to retrieve the number of patients diagnosed for each tumour type; details of the coding can be found in appendix 3. 0-14 year: including children up to 15 years minus 1 day; 15-19 year: including adolescents from 15 years old up to 20 years minus 1 day; N: number of diagnosed children per tumour type; N with known treatment: number of children per tumour type for which information concerning their treatment is available at the Belgian Cancer Registry; N RT: number of children per tumour type considered eligible for radiotherapy; % RT: percentage of children per tumour type considered eligible for radiotherapy (per number of children with known treatment); *: the total numbers may be higher than the 'actual' total number of affected children, due to some overlapping selection criteria.*

3.2 Chordoma & chondrosarcoma

3.2.1 Background[k]

We describe skull base and (para)spinal chordoma and skull base chondrosarcoma in the same chapter because many (clinical) studies also address the two pathologies together. Both tumours are generally slow growing and indolent, therefore they are often clinically silent until the late stages of disease.[82] As they lie in close proximity to the brain stem, optic apparatus, cranial nerve and skull base vessels, they both pose the same challenges for surgery and radiotherapy.[83] Yet, chordomas and chondrosarcomas represent two biologically distinct categories of mesenchymal neoplasms that share morphological similarity and often present in similar locations throughout the neuroaxis; however, they differ in response to treatment.[82]

3.2.1.1 Chordomas

3.2.1.1.1 Clinical pathology & incidence

Chordomas are extra-axial tumours that originate from the remnants of the notochord. Approximately 50% develop in the sacrococcygeal region, 35% in the sphenooccipital region, and 15% in the vertebrae. Chordomas metastasize infrequently.[8] Skull base chordomas account for less than 0.2% of all intracranial neoplasms.[84] Population-based studies using the Surveillance, Epidemiology, and End Results (SEER)[l] database suggest an incidence of chordoma of 0.08 per 100 000, with a predominance in men and a peak incidence between 50–60 years of age. Chordomas have a very low incidence in patients younger than 40 years, and rarely affect children and adolescents (<5% of all chordoma cases).[82] In children and teenagers, chordomas develop more often in the base of the skull, making them hard to remove completely with surgery.[85] Childhood chordoma is linked to the condition tuberous sclerosis, a genetic disorder in which tumours that are benign form in the kidneys, brain, eyes, heart, lungs, and skin.[85]

Chordomas manifest as one of three histological variants: classical (conventional), chondroid, or dedifferentiated.[82] Although histologically considered to be a low-grade neoplasm, chordomas are highly recurrent, making their clinical progression very similar to that of malignant tumours. In addition, chordomas frequently pose a significant challenge to local control because of their location: skull base chordomas occur in close proximity to many critical structures, such as the brainstem or other parts of the brain, cranial nerves, arteries, spinal cord, and/or optic pathways.[8]

3.2.1.1.2 Current treatment regimen & prognosis

Skull base chordomas arise in bone but may grow to involve multiple areas of the cranial base, and occasionally erode into the intradural space to encompass neurovascular structures and compress the brainstem. The selection of an operative approach depends on the tumour location and the relationship to the internal carotid, vertebral, and basilar arteries, cavernous sinus, and brainstem.[84] Where en-bloc resection or gross total resection is not feasible, particularly for lesions in the clivus, radical or near total intralesional resection is advocated. Although subtotal resection is sometimes the goal of surgery, maximally safe resection with an emphasis on neurological preservation, followed by radiation therapy, is an optimum treatment paradigm. Tumour tissue that remains after surgery, particularly when small in volume, can be managed effectively with radiotherapy.[82] Innovative endoscopic, endonasal techniques to access the clivus are minimally invasive and are also highly effective.[82] Aggressive surgical resection upon initial surgery is also advocated in chordomas of the sacrum and mobile spine.[82] In children and adolescents surgery is not commonly curative because of difficulty obtaining clear margins and the likelihood of the chordoma arising in the skull base, rather than in the sacrum, making them relatively inaccessible to complete surgical excision.[85]

In a systematic review the overall 5-year and 10-year survival rates in patients with intracranial chordomas were 63% (299 patients) and 16% (176 patients).[86] There was no difference in the overall survival rates when a cut-off of 40 y.o. was used, but when 5 y.o. was used as cut-off the overall

[k] Not based on a systematic search of the literature.

[l] The Surveillance, Epidemiology and End Results (SEER) database provides population-based incidence and survival data for primary malignant tumours collected from 17 registries in the United States.

survival was better for patients in the group older than 5 years of age (<5 years: 14% vs. >5 years: 66%; p=0.001). Adjuvant radiotherapy and histological type were not associated with a statistically significant improvement of 5-year overall survival.[86]

3.2.1.2 Chondrosarcomas

3.2.1.2.1 *Clinical pathology & incidence*

Chondrosarcomas are uncommon malignant neoplasms of the cartilage that can occur anywhere in the body but are most commonly found in the long bones and pelvis, with less than 10% occurring in the head and neck. Only 1% of chondrosarcomas arise in the skull base, and they account for 6% of all skull-base tumours.[87] Chondrosarcomas are rare in children; when they occur, they tend to be aggressive.[88]

Histopathologically, chondrosarcomas can be of the conventional, mesenchymal, clearcell, or dedifferentiated type. Almost all skullbase tumours are the conventional type, with rare (<10%) mesenchymal lesions reported.[87] Conventional chondrosarcoma can be composed of hyaline or myxoid cartilage, or a combination of the two.[87] The significance of histological subtypes among chondrosarcomas has been reported; however, the prognosis is determined primarily by its World Health Organization (WHO) histological grade.[89] The grading system consists of three categories: grade I (well differentiated), grade II (moderately differentiated) and grade III (poorly differentiated).

3.2.1.2.2 Current treatment regimen & prognosis

Although malignant, the biological behaviour of these tumours is characterized by potentially fatal progressive enlargement and subsequent compression or invasion of local structures such as the brain and the optic pathway.[89] The complete surgical resection of these tumours is most often prevented by their deep location; consequently, a combination of surgery and irradiation has become the mainstay of treatment.[89] Factors such as pathological pattern, previous treatment (surgery or radiation therapy), degree of tumour resection and adjuvant postoperative radiation therapy have all been implicated in the prognosis of patients with chondrosarcoma.[89] A systematic literature review by Bloch et al. revealed a significant reduction in the 5-year rate of disease recurrence from 44% after surgery alone to 9% after additional irradiation.[89] In this evaluation of 560 patients with cranial chondrosarcomas, radiotherapy when used as the only treatment even demonstrated a significantly lower 5-year recurrence rate compared with surgery alone (19% vs. 44%).[89] It should be noted that surgical treatment of chondrosarcomas of the skull base has a high risk of neurological side effects.[90] Samii et al. (2009) reported a neurological complication rate of 33.3% and an incidence of cerebrospinal fluid leakage of 10.3%.[91]

3.2.2 What is the clinical effectiveness of proton beam therapy in children with skull base and (para)spinal chordoma or with skull base chondrosarcoma?

The previous KCE report concluded that there was no clear clinical evidence from comparative studies to assess the clinical superiority in efficacy between proton and classical photon therapies (or their combination or high precision photon therapy) in patients with skull base chordoma.[65] For chondrosarcoma of the skull base, it was concluded that there were no differences in local control or overall survival between photon and proton irradiation in the case series. For other non-skull based chordomas and chondrosarcomas, there was no evidence in favour of proton beam therapy. Yet, despite the poor quality of evidence non-operable skull base chordomas and skull base chondrosarcomas were listed as potential indications for proton therapy in the previous KCE report.[65] Also, with regard to the scope of this update, it should be mentioned that all studies concerning chordoma and chondrosarcoma adopted in the previous KCE report comprised a mixture of paediatric and adult patients.[65]

Only three cases series[8, 92, 93] on proton beam therapy in children were retrieved and as the patients discussed in Rutz et al.[93] were all included in Rombi et al.[8] (personal communication with one of the authors), the former was excluded.

Habrand et al. reviewed 30 children with skull base and cervical canal low-grade bone malignancies who were treated postoperatively with high-dose photon–proton (29 patients) or protons-only (1 patient) radiotherapy.[9] Twenty-six children had skull base chordomas (CH), 3 had low-grade skull base chondrosarcomas (CS), and 1 had an aggressive chondroma. Their mean age was 12.8 years; median follow-up was 26.5 months (range: 5-102 months).[92] As there were only 3 children with chondrosarcoma and the

inclusion criterium was at least 5 patients, the results concerning these children were not considered nor reported.
Rombi et al. included 26 children with a histologically proven diagnosis of chordoma (n=19) or chondrosarcoma (n=7), originating from the skull base (n=17) or the axial skeleton (n=9). They were treated postoperatively with spot-scanning proton radiation therapy. Their mean age was 13.2 years; mean follow-up was 46 months (range: 4.5-126.5 months).[8.]
For more information on these studies, the reader is referred to the evidence tables in Appendix 2.3.1.

3.2.2.1 Chordoma

Overall survival

In Habrand et al., the 5-year overall survival was 81% (95% CI: 56-100%); in Rombi et al., the 5-year overall survival was 89%.

Progression-free survival

In Habrand et al., the 5-year progression-free survival rate was 77% (95% CI: 59-95%); Rombi et al. did not report a progression-free survival rate.

Recurrence rate

After a mean follow-up of 26.5 months, Habrand et al. reported a local failure rate of 5/26 (19%). Rombi et al. reported 2 failures: one boy first had a lung metastasis followed by an in-field recurrence, the other patient had a relapse in the anterior nasal cavity.

Local control rate

In Rombi et al. the 5-year actuarial local control rate was 81%.

Quality of life

There are no data reported with regard to quality of life.

3.2.2.2 Chondrosarcoma

Overall survival

In Rombi et al., the 5-year overall survival was 75% for the 7 children with chondrosarcoma.

Progression-free survival

Rombi et al. did not report data with regard to progression-free survival in chondrosarcoma; the Habrand et al. study only included 3 cases with chondrosarcoma.

Recurrence rate

In Rombi et al., one of the 7 patients (14%) treated for chondrosarcoma experienced a local recurrence.

Local control rate

In Rombi et al. the 5-year actuarial local control rate was 80%.

Quality of life

There are no data reported with regard to quality of life.

3.2.2.3 Chordoma & chondrosarcoma

Complication rate

In the study by Habrand et al., complications were observed in 28 out of 30 patients. Acute toxicity was reported as minor or mild.The reported acute toxicities were: mucositis (n=10), epidermitis (n=14), headaches (n=10), nausea (n=9) and focal alopecia (n=23). Late toxicity was evaluable in only 23 of 30 patients. Late toxicity of radiotherapy was severe in 1 patient (Grade 3 auditory) and minor or mild in 7 patients, mainly related to partial pituitary hormone failure after irradiation (Grade 2). In Rombi et al. PBT was well tolerated with 15 events of grade 2 acute toxicity in 12 of 26 patients. Five patients, all with the tumour localized in the skull base, developed eight events of minor or mild late toxicity (grade 2); no high-grade late toxicities were noted.

Secondary malignancy

Rombi et al. reported that during the follow-up period (range: 4.5-126.5 months) no secondary malignancies were observed. Habrand et al. has not mentioned anything on secondary malignancies.

Results described above should be interpreted with caution since both studies had serious methodological limitations (see evidence tables in Appendix 2.3.1). There were no control groups (patients treated with photon radiotherapy after surgery), hence it was impossible to extract what the added value of PBT was.

Conclusions

- At present there is insufficient scientific evidence to support or to refute the use of PBT in children with skull base and (para)spinal chordoma.
- At present there is insufficient scientific evidence to support or to refute the use of PBT in children with skull base chondrosarcoma.

Other considerations

- According to experts of the field, skull base chordoma is an example of an indication where there is at present no doubt that PBT is the preferred radiotherapy option due to the high dose of radiotherapy needed at a location close to critical parts of the brain.
- The target dose for clival chordoma is higher than the brainstem can support; therefore a sharp demarcation is needed.
- At present two studies, both conducted at the University of Texas, MD Anderson Cancer Center are mentioned on the ClinicalTrials.gov website: one is a randomized phase II (safety/efficacy) evaluation of PBT vs. photon therapy for skull base chordoma and the second is a single-arm phase II (safety/efficacy) evaluation of PBT for skull base chondrosarcoma. The estimated primary completion date of the first is September 2014 and for the second April 2015. None of the study protocols mention whether children were also eligible.

3.3 Craniopharyngioma

3.3.1 Background[m]

3.3.1.1 *Clinical pathology & incidence*

A craniopharyngioma is a non-glial intracranial tumour arising in the suprasellar region near the pituitary gland.[94-96] The WHO defined 2 subtypes: adamantinomatous (ordinary) craniopharyngioma and (squamous) papillary craniopharyngioma.[96, 97] In children, the adamantinomatous form is predominant.[96, 98] Craniopharyngiomas are slow growing tumours; they are typically composed of both a solid portion with an abundance of calcification, and a cystic component which is filled with a dark, oily fluid.[96, 99] Recent evidence suggests that adamantinomatous craniopharyngiomas are locally more aggressive with a significantly higher rate of recurrence compared with the squamous papillary subtype.[4]

Despite their histologically benign nature, craniopharyngiomas frequently cause profound disabilities due to their location near critical structures such as the optic pathway, the middle cerebral arteries, the hypothalamus, the pituitary gland, cranial nerves and the brain parenchyma.[94, 100, 101,102] Uncontrolled growth of the tumour can be fatal.[100]

Craniopharyngiomas are relatively rare tumours, representing 5-10% of all childhood brain tumours[96, 100] with a peak incidence occurring at 5-14 years of age.[100] The overall incidence (children and adults) of craniopharyngioma is 0.13 in 100 000.[100]

3.3.1.2 Current treatment regimen & prognosis

There is no consensus on the optimal treatment of newly diagnosed craniopharyngioma, in part due to the lack of prospective randomized trials comparing different treatment options.[96] However, surgery and radiotherapy are the cornerstones in the management of craniopharyngioma.[103] Seventy percent of craniopharyngiomas are located in the retrochiasmatic region where gross total resection is difficult to achieve without undue morbidity.[99] Gross total resection can be considered in patients with small tumours (< 3-4 cm) and in patients with tumours in the prechiasmatic or purely intrasellar

[m] Not based on a systematic search

location.[102] A systematic review of 109 reports that described the extent of resection, found that subtotal resection plus radiation therapy was associated with similar rates of tumour control as gross total resection and that both approaches were associated with higher progression-free survival (PFS) rates than subtotal resection alone.[104]

The treatment of craniopharyngiomas may be accompanied by serious complications: visual loss, morbid obesity, loss of pituitary function, cognitive dysfunction, development of late strokes and vascular malformations, development of second tumours, and, rarely, malignant transformation of the primary tumour within the radiation field.[96, 100, 103] Therefore, quality of life is an issue of concern. Another challenge in the treatment of craniopharyngiomas is the management of the potential cyst growth, which may require additional invasive procedures (e.g. intracystic catheter placement, Ommaya reservoir) to release the compression of critical structures.[95]

Regardless of the treatment modality, long-term survival is approximately 85% in children with 5- and 10-year overall survival rates greater than 90%.[96] Recurrence occurs in approximately 35% of the patients with childhood craniopharyngioma.[96]

3.3.2 *What is the clinical effectiveness of proton beam therapy in children with craniopharyngioma?*

One comparative study[95] and two retrospective studies[98,101] in children with craniopharyngioma treated with proton beam therapy were retrieved.

Bishop et al. (2014) retrospectively compared PBT with IMRT in terms of disease control, cyst dynamics and toxicity in 52 paediatric patients with craniopharyngioma in 2 centres in Texas (US).[95] The PBT group included 21 patients (median age at diagnosis: 9.1 y.o.; gender: 57% female) and the IMRT photon group included 31 patients (median age at diagnosis: 8.8 y.o.; gender: 55% female). The median radiation dose in both treatment groups was 50.4 Gy. The 2 treatment groups were significantly different in terms of follow-up (median follow-up PBT: 33.1 months (range: 10.5 – 65.6 months) vs. IMRT: 106.1 months (range: 8.9 – 185.3 months)) and extent of first surgery (PBT: gross total resection (n=5), subtotal resection (n=9), cyst drainage, fenestration or shunting (n=7) vs. IMRT: gross total resection (n=1), subtotal resection (n=11), cyst drainage, fenestration or shunting (n=19)). Only 44% of the patients (PBT: n=19 vs. IMRT: n=5) had imaging during RT.

Winkfield et al. (2009) retrospectively investigated craniopharyngioma cyst growth during PBT in 24 children at Massachusetts General Hospital in US (mean age at PBT: 8.4 years (range: 3 – 14 years); histologic type: adamantinomatous (n=18), classification not reported (n=6); cystic component (n=19)).[98] The total PBT dose ranged from 52.2 to 54 GyE in 1.8 GyE per fraction. Median follow-up was 40.5 months (range: 6 – 78 months). Median cyst volume before treatment was 6.3 cm³ (range: 1.8 – 29.8 cm³).

Finally, Laffond et al. (2012) focused on quality of live, mood and executive functioning after childhood craniopharyngioma in 29 patients treated in France with surgery and PBT or PBT combined with photon therapy[101] (total dose range: 54 – 55.2 Gy). The authors surveyed patients and their family by phone and by postal questionnaire (mean age at diagnosis: 7 years 10 months (SD= 4.1; range: 1 year 10 months – 15 years 10 months); mean age at time of the QoL assessment: 14 years (SD=4.1; range: 7 years 1 month – 24 years)).

For more information on these studies, the reader is referred to the evidence tables in the Appendix 2.3.2.

Overall survival

Bishop et al. did not observe a statistically significant difference in 3-year overall survival between treatment groups (PBT: 94.1% vs. IMRT: 96.8%; p= 0.742).

Disease-free survival

Bishop et al. found no statistically significant difference between the PBT and IMRT group with regard to 3-year cystic failure-free survival (PBT: 67.0% vs. IMRT: 76.8%; p= 0.994) nor with regard to 3-year nodular failure-free survival (PBT: 91.7% vs. IMRT: 96.4%; p= 0.546).

Progression-free survival

There are no data reported with regard to progression free-survival.

Recurrence rate

There are no data reported with regard to recurrence rate.

Cyst dynamics during RT

Among the19 patients with a cystic component adopted in the Winkfield et al. study, only 17 had repeat imaging during RT. Six of them (35%) required intervention because of changes in cyst dimensions: cyst growth beyond the original treatment field requiring enlargement of the treatment plan (n=4), decrease in cyst size requiring reduction of the treatment plan (n=1) and cyst drainage to avoid enlargement of the treatment field (n=1).

Cyst dynamics after RT

In the Bishop et al. study, seventeen patients (33%) had imaging evidence of early cyst growth (within 3 months of completing RT), with a greater percentage occurring in the IMRT group (PBT: 19% vs. IMRT: 42%; p= 0.082), but this apparent difference was not statistically significant. Fourteen of the 17 patients with early cyst growth had only transient enlargement that resolved on follow-up imaging.
Fourteen patients (27%) had late cyst growth (>3 months after RT), with no difference between groups (PBT: 19% vs. IMRT: 32%; p=0.353), and 6 patients required additional intervention (3 cyst drainage, 2 catheter placement, and 1 surgical fenestration).

Complication rate

Bishop et al. observed no statistically significant differences in late RT toxicity between the PBT and IMRT treatment group (vascular injuries: PBT 10% vs. IMRT 10%; p= 1.00 – visual dysfunction: PBT 5% vs. IMRT 13%; p= 0.637 – hypothalamic obesity: PBT 19% vs. IMRT 29%; p= 0.523 – panhypopituitarism: PBT 33% vs. IMRT 55%; p= 0.162 – other endocrinopathies: PBT 43% vs. IMRT 23%; p= 0.139).

At the time of the QoL assessment in the Laffond et al. study (i.e. 1 year 8 months – 14 years after PBT), the following late toxicities were reported by the patients: pituitary dysfunction (n=28), visual impairment (n=23), hypothalamic syndrome (n=18), obesity (i.e. BMI > 97th percentile; n=17), recurrent headaches (n=15), depression (n=11; n=8 slight-to-moderate and n=3 modere-to-severe), epilepsy (n=4) and hemiparesis (n=3).

Secondary malignancy

There are no data reported with regard to secondary malignancy.

Quality of life

Laffond et al reported an overall fair quality-of-life measured by the Kidscreen-52 questionnaire[n] (self-report: range from 43.05 to 51.15, proxy (reported by the parents): range from 36.19 to 51.2). Executive deficits in everyday life (i.e. BRIEF[o] global executive composite score ≥ 65) were found in 30% (6/20) of the patients. The mean BRIEF global executive composite score was 52.2 (SD= 12.9; n=20). The majority of the patients had a normal schooling (26/29).

The above results should be interpreted with caution since all studies suffered from serious methodological flaws (see evidence tables in Appendix 2.3.2). Moreover, in one study radiation therapy comprised PBT alone in some children but PBT in combination with photon therapy in others and the results were not separately reported.[101]

Conclusions

- At present there is very low level scientific evidence that the use of PBT compared with IMRT in children with craniopharyngioma does not result in significant differences in terms of 3-year overall survival, 3-year cystic failure-free survival, 3-year nodular failure-free survival, toxicity or cyst dynamics after RT.

[n] For more information see http://www.kidscreen.org/english/questionnaires/kidscreen-52-long-version/

[o] Behaviour Rating Inventory of Executive Function

Other considerations

- According to experts of the field, craniopharyngioma is an example of an indication where there is at present no doubt that PBT is the preferred radiotherapy option due to the location of this non-infiltrative tumour and the need to spare critical parts of the brain.
- At present a phase II trial of limited surgery and PBT for craniopharyngioma or observation after radical resection, which only recruits adults, is running at St. Jude Children's Research Hospital (Memphis, US).
- In Germany children between 5-18 y.o. with a craniopharyngioma that is incompletely resected, are recruited for an RCT that compares the impact of early versus delayed radiotherapy on QoL issues (see http://kraniopharyngeom.net/). The aim of the prospective multicentre study is defining the optimal timing of postoperative irradiation of the residual tumour (immediate postoperative XRT vs. XRT at the time of progression).

3.4 Ependymoma

3.4.1 Background[p]

3.4.1.1 *Clinical pathology & incidence*

Ependymomas are one of the three types of gliomas, tumours of the supporting tissue of the brain. Gliomas are described in a separate chapter (see paragraph 3.8), while this chapter will only focus on ependymomas. Ependymomas arise from ependymal cells that produce cerebrospinal fluid;[105] these cells line the brain ventricles and passageways in the brain and the centre of the spinal cord.[106] The tumours originate most often in the brain (both in the supratentorial and the infratentorial region) and are rarely found in the spinal cord.[107] In children, most ependymomas are infratentorial tumours that arise in or around the fourth ventricle.[105]

According to the WHO classification of brain tumours, ependymal tumours are classified into the following four main subtypes: (1) Subependymomas (grade I): typically slow-growing tumours, (2) myxopapillary ependymomas (grade I): typically slow-growing tumours, (3) ependymomas (grade II): the most common of the ependymal tumours, which can be further divided into the subtypes cellular ependymomas, papillary ependymomas, clear cell ependymomas, and tancytic ependymomas and (4) anaplastic ependymomas (grade III): typically faster-growing tumours.[106] The various types of ependymomas appear in different locations within the brain and spinal column. Subependymomas usually appear near a ventricle. Myxopapillary ependymomas tend to occur in the lower part of the spinal column. Ependymomas are usually located along, within, or next to the ventricular system. Anaplastic ependymomas are most commonly found in the brain in adults and in the lower back part of the skull (posterior fossa) in children. They are rarely found in the spinal cord.

In children, ependymomas account for 6 to 10% of paediatric CNS tumours,[107] with one third of cases being diagnosed under the age of three years and the vast majority being diagnosed by age six years.[11]

3.4.1.2 Current treatment regime & prognosis

Standard treatment for all grades and ages includes maximal surgical resection and adjuvant radiotherapy.[108] The degree of surgical resection is associated with improvement in local control, disease-free survival, and overall survival.[109] For children aged 0-19 years with ependymoma, the overall 5-year relative survival rate is 72.1%. For classical ependymomas and anaplastic ependymomas, the estimated 5-year relative survival rate is 70.2% (patients 0-14 years).[110] Because of the very young age of patients with ependymoma, they can expect to experience worse late adverse effects from radiation to the brain in comparison with older children or adults.[111]

[p] Not based on a systematic search of the literature.

3.4.2 What is the clinical effectiveness of proton beam therapy in children with ependymoma?

Three case series on proton beam therapy in children with ependymoma were retrieved (Amsbaugh 2012, MacDonald 2008 and MacDonald 2013),[107, 111, 112] but as it was confirmed by the first author (personal communication) that all patients included in the MacDonald 2008 publication[111] were also comprised in the MacDonald 2013 report,[112] the former was excluded.

Amsbaugh 2012 et al. collected prospectively data on 8 children with spinal ependymoma (mean age 10.5 y.o. (range: 1.6-16.6 y.o.); 6/8 patients with WHO Grade I ependymoma and 2/8 with WHO Grade II ependymoma). Mean follow-up was 26 months (range: 7-51 months); treatment prior to PBT included resection surgery (8/8), chemotherapy (1/8) and photon therapy (1/8). The mean total dose for PBT treatment was 51.1 CGE (range, 45-54 CGE).[107]

Seventy paediatric patients with intracranial ependymoma (median age: 38 mo (range: 3 mo-20 y.o.); tumour localisation: infratentorial tumours (51/70), supratentorial tumours (19/70); tumour grade: differentiated (classic) ependymoma (37/70), anaplastic ependymoma (33/70)) were reviewed by MacDonald et al in 2013.[112] Mean follow-up was 46 months (range: 12 months-11.7 years); treatment prior to PBT was resection surgery (70/70) and chemotherapy (21/70); the median dose for PBT treatment was 55.8 Gy (range, 50.4-60.0 Gy).[112]

For more information on the included studies, the reader is referred to the evidence tables in Appendix 2.3.3.

Overall survival

The 3-year overall survival rate in the 70 children included between 2000 and 2011 in MacDonald et al.'s study (2013) was 95%. After a mean follow-up of 26 months, the overall survival rate was 8/8 in the Amsbaugh et al.'s study where 8 patients with spinal ependymoma were treated with PBT.

Progression-free survival

The 3-year progression-free survival rate was estimated to be 76% in the 70 children included in the MacDonald et al.'s study (2013).

Recurrence rate

In the MacDonald et al.'s study (2013), the 3- and 5-year local control rates were 83% and 77%, respectively, while the 3- and 5-year distal control rate were 86% and 83%, respectively. In the same study, disease progression was observed in 18/70 patients after a mean follow-up of 18 months (range 5.3-68.1 months). After a mean follow-up of 26 months, local control of the disease was observed in all 8 patients with spinal ependymoma included in Amsbaugh et al.'s study.

Complication rate

A complication rate was not reported in the MacDonald et al.'s study (2013). The authors assessed certain possible toxicities in a subset of the original sample of 70 children with intracranial ependymomas. Endocrine side-effects observed were hypothyroidism (1/32), growth hormone deficiency (2/25), deficient level of insulin-like growth factor 1 (IGF-I)(9/25) and highly variable changes in height recorded in 57 patients. Furthermore, hearing loss was also mentioned in 2/23 patients. Apparently, the treatment offered to the children did not affect the neurocognitive performance nor the adaptive skills and functional independence statistically significantly when measured with MDI[q]/IQ and SIB-R[r], respectively. It should be mentioned that all these outcomes were measured at different time intervals after the PBT.

Secondary malignancies

MacDonald et al. reported that there were no cases of secondary malignancies identified, but it should be realized that the follow-up period ranged between 12 months and 11.7 years.

Quality of life

There are no data reported with regard to quality of life issues.

[q] MDI: Mental Development Index

[r] SIB-R: Scale of Independent Behaviour-Revised

The above results should be interpreted with caution since both studies suffered from serious methodological flaws (see evidence tables in Appendix 2.3.3).

Conclusions

- At present there is insufficient scientific evidence to support or to refute the use of PBT in children with ependymoma.

Other considerations

- Thanks to genome sequencing there have been 9 different molecularly defined types of ependymoma identified so far; this may be helpful in the future to specify treatment pathways and e.g. eligibility for PBT.
- No running trial regarding proton beam therapy in children (or adults) with ependymoma was found on clinicaltrials.gov.

3.5 Esthesioneuroblastoma

3.5.1 Background[s]

3.5.1.1 Clinical pathology & incidence

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is an uncommon malignancy of the head and neck, representing only 3% to 6% of nasal cavity and sinonasal neoplasms.[113] It is a tumour of neural crest origin that is considered to arise from the olfactory neuroepithelium of the olfactory cleft in the superior nasal cavity at the anterior skull base.[114] Local spread of the tumour can extend throughout the paranasal sinuses and skull base with invasion of the orbit, cavernous sinus, and brain.[115] The behaviour of the tumour varies from an indolent slow-growing neoplasm to that of a highly aggressive and locally invasive malignancy with a capacity for regional and distant metastases; ENB is typically diagnosed after extensive local spread.[115]

The reported mean age of presentation ranges from 45 to 56 y.o.; approximately 7% to 20% of patients present at the age of 10 to 24 y.o.[113]

3.5.1.2 Current treatment regimes

As a general rule, sinonasal malignancies are best managed with a multidisciplinary approach. However, the rarity of presentation and lack of controlled trials have resulted in a wide variation in the management of ENB.[115] Traditionally, surgery using a craniofacial resection (with a transfacial approach and craniotomy) and adjuvant radiation therapy have been the mainstay of treatment of patients with resectable disease. Endoscopic resection has gained popularity for selected lesions and can spare some patients the morbidity of facial incisions and even craniotomy while remaining an oncologically sound operation. Neoadjuvant, concurrent, and adjuvant chemotherapy (single agent and combination) has been used in combination with surgery and radiation therapy to exploit ENBs' biologically similarity to other tumours of neural crest cell origin that are also chemosensitive.[115] Complications, short and long term, vary with the therapeutic intervention used and are more likely when extensive local invasion is seen at initial presentation.[115]

Outcomes & prognosis

Based on the Surveillance, Epidemiology, and End Results (SEER) database (which collects cancer incidence and survival data from cancer registries that cover approximately 26% of the US population and) which included a total of 511 esthesioneuroblastoma cases, 5-year overall survival stratified by treatment was estimated. It was 73% for surgery and radiotherapy, 68% for surgery only, 35% for radiotherapy only, and 26% for neither surgery nor radiotherapy.[116] In a retrospective analysis of 50 cases treated by preoperative (photon) radiotherapy and craniofacial resection (Kadish A & B) or preoperative sequential chemotherapy and (photon) radiotherapy followed by a craniofacial resection, 5- and 15-years disease-free survival was 86.5% and 82.6%.[117] In the latter study the recurrence rate was 34%; there was a long interval to relapse (mean: 6 years; longest: 10 years).

Esthesioneuroblastomas require long-term follow-up (>10 years) given the extended time to local and regional recurrence (i.e. up to a decade after definitive treatment).[115]

[s] Not based on a systematic search of the literature.

3.5.2 What is the clinical effectiveness of proton beam therapy in children with esthesioneuroblastoma?

Only two retrospective case series on proton beam therapy in children with Esthesioneuroblastoma were retrieved (Herr et al., 2013[118]; Herr et al., 2014[119]), but as the patients discussed in the former were presumably also included in the latter, only the latter was fully evaluated and will be discussed. Herr et al. included 22 patients (age range: 11-77 y.o.; 10 patients with Kadish[t] stage B and 12 patients with Kadish stage C) who received craniofacial resection followed by proton beam irradiation with or without chemotherapy.[119] Mean follow-up was 6 years (73 months, range: 24-183 months). The median total radiation dose was 66.5 CGE.

For more information on the included study, the reader is referred to the evidence table in the Appendix 2.3.4.

Overall survival

The 5-year overall survival rate was 95.2% (95% CI: 70.7-99.3%).

Disease-free survival

The 5-year disease free survival rate was 86.4% (95% CI: 63.4-95.4%).

Recurrence

At a mean of 73.4 months (range: 13-145 months) after diagnosis 6 of 22 patients (27%) had local and/or regional and/or distant recurrences (1 patient had a regional recurrence, 2 patients had distant recurrences, 2 patients had regional and distant recurrences and 1 patient had local and regional and distant recurrences). The locations of recurrences were: the CNS, the spine, the neck, the parotid gland, the scalp, the vertebrae and the ribs.

Complication rate

Thirteen patients (59%) had several mild to severe complications due to late-radiation toxicity (e.g. 1 patient with blindness in the ipsilateral eye as a result of radiation-induced optic neuritis, 4 patients with persistent sinocutaneous fistulas, 3 patients with infections at the anterior skull base). The authors further state that 13 patients (are these the same patients?) experienced a total of 25 complications from all modalities of therapy. Eight patients had in total 11 ocular complications (e.g. epiphora (i.e. excessive tear production), transient cranial nerve VI palsy, persistent diplopia, blindness in the ipsilateral eye as a result of radiation-induced optic neuritis), 2 had in total 5 CNS complications (e.g. recurrent seizures, postoperative cerebrospinal fluid leak and symptomatic pneumocephalus, asymptomatic postoperative pneumocephalus) and 8 had in total 9 wound healing complications. In addition there were several (no exact number reported) infectious complications. The authors do not report when and how (e.g. at set time points, upon patient's request) the complications were recorded.

Secondary malignancy

There are no data reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life.

Results described above should be interpreted with caution since the study had serious methodological limitations (see evidence table in the Appendix 2.3.4) and patients received a variety of treatment schemes, hence it was impossible to extract what the added value of PBT was. Moreover, it is unclear how many children were included in the study.

Conclusion

- At present there is insufficient scientific evidence to support or to refute the use of PBT in children with esthesioneuroblastoma.

[t] Esthesioneuroblastomas can be classified according to the modified Kadish classification: Kadish A: the tumour is confined to the nasal cavity; Kadish B: the tumour extends to the paranasal sinuses; Kadish C: the tumour extends beyond the nasal cavity and paranasal sinuses and Kadish D: there are regional (lymph node) or distant metastases.[115]

Other considerations

- When conventional photon therapy is offered to children/young adults with esthesioneuroblastoma (or other tumours of the head & neck), this may cause serious malformations (due to growth disturbances) of the face and may have a deleterious effect on the patient's vision.
- At present there is an Italian phase II study ongoing that aims at evaluating a multidisciplinary approach (i.e. chemotherapy, surgery, photon and heavy ion radiotherapy (i.e. carbon ion)) in operable adults with poor prognosis sinonasal tumours (See Appendix 1.3.2). The estimated primary completion date is January 2016; unfortunately it is a single arm study. A second ongoing study will evaluate the same multidisciplinary approach in inoperable adults with poor prognosis sinonasal tumours.

3.6 Ewing sarcoma

3.6.1 Background[u]

3.6.1.1 *Clinical pathology & incidence*

Ewing sarcoma is derived from a primordial bone marrow–derived mesenchymal stem cell. Ewing sarcomas appear to arise mainly in bone and infrequently in soft tissues.[120] While osteosarcomas tend to occur in the metaphyseal areas of long bones of skeletally immature patients, particularly in the knee region, Ewing sarcoma tends to arise in the diaphysis.[121] Primary sites of bone disease include the lower extremity, pelvis, chest wall, upper extremity, spine, hand and foot and the skull.[120]

The annual incidence rate for Ewing sarcoma is 1-3 per million in Europe and in the US. This tumour type is rarer in Asia and Africa.[122] The median age of patients with Ewing sarcoma is 15 years; more than 50% of patients are adolescents. Hence, the incidence in patients aged 10 to 19 years is between 9 and 10 cases per 1 million.[120]

3.6.1.2 *Current treatment regimes*

Current treatment consists of a multimodal approach combining surgery, radiotherapy and chemotherapy.[123, 124] Ewing sarcoma differs from other sarcomas in their greater sensitivity to chemotherapy and radiotherapy.[125] Radiotherapy is used in approximately 60% of Ewing sarcoma patients, e.g. when it occurs in bones not easily resected, in the postoperative setting for patients with close or positive resection margins, sometimes in the setting of a poor or slow clinical response to neoadjuvant chemotherapy and typically radiotherapy is used instead of surgery for children with unresectable tumours or in cases in which surgery would result in too great morbidity.[5] When metastases are diagnosed, stem cell transplant and targeted therapy can be considered.[120]

3.6.1.3 *Outcomes & prognosis*

Dramatic improvements in survival have been achieved for children and adolescents with Ewing sarcoma: between 1975 and 2002, the 5-year overall survival rate has increased from 59% to 76% for children (<15 y.o.) and from 20% to 49% for adolescents (15-19 y.o.).[120] Prognosis is influenced by pretreatment factors (such as tumour site, tumour size, age, gender…) and treatment response but the presence or absence of metastatic disease is the single most powerful predictor of outcome.[120] Metastases at diagnosis are detected in approximately 1 out of 4 patients.[120] While patients with localized disease at primary diagnosis show a long-term event-free survival rate of about 75 %,[124] patients with metastatic disease achieve a 6-year event-free survival of approximately 28% and an overall survival of approximately 30%.[120] The combination of lung and bone/bone marrow metastases presents the worst prognosis (4-years event-free survival of14%).[120] In addition, the prognosis in patients with recurrence is also poor with a 5-year survival after recurrence of approximately 10 to 15%.[120]

[u] Not based on a systematic search of the literature.

3.6.2 What is the clinical effectiveness of proton beam therapy in children with Ewing sarcoma?

Only one retrospective case series on proton beam therapy in children with Ewing sarcoma was retrieved (Rombi et al. 2012[126]). Rombi et al. included 30 children with Ewing sarcoma (median age: 10 y.o., range: 1.8-21 y.o.; tumour localisation: pelvis (n=4), trunk (n=15, among which 14 vertebral body or sacrum), head-and-neck region (n=4), base of skull or cranium (n=7)) who received proton beam irradiation with prior chemotherapy and surgery. Median follow-up was 38.4 months (range: 17.4 months-7.4 years). The median total radiation dose was 54 Gy (range: 45-59.4). For more information on the study, the reader is referred to the evidence table in Appendix 2.3.5.

Overall survival

The 3-year overall survival rate was 89%. During the median follow-up of 38.4 months, 4 patients died: 3 of disease progression and 1 of acute myeloid leukemia.

Disease-specific survival

The 3-year disease-specific survival rate was 68%.

Event-free survival

The 3-year event-free survival rate was 60%.

Disease-free survival

After a median follow-up of 38.4 months, disease free survival rate was 70% (21/30).

Recurrence rate

Local recurrence occurred in 2 patients, distal recurrence in 1 patient and the combination of local and distal recurrence was observed in 2 patients.

Local control rate

The 3-year local control rate was 86%.

Complication rate

All patients suffered from acute skin reactions. Fatigue (21/30) and anorexia (14/30) were the most frequently reported side effects. Nausea and scolioses/kyphoses were both reported in 5 patients. Less frequent acute side effects were hoarseness, swelling and confluent mucositis at radiation portal and grade 2 kerato-conjunctivitis. The following late side effects were reported: skin changes (mild hyperpigmentation or teleangiectasia), occasional mild nosebleeds, permanent alopecia, late effects on eyes, endocrine deficiencies, and unilateral high frequency hearing loss.

Secondary malignancy

No solid secondary tumours were observed. However, acute myeloid leukaemia was observed in 3 patients and myelodysplastic syndrome in 1 patient. This resulted in a 2-year and 3-year cumulative incidence of 7% (95%CI, 1-19%) and 15% (95%CI, 5-32%), respectively.

Quality of life

There are no data reported with regard to quality of life issues after PBT in children with Ewing sarcoma.

The above results should be interpreted with caution since only one study was retrieved. Moreover, this study suffered from serious methodological flaws (see evidence table in Appendix 2.3.5).

Conclusions

- At present there is insufficient scientific evidence to support or to refute the use of PBT in children with Ewing sarcoma.

Other considerations

- The authors suggest that further research is indicated to fully explore the reason for the relatively high (i.e. 15% after 3 years) rate of secondary leukaemia (acute myeloid leukemia (AML)/ myelodysplasia (MDS)) in this cohort of children with Ewing sarcoma.
- One study on PBT in children and young adults with Ewing sarcoma is in progress. Results are expected by January 2019 (see Appendix 1.3.2).

3.7 CNS germinoma

3.7.1 Background[v]

3.7.1.1 Clinical pathology & incidence

Central nervous system (CNS) germ cell tumours (GCTs) generally affect adolescents and account for 3-5% of childhood brain tumours.[127] Germ cell tumours are divided into 2 main histologic subgroups: (1) germinomas, which are the most common and carry the most favourable prognosis, and (2) mixed malignant germ cell tumours (MMGCT, sometimes termed non-germinomatous germ cell tumours (NGGCT)), which are relatively resistant to therapy.[128]

CNS germ cell tumours may arise as solitary or multiple lesions in the pineal and/or suprasellar regions. Pineal region tumours are twice as frequent as suprasellar tumours, but approximately 5% to 10% of patients have both suprasellar and pineal gland involvement at the time of diagnosis. Males have a higher incidence of germ cell tumours than females, with males having a preponderance of pineal region primaries. Other areas that may be involved, though rare, include the basal ganglia, ventricles, thalamus, cerebral hemispheres, and the medulla.[129]

3.7.1.2 *Current treatment regimes & outcomes*

Germinomas are highly radiosensitive and have been traditionally treated with radiation therapy alone; historically, craniospinal irradiation with a boost to the region of the primary tumour has been utilized. This has resulted in 5-year overall survival rates greater than 90%.[129] In order to decrease late effects, the treatment for patients with localized germinomas has been modified to cover the whole ventricular system followed by a boost to the primary site, rather than to deliver radiation therapy to the entire craniospinal axis or even to the whole brain. This change has not resulted in worse outcomes and is expected to minimize the acute and long-term toxicity of radiation therapy. Chemotherapy has been explored in an effort to reduce radiation therapy doses and associated neurodevelopmental morbidity, but the number of treated patients is still small.[129] Chemotherapy alone cannot replace radiotherapy as sole treatment.[130] Several studies have supported the need for irradiation following chemotherapy and the likely requirement for whole-ventricular irradiation when chemoradiotherapy is used in order to avoid ventricular recurrence.[129]

The optimal treatment regimen for mixed malignant germ cell tumours remains unclear. The addition of chemotherapy to radiation therapy has increased survival, but the specific chemotherapy regimen and length of therapy and the optimal radiation field, timing, and dose remain under investigation. Some investigators have proposed radiation therapy fields that are smaller than craniospinal irradiation (e.g., focal or focal whole ventricular) for nondisseminated NGGCT patients. Results of these trials appear promising, although controversy exists over the pattern of relapse for patients treated with chemotherapy and focal radiation.[129] In a phase II study that included 22 children and young adults, multimodality therapy for CNS mixed malignant germ cell tumours resulted in a 6-year relapse-free survival of 63 (+/-10)% and an overall survival of 68 (+/- 9)%. Of 16 M0 patients who received only whole ventricular radiation therapy, four relapsed in the spine, outside the radiation field.[128]

3.7.2 *What is the clinical effectiveness of proton beam therapy in children with CNS germinoma?*

Only one retrospective case series on proton beam therapy in children with germinoma was retrieved (MacDonald, 2011).[127] The records of all 22 children with CNS germ cell tumours (median age: 11 y.o. (range: 6-20 y.o.); primary lesions: pineal gland (n=4), suprasellar region (n=10), multiple midline lesions (n=6), multiple sites of brain involvement (n=2); germinoma (n=13) and nongerminomatous germ cell tumour (NGGCT, n=9)) treated with proton beam therapy at the Massachusetts General Hospital (Boston, US) were reviewed. Median follow-up was 28 months (range: 13-97 months). Total proton beam dose (delivered as three-dimensional conformal proton therapy (3D-CPT)) ranged for germinoma between 30.6-57.6 Gy (RBE) and for NGGCT between 18.6-50.4 Gy (RBE). All patients with NGGCT and the majority (11/13) of patients with germinoma also received pre-radiation chemotherapy; only 1 patient with NGGCT also had surgery.

[v] Not based on a systematic search of the literature.

For more information on the included study, the reader is referred to the evidence tables in Appendix 2.3.6.

Overall survival

The overall survival rate in all 22 children was 100%.

Progression-free survival

The progression-free survival rate in all 22 children was 95%; no separate data for children affected by germinoma were provided.

Local recurrence rate

The local recurrence rate was 0% in children affected by germinoma as well as in children affected by NGGCT.

Distal recurrence rate

The distal recurrence rate was 0% in children affected by germinoma and 11% (1/9) in children affected by NGGCT.

Complication rate

There are no data reported with regard to complications.

Secondary malignancy

There are no data reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life.

Results described above should be interpreted with caution since the study had serious methodological limitations (see evidence table in Appendix 2.3.6), was based on a small sample and patients received a variety of treatment schemes, hence it was impossible to extract what the added value of PBT was.

Conclusion

- At present there is insufficient scientific evidence to support or to refute the use of PBT in children with germinoma.

Other considerations

- At present there is 1 study ongoing that evaluates proton beam therapy in children with CNS germ cell tumours (Phase II Study of Proton Radiation Therapy for CNS Germ Cell Tumors: Evaluation of Acute and Late Side Effects – See Appendix 1.3.2). Unfortunately it is a single arm study.
- In addition, there are some (non-proton beam therapy) prospective trials (e.g. SIOP CNS GCT II - http://clinicaltrials.gov/show/NCT01424839; COG-ACNS1123 - http://www.cancer.gov/clinicaltrials/search/view?cdrid=734032&version=HealthProfessional) ongoing which aim at improving the therapeutic ratio between high cure rates and a low risk for long-term side effects, in particular neurocognitive function and quality of survival.[130]

3.8 Low-grade glioma (incl. optic pathway glioma)

3.8.1 Background[w]

3.8.1.1 Clinical pathology & incidence

Glioma is a generic term that refers to any tumour that arises from glial cells (i.e. non-neuronal cells that maintain homeostasis, form myelin, and provide support and protection for neurons in the brain and peripheral nervous system). These tumours of the supportive tissue of the brain can occur in the midbrain, pons or medulla (brain stem glioma) or in the optic nerve (optic nerve glioma). Three types of normal glial cells can produce tumours: astrocytes (astrocytoma, overall incidence in Europe 4.8 per 100 000[131]), ependymal cells (ependymoma, overall incidence in the US 0.26 per 100 000[110]) and oligodendrocytes (oligodendroglioma, overall incidence in Europe 0.4 per 100 000[131]). Sometimes, gliomas contain more than one cell type, usually a mixture of astrocytes and oligodendrocytes (mixed glioma also called oligoastrocytoma).[106, 132] Between 2004 and 2008, glial tumours

[w] Not based on a systematic search

constituted in the US the most common histology in the 0–14-year and 15–19-year age groups (56 and 45%, respectively) within the overall paediatric tumours.[133]

There are low-grade astrocytomas and high-grade astrocytomas. Low-grade astrocytomas are usually localized and grow slowly whereas high-grade astrocytomas grow at a rapid pace and require a different course of treatment. Most astrocytoma tumours in children are low grade; in adults, the majority are high grade.[4] Low-grade gliomas are the most common paediatric brain tumour, representing over 30 % of all childhood primary brain tumours while high-grade gliomas comprise 8-12 %.[134] The various grades of astrocytoma are: Pilocytic Astrocytoma (Grade I, also called Juvenile Pilocytic Astrocytoma, most commonly seen in children; they account for 64% of paediatric astrocytomas and 17 % of all primary paediatric brain tumours,[135] Diffuse (Infiltrating) Astrocytoma (also called Low-Grade or Astrocytoma Grade II), Anaplastic Astrocytoma (Grade III tumour; these rare tumours require more aggressive treatment than benign pilocytic astrocytoma), Astrocytoma Grade IV (also called Glioblastoma, previously named Glioblastoma Multiforme or GBM) and Subependymal Giant Cell Astrocytoma (ventricular tumours associated with tuberculous sclerosis).

Oligodendrogliomas can be low-grade (grade II) or high-grade (grade III, or anaplastic). Only 6% of these tumours are found in infants and children. Most oligodendrogliomas occur in adults (ages 50-60 y.o.), and are found in men more often than women.[4] The subtype ependymoma is discussed in the dedicated chapter (see 3.4).

3.8.1.2 *Current treatment regimes*

In general, low-grade gliomas are frequently amenable to surgical resection.[99] However, deep seated tumours in the region of the hypothalamus, optic chiasm and brainstem as well as more peripheral tumours in areas of critical function are generally not removed surgically because of the high risk of morbidity. These tumours can respond to chemotherapy which is often the first line of treatment for children under 7-10 years of age and is often effective in delaying the need for radiotherapy. Radiation therapy is used when tumours progress after chemotherapy or in older children.[99]

Treatment options for astrocytoma depend on the type, size, and location of the tumour, if and how far it has spread, previous treatment received, and the patient's overall health.[4] For instance, Pilocytic Astrocytomas are often removed by surgery alone. In adults and older children, radiation may follow surgery if the tumour cannot be completely removed. Or, the patient may be watched carefully for signs that the tumour has returned.

For oligodendroglioma, standard treatment is surgical removal of as much of the tumour tissue as possible if the tumour is accessible.[4] Biopsy is typically performed on tumours that are not accessible to confirm the diagnosis and determine the grade of tumour. Recurrent low-grade oligodendrogliomas can be treated with surgery, radiation therapy (if not given initially), and chemotherapy.[4]

3.8.1.3 *Outcomes & prognosis*

Prognosis depends on the histology/ grading of the tumours (e.g. the median survival for children with diffuse intrinsic pontine glioma is less than 1 year whereas focal pilocytic astrocytomas have a markedly improved prognosis, with a 5-year overall survival exceeding 90%), the location and the age at diagnosis (prognosis is better for children younger than 3 years).[3,133] Children with neurofibromatosis type 1 (NF1) are at an increased risk of developing a brain stem glioma. Children with NF1 and brain stem gliomas may have a better prognosis than other patients who have intrinsic lesions.[3]

3.8.2 *What is the clinical effectiveness of proton beam therapy in children with low-grade glioma?*

The effectiveness of proton beam therapy in children with glioma was studied in 2 trials (Bian et al. 2013, Greenberger et al. 2014).[135, 136]

Greenberger et al reviewed 32 paediatric patients with low-grade glioma of the brain (n=29) or spinal cord (n=3) (median age: 11.0 y.o. (range: 2.7-21.5 y.o); male: 17/32; histology: pilocytic astrocytoma WHO grade I (n=19), WHO grade II (n=6), low grade without other specification (n=2), no pathology (n=5)). Patients were treated with PBT or with PTB in combination with photons between 1995 and 2007 in Harvard Cyclotron and Massachusetts General Hospital in Boston (US). The median dose was 52.2 Gy (RBE) (range: 48.6-54 Gy (RBE)). In addition to RT, patients received surgery (resection (n=21), biopsy only (n=6), none (5/32), shunts (n=6) and/or chemotherapy (n=16). Last, it should be noted that patients treated

before 2002 received 20% of the treatment with 3-D conformal photons because the cyclotron was closed 1 day per week.

Bian et al. described 6 cases of children with disseminated pilocytic astrocytoma (median age: 7 y.o (range: 2-15 y.o), male: 5/6) treated with PBT (initial radiation dose range: 30.6-48.6 Gy (RBE) and the total boost dose range: 43.2-54 Gy (RBE)) in the Anderson Cancer Centre in Houston (US). All patients received surgery prior to PBT (subtotal resection (n=5), gross total resection (n=1). In addition, two patients received chemotherapy before PBT. Median follow-up was 24 months (range: 5-95 months).

For more information on the included studies, the reader is referred to the evidence tables in Appendix 2.3.7.

Overall survival

In the Greenberger et al. study, which included 32 children with low-grade glioma, the 8-year overall survival was 100%.
At a median follow-up of 24 months (range: 5-95 months), Bian et al., who included 6 patients with disseminated pilocytic astrocytomas, observed an overall survival of 83.3%. .

Progression-free survival

In Greenberger et al., the 6-year and 8-year progression-free survival rates were 89.7% and 82.8%, respectively.

Response rate

Bian et al. reported stable disease in 5 patients out of 6 and progressive disease after PBT and resection in one patient.

Recurrence rate

There are no date reported with regard to recurrence rate.

Complication rate

In none of the included studies, a complication rate is reported. However, Greenberger et al. assessed neurocognitive outcomes in a subset of patients who exclusively received proton therapy. Between baseline and follow-up there were no significant declines in Full-Scale Intelligence Quotient (mean change: -0.7 (SD: 9.2), n=11, p=0.80), in Verbal Comprehensive Index (mean change: -0.5 (SD: 11.7), n=12, p=0.88) and in Perceptual Reasoning Index (mean change: -0.17 (SD: 9.8), n=12, p=0.95). Subgroup analysis indicated some significant decline in neurocognitive outcomes for young children (<7 y.o.) and those with significant dose to the left temporal lobe/hippocampus. In addition, deterioration of visual acuity was observed in 3 out of 18 patients and vasculopathy in 2 patients. It is important to mention that all complications were assessed in (variable) subsets of the original sample.

Secondary malignancy

There are no date reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life issues.

The above results should be interpreted with caution since both studies suffered from very serious methodological flaws (see evidence tables in Appendix 2.3.7), were based on a small sample size, patients received a variety of treatment schemes, PBT was delivered alone or in combination with photon RT and patients were not compared to control groups, hence it was impossible to extract the added value of PBT.

Conclusions

- At present there is insufficient scientific evidence to support or to refute PBT in children with low-grade glioma.

Other considerations

- In clinical practice, only low-grade optic pathway gliomas are treated with PBT. According to experts of the field, low-grade glioma is an example of an indication where there is at present no doubt that PBT is the preferred radiotherapy option due to the location of this non-infiltrative tumour and the need to spare critical parts of the brain.
- One phase II study on PBT for low grade and favourable Grade 3 gliomas is at present recruiting (at Massachusetts General Hospital, see Appendix 1.3.2).

3.9 Medulloblastoma & other primitive neuroectodermal tumours (PNET)

3.9.1 Background[x]

3.9.1.1 Clinical pathology & incidence

Embryonal tumours are a collection of biologically heterogeneous lesions that share the tendency to disseminate throughout the nervous system via cerebrospinal fluid pathways.[137] The WHO categorizes them as follows: (1) Medulloblastoma, (2) other CNS primitive neuroectodermal tumours (supratentorial PNET, ependymoblastoma, medulloepithelioma) and (3) atypical teratoid/rhabdoid tumour (ATRT).[97] Embryonal tumours comprise 20% to 25% of primary CNS tumours arising in children. They occur throughout the paediatric age spectrum, but tend to cluster early in life.[137] This chapter focuses on medulloblastoma and other PNET.

Medulloblastomas arise infratentorially in the cerebellum or fourth ventricle;[138] it is unusual for medulloblastomas to spread outside the brain and spinal cord.[139] Five different histologic variants are classified by the WHO[97, 139-141]: classic medulloblastoma, desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma and large cell medulloblastoma. The two main variants are classic medulloblastoma (80%) and desmoplastic/nodular medulloblastoma (15%).[138] The WHO classification does not influence the treatment plan but allows to stratify patients into low-risk (or standard-risk) and high-risk groups. Desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity are considered as low-risk while large cell medulloblastomas and anaplastic medulloblastomas as high-risk.[140, 141] Medulloblastomas are rapid growing tumours[139] and are classified as WHO grade IV lesions.[138] They are further characterized by a relatively high rate of spinal metastases (by leptomeningeal spreading at the time of diagnosis.[22]

Eighteen to thirty percent of all paediatric brain tumours are medulloblastomas.[139, 141-143] More than 70% of all paediatric medulloblastomas are diagnosed in children under 10 years old; they are rarely observed in children under 1 year old.[139] A slight male preponderance is observed.[138, 140, 143] In the UK, the incidence rate is 4.5 cases per million child years.[138]

CNS primitive neuroectodermal tumours (PNETs) are a heterogeneous group of other embryonal tumours that occur predominantly in children and adolescents and show aggressive clinical behaviour. They can be further subdivided in CNS neuroblastoma, CNS ganglio-neuroblastoma, medulloepithelioma and ependymoblastoma.[97] PNETs occur primarily in the cerebrum; they are highly malignant, and tend to spread throughout the central nervous system. These tumours often contain areas of dead tumour cells (necrosis) and cysts. Fluid surrounding the tumour is not uncommon.[139] PNETs account for only 1 to 2.5 % of all childhood tumours. The mean age of onset is around 3 years of age.[144]

3.9.1.2 Current treatment regimes

Surgical resection is the mainstay of therapy for all PNET, including medulloblastoma. The primary goal is gross total resection (GTR). Medulloblastomas/PNETs are also radiosensitive tumours and adjuvant therapy with radiation has been the standard of care in children older than 3 years. Due to the high metastatic tendency within the central nervous system, all patients receive a “prophylactic” radiation therapy on the whole CNS (for elimination of invisible micrometastases). A higher dose of craniospinal irradiation is needed for patients with a clearly involved CSF. The local radiotherapy as well as the craniospinal radiotherapy may lead to substantial long-term side effects such as hearing loss, cognitive decline, endocrine abnormalities, cerebrovascular complications, as well as secondary tumours (vascular, benign or malign). A range of different chemotherapeutic agents has been used and is now standard of care in the management of children with medulloblastoma in all risk groups.[144] The third standard component of the treatment of medulloblastoma/PNET which further increases the cure rate is chemotherapy.

[x] Not based on a systematic search

3.9.1.3 Outcome & prognosis

The five-year overall survival for children with standard risk **medulloblastoma** is 75 – 85%.[22] In the subset of children with medulloblastoma diagnosed when they are younger than 5 y.o., long-term disease control is in general far worse (e.g. ranging from 14% to 55% depending on tumour histology),[145] although others reported five-year progression-free and overall survival rates of 85±8% and 95±5%, respectively, in children younger than 3 y.o. with desmoplastic medulloblastoma.[146] Paediatric PNETs carry an even more dismal prognosis: the 5-year overall survival ranges between 30 and 40%.[145]

3.9.2 What is the clinical effectiveness of proton beam therapy in children with medulloblastoma and PNET?

Two retrospective case series were retrieved: one on proton beam therapy in children with medulloblastoma and PNET (Jimenez 2013[145]) and one on proton beam therapy in children with medulloblastoma (Sethi 2013[147]). In addition, one prospective case series on ototoxicity of proton beam therapy in children with medulloblastoma was also retrieved (Moeller 2011[148]).

Sethi et al. (2014) reported on 109 paediatric patients with medulloblastoma (median age at diagnosis: 7.4 y.o. (range: 2.2 – 22.7 y.o.); histology: classic (n=81), anaplastic (n=17), desmoplastic (n=10), anaplastic + desmoplastic (n=1; metastatic disease at diagnosis: n=20; high-risk: n=35)) treated with proton beam therapy at the Massachusetts General Hospital (Boston, US).[147] The median follow-up was 38.8 months (range: 1.4-119.2 months). All patients received craniospinal irradiation (range: 18 to 36 Gy [RBE]) and either an involved field boost (n=70) or a whole posterior fossa boost (n=39); sites of metastatic disease were also boosted. All patients had surgery (gross total resection (n=80), subtotal resection (n=27) and biopsy (n=2)) and chemotherapy according to various protocols.

The records of 12 cases of medulloblastoma and 3 cases of supratentorial primitive neuroectodermal tumours treated with proton beam therapy at the Massachusetts General Hospital (Boston, US) were reviewed by Jimenez et al. (2013).[145] Patients' median age at diagnosis was 35 months (range: 23 - 55 months). They were followed during a median period of 39 months (range: 3 – 102 months). All patients underwent maximal surgical resection (gross total resection (n=11), subtotal resection (n=3), partial resection (n=1)), chemotherapy according to various protocols and either craniospinal irradiation followed by involved-field radiation therapy (n=11) or involved-field radiation therapy alone (n=4). Median craniospinal irradiation dose was 21.6 Gy (RBE); median boost dose was 54.0 Gy (RBE).

It should be noted that both studies were performed in Massachusetts General Hospital and had approximately the same enrolment period. Eleven children described in the Jimenez et al. study also received craniospinal irradiation (CSI); it is not clear whether all or some of them were also adopted in the Sethi et al. study. Personal communication with the corresponding author did not resolve this concern.

The third study (Moeller et al., 2011[148]) measured prospectively the ototoxicity in 19 children with medulloblastoma treated with proton beam therapy at Anderson Cancer Center (Houston, US). Patients' median age was 6 y.o. (range: 3 - 16 y.o.); ototoxicity was assessed at baseline and after a mean period of 11 months (range: 8-16 months). All patients received surgery (no details reported on the extent of the surgery) and platinum-based chemotherapy (n=19). High-risk patients received craniospinal irradiation to a dose of 36 CGE whereas standard-risk patients received CSI to a dose of 23.4 CGE. The tumour bed plus a CTV expansion was boosted to a total dose of between 54 and 55.8 CGE. The cochlear dose ranged between 19 and 43 CGE.

For more information on the included studies, the reader is referred to the evidence tables in Appendix 2.3.8.

Overall survival

Sethi et al. noted an overall survival rate of 89% at a median follow-up of 38.8 months (range: 1.4-119.2 months) in 109 children with medulloblastoma. Jimenez et al reported a 3-year overall survival of 85.6% (no reliable 95% CI reported) in 15 children with medullablostoma or supratentorial PNET.

Progression-free survival

There are no date reported with regard to progression-free survival.

Recurrence rate

Among the 109 cases reported by Sethi et al., 16 patients (14.7%) experienced a treatment failure after a median follow-up of 38.8 months (range: 1.4-119.2 months). These patients were mostly males (n=14) and had a diagnosis of classic medulloblastoma in 11 out of 16 cases. The other cases were anaplastic medulloblastoma (n=4) and desmoplastic medulloblastoma (n=1). The localisations of failure were the following: spine (n=6), supratentorial (n=4), supratentorial + spine (n=1), diffuse (n=3), tumour bed (n=1), tumour bed + spine (n=1). At the latest disease status, 12 patients were dead of disease, 2 patients showed no evidence of disease and 2 other patients were alive with disease.

In a smaller group of patients with medulloblastoma (n=12) or PNET (n=3), Jimenez et al. reported a 3-year local failure rate of 7.7% (95% CI: 0.4 – 30.6%).

Complication rate

After a median follow-up of 38 months (range: 12 – 81 months), high-frequency hearing loss was observed in 9 out of 13 patients among whom 3 required hearing aids and 3 FM amplifier (Jimenez et al.). Ototoxicity Grade 3 was observed in 2 patients. It should be noted however that 6 patients had hearing evaluations after chemotherapy (i.e. before radiation therapy). Of these 6 patients, 5 exhibited bilateral sensorineural hearing loss before the initiation of radiation therapy. In the same study, 3 patients developed grade 2 endocrinopathies requiring hormone replacement, including 1 patient with clinical growth hormone deficiency, 1 patient with growth hormone and thyroid-stimulating hormone deficiency and 1 patient with growth hormone and adrenocorticotropic hormone deficiency and premature puberty. It should be noted however that endocrinopathies were evaluated in 12 of 13 non-deceased patients. When all 3 patients with documented GH deficiency were excluded from the analysis, there was no significant difference in age-adjusted height compared with baseline. Neuropsychological function was only assessed in 8 patients. At a median follow-up of 26 months from completion of treatment (range: 15-38 months), there were no significant differences between baseline and follow-up in mean IQ scores (n=5) or baseline and follow-up SIB-R (functional independence) scores (n=8). Moeller et al. reported a clinically and statistically significant worsening of hearing threshold across all frequencies tested ($p<0.05$) and a modest threshold change in the audible speech range (0.5-6 kHz) after therapy. Following PBT the incidence of high-grade (grade 3-4) ototoxicity was 5%.

Secondary malignancy

There are no date reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life issues after PBT in children with medulloblastoma.

The above results should be interpreted with caution since the included studies all had serious methodological flaws (see evidence tables in Appendix 2.3.8) and the included patients received a variety of treatment schemes, hence it was impossible to unravel the added value of PBT.

Conclusions

- At present there is insufficient scientific evidence to support or to refute PBT in children with medulloblastoma.
- At present there is no scientific evidence to support or to refute PBT in children with PNET.

Other considerations

- Sethi et al. (2014) commented that the pattern of failures in medulloblastoma patients treated with proton radiation is generally similar to the pattern of failure in medulloblastoma patients treated with photon radiation.
- Two studies on the impact of PBT in children and young adults with medulloblastoma and pineoblastoma are in progress. Results are expected in December 2014 and April 2018. Results of a third study including children and young adults with medulloblastoma are expected in June 2023 (see Appendix 1.3.2).

- Children affected by atypical teratoid/rhabdoid tumour (ATRT) may also be eligible for PBT. ATRT is a rare CNS tumour and commonly affect infants and small children under the age of three years. The exact incidence of AT/RT is not known, however based on institutional reviews and data of institutional cancer registries it is suggested that in children younger than one year AT/RT constitutes 50% of all malignant brain tumours.[149] Macroscopically, AT/RT resembles PNET/medulloblastoma. A multimodality treatment is essential: like in PNET surgical resection is the mainstay and radiotherapy and chemotherapy are also important components in the therapy. A new multinational registry for these rare rhabdoid tumours of any anatomical site (European Rhabdoid Registry or EU-RHAB) is in construction. EU-RHAB will also try to bring an optimization of the management of affected patients by obtaining epidemiologic and molecular biology data in a cohort of patients that have been treated on a standard therapeutic schedule.
- Thanks to genome sequencing there have been 4 different molecularly defined types of medulloblastoma identified; this may be helpful in the future to specify treatment pathways and e.g. eligibility for PBT.

3.10 Non-resectable osteosarcoma

3.10.1 Background[y]

3.10.1.1 Clinical pathology & incidence

Conventional osteosarcoma is the most common non-haematopoietic primary malignant tumour of the bone. It is an aggressive, malignant bone-forming mesenchymal tumour, predominantly affecting the long bones (particularly distal femur, proximal tibia, and proximal humerus) of adolescents and young adults. Aggressive local growth and rapid haematogenous systemic dissemination are typical features. It may metastasize to other anatomic sites, particularly the lungs.[150] Depending on the type of matrix produced, three major subtypes have been defined: osteoblastic osteosarcoma, chondroblastic osteosarcoma and fibroblastic osteosarcoma.[150]

Osteosarcoma has an incidence rate of 4-5 cases/million population/year.[150] It occurs most frequently in adolescents – it accounts for approximately 5% of childhood tumours,[151] but there is a second incidence peak among individuals aged >60 years.[152] At all ages, males are affected more frequently than females.[152]

3.10.1.2 Current treatment regimes

Successful treatment generally requires the combination of effective systemic chemotherapy and complete resection of all clinically detectable disease. Protective weight bearing is recommended for patients with tumours of weight-bearing bones to prevent pathological fractures that could preclude limb-preserving surgery.[151] Osteosarcoma is generally considered to be a relatively radioresistant tumour entity, but it has been suggested that radiotherapy may be effective, if a sufficient dose in a large fraction is given to an adequate volume.[153] The ESMO guideline states: "In general, there is no indication for radiation therapy, but there are anatomical locations in which the possibility of complete surgical resection is limited. In these cases, radiation therapy may be an option to try to extend the progression-free interval. New radiation techniques may extend the indications for this.[154]"

3.10.1.3 Outcomes & prognosis

Randomized clinical trials have established that both neoadjuvant and adjuvant chemotherapy are effective in preventing relapse in patients with clinically nonmetastatic tumours.[151] In one of these trials where patients were randomized to receive either adjuvant chemotherapy or observation after surgical resection, the 25-year disease-free survival rate was 28% for patients who received adjuvant chemotherapy compared with 15% for the untreated patients (p=0.02). The overall survival rate at 25 years was also significantly higher for treated patients versus untreated patients (38% vs 15%; p=0.02).[155]

Local control of the tumour is absolutely critical, because the chances of long term survival are <10% if a complete surgical resection of the tumour is not possible.[156] In a minority of patients, the tumour cannot be completely resected without unacceptable mutilation. In such patients local

[y] Not based on a systematic search of the literature.

radiotherapy has been used. Published small series of such patients have documented that radiotherapy can achieve local control,[153] although the success rate of this strategy has not been analysed in systematic trials.[156] Oya et al. reported on 39 patients with osteosarcoma who received very high-dose definitive intraoperative radiotherapy (IORT), with the intention of saving the affected limb. The cause-specific and relapse-free 5-year survival rate was 50% and 43%, respectively; distant metastasis developed in 23 patients.[153]

3.10.2 What is the clinical effectiveness of proton beam therapy in children with non-resectable osteosarcoma?

Only 1 retrospective case series on proton beam therapy in patients (children and adults) with non-resectable osteosarcoma was retrieved (Ciernik et al. 2011[157]). Ciernik et al. reviewed the charts of 55 patients treated with proton beams between 1983 and 2009 (age range: 2-76; male: female: 5/6). The osteosarcomas were located in the head/cranium (n=22), spine (n=17), pelvis or sacrum (n=13), femur (n=1), hip (n=1), rib/chest wall (n=1); according to the TNM staging, they could be classified as stage I (n=12), stage II (n=38), stage IV (n=5); according to histology, they could be classified as osteoblastic (n=29), chondroblastic (n=21), osteosarcoma with giant cells (n=2), fibroblastic (n=2) and myxoid (n=1). The total radiation dose was variable (50.4-59.4Gy (n=5), 60-70Gy (n=22), ≥70Gy (n=28)) and a variable proportion of the total dose was delivered with proton beams (100% (n=11), 50-99% (n=17), <30% (n=9), no information for 18 patients). In addition, some patients had surgical resection (partial resection/debulking (n=19), gross resection with positive margins (n=24), no surgery (n=12)) and some patients had chemotherapy (some chemotherapy (n=31), intensive chemotherapy (n=19), no systemic treatment (n=5)). Median follow-up was 27 months (range: 0-196 months).

For more information on the included study, the reader is referred to the evidence tables in Appendix 2.3.9.

Overall survival

The 2-year and 5-year overall survival were 84% (95% CI: 69-92%) and 67% (95% CI: 47-80%), respectively. The authors further reported that 2 patients died because of therapy related causes (acute lymphatic leukaemia and squamous cell carcinoma of the maxilla) and 2 patients died of non-cancer related disease.

Disease-free survival

The 2-year and 5-year disease free survival were 68% (95% CI: 53-80%) and 65% (95% CI: 49-77%), respectively.

Local & distal control rate

The 3-year and 5-year local control rate were 82% (95% CI: 68-90%) and 72% (95% CI: 52-84%), respectively. In addition, 11 patients had distant failure. It should be noted that 4/12 patients with local failure also had distant failure.

Complication rate

The majority of patients (46/55 or 84%) patients had a significant late treatment associated toxicity. They were classified as Grade 1 toxicity (n=12), Grade 2 toxicity (n=12; pain, paraesthesia, atrophy, ineffective gait and foot drop, radiation myelopathy, and distal neuropathy) and Grade 3 and 4 toxicity (n=17; grade 3: severe pain requiring morphine-based medication, cranial nerve damage with diplopia, immobility of limb, severe bowel dysfunction with distal functional obstruction because of denervation and severe headaches; grade 4: loss of organ or complete loss of organ function). The authors suggest that the complaints were possibly caused by radiation alone in some patients, whereas most cases of neuronal dysfunction were either pre-existing or possibly related to surgery.

Risk of secondary malignancies

There are no data reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life.

The results should be interpreted with caution since the study had serious methodological flaws (see evidence table in Appendix 2.3.9) and the included patients received a variety of treatment schemes, hence it was impossible to unravel the added value of PBT. Moreover, it is unclear how many children were included in the study.

Conclusion

- At present there is insufficient scientific evidence to support or to refute PBT in children with non-resectable osteosarcoma.

Other considerations

- According to experts of the field, skull base osteosarcoma is an example of an indication where there is at present no doubt that PBT is the preferred radiotherapy option due to the high dose of radiotherapy needed at a location of the tumour close to critical parts of the brain.
- At present there is a phase 2 study recruiting patients (up to 30 y.o.) in Massachusetts General Hospital, Boston, US. The main purpose of this study is to assess the short term and the long term side effects of proton beam radiation for paediatric bone and non-rhabdomyosarcoma soft tissue sarcomas. The estimated primary completion date is June 2015.

3.10.3 What is the clinical effectiveness of carbon ion radiotherapy (CIRT) in children with non-resectable or incompletely resected high-grade osteosarcoma?

Only 1 retrospective case series on carbon ion therapy in patients (children and adults) with non-resectable osteosarcoma was retrieved (Matsunobu et al. 2012[48]). Matsunobu et al. reviewed the charts of 78 patients treated with carbon ion therapy between 1996 and 2009 (age range: 11-83; female: 37%). The osteosarcomas were located in the pelvis (n=61), spine or paraspinal region (n=15), mediastinum and chest wall (n=2); according to histology, they could be classified as osteoblastic (n=36), chondroblastic (n=16), fibroblastic (n=14), other or unclassified (n=12). The total radiation dose was variable (52.8 GyE (n=3), 57.6 GyE (n=3), 64.0 GyE (n=8), 70.4 GyE (n=57), 73.6 GyE (n=7)); all patients could complete the planned CIRT without interruption. In addition, some patients had surgical resection (n=11) and some patients had chemotherapy (n=61). Median follow-up was 24 months (range: 2-166 months).
For more information on this study, the reader is referred to the evidence tables in the Appendix 2.3.9.

Overall survival

The 2-year and 5-year overall survival rate was 58% (95% CI: not reported) and 33% (95% CI: not reported), respectively. The median survival was 28 months (range: 2-166 months). After a median follow-up of 24 months, 48 patients had died; 45 patients died of their disease and 3 patients died of other causes. In total, 12 patients survived more than 5 years; 9 patients remained continuously disease free, 3 patients died after 5 years.

Disease-specific survival

The 2-year and 5-year disease-specific survival rate was 60% (95% CI: not reported) and 34% (95% CI: not reported), respectively.

Progression-free survival

The 2-year and 5-year progression-free survival rate was 34% (95% CI: not reported) and 23% (95% CI: not reported), respectively.

Local & distal control rate

The 2-year and 5-year local control rate was 73% (95% CI: not reported) and 62% (95% CI: not reported), respectively. Local recurrences were observed in 21 (27%) patients. The median time to diagnosis of a local recurrence was 15 months (range: 4-96 months). In addition, 41 (53%) patients had a distant metastasis; the most frequent site was the lung (n=28).

Complication rate

The authors noted that no fatal toxicities were observed during follow-up after CIRT, but the number of patients with acute or late side effects was not reported. The reported side effects were skin and soft tissue reactions (Grade 3 acute skin reactions: n=3, Grade 3 late skin/soft tissue reactions: n=4 and Grade 4 late skin/soft tissue reactions requiring skin grafts: n=3) and functional deficits of various degrees, depending on the location and extent of the tumour before CIRT (i.e. permanent neurologic complications (for which radiotherapy was believed to be the sole cause): n=4 and bone fractures (requiring surgery): n=2).

Risk of secondary malignancies

There are no data reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life.
The results described above should be interpreted with caution since the study had serious methodological flaws (see evidence table in Appendix 2.3.9) and the included patients received a variety of treatment schemes, hence it was impossible to unravel the added value of PBT. Moreover, it is unclear how many children were included in the study.

Conclusions

- At present there is insufficient scientific evidence to support or to refute carbon ion therapy in children with non-resectable osteosarcoma.

Other considerations

- At present, there is a phase I/II therapy trial ongoing in Heidelberg (Germany) to determine the safety and efficacy of heavy ion radiotherapy (C12) in patients (older than 6 years) with non-resectable osteosarcoma. The estimated primary completion date is January 2015.

[z] Not based on a systematic search of the literature.

3.11 Pelvic sarcomas

3.11.1 Background[z]

3.11.1.1 Clinical pathology & incidence

Based on the data collected in the SEER[aa] database (n=1185 pelvic sarcoma cases from 1987 to 2006, age range: 0 - >60 y.o.) the incidence of pelvic sarcoma in 2006 was 89 per 100 000 persons; it has significantly increased in the US since 1973 (P < .05).[158]

3.11.1.2 Current treatment regimes

Treatment of malignant sarcomas of the pelvis poses a challenge for local disease control and oncologic outcome.[158] Surgical resection is difficult because of the anatomic proximity of the pelvis to many neurovascular structures and the urinary and intestinal tracts. In addition, extensive resection of pelvic sarcomas often necessitates reconstruction to avoid severe functional disabilities from the impairment of the load-bearing axis.[159] At present, there is no consensus yet whether a uniform treatment strategy should be applied to all patients regardless of the histopathology, as previously suggested, or each disease should be treated as a separate entity.[158] For instance, for pelvic Ewing sarcoma some authors have suggested considering radiotherapy as an alternative to surgery[160] whereas others have stressed the importance of wide excision of the primary disease for this and other sarcomas.[161]

3.11.1.3 Outcomes & prognosis

Evaluation of the SEER database revealed a 5-year overall survival of 47% with osteosarcoma having the worst 5-year survival at 19% and patients with chordoma having the best 5-year survival at 60%.[158] A review of 44 patients (median age: 39 years, age range: 11-74 years) who underwent pelvic resection for primary sarcomas involving the pelvis, with an average follow-up period of 39 months (range, 0 to 146 months), revealed an overall 5-year survival rate of 40%.[159]

[aa] The Surveillance, Epidemiology and End Results (SEER) database provides population-based incidence and survival data for primary malignant tumours collected from 17 registries in the United States.

3.11.2 What is the clinical effectiveness of proton beam therapy in children with pelvic sarcomas?

No studies were retrieved from the searches.

Conclusions

- At present there is no scientific evidence to support or to refute PBT in children with pelvic sarcoma.

Other considerations

- Most sarcomas in the pelvis of children are either Ewing's sarcomas or rhabdomyosarcomas; the reader is therefore referred to the dedicated chapters.
- Sarcomas of the pelvis should preferably be treated with pencil beam scanning proton therapy, which was recently introduced in clinical care. As a result there are at present no results yet.

3.12 Pineal parenchymal tumours

3.12.1 Background[bb]

3.12.1.1 Clinical pathology & incidence

The pineal gland, also known as the pineal body or epiphysis cerebri, is a small endocrine gland that produces the serotonin derivative melatonin. It is located in the epithalamus, near the centre of the brain, between the two hemispheres.

Tumours originating from the pineal region are very rare; they account for less than 1% of all primary central nervous system tumours.[162] They represent a very heterogeneous pathologic collective: many types of central nervous system tumours like gliomas, meningeomas, choroid plexus papillomas and ependymomas can occur in the pineal region.[163] The most common tumours in the pineal region (21-70%) are germ cell tumours (see dedicated chapter); pineal parenchymal tumours (PPT) are the second largest subgroup of pineal tumours and represent about 10-30%. Pineal parenchymal tumours derive from pinealocytes, the cells the pineal gland is predominantly composed of.[163]

According to the WHO classification for tumours of the central nervous system revised in 2007, PPTs are subdivided into well differentiated pineocytomas (PC), PPT with intermediate differentiation (PPTID) and poorly differentiated pineoblastomas (PB).[97] In the literature, the incidence of PPT subtypes varies greatly, i.e., the incidence of pineocytoma ranges from 14% to 60%; that of pineoblastoma is 45% and that of PPT with intermediate differentiation is 10%.[162]

3.12.1.2 Current treatment regimes

Treatment may consist of surgery, radiotherapy and/or chemotherapy. Stoiber et al. suggested that local radiotherapy may be effective in patients with PC and some PPTIDs, but that the treatment of patients with more aggressive variants of PPTIDs as well as treatment of PB need further improvement, since local and spinal failure is common even despite craniospinal irradiation (CSI).[163]

3.12.1.3 Outcomes & prognosis

In general, survival of patients with PPT is considered much more doubtful compared to that of patients with other pineal region tumours. Evaluation of the SEER[cc] database (n=187, median age: 21 y.o., age range: 0-82 y.o.) revealed a 5-year overall survival of 47.2% and a median survival of 4.5 years.[162]

[bb] Not based on a systematic search of the literature.

[cc] The Surveillance, Epidemiology and End Results (SEER) database provides population-based incidence and survival data for primary malignant tumours collected from 17 registries in the United States.

3.12.2 What is the clinical effectiveness of proton beam therapy in children with pineal parenchymal tumours?

No studies were retrieved from the searches. In the recent HTA report of the American Institute for Clinical and Economic Review[78] only 1 study covering proton beam therapy in patients with pineal parenchymal tumours was mentioned (Barney, 2014[164]). Since all seven patients with pineoblastoma in that study were adults, the study was excluded here.

Conclusions

- At present there is no scientific evidence to support or to refute PBT in children with pineal parenchymal tumours.

Other considerations

- Pineal tumours are located in the most difficult to reach region in the brain.
- According to experts in the field, the main rationale for using proton beam therapy in this tumour type is to avoid damage to critical structures surrounding the pineal gland.
- Two studies on the impact of PBT in pineoblastoma are in progress (see Appendix 1.3.2). One study will be finished in December 2014; the second started in 2010 and will be finished in 2018. Unfortunately they are both single arm studies.

3.13 Retinoblastoma

3.13.1 Background[dd]

3.13.1.1 Clinical pathology & incidence

Retinoblastoma is a relatively uncommon tumour of childhood that arises in the retina (the light-sensitive layers of nerve tissue at the back of the eye) and accounts for about 3% of the cancers occurring in children younger than 15 years. Ninety-five percent of cases are diagnosed before age 5 years, and two-thirds of these cases occur before age 2 years. Older age is usually associated with more advanced disease and a poorer prognosis.[165] Retinoblastoma exists in a heritable (25% to 30%) and a nonheritable (70% to 75%) form.[165] The non-hereditary variant is always solitary, while heritable retinoblastoma may manifest as unilateral or bilateral disease.[166] In the early stages, the tumour is confined to the eye and cure rates for intraocular retinoblastoma can be as high as 95%.[167] Treatment requires significant multidisciplinary input, with local ophthalmic treatment, systemic chemotherapy and external beam or plaque radiotherapy, or surgery to remove the affected eye.[167] Chantada et al. noted a 5-year disease free survival rate of 98% in 118 patients with intraocular disease, including 54 patients with choroidal invasion.[168]

3.13.1.2 Current treatment regimes

Due to the radiosensitive nature of retinoblastoma, external beam radiation therapy (EBRT) has been thought to be the first line and major treatment method for retinoblastoma.[169] However, there is a very high incidence of secondary malignant neoplasms among the survivors of heritable retinoblastoma, as well as cosmetic problems of orbital bone growth retardation in those who received EBRT, particularly in younger children. Therefore, treatment modalities were shifted toward primary systemic chemotherapy for reducing tumour volume initially (chemo reduction) and additional focal treatment such as cryotherapy, thermotherapy, or brachytherapy.[169] Recently published, large retrospective studies have developed the current understanding that patients bearing the germline RB1 mutation have an underlying vulnerability to additional cancers that is

[dd] Not based on a systematic search of the literature.

exacerbated by radiotherapy. Hence, in "developed" countries, the leading cause of death in patients with hereditary retinoblastoma is secondary malignancy, particularly bone and soft tissue sarcomas.[170, 171]

3.13.1.3 Outcomes & prognosis

Analysis of data collected in the SEER[ee] database (n=992 retinoblastoma cases from 1975 to 2004) revealed that the 5-year observed actuarial survival rate increased from 92.3% (1975–84) to 93.9% (1985–94) to 96.5% (1995–2004).[172] Extraocular spread carries a very poor prognosis, with cure rates below 5–10%.[167] Early diagnosis and prompt treatment is therefore crucial to save life and vision.

3.13.2 What is the clinical effectiveness of proton beam therapy in children with retinoblastoma?

Only one (comparative) observational study on proton beam therapy in children with retinoblastoma was retrieved (Sethi, 2014).[171] Sethi et al. retrospectively analysed the risk for secondary malignancies after proton beam therapy vs. photon radiotherapy in 86 infants who were treated for retinoblastoma and followed for a median of 7 years (PBT) or 13 years (photon radiotherapy).[171] Kaplan-Meier analyses were controlled for differential follow-up but not for other differences between groups.

For more information on the included study, the reader is referred to the evidence table in Appendix 2.3.10.

Overall survival

There are no data reported with regard to overall survival. As survival rates for patients with retinoblastoma are very high, even among those with advanced disease, the impact of proton beam therapy on medium term survival is not really an issue of concern.[168]

Progression-free survival

There are no data reported with regard to disease-free survival.

Local control rate

There are no data reported with regard to local control rate.

Complication rate

There are no data reported with regard to complication rate.

Risk of secondary malignancies

In Sethi et al. the 10-year cumulative incidence of secondary malignancy was not statistically significantly different between groups (PBT: 5% vs. photon: 14%, p=0.12).[171] However, when restricted to radiotherapy-induced or in-field malignancies, patients treated with PBT had a significantly lower risk of developing a secondary malignancy compared to those treated with photon radiotherapy (PBT: 0% vs. photon: 14%, p=0.015). In addition, in the subgroup of patients with hereditary disease, the authors report significant differences in favour of PBT in 10-year cumulative incidence (PBT: 5% vs. photon: 22%, p=0.021) as well as radiotherapy-induced or in-field malignancy (PBT: 0% vs. photon: 22%, p=0.005). It should be noted however that these analyses were performed in small subgroups assigned hereditary disease (i.e. bilateral disease and/or a family history; 46 patients treated with PBT and 19 patients treated with photon radiotherapy) and that the authors did not provide any information on the number of patients bearing the germline RB1 mutation. In addition, as chemotherapy itself may also introduce secondary tumours, it should be noted that more patients from the proton cohort received chemotherapy (PBT: 56% vs. photon: 16%, p<0.001).

Quality of life

There are no data reported with regard to quality of life.

The results should be interpreted with caution since the study had serious methodological flaws (see evidence tables in Appendix 2.3.10). In addition, several malignancies were not included in the analysis (e.g. 1 pineoblastoma, 1 osteosarcoma and 2 benign neoplasms)

[ee] The Surveillance, Epidemiology and End Results (SEER) database provides population-based incidence and survival data for primary malignant tumours collected from 17 registries in the United States.

Conclusions

- At present there is no scientific evidence that the use of PBT in children with retinoblastoma results in higher or lower progression free survival rates, local control rates, complication rates or quality of life measures.
- At present there is very low level scientific evidence that the use of PBT in children with retinoblastoma results in a significantly lower risk of developing radiotherapy-induced in-field malignancies.

Other considerations

- Photon therapy has improved tremendously since the inclusion of the first patients (1986) in the included study; in fact, PBT should be compared with actual methods of photon therapy applied in retinoblastoma (e.g. brachytherapy). Plaque therapy would be expected to have an even lower risk of second malignant neoplasms than proton external beam therapy.
- Two studies on the impact of PBT in retinoblastoma are in progress (see Appendix 1.3.2). One study was finished in February 2014; the second started in 2007 and will be finished in 2020.

3.14 Rhabdomyosarcoma

3.14.1 Background[ff]

3.14.1.1 Clinical pathology & incidence

Rhabdomyosarcomas (RMS) are a heterogeneous group of malignancies of mesenchymal cell origin that arise primarily in striated muscle tissues.[11, 173] The most common primary sites for rhabdomyosarcoma are the head, the genitourinary tract, and the extremities;[174] it can spread to lungs, bone marrow, bones, lymph nodes, and other sites.[175] In children, the most common primary sites are the orbit, representing 35 to 45% of all cases of childhood RMS,[176] and the genitourinary tract.[174]

There are two main histological types, embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS) representing respectively 80% and 15-20% of RMS[177] and a less prevalent type called pleomorphic (undifferentiated or anaplastic) rhabdomyosarcoma. In addition to the conventional type of ERMS, two other subtypes were identified: botryoid RMS and spindle cell RMS. These two subtypes tend to have a better prognosis than the conventional type of ERMS.[175]

Rhabdomyosarcoma is the most common type of soft-tissue sarcoma during the first two decades of life, accounting for 3-5% of paediatric cancers.[11, 173,178] The annual incidence is 4.3 cases per million[177] and presents a bimodal distribution with a first peak at age 6 years and a second peak at adolescence.[11]

3.14.1.2 Prognosis

The prognosis of RMS depends on the histologic type and the tumour site. For instance, orbital ERMS has a more favourable prognosis than orbital ARMS: the 5-years overall survival is 94% and 74%, respectively).[179] ”Favourable” sites are the orbit/eyelid, nonparameningeal head and neck, the genitourinary tract other than the kidney, bladder, or prostate and finally the biliary tract.[175]

[ff] Not based on a systematic search of the literature.

3.14.1.3 Current treatment regimes

RMS therapy requires a multidisciplinary approach including surgery, chemotherapy and radiotherapy.[179] The Intergroup Rhabdomyosarcoma Study group (IRS) studies II and III prescribed treatment plans based on the Surgical-pathologic Group system. In this system, groups are defined by the extent of disease and by the completeness or extent of initial surgical resection after pathologic review of the tumour specimen(s)[gg].[174] The treatment of rhabdomyosarcoma differs in management and overall treatment philosophy.[174] In the MMT (i.e. International Society of Paediatric Oncology Malignant Mesenchymal Tumour Group) trials, the main objective is to reduce the use of local therapies using initial front-line chemotherapy followed by second-line therapy in the presence of poor response. Subsequent surgical resection is preferred over radiotherapy, which is used only after incomplete resection, documented regional lymph node involvement, or a poor clinical response to initial chemotherapy. This approach is designed to avoid major surgical procedures and long-term damaging effects from radiotherapy. Conversely, the primary Children's Oncology Group Soft Tissue Sarcoma Committee (COG-STS, US) objective has been to employ local therapy soon after the initial operation or biopsy (except in patients with metastatic disease), using RT for patients with residual disease.

3.14.1.4 Outcomes

The MMT Group approach led to an overall survival (OS) rate of 71% in the European MMT89 study, compared with an OS rate of 84% in the IRS-IV study. Similarly, event free survival (EFS) rates at 5 years were 57% in the MMT89 study versus 78% in the IRS-IV study. Differences in outcome were most striking for patients with extremity and head and neck non-parameningeal tumours. The overall impression is that survival for most patient subsets is superior with the use of early local therapy, including RT. However, in the MMT trials, some patients are spared aggressive local therapy, which may reduce the potential for morbidities associated with such therapy.[174]

3.14.2 What is the clinical effectiveness of proton beam therapy in children with rhabdomyosarcoma?

Three retrospective studies on proton beam therapy in children with rhabdomyosarcoma were retrieved (Childs 2012[180], Cotter 2011[178], Timmermann 2007[181]).

Childs et al. reported on 17 patients with parameningeal rhabdomyosarcoma (age range: 0.4-17.6 y.o.; 15 with IRS group III and 2 with IRS group IV; 11 with ERMS and 6 with ARMS or undifferentiated RMS).[180] Median follow-up was 5.0 years (range: 2-10.8 years); median prescribed dose to the gross tumour volume was 50.4 cobalt gray equivalent (range: 50.4-56).

In the study of Cotter et al. the files of 7 children with bladder or prostate rhabdomyosarcoma were reviewed (age range: 11-70 months; 1 with IRS group II and 6 with IRS group III; all with ERMS).[178] Median follow-up was 27 months (range: 10-90 months); radiation doses ranged between 36 and 50.4 cobalt gray equivalent.

Paediatric soft tissue sarcomas, not only rhabdomyosarcoma, were studied in the Timmermann et al. paper (median age: 3.3 y.o.; 11 with IRS group III and 1 with IRS group IV; 10 with ERMS (parameningeal (n=6), prostate (n=1), orbital (n=3)) and 1 with ARMS (orbital) and 1 with undifferentiated parapharyngeal RMS).[181] Median follow-up was 1.5 years; the median total dose of PBT was 50.0 cobalt gray equivalent. Two children also received photon radiation.

[gg] Group I (incidence: +/- 13%): Localized tumour, completely removed with microscopically clear margins and no regional lymph node involvement. Lymph node biopsy or sampling is encouraged if lymph nodes are clinically or radiographically suspicious. Group II (incidence: +/- 20%): Localized tumour, completely removed with: (a) microscopic disease at the margin, (b) regional disease with involved, grossly removed regional lymph nodes without microresidual disease, or (c) regional disease with involved nodes, grossly removed but with microscopic residual and/or histologic involvement of the most distal node from the primary tumour. Group III (incidence: +/- 48%): Localized tumour, incompletely removed with gross, residual disease after: (a) biopsy only, or (b) gross major resection of the primary tumour (>50%). Group IV (incidence: +/- 18%): Distant metastases are present at diagnosis. This category includes: (a) radiographically identified evidence of tumour spread, and (b) positive tumour cells in cerebral spinal fluid, pleural, or peritoneal fluids, or implants in these regions.

For more information on the included studies, the reader is referred to the evidence tables in Appendix 2.3.11.

Overall survival

Childs et al. reported a 5-year overall survival of 64% (95% CI: 37-82%) in children with parameningeal RMS.[180] Again, patients with intracranial extension (n=10) experienced a lower overall survival rate compared with their peers (n=7) without intracranial extension (60%, 95% CI: 25-83% vs. 71%, 95% CI: 26-92%). At the completion of the Timmermann et al. study, 10/12 patients were still alive. It should be noted however that for half of these children the follow-up time was shorter than 1 year.[181]

Failure-free survival

Childs et al. observed in 17 children with parameningeal RMS a 5-year failure free survival rate of 59% (95% CI: 33-79%). Patients with intracranial extension (n=10) experienced a lower 5-year failure free survival rate compared with their peers (n=7) without intracranial extension (50%, 95% CI: 18-75% vs. 71%, 95% CI: 26-92%). The difference was not statistically significant, probably due to the small sample size.

Recurrence rate

In Childs et al. 7/17 (41%) patients with parameningeal rhabdomyosarcoma had recurrences (local only (n = 2), regional only (n = 2), distant only (n = 2), and local and distant (n = 1)) at a median time[2] of 10.5 months (range: 7-18.5 months).[180] Cotter et al. reported 1 local recurrence (in the bladder) and 1 regional recurrence (in the rectum and inguinal nodes) after a median follow-up of 27 months.[178] When only the patients with RMS are taken into account, the local recurrence rate in the Timmermann et al. study was 2/12 patients.[181]

Complication rate

A complication rate for the whole Childs et al. sample was not reported.[180] The late effects likely related to PBT in the 10 patients without recurrence were: failure to maintain height velocity (n=3), endocrine deficits (n = 2), mild facial hypoplasia (n = 7), failure of permanent tooth eruption adjacent to the treatment field (n = 3), dental caries adjacent to the treatment field (n = 5) and chronic nasal/sinus congestion (n = 2).[180] Cotter et al. described a complication rate of 3/7 patients; it should be noted that it was not possible to reveal which side effects were due to proton beam therapy.[178] They observed urinary sphincter dysfunction (1/7), intermittent hematuria (1/7), enuresis/hydronephrosis/ vesicoureteral reflux (grade IV) as treatment side effects.[178] Furthermore, they noted that there were no skeletal or gastrointestinal side effects.
In the Timmermann et al. study, data on acute toxicity were not reported separately for children with rhabdomyosarcoma. They noted that the acute side effects (in the whole sample) were mild; grade 3 or 4 toxicity occurred only for bone marrow when parallel chemotherapy was applied. In addition, only 3 surviving children with RMS were followed for more than 1 year, hence for the others follow-up was too short to evaluate late sequelae. Late effects were seen in 2 of those 3 children.

Secondary malignancies

There are no date reported with regard to secondary malignancies.

Quality of life

There are no data reported with regard to quality of life issues after PBT in children with RMS.

The above results should be interpreted with caution since all three studies suffered from serious methodological flaws and were based on small samples.

Conclusions

- At present there is insufficient scientific evidence to support or to refute PBT in children with rhabdomyosarcoma.

Other considerations

- As a primary rhabdomyosarcoma tumour, just like Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcoma, can occur in multiple different locations throughout the body, the value of proton external beam therapy versus photon external beam therapy is also dependent upon tumour location. For instance, the risk of normal tissue injury is substantially different if the primary rhabdomyosarcoma is in the orbit, prostate, or vagina of a 4 year old child than if it is in the non-dominant forearm of a 17 year old. (EC Halperin, personal communication)

- Two studies on the clinical effectiveness of PBT in RMS are in progress (see Appendix 1.3.2). One study will be finished in June 2015, the second in 2021. However, these two studies only include adults.

3.15 (Para-)spinal 'adult type' soft tissue sarcoma

3.15.1 Background[hh]

3.15.1.1 Clinical pathology & incidence

Soft tissue sarcomas (STS) are a rare group of malignant tumours, originating from primitive mesenchymal tissue; they account for 7% of all childhood tumours.[182] The most common soft tissue sarcoma in children younger than 15 y.o. is rhabdomyosarcoma, a tumour of striated muscle which is discussed in a separate chapter. The remaining soft tissue sarcomas are commonly referred to as non-rhabdomyosarcomatous STSs and account for about 3% of all childhood tumours. Non-rhabdomyosarcomatous STSs are characterized by local aggressiveness and a propensity to metastasize that is correlated to their grade of malignancy.[183] The group of non-rhabdomyosarcomatous STSs is very heterogeneous; includes neoplasms of the connective tissue (e.g. desmoid fibromatosis, liposarcoma), the peripheral nervous system (e.g. malignant peripheral nerve sheath tumour), the smooth muscle (e.g. leiomyosarcoma) and the vascular tissue (blood and lymphatic vessels, e.g. angiosarcoma). In children, synovial sarcoma, fibrosarcoma, fibrohistiocytic tumours, and malignant peripheral nerve sheath tumours predominate.

3.15.1.2 Current treatment regimes

As non-rhabdomyosarcomatous STSs are more common in adolescents and adults, most of the experience gained in the treatment of paediatric non-rhabdomyosarcomatous STSs either derives from managing soft tissue sarcomas in adults or relies on the principles derived from the management of rhabdomyosarcoma.[183] Like their adult counterparts, paediatric non-rhabdomyosarcomatous STSs seem to be relatively insensitive to chemotherapy, making local therapy (and surgery in particular) the unquestioned cornerstone of their treatment.[184] Although radiotherapy plays a dominant role in those tumours which cannot be surgically removed without leading to major impairment, the knowledge of severe late effects of radiotherapy has led to significant differences in treatment philosophies between American and European physicians. It is estimated that in the American protocols approximately 70% of all children with sarcomas are treated with radiotherapy as compared with approximately 50% in the German and European Cooperative Childhood Soft Tissue Sarcoma trial (CWS) protocols.[181]

3.15.1.3 Outcomes & prognosis

Given the heterogeneity of these tumours, clinical studies should actually target diagnostic subgroups as specifically as possible, but the rarity of each histotype prevents the performance of clinical trials on a single tumour type, and consequently, non-rhabdomyosarcomatous STSs have to be analysed as a group.[183] In a relatively homogeneous subgroup of 182 patients younger than 18 years with adult-type histotypes of non-rhabdomyosarcomatous STSs, 5-year overall survival was 89% in patients who underwent complete resection at diagnosis, 79% in patients who had marginal resection, 52% in initially unresected patients, and 17% in patients with metastases at onset.[183] In this patient group, surgery was the mainstay of treatment; radiotherapy was administered to 73 patients, and chemotherapy was administered to 114 patients (70 received chemotherapy as adjuvant therapy). More recently, the pooling of data from 304 patients younger than 21 years old from various groups confirmed the poor prognosis for patients with non-rhabdomyosarcoma STSs with initially unresected tumours: the 5-year and 10-year overall survival was 60.0% and 51.5%, respectively, and it was significantly associated with patient's age, histological subtype, tumour site and size, quality of delayed surgical resection, radiotherapy administration and response to induction chemotherapy.

[hh] Not based on a systematic search of the literature.

3.15.2 What is the clinical effectiveness of proton beam therapy in children with (para)spinal adult-type soft tissue sarcomas?

No studies were retrieved from the searches. In the recent HTA report of the American Institute for Clinical and Economic Review[78] 2 studies covering proton beam therapy in patients with soft tissue sarcomas were mentioned (Yoon 2010[34] and Weber 2007[185]), but since both studies included only adults, both studies were excluded here.

Conclusions

- At present there is no scientific evidence to support or to refute PBT in children with (para)spinal adult-type soft tissue sarcomas.

Other considerations

- At present several studies on proton beam therapy in patients with soft tissue sarcomas are undertaken, so far only one, run at Massachusetts General Hospital, recruits children (see Appendix 1.3.2).

3.16 Summary of selected studies

Proton beam therapy						
Study	**Method**	**FU**	**Additional treatment[ii]**	**Control group**	**Reported outcomes[jj]**	**Conclusions**
Skull base chondrosarcoma (1 study)						
Rombi et al. 2013; Villigen, Switzerland	Retrospective; case series; enrolment: 2000-2010; n=7; age: 3.7-20.8 y.o. (whole sample, incl. n=19 with chordoma)	4.5-126.5 months (whole sample)	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS (5yr)**: 75% (95% CI NR) • **RcR**: 1/7 (14%) • **LCR (5yr)**: 80% (95% CI NR)	At present **insufficient scientific evidence** to support or to refute
Skull base & (para)spinal chordoma (2 studies)						
Rombi et al. 2013; Villigen, Switzerland	Retrospective; case series; enrolment: 2000-2010; n=19; age: 3.7-20.8 y.o. (whole sample, incl n=7 with chondrosarcoma)	4.5-126.5 months (whole sample)	Variable[kk] (incl. surgery)	No	• **OS (5yr)**: 89% (95% CI NR) • **RcR**: 2/19 (11%) • **LCR (5yr)**: 81% (95% CI NR)	At present **insufficient scientific evidence** to support or to refute
Habrand et al. 2008; Orsay, France	Retrospective; case series; enrolment: 1996-2006; n=26; age: 6-17 y.o. (whole sample, incl n=3 with chondrosarcoma and n=1 with chondroma)	5-102 months	Variable[kk] (incl. surgery & photon RT)	No	• **OS (5yr)**: 81% (95% CI: 56-100) • **PFS (5yr)**: 77% (95% CI: 59-95) • **RcR**: 5/26 (19%)	
Craniopharyngioma (3 studies)						
Bishop et al. 2014; Houston, US	Retrospective; comparative study; enrolment: 1996-2012; n=52 (PBT: n=21; IMRT: n=31); median age (range NR): 8.9 y.o.	PBT: 10.5-65.6 months; IMRT: 8.9-185.3 months	Variable[kk] (incl. surgery)	31 patients who had IMRT	• **OS (3yr)**: PBT: 94.1% (95% CI NR) vs. IMRT: 96.8% (95% CI NR) (p=0.742) • **CFFS (3yr)**: PBT: 67.0% (95% CI NR) vs. IMRT: 76.8% (95% CI NR)(p=0.994)	At present **very low level scientific evidence** that PBT compared with IMRT **does not result in**

[ii] Before, during or after radiation therapy

[jj] CFFS: cystic failure-free survival; CI: confidence interval; CoR: complete remission; CR: complication rate; CIn: cumulative incidence; DFS: disease free survival; DR: distal recurrence rate; DSS: disease specific survival; EFS: event free survival; FFS: failure free survival; incl.: including; LCR: local control rate; LR: local recurrence rate; NFFS: nodular failure-free survival; NGGCT: nongerminomatous germ cell tumour; NR: not reported; OS: overall survival; PFS: progression free survival; PP: pseudo progression; PR: partial remission; RcR: recurrence rate; RpR: Response rate; RT-ind: radiotherapy induced; SM: secondary malignancy; StD: stable disease;

[kk] Variable: indicating that not all patients received (the same type of) surgery, not all patients received (the same) chemotherapy (regimen)

					• **NFFS (3yr)**: PBT: 91.7% vs. IMRT: 96.4% (p=0.546) • **Early cyst growth**[ll]: PBT: 4/21 (19%) vs. IMRT: 13/31 (42%) (p=0.082) • **Late cyst growth**[mm]: PBT: 4/21 (19%) vs. IMRT: 10/31 (32%) (p=0.353)	**significant differences** in 3-yr OS, 3-yr CFFS, 3-yr NFFS, toxicity or cyst dynamics.
Laffond et al., 2012; Orsay, France	Retrospective; case series; enrolment: 1995-2007; n=29; age: 22-190 months	NA	Variable[kk] (incl. photon RT & surgery)	No	• **QoL**: satisfactory	
Winkfield et al., 2009; Boston, US	Retrospective; case series; enrolment: 2001-2007; n=24; age: 3-14 y.o.	6-78 months	Variable[kk] (incl. surgery)	No	• **LCR**: 100%	
Ependymoma (2 studies)						
MacDonald et al. 2013; Boston, US	Retrospective; case series; enrolment: 2000-2011; n=70; age: 3 mo-20 y.o.	1-11.7 years	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS (3yr)**: 95% (95% CI NR) • **PFS (3yr)**: 76% (95% CI NR) • **LCR (3yr)**: 83% (95% CI NR) • **LCR (5yr)**: 77% (95% CI NR) • **DCR (3yr)**: 86% (95% CI NR) • **DCR (5yr)**: 83% (95% CI NR)	At present **insufficient scientific evidence** to support or to refute
Amsbaugh et al. 2012; Texas, US	Prospective; case series; enrolment: 2006-2010; n=8; age: 1.2-16.5 y.o.	7-51 months	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS**: 100% • **EFS**: 100% • **LCR**: 100%	
Esthesioneuroblastoma (1 study)						
Herr et al. 2014; Boston, US	Retrospective; case series; enrolment: 1997-2013; n=22; age: 11-77 y.o. (n children NR)	24-183 months	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS (5yr)**: 95.2% (95% CI: 70.7-99.3%) • **DFS (5yr)**: 86.4% (95% CI: 63.4-95.4%) • **RcR (LR+DR)**: 6/22 (27%) • **CR**: 13/22 (59%) (mild to severe)	At present **insufficient scientific evidence** to support or to refute

[ll] Early cyst growth: ≤ 3 months after RT

[mm] Late cyst growth: > 3 months after RT

Ewing sarcoma (1 study)						
Rombi et al. 2012; Boston, US	Retrospective; case series; enrolment: 2003-2009; n=30; age: 1.8-20 y.o.	17.4 months – 7.4 years	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS (3yr)**: 89% (95% CI NR) • **DSS (3yr)**: 68% (95% CI NR) • **EFS (3yr)**: 60% (95% CI NR) • **DFS**: 21/30 (70%) • **LCR (3yr)**: 86% (95% CI NR) • **RcR**: 5/30 (17%) • **CR (acute)**: 100% (95% CI NR) • **SM – CIn (2yr)**: 7% (95%CI: 1-19%) • **SM – CIn (3yr)**: 15% (95%CI: 5-32%)	At present **insufficient scientific evidence** to support or to refute
CNS germinoma (1 study)						
MacDonald et al. 2011; Boston, US	Retrospective; case series; enrolment: 1998-2007; n=22 (Germinoma: n=13, NGGCT: n=9); age: 6-20 y.o.	13-97 months	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS**: 100% (95% CI NR) • **PFS**: 95% (95% CI NR) • **RcR**: LR: 0%; DR: 0% (Germinoma), 1/9 (11%)(NGGCT)	At present **insufficient scientific evidence** to support or to refute
Low-grade glioma (2 studies)						
Greenberger et al. 2014; Boston, US	Retrospective; case series; enrolment: 1995-2007; n=32; age:2.7-21.5 y.o.	3.2-18.2 years	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS (8yr)**: 100% (95% CI NR) • **PFS (6yr)**: 89.7% (95% CI NR) • **PFS (8yr)**: 82.8% (95% CI NR)	At present **insufficient scientific evidence** to support or to refute
Bian et al. 2013; Houston, US	Retrospective; case series; enrolment: NR; n=6; age: 2-15 y.o.	5-95 months	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS**: 83.3% • **RpR**: StD: 4/6 (67%)	
Medulloblastoma (3 studies)						
Sethi et al. 2014; Boston, US	Retrospective; case series; enrolment: 2002-2011; n=109; age: 2.2-22.7 y.o. (n children NR)	1.4-119.2 months	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS**: 97/109 (89%) • **RcR**: 16/109 (15%)	At present **insufficient scientific evidence** to support or to refute

Jimenez et al., 2013; Boston, US	Retrospective; case series; enrolment: 2002-2010; n=15[nn]; age: 23-55 months	3-102 months	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS (3yr)**: 85.6% (no reliable CI reported) • **DFS**: 13/15 (87%) • **RcR (L)(3yr)**: 7.7%	
Moeller et al. 2011; Houston, US	Prospective; case series; enrolment: 2006-2009; n=23; age: 3-16 y.o.	NA	Variable[kk] (incl. chemotherapy & surgery)	No	• **CR (1 yr grade 3-4 ototoxicity)**: 5%	
Non-resectable osteosarcoma (1 study)						
Ciernik et al. 2011; Boston, US	Retrospective; case series; enrolment: 1983-2009; n=55; age: 2-76 y.o. (n children NR)	0-196 months	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS (2yr)**: 84% (95% CI: 69-92%) • **OS (5yr)**: 67% (95% CI: 47-80%) • **DFS (2yr)**: 68% (95% CI: 53-80%) • **DFS (5yr)**: 65% (95% CI: 49-77%) • **LCR (3yr)**: 82% (95% CI: 68-90%) • **LCR (5yr)**: 72% (95% CI: 52-84%) • **CR**: 46/55 (84%) (mild to severe)	At present **insufficient scientific evidence** to support or to refute
Pelvic sarcomas (no studies with children included)						
						At present **no scientific evidence** to support or to refute
Pineal parenchymal tumours (no studies with children included)						
						At present **no scientific evidence** to support or to refute
PNET (no studies with children included)						
						At present **no scientific evidence** to support or to refute

[nn] All or some children also included in the Sethi et al. 2014 study?

Retinoblastoma (1 study)						
Sethi et al. 2014; Boston, US	Retrospective; comparative; enrolment: 1986-2011; n=86 (PBT: n=55; photon: n=31); age: 0-11.7 y.o.	PBT: 1.0-24.4 years; photon: 1.4-23.9 years	Variable[kk] (incl. chemotherapy)	31 patients who had photon RT	• **SM (10yr CIn)**: PT: 5% (95% CI: 0-21) vs. photon: 14% (95% CI: 3-31) (p=0.12) • **SM (10yr CIn RT-ind or in-field)**: PT: 0% (95% CI undefined) vs. photon: 14% (95% CI: 3-31) (p=0.015)	At present **very low level scientific evidence** that PBT results in lower risk of developing RT-induced in-field secondary malignancies
Rhabdomyosarcoma (3 studies)						
Childs et al. 2012; Boston, US	Retrospective; case series; enrolment: 1996-2005; n=17; age: 0.4-17.7 y.o.	2-10.8 years	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS (5yr)**: 64% (95% CI: 37-82%) • **FFS (5yr)**: 59% (95% CI: 33-79%) • **RcR (L+D)**: 7/17 (41%)	At present **insufficient scientific evidence** to support or to refute
Cotter et al. 2011; Boston, US	Retrospective; case series; enrolment: 2002-2008; n=7; age: 10-70 months	10-90 months	Variable[kk] (incl. chemotherapy & surgery)	No	• **DFS**: 5/7 (71%) • **RcR (L)**: 14% • **RcR (D)**: 14% • **CR**: 43%	
Timmerman et al. 2007; Villigen, Switzerland	Retrospective; case series; enrolment: 1997-2005; n=16 (n=12 with rhabdomyosarcoma); age: 0.9-12.1 y.o.	4.3-70.8 months	Variable[kk] (incl. chemotherapy, photon RT & surgery)	No	• **OS[oo] (1yr)**: 90.9% (95% CI NR) • **OS[oo] (2yr)**: 69.3% (95% CI NR) • **PFS[oo] (1yr)**: 81.8% (95% CI NR) • **PFS[oo] (2yr)**: 71.6% (95% CI NR) • **RpR**: StD: 6/12; PR: 3/12; CoR: 3/12 • **RcR (LR)**: 2/12 (17%)	
(Para-)spinal "adult type" soft tissue sarcoma (no studies with children included)						
						At present **no scientific evidence** to support or to refute

[oo] Reported for all 16 patients (not separately for children with rhabdomyosarcoma)

Carbon ion therapy						
Study	**Method**	**FU**	**Additional treatment[ii]**	**Control group**	**Reported outcomes[jj]**	**Conclusions**
Non-resectable osteosarcoma (1 study)						
Matsunobu et al. 2012; Chiba, Japan	Retrospective; case series; enrolment: 1996-2009; n=78; age: 11-83 y.o.	2-166 months	Variable[kk] (incl. chemotherapy & surgery)	No	• **OS (2yr)**: 58% (95% CI NR) • **OS (5yr)**: 33% (95% CI NR) • **DSS (2yr)**: 60% (95% CI NR) • **DSS (5yr)**: 34% (95% CI NR) • **PFS (2yr)**: 34% (95% CI NR) • **PFS (5yr)**: 23% (95% CI NR) • **LCR (2yr)**: 73% (95% CI NR) • **LCR (5yr)**: 62% (95% CI NR)	At present **insufficient scientific evidence** to support or to refute

4 DISCUSSION & CONCLUSIONS

After selection, we retrieved only 21 full text articles on the 16 potential indications under study. The majority of these studies (n=16) were retrospective case series, 2 were retrospective comparative studies and 3 were prospective case series. When the upper age limit is applied in a flexible way, the majority of retrieved studies (n=18) were based on children only (i.e. younger than 22 y.o.); for 3 indications under study (i.e. esthesioneuroblastoma, osteosarcoma with PBT and osteosarcoma with CIRT) no children-only studies were found, hence we had to resort to publications with a mixed population. With regard to geographical aspects: 16 studies were performed in the US, 4 in Europe and 1 in Japan. This is in line with the recent HTA published by the Washington State Health Care Authority, which identified no comparative studies of the clinical effectiveness of primary PBT nor for recurrent disease in patients with paediatric cancers; only case series of PBT in a variety of childhood cancers were identified.[78]

On top of the non-randomized, non-controlled and retrospective nature of the majority of retrieved studies - with the limitations characteristic of these types of studies (e.g. selection bias, recall bias) - all studies suffered from very serious methodological limitations (among others small sample size, long enrolment period, no clear inclusion nor exclusion criteria, variable treatment schemes, short follow-up, no information on the methods and intervals of follow-up, complications only assessed in a subset of patients) and hence when GRADE[81] was applied, the level of scientific evidence for all outcomes in all indications was regarded as very low. As a result, we had to conclude for most indications that anno 2014 there was insufficient[pp] or even no[qq] scientific evidence to support or to refute the use of PBT (or CIRT) in children. For craniopharyngioma it was concluded that there was very low level scientific evidence that PBT compared with IMRT did not result in significant differences in overall survival, cystic failure-free survival, nodular failure-free survival, toxicity or cyst dynamics. Only for retinoblastoma it was concluded that there was very low level scientific evidence that PBT results in a lower risk of developing RT-induced in-field secondary malignancies, but as it was pointed out in the introduction, as radiation-induced solid malignancies develop a minimum of at least 5 to 10 years after treatment[15] and for some children in the retinoblastoma study[171] the follow-up was short, the results should be interpreted with caution.

- For chondrosarcoma, chordoma, ependymoma, esthesioneuroblastoma, Ewing sarcoma, CNS germinoma, glioma, medulloblastoma, non-resectable osteosarcoma (for PBT as well as CIRT) and rhabdomyosarcoma there is **insufficient scientific evidence to support or to refute** the use of PBT (or CIRT) in children.
- For pelvic sarcoma, pineal parenchymal tumour, PNET and (para-) spinal “adult type” soft tissue sarcoma there is **no scientific evidence to support or to refute** the use of PBT in children.
- For **craniopharyngioma** there is **very low level scientific evidence that PBT compared with IMRT did not result in significant differences** in overall survival, cystic failure-free survival, nodular failure-free survival, toxicity or cyst dynamics.
- For **retinoblastoma** it was concluded that there was **very low level scientific evidence that PBT results in a lower risk of developing RT-induced in-field secondary malignancies,** but as radiation-induced solid malignancies develop a **minimum of at least 5 to 10 years after treatment** and for some children the **follow-up** was short, the results should be interpreted with caution**.**

Essentially, there are two rationales for using proton beam therapy. First, the dose to organs at risk (OAR) can be reduced and/ or the risk for second malignancies can be lowered *(Radioprotection philosophy, ALARA)*. Second, the dose to the tumour can be increased without putting the organs at risk to a higher dose *(Dose escalation)*.

[pp] Insufficient scientific evidence was the case for chondrosarcoma, chordoma, ependymoma, esthesioneuroblastoma, Ewing sarcoma, CNS germinoma, glioma, medulloblastoma, non-resectable osteosarcoma (for PBT as well as CIRT) and rhabdomyosarcoma.

[qq] No scientific evidence was the case for pelvic sarcoma, pineal parenchymal tumour, PNET and (para-)spinal “adult type” soft tissue sarcoma.

Reducing the dose to organs at risk has been used for many years in radiotherapy.[186] The underlying observation is that more dose to OAR will lead to more side effects, mostly following a sigmoid dose-response relation. The uncertainty is not the concept, it is the precise quantification of this dose-response relationship. A subtle dose reduction to OAR may therefore theoretically be beneficial for an individual patient, but it will not be detectable in clinical trials. Because proton beam therapy nearly universally leads to sparing of OAR compared to photon therapy,[23] the wide confidence intervals on the dose-response relations preclude to conclude that all patients should be treated with protons. Instead, it is reasonable only to consider proton therapy when the 95 % CI of the estimation of the side effects with protons and photons are non-overlapping. In this case, the differences in side effects are real. As a second criterion, the side effect should be important for the patient. As an example, sparing of brain structures such as the hippocampus without hampering the dose to the tumour is clearly of potential clinical benefit, for the child may have less neurocognitive deficits. This strategy is based on validated dose-response relationships and is thus scientifically sound, even without randomised studies.

Reducing the probability to develop second radiation-induced cancer is a concept that is widely used in radioprotection for the community. In the ALARA (as low as reasonably achievable) principle, it is assumed that no safe threshold exists for the development of second cancers due to radiation exposure. In patients that are at risk for second cancers, that is all patients with a life expectancy over 5 to 10 years, reducing the integral dose is the consequent application of the ALARA principle. A life expectancy of 5 to 10 years or more is based on the latency time between radiation exposure and the development of second malignancies. Obviously, the integral dose should take into account the neutron leakage of the machine. This is measurable and should be included in the calculations. It is hardly justifiable to enrol patients in prospective studies to detect second cancers that will take decades to accomplish and need high patient numbers, whereas the same radioprotection rules are implemented in public health without prospective validation.

Completely separate from sparing of OAR is dose escalation of the tumour, whilst keeping the dose to the OAR constant. Although this approach is appealing, the dose-response relationship for tumours is less well established than those for normal tissues. Dose-escalation and hypofractionation are therefore, both in photon and proton therapy, experimental approaches that should be restricted to clinical trials.

Worldwide a growing number of children is being treated with proton beam therapy. As we have no Belgian data and as a European registry has not been installed (yet), we have to rely on American data. A survey among all American proton centres[rr] disclosed that in 2012 a total of 694 paediatric patients were treated, an increase from 613 patients in 2011 and 465 patients in 2010.[187] The six most common tumour types treated were ependymoma, medulloblastoma, low-grade glioma, rhabdomyosarcoma, Ewing sarcoma, and craniopharyngioma;[187] indications for which we found either no or insufficient scientific evidence to support or to refute proton beam therapy.

It is remarkable that only a fraction of children treated with PBT are enrolled in clinical trials.[12] There may be several reasons for that. First of all, clinicians/researchers have to be convinced that clinical research in the field is still necessary. They have to spend time explaining it to patients and their legal representatives in order to obtain their consent.[188] Parents may not be eager to be involved in clinical research as they are too occupied with the care of an extremely ill child; they may dread extra efforts (e.g. extra evaluation sessions, completing surveys). The superior dose distribution and lower integral dose may introduce bias that a proton beam treatment is superior to photon therapy and this may hamper the accrual for randomized trials. The same reasons are applicable for more limited as compared to extensive surgery. Long-term follow-up, pivotal to assess secondary cancer risk, may be jeopardized when patients travel from another hospital or from abroad. Moreover, after an intensive period of multimodality treatment and follow-up, patients and their parents may opt not to be confronted anymore with anything that reminds them of the “cancer period” and hence they are lost to follow-up (personal communication). Certainly, clinical practice (and patients) would benefit from large, multicentre studies on the clinical impact of proton beam therapy, but apparently the international collaboration between centres is not going without a hitch. In order to keep centres running, there is quite some rivalry between them, but also funding for this research is lacking.

[rr] In 2010 and 2011 there were 9 proton therapy centres in operation in the US (3 of which began treatments mid-2010) and 10 centres in 2012[187].

In the medical literature animated debates have been held on the necessity or ethical justification of performing randomized controlled trials to test proton beam therapy.[62, 188-190] The proton protagonists argue that it is ethically unacceptable to conduct RCTs comparing protons with photon RT, as the central requirement for performing RCTs, namely that there be equipoise between the arms of the trial, is not met.[189] The theoretical potential of PBT to lower radiation-induced toxicity in children (who are at least 10 times more sensitive to radiation-induced cancer[9]), supported by dosimetry, planning, and simulation studies, serves as their evidence base. The opponents argue that the equipoise required for an RCT is not between the treatment arms, but in the opinion of clinicians who manage the patients.[190] In the case of PBT, there may well be equipoise in the wider clinical community.[190] An improved dose distribution is not the equivalent of an improved clinical outcome; for most tumours, protons have not met the test of improved outcomes.[191] Given the fact that systematic reviews fail to demonstrate clear evidence of a clinical superiority for protons, it is difficult to understand why it would be unethical to perform randomized trials,[188, 190] except in those cases where there are manifest anatomical and physical reasons against the use of photons (e.g. low-grade glioma, craniopharyngioma, skull base chordoma and skull base osteosarcoma). Most certainly for prevalent indications (e.g. in adults), there should be no discussion on the necessity of proving PBT's superiority and cost-effectiveness through randomized clinical trials.

For children (and for adults with rare cancers), some mitigating factors may apply: in addition to the factors mentioned before, the number of children with cancer requiring radiotherapy as part of their treatment is so small that the likelihood that prospective randomized trials can be conducted to test if different dose distributions indeed make a clinical difference is very small.[192] In the meantime, it should not be ignored that the passive modulation of a proton beam results in a significant total-body dose of neutrons, which are very carcinogenic.[50, 70]

What we also learn from the literature is that, when compared to the total number of patients treated in proton centres, the proportion of children is small: in the US paediatric patients consisted of 10% (range, 2% to 24%), 12% (range, 1% to 30%), and 13% (range, 2% to 40%) of the total patients treated in 2010, 2011, and 2012 respectively. The surveyed centres treated at least one paediatric patient a year, with a range of 1 to 111 patients in 2010, 4 to 124 patients in 2011, and 6 to 140 in 2012.[187] As the treatment of children demands specific skills and precautions (e.g. anaesthesia is required in nearly half of the children in some or all sessions of the treatment[187]), the concentration of children in a restricted number of centres should be considered. In addition, some have plead for paediatric accreditation as a prerequisite for proton therapy in children.[12] Based on the BCR data (2004-2011), limited to the indications under study, it can be estimated that on average no more than 37 children (0-14 y.o.) and 14 adolescents a year may be eligible for proton beam therapy in Belgium.

In addition, as was pointed out earlier, the clinical application of proton beam therapy still has to contend with other serious technical limitations and disadvantages: the magnitude of the lateral penumbra, the uncertainty about the distal edge degradation, range inaccuracies, patient-position related uncertainties, operational difficulties and last but not least cost-effectiveness issues. With an increase in cost which was estimated at between 70% and 150%,[193, 194] anyone paying for the treatment - whether an individual patient, an insurance company, a health maintenance organization, or taxpayers - deserves to know how much better the outcomes are that they are buying. For prostate cancer this is since very recently an open-and-shut case (in the US): in June 2014, the American Society for Radiation Oncology (ASTRO) stated that proton therapy is not recommended for the primary treatment of prostate cancer outside of a prospective clinical trial or registry because the evidence for efficacy is not clear cut.[195] Meanwhile prostate cancer is in the US the most common indication for proton therapy referrals despite there being no evidence base to support it.[196] Actually, some stated that proton centres need to treat the prostates to subsidize the machine needed to treat the kids and the skull-based tumours; prostate cancer patients are considered as maintenance to enable the delivery of this unique therapy to the kids.[76]

Likewise, the ethical problem of opportunity costs, i.e. costs produced by doing one thing rather than another, deserves attention. When society spends about 30 million euros building a proton unit and every year a great deal of money maintaining that unit, then society is not spending those euros on something else. Maybe it would be better to spend cancer resources on tobacco control or HPV vaccination to reduce the risk of cervix cancer rather than proton therapy? (EC Halperin, personal communication)

In conclusion, to date clinical data on PBT in several paediatric cancers is lacking critical information on measures of long-term effectiveness and harm. Hence, prospective comparative clinical trials in the field are urgently needed. It is important that comparisons are made with contemporary radiation techniques (e.g. intensity-modulated radiation therapy, stereotactic body radiation therapy), as conventional radiotherapy planning and delivery have also evolved the last decades. In addition, as was suggested earlier, the establishment of a European Hadron Therapy Registry (EHTR), which holds (anonymised) data on patients treated by European centres providing hadron therapy would provide a simple but effective solution to the current lack of coherent published data.[197] In the US the Pediatric Proton Consortium Registry (PPCR) was recently installed for that purpose.[198]

Quality assurance is another important aspect not to be neglected; the protocols being developed by the PTCOG are an important initiative in that respect (http://www.ptcog.ch/index.php/clinical-protocols).

5 RECOMMENDATIONS[ss]

To the clinicians:

- **Patients (or their parents or representatives) should be fully informed that despite the physical underpinning of proton beam therapy, its clinical efficacy for the indications considered in this report has not yet been confirmed in clinical studies.**
- **Children should be referred to proton beam centres with the necessary expertise in treating children with that specific pathology and involved in clinical studies with long-term follow-up (if recruiting in Europe).**
- **The registration in the Belgian Cancer Registry (BCR) database of the chemotherapy regimen and radiotherapy schedule (including hadron therapy) administered in children is recommended. This registration can allow, amongst others, the monitoring of secondary malignancies occurrence.**

To the Technical Medical Council & the Insurance Committee of the RIZIV - INAMI:

- **The current reimbursement for PBT should be reevaluated periodically as new scientific evidence on effectiveness and safety becomes available. Meanwhile, the 15-year age limit should be reconsidered for certain indications.**
- **The amount reimbursed for radiotherapy in children should take into account the complexity of treatment administration, including the potential need for anaesthesia. The reimbursement should be made conditional to the registration into the BCR database.**

To the RIZIV - INAMI, BCR & FANC - AFCN and scientific/professional associations:

- **Our country should actively promote the set-up of a European Hadron Therapy Registry.**

Research agenda:

- **There is an urgent need for more research, not only on the clinical efficacy, side effects, and harms, but also on the economical aspects, and on the physics and biology. Clinical research should preferentially be conducted in an internationally coordinated way.**

[ss] KCE has the sole responsibility for the recommendations

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