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Australia and New Zealand Horizon Scanning Network

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Horizon Scanning Report

Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures

May 2007

ASERNIP-S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

Royal Australasian College of Surgeons

ISBN: 1-74186-257-4
Publications Approval Number: P3 -1873

Electronic copies can be obtained from http://www.horizonscanning.gov.au

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The production of this *Horizon scanning report* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and the New Zealand District Health Boards. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning report was prepared by Mr. Irving Lee from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

We acknowledge the contribution of Mr. David Tayler (New Zealand Health Information Service) for the data on number of registered cancer cases and public hospital separations in New Zealand.

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Executive Summary

In Australia, there were 85,231 new cancer cases and 35,366 cancer-related deaths in the year 2000 alone, while New Zealand reported 17,943 new cancer registrations in 2002. Cancer in responsible for approximately 30% of male deaths and 25% of female deaths in Australia, and is therefore a significant cause of mortality within this population. Contemporary management of cancers or life-threatening benign tumours often includes a multidisciplinary approach using a combination of surgery, radiotherapy, and chemotherapy specific for the tumour type, histologic grade and the stage of disease. Conventional radiotherapy commonly involves the use of ionising radiation in the form of X-rays or gamma rays (photons) which achieves tumour control by inducing DNA damage leading to cell death. However, the dose-distribution of photon radiotherapy leads to the irradiation of healthy tissue adjacent to the target tumour, potentially leading to substantial radiation-induced damage which may result in long-term morbidity or the development secondary tumours (see Figure 1). Currently there is a substantially more advanced photon beam delivery method known as intensity-modulated radiation therapy (IMRT) which enables delivery of higher radiation doses to the target tumour while reducing the dose delivered to healthy tissues. However, a key concern is that IMRT results in increased volume of healthy tissues irradiated due to the application of numerous radiation fields from different directions.

Proton beam therapy is a form of radiotherapy which is intended to treat tumours in patients where surgical excision is deemed impossible, too dangerous or unsuccessful. The key advantage of protons compared to photons is its superior dose-distribution profile (see Figure 1). Protons have a very rapid energy loss in the last few millimetres of penetration and therefore has a sharply localised peak dose known as the Bragg peak. By modulating the penetration depth of the protons (determined by the initial energy of the proton), it is possible to target the Bragg peak precisely to the target tumour while sparing the healthy tissue beyond the tumour from radiation. This could prove to be very useful in neoplasms involving, or adjacent to, cranial structures due to the proximity of the tumour(s) to critical structures. The proton beam procedure involves the construction of detailed treatment plans with the aid of 3D PET or CT scans to ensure the accurate delivery of the proton beam. The treatment plan is constructed with input from clinicians, medical physicists and dosimetrists, which will determine the precise angle, proton beam energy (to determine penetration) and the dose per treatment for each individual patient. During the actual treatment session, patients are immobilised with the use of custom made moulds which hold the entire body or the head and neck region completely still to prevent any movement that may compromise the accuracy of the proton beam.

To date, model studies/treatment-planning studies have unanimously concluded that proton beam therapy results in substantial dose-sparing to adjacent critical structures which should translates to lower toxicity and thus increased survival. Unfortunately, clinical studies have not consistently proven that proton beam therapy is significantly better compared to conventional photon therapy. The prevalence of proton radiation-

induced side effect in the studies included in this assessment appears to be within the range expected for conventional photon therapy, with some studies inferring that proton therapy is substantially safer. However the lack of consistency across studies and the lack of direct comparative studies severely limit the conclusiveness of these results. Meanwhile, most included studies reported local tumour control rates which are similar to conventional photon radiotherapy as well.

Goitein and Jermann (2003) estimated that the construction of a two-gantry proton facility would cost approximately €62,500,000; in comparison construction of an X-ray facility would cost €16,800,000. Operational costs per fraction were estimated to be €1025 for proton therapy and €425 for X-ray/photon therapy. It is likely that proton beam therapy will continue to be substantially more expensive compared to conventional photon therapy despite accounting for future cost reductions. Meanwhile, Lundkvist et al. (2005) reported that the average cost per QALY gained for the treatment of left-sided breast cancer, prostate cancer, head and neck cancer and childhood medulloblastoma with proton therapy was €10,130. However these calculations were attained utilising various assumptions which dilutes its conclusiveness and hence should be interpreted with caution.

In conclusion, the evidence for proton beam therapy in neoplasms involving, or adjacent to, cranial structures remains inconclusive. Further studies are required to determine if proton therapy is indeed substantially better compared to conventional radiotherapy, as inferred by numerous model/treatment-planning studies.

HealthPACT Advisory

The use of proton beam therapy as another form of radiotherapy for neoplasms has theoretical appeal but insufficient clinical evidence to contemplate its routine application at this time. Australia needs to maintain a watching brief on the ongoing international research, and revisit the evidence when contemplating the development of major new radiotherapy or synchrotron facilities in the larger capital cities.

Its introduction into Australia for treatment of the range of neoplasms studied thus far could only be considered in the context of research, and it would be more prudent to await the outcome of international research involving larger numbers of patients, preferably in randomised trials, before contemplating a commitment to such a substantial capital investment. The magnitude of the required capital investment, the strategic siting of such a facility, and the clinical governance arrangements would dictate the need for a national summit if the use of proton beam therapy was to be seriously considered in this country.

Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (HealthPACT) on the state of play of the introduction and use of proton beam therapy.

Proton beam therapy was developed as a means of treating tumours located adjacent to critical structures. If approved, this technology will be offered through a radiologist or specialist medical institutions.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with proton beam therapy.

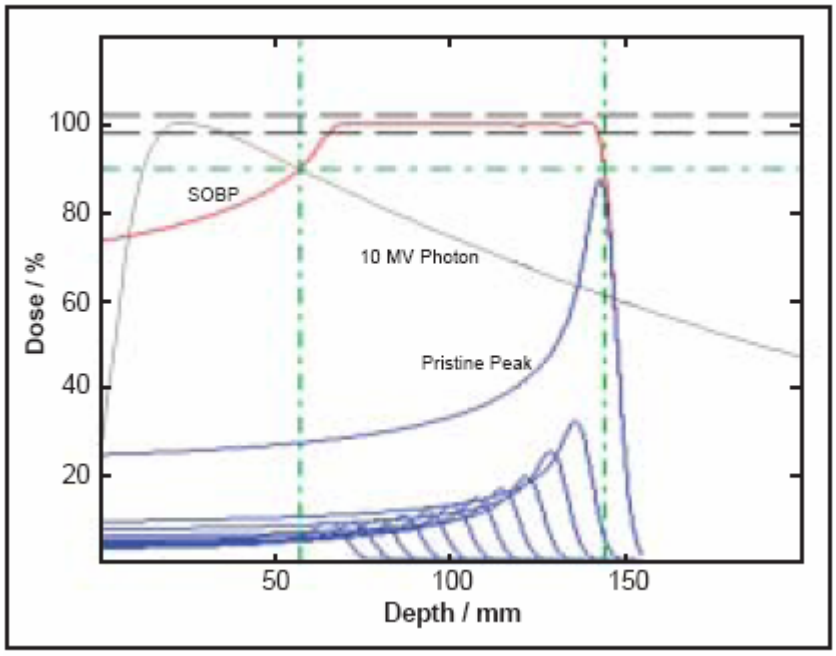
Description of the Technology

The Procedure

Conventional radiation therapy for the treatment of cancer involves the use of ionising radiation in the form of X-rays or gamma rays, both of which utilise photons. Radiation therapy is commonly used in the locoregional treatment of cancer whereby destruction of the tumour is achieved via radiation-induced DNA damage of tumour cells. However, the precise targeting of tumour cells is challenging in situations where the anatomical location of the target tumour is adjacent to radiation-sensitive critical structures. Further compounding the complexity of radiotherapy is the fact that lethal tumour doses are not always achievable, as high doses of conventional photon radiotherapy may induce damage to the surrounding healthy tissue, increasing the likelihood of radiation-induced long-term morbidity or secondary tumour growth (Levin et al. 2005). Recent advances in imaging and treatment planning software has resulted in the development of conformal radiotherapy treatments which enable better targeting of tumours. One of the latest developments is intensity-modulated radiation therapy (IMRT). IMRT delivers higher doses of photon radiation to the target tumour while reducing the dose delivered to surrounding normal tissues by applying numerous radiation fields of varying intensities from different directions (DeLaney et al. 2005). However, concerns have been highlighted that IMRT actually increases the volume of tissue exposed to irradiation (due to the multidirectional radiation). Although the overall dosage to normal tissues is lower, this increased exposure of healthy tissue to low-dose radiation may result in a second malignancy or other potentially dangerous tissue defects (DeLaney et al. 2005, Levin *et al.* 2005).

Charged particle radiotherapy has garnered substantial interest, in particular proton therapy techniques due to the fact that protons have a superior dose distribution compared to photons. Protons deposit very little energy in the tissues until the end of the proton energy range. This results in a sharply localised peak of radiation dose known as the Bragg peak (Figure 1). The penetration depth of the Bragg peak is directly related to the initial energy of the charged particle, therefore the desired dose can be precisely targeted to the culprit tumour. When proton beams are utilised for tumour irradiation, the beam energy is modulated by superimposing multiple Bragg peaks of descending energies and weights to create a spread (spread Bragg peak) of uniform radiation dose over the depth of the target tumour (DeLaney et al. 2005). A spread Bragg peak is essential for the successful application of this technology in tumour control as a single concentrated Bragg peak is considered too narrow for practical clinical applications (Figure 1) (DeLaney *et al.* 2005). Importantly, the application of multiple Bragg peaks does not alter the proton's dose distribution and it is still characterised by a lower-dose region in the healthy tissue proximal to the tumour, a uniformly high-dose region within the tumour and zero dose beyond the tumour (DeLaney et al. 2005). In comparison, photon therapy (X-rays) delivers the maximum radiation dose to the surrounding normal tissue instead of the tumour itself (Figure 1) (Levin et al. 2005).

Figure 1: Depth-dose curve



Depth-dose distributions for a spread-out Bragg peak (SOBP), its constituent pristine proton Bragg peaks and a 10MV photon beam.

DeLaney et al. (2005)

Patients undergoing proton beam therapy are immobilised to ensure the same position is maintained throughout the treatment with respect to the proton beam. This is achieved with the use of custom made moulds which either hold the entire body or just the head or neck (for tumours of the head and neck region) completely still to ensure that the tumour is accurately targeted by the proton beam. Patients receiving this treatment will be required to undergo computed tomography (CT) sometimes complemented by positron emission tomography (PET) scanning to document the exact location of the tumour as well as the density of the surrounding tissue. Utilising the 3D scans obtained from CT/PET scanning, a treatment plan is constructed with specialised software in conjunction with clinician, medical physicist and dosimetrist input; therefore determining the target angle, proton beam energy and dose per treatment (similar to that of conventional photon therapy). The proton beam is delivered at the precise angle set by the treatment plan via large gantries which can be rotated 360˚. According to the Loma Linda University Medical Centre (LLUMC), each treatment cycle lasts between 20 to 40 minutes with most of this time spent on positioning the patient correctly. Protons are generated within a linear accelerator and are injected into a synchrotron where they are accelerated to high energies. When the protons are extracted, they can be delivered down a beam line either via the gantry or to horizontal beam lines (LLUMC 2006).

Intended Purpose

Proton beam therapy is intended to treat tumours in patients where surgical excision is deemed impossible, too dangerous, or unsuccessful. The first published use of proton

beam therapy was in 1954 (Chalmers 2003), however the extremely high cost of producing charged particles like protons has inhibited its widespread usage.

The improved dose-distribution that can be achieved with proton beam therapy enables this form of radiotherapy to be considered for the treatment of tumours that are located close to critical structures such as the spinal cord, eyes and brain. To date, proton beam therapy has been utilised in the treatment of various cancers, including: ocular/uveal melanoma, skull base and spine sarcomas, benign meningiomas, paranasal sinus, nasal and nasopharyngeal tumours, carcinoma of the prostate, hepatocellular carcinomas and early-stage lung cancers (Bush et al. 2004, Chiba et al. 2005, Levin et al. 2005).

Clinical Need and Burden of Disease

In comparison to adult cancers, paediatric malignancies are considered rare, usually accounting for less than 1% of all tumours diagnosed annually (Noel et al. 2003a). Approximately 20% of all paediatric malignancies are central nervous system tumours (Kirsch et al. 2004). Although many childhood malignancies are cured, the acute toxicity of therapy and significant late treatment effects make these tumours a substantial burden for patients, their families and society. Radiation therapy is frequently employed alone or as part of a multi-modality treatment approach in combination with surgery and chemotherapy. This is due to the fact that successful excision of the tumour is difficult, and is often impeded by the location of the tumour (adjacent to critical structures) (Kirsch et al. 2004). Cranial irradiation in paediatric patients can result in hearing loss, interfere with intellectual development, and affect the hypothalamic-pituitary axis (leading to growth retardation). Proton beam therapy therefore has a potentially significant role in this area due to the high level of precision and potentially advantageous dose-distribution characteristics required to prevent or minimise damage to surrounding critical structures.

In adults, the treatment of neoplasms involving, or adjacent to, cranial structures are considered very challenging due to the close proximity of critical structures. Sarcoma of the skull base and spine are adjacent to the brain, brainstem, cervical cord, optic nerves, optic chiasm and the spinal cord. Meanwhile, chordomas and chondrosarcomas (uncommon, slow-growing neoplasms) often arise in the clival area and both tumours tend to grow posteriorly towards the brain stem. In addition, adjacent structures, the medulla oblongata and brainstem, have relatively low radiation tolerance (Blomquist et al. 2005). Surgery-related complications are frequently observed with figures up to 40% reported in previous studies (Noël et al. 2002). Another example, pituitary adenomas, comprise approximately 10% to 12% of all intracranial tumours (Ronson et al. 2006) and despite their benign histology they can cause substantial morbidity and occasional mortality due to their detrimental effects on hormonal balance and functional deficits while craniopharyngiomas (within the sellar and supersellar region) may cause blindness, permanent hormonal deficiency, or death despite being benign (Fitzek et al. 2006).Therefore, more specific radiation therapy that reduces the risk of sequelae as a result of therapy could be highly beneficial in children and adults with these forms of tumours.

In the year 2000, excluding skin cancers other than melanoma, there were 85,231 new cancer cases and 35,466 deaths due to cancer in Australia. At the incidence rates prevailing in 2000, it would be expected that 1 in 3 men and 1 in 4 women would be diagnosed with a malignant cancer in the first 75 years of life. In addition to this, the Australian Institute of Health and Welfare estimated that 253,000 potential years of life would be lost to the community as a result of people dying of cancer in 2000 before the age of 75. The latest data states that cancer accounts for 30% of all male deaths and 25% of female deaths. A total of 35,628 deaths registered in 2000 had malignant cancer as the underlying cause while cancer was attributed as the associated cause of death in 4,289 Australians (AIHW 2006). Between 1990 and 2000, the age-standardised incidence rates for all cancers combined (except skin cancers other than melanoma) increased for males by an average of 4.4% per annum until 1994 then declined by an average 2.1% per annum until 2000. For females, the age-standardised rates increased by an average of 1.9% until 1995 and remained relatively stable up to 2000 (AIHW 2006).

In New Zealand, the number of new cancer registrants in 2002 was 17,943 of which 52.4% were male and 47.6% were female. The number of new registrations was 1.7% lower compared to 2001 for males and 2.3% higher for females, meanwhile new cancer registrations for the Māori population increased by 6.3% from 1135 in 2001 to 1207 in 2002. There were a total of 7800 cancer deaths in 2002, 4,125 males and 3,675 females, which was similar to 2001 (7810 deaths). The age-standardised cancer mortality rate for males was 142.8 per 100,000 male population, while the female age-standardised rate was 104.9 per 100,000 female population. The overall New Zealand mortality rate for cancer was 120.9 per 100,000 population, a reduction from the 2001 mortality rate of 125.8 deaths per 100,000 population (New Zealand Health Information Service 2006).

The following table summarises the incidence for intracranial and paediatric cancers in Australia and New Zealand that could potentially be treated with proton beam therapy (Table 1).

Table 1: Incidence rates of selected cancers in Australia and New Zealand.

a) Brain and other central nervous system

Principal diagnosis	Number of new cases, Australia (2001)	Number of public hospital separations, Australia (2001-2002)	Number of registered cases, New Zealand (2002)	Number of public hospital separations, New Zealand (2002)
Brain (C71)	1348	4620	280	713
Meninges and other central nervous system (C70, C72)	73	250	9	50

b) Paediatric cases (age 0 – 14 years)

Principal diagnosis	Number of new cases, Australia (2001)	Number of public hospital separations, Australia (2001-2002)	Number of registered cases, New Zealand (2002)	Number of public hospital separations, New Zealand (2002)
All cancer sites (C00-C97)	603	11000	112	1539

AIHW 2006, New Zealand health Information Service 2006

Stage of Development

At the time of writing, over 39,000 patients worldwide have received part or all of their radiation therapy by proton beams (Levin *et al.* 2005). As stated previously, proton beams were initially used for high-energy physics research and therefore the initial clinical use of proton therapy very cumbersome due to the large equipment. One of the pioneering centres of proton beam therapy was the Harvard Cyclotron Laboratory in Cambridge, Massachusetts. Patient treatment with proton therapy began in the centre in 1961 up to 2002; at that point the clinical programme was transferred to the Northeast Proton Therapy Centre at Massachusetts General Hospital (Levin *et al.* 2005).

As technology progressed, hospital-based cyclotrons were developed and were capable of producing higher energy beams (hence deeper penetration) with field sizes comparable to linear accelerators and rotational gantries that assist in ensuring accurate targeting of the tumour. One of the first hospital-based facilities was opened at the Loma Linda University in California, 1990 (Levin *et al.* 2005, LLUMC 2006). A list of operational proton therapy centres is provided in Table 2:

Table 2: Operational proton therapy centres

Country/Facility	Date of first treatment	Recent patient total	Date of total
Canada			
TRIUMF	1995	89	December 2003
England			
Clatterbridge	1989	1287	December 2003
France			
Nice	1991	2555	April 2004
Orsay	1991	2805	December 2003
Germany			
HMI, Berlin	1998	439	December 2003
Italy			
INFN-LNC, Catania	2002	77	June 2004
Japan			
Chiba	1979	145	April 2002
NCC, Kashiwa	1998	270	June 2004
HIMBC, Hyogo	2001	359	June 2004
PMRC, Tsukuba	2001	492	July 2004
WERC	2002	14	December 2003

Shizuoka	2003	69	July 2004
Russia			
ITEP, Moscow	1969	3748	June 2004
St. Petersburg	1975	1145	April 2004
Dubna	1999	191	November 2003
South Africa			
iThemba Labs	1993	446	December 2003
Sweden			
Uppsala	1989	418	January 2004
Switzerland			
PSI	1984	4066	June 2004
PSI	1996	166	December 2003
United States			
Loma Linda	1990	9282	July 2004
UCSF-CNL	1994	632	June 2004
NPTC, MGH	2001	800	July 2004

Levin et al. 2005

Australian Therapeutic Goods Administration approval

Proton beam therapy is currently not available in Australia or New Zealand in clinical practice or trials.

Treatment Alternatives

Existing Comparators

To date, the treatment of tumours is rather diverse and the selection of a treatment modality is dependant on the type and location of the tumour. Chemotherapy, radiotherapy, biological therapy, photodynamic therapy, laser therapy, gene therapy and anti-angiogenesis drugs are some of the options currently available for the treatment of tumours. These treatment modalities may be utilised in combination to ensure effective locoregional and systemic control of the target tumour (National Cancer Institute 2006, Cancer Research UK 2006).

Radiation therapy in itself is a varied treatment, which can be categorised into external radiation therapy, internal radiation therapy and systemic radiation therapy:

a) External radiation therapy
External radiation therapy[1] is utilised to treat various solid tumours, such as cancer of the bladder, brain, breast, cervix, larynx, lung, prostate, and vagina. Intraoperative radiation therapy (IORT) is a form of external radiation given during surgery after surgical resection to treat localised cancers that cannot be completely removed or have a high risk of recurring in adjacent tissues. Another form of external irradiation is prophylactic cranial irradiation; this technique is targeted to the brain in situations where the primary cancer has a high risk of spreading to the brain (National Cancer Institute 2006). The latest developments in external radiation therapy also include

[1] External radiation therapy often uses a photon energy source (X-ray, gamma rays etc.)

intensity-modulated radiation therapy (IMRT) and other charged particle radiation therapies (e.g. carbon ions and protons) (Levin *et al.* 2005).

b) Internal radiation therapy
Internal radiation therapy (also known as brachytherapy) involves the implantation of a radiation source[2] within (or adjacent to) the tumour to induce cell death. This treatment is used to treat prostate, cervical, ovarian, breast, oral, rectal, uterine, head and neck tumours (National Cancer Institute 2006).

c) Systemic radiation therapy
Systemic radiation therapy involved the ingestion or injection of radioactive materials such as Iodine 131 and Strontium 89. This therapy is sometimes used to treat cancer of the thyroid and adult non-Hodgkin's lymphoma (National Cancer Institute 2006).

Clinical Outcomes

There is a considerable amount of literature describing the use of proton beam therapy for patients with various types of cancer. The majority of studies included in this assessment are case series (level IV Intervention evidence) which limits the validity of comparisons with other approaches. This Horizon Scanning report will focus on central nervous system, head and neck tumours in children and adults only, with a second report to be produced on ocular tumours at a later date.

It is important to note that due to the heterogeneity between the included studies, it may be impossible to compare results in a meaningful manner. The studies presented in this assessment will include case series that utilised proton beam therapy in combination with other treatment modalities (e.g. photon therapy), therefore potentially large variations in clinical outcomes are expected.

The radiation dose administered is reported in Gy (Grays) or CGE (Cobalt Gray Equivalent). CGE is defined as 'Gy x Relative Biological Effectiveness (RBE)[3]'. The RBE for protons is 1.1 (photon RBE: 1.0).

The main effectiveness outcomes were overall survival, disease/recurrence free survival and local control.

[2] An implant in the form of wires, catheters, ribbons, capsules or seeds.
[3] RBE: A measure of the capacity of a specific ionising radiation to produce a specific biological effect, expressed relative to a reference radiation.

Safety

Safety outcomes will be subdivided to paediatric and adult tumours. In addition, the stage and type of tumour affects the frequency and severity of acute and late adverse events, therefore making it difficult to differentiate between normal survival rates/adverse events and those associated with proton beam therapy treatment.

Certain studies present normal tissue complications/toxicity according to the Late Effects on Normal Tissues (LENT) - Subjective, Objective, Management and Analytic (SOMA) (a.k.a. LENT/SOMA) evaluation scales. The higher the grade allocated, the more severe the complication. Grade 1 and 2 toxicities/complications/side-effects are considered mild while Grade 3 and upwards are considered severe.

Cancer related mortality is not reported in the safety section as survival is one of the main effectiveness outcomes reported in the next section. Treatment related mortality was rarely reported in the included studies.

Paediatric head and neck tumours

Clinical studies on paediatric neoplasms involving, or adjacent to, cranial structures will be presented followed by a discussion on several comparative model/treatment-planning studies.

Clinical Studies

The following table (Table 3) summarises the safety outcomes of several clinical case series studies where paediatric patients with cranial, central nervous system (CNS) or brain tumours were treated with proton beam therapy:

Table 3: Safety outcomes of paediatric patients treated with proton beam therapy.

Study	Study Design	Population (Mean/Median follow-up)	Safety outcomes
Benk *et al.* (1995) Case series *Photon and proton irradiation for base of skull and cervical spine chordomas*	Case series (Level IV evidence) Fractionated proton + photon RT All patients had undergone surgical resection (incomplete) <u>Median dose</u>	18 paediatric patients (median: 72 months)	<u>Late side effects</u> Two patients (11.1%) developed growth hormone deficit that was corrected with hormone replacement. Three patients (16.7%) had some hearing impairment. One case (5.5%) of temporal lobe necrosis. One case (5.5%) of fibrosis of the temporalis muscle, improved with surgery.

	69 CGE		
Hug *et al.* (2002a) *Proton radiotherapy of base of skull tumours*	Case Series (Level IV evidence) Fractionated proton+photon RT All patients had undergone either surgical resection or biopsy. <u>Median dose</u> Malignant: 71.1 CGE Benign: 60.4 CGE Some patients may have received concurrent chemotherapy.	29 paediatric patients (14 males, 15 females) with mesenchymal tumours. (mean: 40 months)	<u>Acute side effects</u> Most patients had side effects consisting: temporary epilation of treatment area, skin erythema, occasional headaches, fatigue, loss of appetite, oropharyngeal muscositis. One patient developed a late acute reaction with severe headaches 4 weeks post-proton therapy. No treatment breaks required for patients who underwent proton therapy alone. One patient who had concurrent chemotherapy experienced 2 weeks treatment interruption. <u>Late side effects</u> Severe late effects noted in 2 patients (7%): One patient required 2 additional surgical resections for posterior fossa tumour regrowth. One patient developed temporal lobe damage within 6 months. Eight patients (27%) with intra- and parasellar tumours developed pituitary insufficiencies and required hormone replacement therapy.
Hug *et al.* (2002b) *Conformal proton radiation for astrocytomas*	Case series (Level IV evidence) Conformal fractionated proton RT Some patients had surgical resection <u>Mean dose</u> 55.2 CGE	27 paediatric patients (14 males, 13 females) with progressive or recurrent low-grade astrocytoma. (mean: 36.9 months)	Side effects were within the expected range of Grade 1-2 on the LENT-SOMA scale. Treatment related side effects: Four patients (14.8%) with tumours in the immediate proximity of the pituitary gland developed hypopituitarism post-treatment. One case (3.7%) of asymptomatic changes of the brain parenchyma near the irradiated tumour. One case (3.7%) of acute onset of Moyamoya disease, resolved with bilateral vascular bypass.
McAllister et al. (1997) *Proton therapy for paediatric cranial tumours*	Retrospective Case series (Level IV evidence) Fractionated proton alone/photon with proton boost 16 patients	28 paediatric patients with various cranial tumours (median: 25 months)	Four patients with site-specific treatment related morbidity: Two patients (7%) had new onset of seizures One patient (3.5%) developed cataract One patient (3.5%) required more hormonal replacement treatment for pituitary adenoma

	had undergone surgical resection(s), 10 had chemotherapy. <u>Median dose</u> Proton alone: 54 CGE Photon + proton boost: 36 Gy + 18 CGE		
Noel *et al.* (2003a) Case series *Proton beam therapy for CNS tumours*	Case series (Level IV evidence) Fractionated proton + photon RT 15 patients had undergone surgical resection. <u>Median dose</u> Photon: 40 Gy Proton: 20 CGE	17 paediatric patients (11 males, 6 females) with benign (6 cases) or malignant (11 cases) intracranial tumours. (mean: 27 months)	<u>Acute treatment related side effects</u> Various degrees of localised alopecia, erythema, headaches, and moderate hearing loss related with external or medial otitis. All side effects resolved within 1 month. <u>Late side effects</u> One case (5.9%) of neuropsychological impairment the resulted in grade 1 memory loss. One case (5.9%) of panhypopituitarism that improved after hormonal replacement. One case (5.9%) of neurological deterioration.

* Interpretation of some of these studies was confounded by concomitant use of photons, chemotherapy or prior surgical resection.

Overall, the clinical studies presented above indicate that proton beam therapy does not result in high rates of treatment-related adverse events when utilised to treat intracranial tumours in paediatric patients (Table 3). The acute side effects observed in the selected studies were judged to be within acceptable ranges considering the anatomic locations and the high doses required in patients with malignant histology. The most common toxicity across all studies was pituitary insufficiency, occurring in 3.5% to 27% of patients post-treatment (Table 3).

Model/treatment planning studies

The retrospective treatment planning study by Lee et al. (2005) compared the amount of radiation imposed upon surrounding tissues between conventional techniques (3D-conformal radiation therapy and electron therapy) and the newer modalities of IMRT and proton therapy in paediatric patients. Utilising treatment planning CT images, Lee et al. (2005) outlined pertinent structures appropriate for each tumour type and transferred it to three different software systems (Philips 3D treatment planning

system, NOMOS Corvus 5.0 and Varian Eclipse Proton Treatment Planning System) to generate optimised treatment plans. Table 4 outlines the medulloblastoma posterior fossa irradiation dose-volume histogram (DVH) analysis obtained from this study. Overall, all three techniques demonstrated good target coverage with a minimum of 96% of the volume receiving the prescribed dose of 30.6 Gy. However, substantial reduction in total tissue volume irradiated was observed for proton therapy, particularly in regards to the cochlea and hypothalamus-pituitary axis, compared to 3D-CRT and IMRT (Lee et al. 2005). This decreased volume of irradiation should correspond to lower risk of developing hearing, hormonal and growth defects secondary to radiotherapy. Unfortunately direct comparative clinical studies have not been published to verify this.

Table 4: Medulloblastoma posterior fossa irradiation DVH analysis

Structure, DVH dose level	Mean % volume for each technique		
	3D-CRT	IMRT	Protons
Target volume coverage	96	96	97
Cochlea			
20 Gy	89	87	34
25 Gy	64	33	6
Hypothal-pituitary			
10 Gy	91	81	21
30 Gy	0	0	0
Mandible			
10 Gy	21	1	0
15 Gy	0	0	0
Optic chiasm			
20 Gy	19	2	0
30 Gy	0	0	0
Eye			
20 Gy	0	0	0
Spinal cord			
30 Gy	0	0	0

3D-CRT: Three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy.

Lee et al. (2005)

Further to this, the model study performed by Lin et al. (2000) comparing proton therapy and conformal photon therapy of the posterior fossa reported comparable results, with > 99% of the posterior fossa receiving > 95% of the prescribed dose (54 Gy) in both treatment modalities and substantial reduction in unwanted radiation within sensitive auditory structures when utilising proton therapy. The average mean dose received by adjacent auditory structures (as a percentage of the prescribed dose) is presented in Table 5.

Table 5: Average mean (± SD) doses received by adjacent auditory structures as a percentage of the prescribed dose (54 Gy).

	Cochlea	Inner ear	Middle ear	Temporal lobe
Proton therapy	25 ± 4%	46 ± 6%	10 ± 6%	22 ± 5%
Photon therapy	75 ± 6%	90 ± 3%	54 ± 4%	64 ± 5%

Lin et al. (2000)

Both model studies (Lee et al. 2005, Lin et al. 2000) on paediatric patients demonstrated substantial dose reduction to adjacent structures, with results indicating approximately three- to four-fold reduction in volume irradiated (Lee et al. 2005) or two- to five-fold reduction in average mean dose (Lin et al. 2000). In addition to this, two other model/treatment planning studies based on paediatric medulloblastomas have concluded that proton therapy offers substantial advantages in dose reduction to critical structures (St. Clair et al. 2004) and predicted reduction of neuropsychologic morbidity (Miralbell et al. 1997) compared to various photon treatment plans. However, it is important to note that despite the apparent large advantage proton therapy confers compared to photons, IMRT is capable of substantial dose reduction to adjacent structures as well. This can be noted in Table 4 where volume irradiated was two-fold lower for the cochlea (at 25 Gy) and 21-fold lower for the mandible in IMRT plans (Lee et al. 2005) and outcomes from these reduced doses is not determined.

Miralbell et al. (2002) attempted to quantify the potential reduction of radiation induced secondary cancer incidence when utilising proton beam therapy in the treatment of paediatric tumours. The estimation of secondary cancer incidence was conducted with a model based on the guideline of the International Commission on Radiologic Protection (ICRP) utilising two sets of CT images, one from a patient with parameningeal rhabdomyosarcoma and another from a patient with medulloblastoma. This model permits the estimation of absolute risks of secondary cancer for each treatment plan based on dose-volume distributions of non-target organs. The estimated absolute yearly rate of secondary cancer for both cases (rhabdomyosarcoma and medulloblastoma) is presented in Table 6.

Table 6

a) Estimated absolute yearly rate (%) of secondary cancer incidence after treating a parameningeal rhabdomyosarcoma with either X-rays, intensity modulated X-rays, proton beams or intensity modulated proton beams.

	X-rays	IM X-rays	Protons	IM protons
Yearly rate (%)	0.06	0.05	0.04	0.02
Relative risk compared to standard X-ray plan	1	0.8	0.7	0.4

IM: Intensity modulated

b) Estimated absolute yearly rate (%) of secondary cancer incidence after treating a medulloblastoma case with either conventional X-ray, intensity modulated X-ray or proton beams.

Tumor site	X-rays (%)	IM X-rays (%)	Protons (%)
Stomach and oesophagus	0.15	0.11	0.00
Colon	0.15	0.07	0.00
Breast	0.00	0.00	0.00
Lung	0.07	0.07	0.01
Thyroid	0.18	0.06	0.00
Bone and connective tissue	0.03	0.02	0.01
Leukemia	0.07	0.05	0.03
All secondary cancers	0.75	0.43	0.05

Relative risk compared to standard X-ray plan	1	0.6	0.07

IM: Intensity modulated

Miralbell et al. 2002

The model suggested that for both cases (rhabdomyosarcoma and medulloblastoma) proton therapy was associated with lower risks of secondary cancer incidence, particular in the case of medulloblastoma (Table 6b) where the relative risk was estimated to be approximately 14-fold lower compared to standard X-ray treatment. The relative risk of secondary cancers for proton therapy in the parameningeal rhabdomyosarcoma case was less pronounced (relative risk: 0.7), however the implementation of intensity modulated proton therapy resulted in substantial risk reduction, which was estimated to be 2.5-fold lower compared to conventional X-ray and 2-fold lower compared to intensity modulated X-ray therapy (Table 6a) (Miralbell et al. 2002).

Neoplasms involving, or adjacent to, cranial structures in adults

The following tables (Table 7 - 12) summarises the safety outcomes for patients treated with proton beam therapy (possibly in combination with other modalities) for adults with various neoplasms involving/adjacent to cranial structures.

a) Meningiomas

Meningiomas constitute approximately 15% to 20% of all primary intracranial neoplasms in adults with benign meningiomas being the most common histology. Total surgical resection is the standard treatment for meningiomas. However, skull base meningiomas, especially around the cavernous sinus and petro clival area, are difficult to mange surgically due to the anatomical location and critical structures within the proximity. Based on these facts, it is not surprising that surgical excision carries a high risk of neurologic morbidity (54% to 60%) (Vernimmen et al. 2001). Radiotherapy has been utilised as an alternate treatment with varying success, the following table (Table 7) outlines the safety outcomes of patients treated with proton therapy for meningiomas (benign, atypical and malignant):

Table 7: Safety outcomes for adult patients treated with proton beam therapy for meningiomas.

Meningiomas			
Study	**Study Design**	**Population (Mean/Median follow-up)**	**Safety outcomes**
Gudjonsson et al. (1999) Case series *Stereotactic proton irradiation of skull base meningiomas*	Case Series (Level IV evidence) Stereotactic fractionated proton RT Most patients had undergone	19 patients with meningiomas (4 males, 15 females) (mean: 36 months)	Two patients (11%) developed corticosteroids responsive oedema in the target area 6 months after treatment. <u>Late side effects</u> One late side effect (5%) noted, no details provided.

	surgical resection. <u>Mean dose</u> 24 Gy		
Hug et al. (2000) Case series *Proton and photon therapy for atypical and malignant meningiomas*	Case Series (Level IV evidence) Proton + photon RT (48% had photon only) Most patients had undergone gross total or subtotal resection. <u>Mean dose</u> Atypical: 62.5 CGE Malignant: 58 CGE	31 patients with meningioma - 15 atypical, 16 malignant. (mean: 59 months)	No treatment breaks required due to severity of acute side effects. All early side effect were within the expected range (details not provided). <u>Late side effects</u> 3 patients (9%) experienced late side effects: 1 patient developed necrosis of brain parenchyma. 1 patient developed symptomatic necrosis within the high-dose region. 1 patient developed extensive visual deficits.
Nöel et al. (2002) Case series *Conformal fractionated proton beam therapy for meningiomas*	Case Series (Level IV evidence) Proton + photon RT Some patients had undergone partial (n=6) or gross (n=2) resection. <u>Mean dose</u> GTV: 61 CGE CTV: 55 CGE	17 patients (7 males, 10 females) with meningioma (mean: 37 months)	<u>Acute side effects</u> 3 patients (18%) who presented cephalgia during irradiation required steroid treatment <u>Late side effects</u> One patient (6%) had partial hypopituitarism at 12 month. One patient (6%) had transient paresthesia of the extremities at 6 months without evidence of tumour progression. Two patients (12%) had slight memory troubles (grade 1) at 23 and 28 months. One patient (6%) experienced mild hearing loss (grade 2) at 35 months. Two patients (12%) had prolonged alopecia (grade 3) for more than 6 months.
Vernimmen et al. (2001) Case series *Stereotactic proton beam therapy for skull base meningiomas*	Case Series (Level IV evidence) Stereotactic (SRT)/ Hypofractionated (HSRT) proton RT Some patients (65%) had undergone	27 patients with intracranial meningiomas (mean: HSRT 40 months, SRT 31 months)	<u>Acute side effects</u> 2 patients (11%) in the hypofractionated stereotactic radiotherapy (HSRT) group developed transient new cranial nerve neuropathy. No patients suffered from nausea or vomiting post therapy. No stereotactic radiotherapy (SRT) patients had acute side effects. <u>Late side effects</u> 2 HSRT patients (11%) developed late side

	surgical resection/biopsy <u>Mean dose</u> HSRT: 16.3 – 20.3 CGE SRT: 54 – 61.6 CGE		effects: 1 patient had ipsilateral partial hearing loss. 1 developed temporal lobe epilepsy. One SRT patient had short-term memory disturbance.
Weber *et al.* (2004) Case series *Proton radiotherapy for intracranial meningiomas*	Case Series (Level IV evidence) Proton RT Most patients had undergone surgical resection. <u>Mean dose:</u> GTV: 55.8 CGE CTV: 54.5 CGE	16 patients (3 males, 13 females) with intracranial meningioma (mean: 34.1 months)	<u>Acute side effects</u> Focal alopecia and skin erythema were most common transient (numbers not stated). Five cases (31%) of discrete gum lesions after mechanical positioning of vacuum-bite block. <u>Late side effects</u> Three patients (19%): One case optic nerve sheath meningioma causing sudden visual field deterioration. One case extensive left sphenoid sinus meningioma. One case of left-side hemiparesis due to right frontal lesion associated with severe oedema. <u>Visual complications</u> One case of retinitis (9.1%). One case of radiation optic neuropathy (9.1%). One case of worsening visual acuity and was registered blind 36 months post-treatment (9.1%).
Wenkel et al. (2000) Case series *Combined proton and photon therapy for benign meningiomas*	Case Series (Level IV evidence) Fractionated proton+photon RT All patients had undergone biopsy or subtotal resection. <u>Mean dose</u> GTV: 61.4 CGE CTV: 52.1 CGE	46 patients with partially resected, biopsied or recurrent meningiomas. (mean: 73 months)	<u>Acute side effects</u> 5 patients (11%) had acute toxicity: 3 patients developed moist desquamation in the skin and scalp. 1 patient severe otitis. 1 patient developed fibrinous mucisitis. <u>Late side effects</u> 8 patients (17%) developed long-term toxicities of grade 3 or 4: This includes 4 ophthalmologic, 4 neurologic and 2 otologic complications.

* Interpretation of some of these studies was confounded by concomitant use of photons or prior surgical resection.

The reported frequency of acute side effects ranged from 11% to 18% while late side effects ranged from 9% to 42% in studies which utilised proton beam therapy for the treatment of meningiomas (Table 7). Previous studies utilising photon radiotherapy have reported treatment-related morbidity to range between 2.2% to 30% (Wenkel *et al.* 2000), with the complication rate closely related to the applied dose, volume irradiated and the percentage of patients with tumours adjacent to sensitive intracranial structures. Wenkel et al. (2000) reported relatively high rates of long-term grade 3 and 4 toxicities (17%); however the authors have cited the unfavourable location of tumours in this series and the relatively high dose (median: 59 CGE) required to achieve local control as the contributing factors to the high rate of severe toxicity observed in this study. It appears therefore, that the rates of severe long-term toxicity were probably acceptable owing to the disadvantageous location of the tumours within this cohort. Interestingly, all patients treated with ≤ 54 CGE did not experience any form of ophthalmologic toxicity (Wenkel *et al.* 2000), indicating that perhaps the optic nerves and chiasm are resistant to damage up to 54 CGE. Weber et al. (2004) reported that ophthalmic toxicities were confined to patients who received excessive radiation doses (Weber et al. 2004) therefore leading to the conclusion that radiation dose to the optic structures should be limited to 54 CGE, reflecting the findings of Wenkel et al. (2000). Noël et al. (2002) reported relatively high rates of complications, however in contrast to Wenkel et al. (2000) there were no incidences of severe side effects despite the high dose administered (median: 61 CGE). This may be due to the implementation of fractionated doses, therefore limiting the amount of radiation administered at each treatment session.

b) Chordoma and chondrosarcomas

The following table (Table 8) summarises the results of proton therapy for the treatment of chordomas and chondrosarcomas in adults.

Table 8: Safety outcomes for adult patients treated with proton beam therapy for chordoma and chondrosarcomas.

Chordoma and chondrosarcoma			
Study	**Study Design**	**Population (Mean/Median follow-up)**	**Safety outcomes**
Hug *et al.* (1999) Case series *Proton therapy for chordoma and chondrosarcomas of skull case*	Case Series (Level IV evidence) Proton RT Most patients (n=55) had undergone surgical resection. <u>Mean dose</u> 70.7 CGE	58 patients with skull base chordomas or chondrosarcomas (mean: 33.2 months)	<u>Acute side effects</u> Varying degrees of temporal epilation, headaches, loss of appetite, fatigue, as well as occasional nausea and vomiting. All controlled symptomatically. <u>Late side effects</u> Four patients (7%) had grade 3 or 4 toxicities. 3 (5%) were symptomatic. Four patients (7%) had partial pituitary insufficiency, all required hormone replacement therapy (Grade 1 and 2). Four patients (7%) had unilateral hearing deficits

			(Grade 1 and 2).
Igaki *et al.* (2004) Case series *Proton beam therapy for skull base chordoma*	Case Series (Level IV evidence) Proton + photon RT All patients had partial/ subtotal resection or biopsies. <u>Median dose</u> 72 Gy	13 patients with skull base chordoma. (median: 69.3 months)	<u>Acute side effects</u> Three cases of headaches (two grade 1, one grade 2) (23%). One case of nausea (grade 1) (7.7%). <u>Late side effects</u> Two cases of brain necrosis (grade 4 and grade 5) (15.4%). One case of oral ulceration (7.7%).
Nöel et al. (2003b) Case series *Proton and photon therapy for chordoma and chondrosarcoma*	Case Series (Level IV evidence) Fractionated proton + photon Most patients had undergone surgical resection <u>Mean dose</u> 66.7 CGE	67 patients (49 with chordoma, 18 with chondrosarcoma) (median: 29 months)	<u>Acute side effects</u> Various degrees of partial alopecia, erythema, headaches, and moderate hearing loss associated with external or medial ostitis (numbers not stated). All subsided within 1 month. <u>Late side effects</u> Total of 32 patients (49%) had late side effects: 16 (24%) experienced total (14) or partial (2) failure of the anterior pituitary. Most common symptom was fatigue. All patients required hormone replacement (grade 2, RTOG). 12 patients (grade 2, RTOG, 18%) had mild hearing loss. One patient had memory impairments and a mild decline in psychomotor speed. Four cases (6%) of severe late adverse effects (grade 3 or 4 LENT-SOMA): Two cases of oculomotor impairment. One case of severe hearing loss requiring hearing aid. One case of rapid bilateral vision loss down to light perception.
Nöel et al. (2001)* Case series *Proton and photon therapy for chordoma and chondrosarcomas*	Case Series (Level IV evidence) Fractionated proton + photon Most patients had undergone	45 patients (26 males, 19 females) with chordoma (34 patients) or chondrosarcoma (11 patients)	<u>Acute side effects</u> Various degrees of localised alopecia, erythema, headaches, and moderate hearing loss related to external or medial otitis (numbers not stated). All acute side effects occurred within a month of treatment. <u>Late side effects</u> Grade 3 and 4 symptomatic toxicities documented in 2 patients (4.5%): The patient who had the grade 3 event

	surgical resection <u>Mean dose</u> 66.7 CGE	(mean: 30.5 months)	experienced bilateral temporal lobe enhancement on MRI and had memory trouble as well as mild decline of psychomotor speed at 17 months. The patient with a grade 4 event developed rapid bilateral vision loss at 8 months. Grade 1 and 2 complications recorded in 9 patients (20%): Four (9%) cases of mild hearing loss. Five (11%) cases of complete pituitary insufficiency requiring hormone replacement.
Weber *et al.* (2005) Case series *Proton atherapy for skull base chordoma and chondrosarcoma*	Case Series (Level IV evidence) Proton RT All patients had undergone surgical resection. <u>Mean dose</u> Chordoma: 74 CGE Chondrosarcoma: 68 CGE	29 patients with skull base chordomas or chondrosarcomas (median: 29 months)	<u>Late side effects</u> Four patients (14%) had late adverse events (pituitary insufficiency).

* Potential patient overlap with Noel et al. (2003)

* *Interpretation of some of these studies was confounded by concomitant use of photons or prior surgical resection.

Only one study reported details on acute side effects (Igaki et al. 2004), all studies stated that acute side effects were within the expected range and all either subsided within a month or were controlled symptomatically (Table 8). Meanwhile, late side effects occurred in 23% to 39% of patients, with severe late side effects (grade 3 to 5) accounting for 5% to 15.4% (Table 8) of the patient population. The high rate of brain necrosis observed by Igaki et al. (2004) (which accounted for the 15.4% severe late adverse event) was attributed by the authors to the use of large daily fraction doses, up to 3.5 Gy (Igaki et al. 2004). It is interesting to note that the three studies (Nöel et al. 2003, Nöel et al. 2001, Weber et al. 2005) which utilised a combination of proton and photon therapy all reported cases of pituitary insufficiency (11% to 24%) requiring hormone replacement while Igaki et al. (2004), which utilised proton therapy only, did not report any incidences of pituitary insufficiency.

c) Pituitary tumours (including craniopharyngiomas)

The safety outcomes of studies included in this assessment for pituitary tumours are presented in Table 9.

Table 9: Safety outcomes for patients treated with proton beam therapy for pituitary tumours.

Pituitary tumours (including craniopharyngiomas)			
Study	**Study Design**	**Population (Mean/Median follow-up)**	**Safety outcomes**
Fitzek *et al.* (2006) Case series *Fractionated proton and photon radiation for craniopharyngioma*	Case Series (Level IV evidence) Proton + photon RT All patients had undergone surgical resection. <u>Mean dose</u> 56.9 CGE	15 patients (5 children - 4 male, 1 female; 10 adults) with craniopharyngioma. (median: 186 months)	One nausea (6.7%) Three fatigue (20.0%) Four headaches (26.7%) Two visual injuries - hemianopsia and total vision loss respectively (13.3%). All patients (100%) required endocrine replacement therapy, 7/10 patients alive were taking multiple endocrine drugs. All four boys required testosterone substitution after radiotherapy
Ronson et al. (2006) Case series *Fractionated proton beam therapy for pituitary adenomas*	Case Series (Level IV evidence) Proton RT Most patients (n=42) had undergone surgical resection. <u>Median dose</u> 54 CGE	47 patients (25 males, 22 females) with pituitary adenomas. (median: 47 months)	<u>Acute side effects</u> One patient had CNS complication due to radiation, resulting in progressive headaches at 19 months post-radiation. Visual complications were detected from targeted visual follow-up tests in 43 patients: 7 cases (16%) of new minor visual deficits. 2 cases (4.6%) of new major visual complications. Endocrinological complications were assessed in 37 patients: 11 cases (29.7%) of hormonal deficiencies which required hormone supplements. 2 cases (5.4%) of panhypopituitarism. The actuarial rate of developing new hormonal deficiency at 5 and 10 years are 21.7% $\pm$ 7.3% and 44.2% $\pm$ 11.3%, respectively. Hypopituitarism due to radiation was noted in 4/20 (20%) patients with non-secreting adenomas and 7/20 (35%) with secreting adenomas. Among patients with secreting tumours, incident hypopituitarism developed in: None (0%) of the 4 patients with ACTH-secreting tumours. 2/10 (20%) patients with GH-secreting tumours.

			3/5 (60%) with prolactin-secreting adenomas. 2/2 (100%) patients with TSH-secreting and mixed adenomas. ***No significant differences in these measurements* <u>Late side effects</u> No radiation-related second tumours or vascular injuries.

* Interpretation of these studies was confounded by concomitant use of photons or prior surgical resection.

Both studies utilised fractionated radiotherapy and both reported that the most prevalent complication was endocrinological (hormonal deficiencies which required hormone replacement therapy), with rates ranging from 29% to 100% in the two studies retrieved (Ronson et al. 2006, Fitzek et al. 2006). Interestingly, it was the study that utilised a combination of proton and photon therapy (Fitzek et al. 2006) which reported the higher endocrinological complication rate. In comparison, 20% to 60% of patients developed hypopituitarism in previous studies utilising fractionated photon therapy (Ronson et al. 2006). Meanwhile visual complications (both minor and major) occurred in 13.3% to 21% of patients, with the higher incidence noted in the study that specifically evaluated visual complications. Ronson et al. (2006) conceded that despite the high dose-conformity of protons, it is still not possible to prevent visual morbidity in patients with tumours close to the optic chiasm.

d) Nasopharyngeal tumours

Two nasopharyngeal tumours were represented in the included studies, nasopharyngeal carcinomas and adenoid cystic carcinoma. Safety outcomes for both clinical studies are summarised in Table 10.

Table 10: Safety outcomes for patients treated with proton beam therapy for nasopharyngeal tumours

Nasopharyngeal tumours			
Study	**Study Design**	**Population (Mean/Median follow-up)**	**Safety outcomes**
Lin et al. (1999) Case series *Repeat conformal proton therapy for nasopharyngeal tumours*	Case Series (Level IV evidence) Proton RT Most patients (n=15) had undergone conventional RT (photon). Mean dose 62.8 CGE Some patients received concurrent chemotherapy.	16 patients with nasopharyngeal carcinoma initially treated with photons. (mean: 23.7 months)	Acute side effects Acute toxicity included worsening dry mouth, fatigue, skin erythema, tinnitus and serous otitis: 1/9 (11%) surviving patients developed osteonecrosis. 1/9 (11%) patient developed chronic ulceration of the nasopharynx. 1/9 (11%) patient developed trismus. 2/9 (22%) patients developed chronic serous otitis. No central nervous system complications noted. Late side effects None stated
Pommier et al. (2006) Case series *Combined proton and photon therapy for skull base adenoid cystic carcinoma*	Case Series (Level IV evidence) Proton + photon RT Some patients (n=12) had undergone gross or partial resection. Mean dose 75.9 CGE	23 patients with adenoid cystic carcinoma (median: 64 months)	All patients tolerated the treatment without any treatment break. Acute side effects 3 patients (13%) experienced grade 2 visual toxic effect as the highest toxic effect during radiation treatment. There were no grade 3, 4 or 5 acute visual toxic effects. Late side effects 1 patient developed chronic grade 4 retinopathy. 3 patients (13%) developed chronic grade 3 toxic effects requiring surgical intervention. 12 patients (52%) developed chronic grade 2 toxic effect (4 epiphora, 6 dry eye, 1 ectropion, 1 cataract, 1 retinopathy, and 3 nasolacrimal duct obstruction). 12 patients (52%) had radiographic brain change after radiation: 2 (9%) grade 2 toxic effects (asymptomatic) 10 (43%) grade 3 toxic effects (7 seizures, 3 decreased short-term memory) 2 patients had grade 5 toxic effects, one at 61 months and the other at 9 months after treatment.

			6 patients developed grade 2 (asymptomatic) hypothyroidism.

* Interpretation of some of these studies was confounded by concomitant use of photons, chemotherapy or prior surgical resection.

As expected, acute and late side effects varied greatly between the two studies retrieved for nasopharyngeal tumours (Pommier et al. 2006, Lin et al. 1999) due to the differences in tumour and treatment modalities and because one study reported in a limited fashion (based on the less than 50% of patients that survived). No meaningful comparison could be made between these studies.
The model study by Mock et al. (2004) compared the treatment plans of conventional, 3D conformal and IMRT photon therapy to proton therapy for paranasal sinus carcinoma in 5 patients. In order to evaluate possible dose reductions to non-target structures utilising proton beams, the 95% isodose area of the proton plan was related to the other isodose levels and treatment planning techniques (conventional, 3D conformal and IMRT proton therapy). The results obtained for isodose volume increase are presented below (Table 11):

Table 11: Isodose volume increase (normalised to 95% proton isodose volume) according to different dose level and treatment planning techniques.

Isodose (%)	Conventional photon	3D conformal photon	IMRT photon	Proton
10	8.1 (3.1)	10.0 (3.8)	9.6 (3.7)	2.6
30	4.2 (2.1)	3.7 (1.8)	3.6 (1.8)	2.0
50	2.7 (1.6)	2.2 (1.3)	2.3 (1.3)	1.7
70	1.9 (1.3)	1.6 (1.1)	1.5 (1.1)	1.4
90	1.1 (1.0)	1.1 (1.0)	1.1 (1.0)	1.1
95	1.1 (1.1)	0.8 (0.8)	1.8 (08)	1.0

Values presented are mean values for 5 patients. Numbers in parentheses express increased in volumes with regard to related proton-based data at defined isodose levels.

Mock et al. 2004

From the results presented (Table 11), dose reduction to normal adjacent tissue using protons was recorded at virtually all dose levels but was evidently more pronounced from the 10% to 70% isodose levels. The mean radiation dose to organs at risk revealed that 3D conformal photon and IMRT plans resulted in substantial dose reduction compared to conventional photon. However the use of protons further reduced the mean dose by up to 65% and 62% compared to 3D conformal photon and IMRT planning techniques, respectively (Mock et al. 2004). However these results only confer a theoretical advantage to proton techniques and require confirmation in comparative clinical trials.

e) Acoustic neuromas/vestibular schwannomas

Summarised safety outcomes of included studies for acoustic neuromas are presented in Table 12. New facial neuropathies after treatment were recorded in two of three studies, ranging from 8.9% to 11% (Weber et al. 2003, Harsh et al. 2002). In the one study where proton therapy was given in fractions of 1.8 to 2.0 Gy per day, there were no incidences of facial neuropathy in any patient (Bush et al. 2002). This infers that

fractionated proton therapy may be beneficial in reducing the risks of side effects, an observation that has been previously confirmed in neurological tissues (Fowler et al. 1989). Incidentally, no evidence of trigeminal dysfunction was noted in this study as well (Bush et al. 2002).

Table 12: Safety outcomes for patients treated with proton beam therapy for acoustic neuromas (vestibular schwannomas).

Acoustic neuromas			
Study	**Study Design**	**Population (Mean/Median follow-up)**	**Safety outcomes**
Bush *et al.* (2002) Case series *Fractionated proton beam therapy for acoustic neuroma*	Case Series (Level IV evidence) Fractionated proton RT 8 patients had undergone surgical resection. <u>Mean dose</u> 54 – 60 CGE	30 patients with acoustic neuroma (mean: 34 months)	Hearing preservation rate of 31% in the 13 patients with grade I or II hearing before treatment. Two cases (6.7%) of new vertigo/ataxia post-treatment. No evidence of transient or permanent treatment-related dysfunction of the trigeminal or facial nerve.
Harsh et al. (2002) Case series *Proton beam radiosurgery of vestibular schwannomas*	Case Series (Level IV evidence) Proton RT 9 patients had undergone surgical resection. <u>Mean dose</u> 12 Gy	68 patients (36 males, 32 females) with vestibular schwannomas (mean: 34 months)	3 patients (4.7%) experienced hydrocephalus that presented as increased ataxia. 4/6 patients who had functional hearing ipsilaterally pre-treatment progressively lost hearing. 2/21 patients who had tinnitus pre-treatment reported worsening of tinnitus while 3 patients reported new tinnitus post-treatment. 3 patients (4.7%) had severe facial hyperasthesia. 6 patients (9.4%) had minor intermittent facial paresthesias (5 new cases). 3 patients (4.7%) had severe facial weakness that required oculoplasty (2 new cases) (level VII). 6 patients (9.4%) had transient partial facial weakness (level VII). 6 patients (9.4%) had transient, infrequent, involuntary periocular twitching (level VII)

Weber *et al.* (2003) Case series *Stereotactic proton beam radiosurgery for vestibular schwannoma*	Case Series (Level IV evidence) Proton RT 15 patients had undergone surgical resection. <u>Median dose</u> 12 CGE	88 patients (46 males, 42 females) with acoustic neuroma. (median: 38.7)	Four patients (5%) developed asymptomatic adjacent parenchymal changes on post-treatment T2-weighted MRI scans. Actuarial hearing preservation rates were 79.1% at the 2-year follow-up examination and 21.9% at the 5-year follow-up examination. <u>Facial neuropathy</u> 11 patients had facial neuropathy before proton beam radiosurgery. *After proton radiosurgery:* 4 cases of mild facial nerve dysfunction. 1 cases of moderate facial dysfunction. 2 cases of moderately severe facial dysfunction. 2 cases of severe facial dysfunction. *Note: 7 patients (8.9%) developed new permanent facial nerve dysfunction post-treatment.* *12 months post-radiosurgery*: 4 reverted to normal facial function, 6 cases of mild to moderate facial dysfunction and one case of moderately severe facial dysfunction. The 2- and 5-year actuarial normal facial nerve function preservation rate was 91.1%. <u>Trigeminal neuropathy</u> Four cases (5%) of transient trigeminal nerve dysfunction. Eight cases (10.1%) of new permanent trigeminal nerve dysfunction after treatment (2 cases significant neuropathy, 6 cases mild neuropathy). Three patients (33%) with pre-existing trigeminal nerve neuropathy experienced complete resolution post-treatment.

* Interpretation of these studies was confounded by prior surgical resection.

Weber et al. (2003) noted that higher prescribed and maximal doses were the most significant risk factors for delayed facial neuropathy and that maximal doses of 17.1 Gy or greater are associated with a significantly higher risk of cranial neuropathy ($p = 0.021$). Harsh et al. (2002) concluded that lower rates of cranial nerve complications can be achieved by selecting tumours < $15cm^3$, utilising a minimal marginal prescribed dose of 12 CGE, and limiting brainstem exposure to < 12 CGE.

Hearing preservation rates varied substantially between the included studies, Weber et al. (2003) reported 2- and 5-year hearing preservation rates of 79.1% and 21.9%, respectively, Harsh et al. (2002) reported that only 33% of patients with functional

ipsilateral hearing retained this ability while Bush et al. (2002) reported hearing preservation rates of 31%. Bush et al. (2002) acknowledges that previous studies have reported improved hearing preservation (69% - 77%) with fractionated stereotactic photon radiotherapy at does of 42 to 44 Gy (which is approximately 20% less than the dose administered in this study) and therefore recommended that dose reduction should be considered but only if tumour control rates are not compromised (Bush et al. 2002).

Effectiveness

The effectiveness of proton beam therapy for the treatment of tumours were assessed primarily via local control and survival rates. Most studies included in this assessment report the observed survival rates and an actuarial control. The actuarial control is an estimate of what would happen without treatment but it is not as reliable as a concurrent comparison in the study population. The survival rates were analysed according to the Kaplan-Meier method, which computes survival taking account of the different lengths of follow-up and any censoring due to dropout.

Paediatric tumours

Local tumour control and survival for paediatric patients treated with proton therapy are summarised in Table 13. All included studies utilised fractionated radiotherapy (1.8 – 2.0 CGE per fraction) with 4/5 studies making use of photon radiation in conjunction with protons.

Table 13: Local tumour control and survival for paediatric patients.

	Benk et al. (1995)	Hug et al. (2002a)	Hug et al. (2002b)	McAllister et al. (1997)	Noel et al. (2003a)
Tumour type	Base of skull or cervical spine chordomas	Mesenchymal neoplasms invading skull base*	Progressive or recurrent low-grade astrocytoma	Cranial tumours (pituitary adenoma, craniopharyngioma, astrocytoma etc.)	Intracranial neoplasms
No. of patients	18	29	27	28	17
Type of radiotherapy	Fractionated proton + photon	Fractionated proton/proton + photon	Conformal fractionated proton	Fractionated proton alone/ photon with proton boost	Fractionated proton + photon
Prior surgical resection	All patients underwent surgical resection (incomplete)	All patients underwent surgical resection or biopsy	Several patients underwent surgical resection	16 patients underwent surgical resection, 10 patients underwent chemotherapy	15 patients underwent surgical resection
Mean tumour volume (cm3)	Median: 80 (13.9 – 282)	N/A	N/A	N/A	14 (0 – 104)
Dose (Gy/CGE)	Median dose: 69 (55.8 – 75.6) [1.8 CGE per fraction, 5 days a week]	<u>Malignant</u> Median dose: 71.1 (50.4 – 78.6) <u>Benign</u> Median dose: 60.4 (45 – 71.8) [1.8 – 2.0 CGE per fraction, 5 days a week]	55.2 (50.4 – 63.0) [1.8 CGE per fraction, 5 days a week]	<u>Protons alone</u> Median: 54 (40.0 – 70.2) <u>Photon with proton boost</u> X-ray median: 36 (18 – 45) Proton boost median: 18 (12.6 – 31.6) [1.8 – 2.0 CGE per	<u>Photons</u> Median dose: 40 (24 – 54) <u>Protons</u> Median dose: 20 (9 – 31) [1.8 CGE per fraction for both, 5 days a week]

				fraction, 5 days a week]	
Mean follow-up (months)	Median: 72 (19 – 120)	40 (13 – 92)	39.6 (7.2 – 81.6)	Median: 25 (7 – 49)	27 (3 – 81)
Local control (at time of analysis)	Vertebral chordomas 33% Base of skull chordomas 80%	Malignant 75% Benign 86%	Overall: 78% Hemispheric and central gliomas 82% Brainstem gliomas 60%	85.7%	Overall: 88.2%
Local control (actuarial)	N/A	Malignant 5-year: 72% Benign 5-year: 88%	5-year: 78%	N/A	Overall 1-, 2- and 3-year: 92 ± 8%
Survival	**Overall (end of study)** 77.8% **Actuarial** 5-year: 68% **Disease-free** 5-year: 63% **Recurrence free** 5-year: 78%	**Overall (end of study)** Malignant 65% Benign 100% **Actuarial** Malignant 5-year: 56% Benign 5-year: 100%	**Overall (end of study)** 85% Hemispheric and central gliomas Hemispheric: 86% Central: 93% Brainstem gliomas 60% **Actuarial** Central 5-year: 88% Brainstem 5-year: insufficient data A trend towards decreased survival was evidence for patients with brainstem location (p = 0.12)	**Overall (end of study)** 89%	**Overall** 1-, 2- and 3-year: 93 ± 6%, 83 ± 11% and 83 ± 11%

The actuarial 5-year local tumour control rates (Hug et al. 2002a, Noël et al. 2003a) achieved for CNS tumours in paediatric patients ranged from 72% to 78%. There were large variations in results, depending on the type of tumour, location of tumour, treatment modality and dose administered. Malignant mesenchymal tumours exhibited substantially lower local control rates; this was evident from the 72% control rate at 5-years post-treatment compared to 88% for benign tumours (Hug et al. 2002a). As expected, this translated to lower survival rates as well (Table 12). The heterogeneity of patients and the concomitant use of photons in many instances in the included studies limit the amount of meaningful comparisons that can be extracted from the results.

Adult head and neck tumours

a) Meningiomas

Local tumour control rates and survival rates achieved in the six studies of meningiomas are presented in Table 14. Overall, the local control rates achieved for meningiomas was approximately 90% in the included studies (Table 14), with the exception of Hug et al. (2000) where the study cohort consisted of patients with malignant and atypical meningiomas. The data suggest that local control and survival

for atypical and malignant histology is markedly inferior compared to benign meningiomas, regardless of therapeutic modality. However, atypical histology appears to have better survival compared to malignant histology (Hug et al. 2000).

Table 14: Local tumour control and survival (meningiomas)

	Gudjonsson et al. (1999)	**Hug et al. (2000)**	**Noel et al. (2002)**	**Vernimmen et al. (2001)**	**Weber et al. (2004)**	**Wenkel et al. (2000)**
No. of patients	19	31	17	27	16	46
Type of radiotherapy	Stereotactic proton	Proton + photon	Proton + photon	Stereotactic proton (SRT) or hypofractionated proton (HSRT)	Proton	Fractionated proton + photon
Prior surgical resection	15 patients underwent surgical resection (incomplete)	29 patients underwent surgical resection (8 total, 21 subtotal)	11 patients underwent surgical resection	15 patients underwent surgery or biopsy	8 patients treated in an adjuvant/post-operative setting after subtotal resection, 5 patients treated for recurrence after surgical resection	38 patients underwent surgical resection
Mean tumour volume (cm3)	17.5 (2 – 53)	N/A	N/A	HSRT 15.6 (2.6 – 63) SRT 43.7	Median: 17.5 (0.8 – 87.6)	GTV 34 (2 – 243) CTV 76.5 (9 – 287)
Mean dose (Gy/CGE)	24 (4 consecutive daily 6 Gy sessions)	Atypical meningioma 62.5 (50.4 – 68.4) Malignant meningioma 58 (40 - 72)	GTV Median: 61 (25 – 69) CTV Median: 55	HSRT Max TD: 20.3 (17.3 – 24.7) Min TD: 16.3 (14.5 – 18.3) [Twice a week] SRT 54 (27 fractions) 61.6 (16 fractions) [4 daily fractions per week]	GTV 55.8 (51.9 – 65.5) PTV 54.5 (50 – 61.9)	GTV 61.4 (53.1 – 74.1) CTV 52.1 (45.9 – 53.3) [Dose fractions: 1.8 for protons, 1.92 for photons, 5 days a week]
Mean follow-up (months)	36	59 (7 – 155)	36 (17 – 60)	HSRT 40 SRT 31	Median: 34.1 (6.5 – 67.8)	73 (12 – 207)
Local control (at time of analysis)	100%	Atypical meningioma 47% Malignant meningioma 46%	94%	N/A	N/A	93.5%
Actuarial control	N/A	Atypical meningioma 5-, 8-years: 38%, 19% Malignant meningioma 52%, 17%	4-year: 87.5% ± 12%	HSRT 88% SRT 100%	3-year: 91.7%	**Recurrence free** 5 years: 100% 10 years: 88%
Survival	**Overall** 100%	**Overall** Atypical meningioma 93% Malignant meningioma 38%	**Overall** 94% **Actuarial survival** 4-year: 88.9% ± 11%	N/A	**Actuarial survival** 3-year: 92.9% **Recurrence free**	**Overall** 5 years: 93% 10 years: 77% **Survival without**

		Actuarial survival Atypical meningioma 5 years: 89% 8 years:51% Malignant meningioma 5 years: 89% 8 years:51% **Disease free** Atypical meningioma 67% Malignant meningioma 38%	**Cause specific** 4-year: 100%		3-year: 91.7%	**severe toxicity** 5 years: 80% 10 years: 80%

The 5-year recurrence-free rate of 100% reported by Wenkel et al. (2000) (proton and photon therapy) was a substantial improvement compared to previous studies with conventional radiotherapy which reported recurrence-free rates ranging from 71% in 29 patients with subtotal tumour resection (Wara et al. 1975) to 85% in 117 benign meningiomas (Goldsmith et al. 1994) at 5-years post-treatment. In other studies utilising proton therapy, control rates ranging from 91% at 3-years (Weber et al. 2004) to 87% at 4-years (Noël et al. 2002) were reported.

Previous studies on radiotherapy for the treatment of meningiomas have utilised doses ranging from 45 to 70 Gy, however there are converging data which support the use of higher doses (Noël et al. 2002). Goldsmith et al. (1994) showed a cut-off dose at 53Gy for benign meningiomas with a 5-year disease-free survival of 93% for patients treated above this dose and 65% for those treated below. Meanwhile, for both atypical and malignant meningiomas, target doses $\geq$ 60 Gy/CGE (proton and photon therapy) resulted in statistically significant improvement in local control rates in the study by Hug et al. (2000). Consequently significantly improved survival for patients with malignant meningiomas was achieved compared to previous studies utilising conventional radiotherapy. However, Wenkel et al. (2000) utilised a dose range of 53.1 to 74.1 CGE and did not observe any correlation for dose and tumour control. Gudjonsson et al. (1999) utilised fractionated proton therapy and reported no incidences of tumour progressive despite the lower dose of 24 CGE delivered in four consecutive fractions of 6CGE. Therefore at the time of writing, no clear dose-response relationship for meningiomas has been defined.

b) Chordomas and chondrosarcomas

Table 15 summarises the results of the five studies included in this assessment for chordoma and chondrosarcoma treatment with proton therapy.

Table 15: Local tumour control and survival (chordomas and chondrosarcomas)

	Hug et al. (1999)	**Igaki et al. (2004)**	**Noel et al. (2003b)**	**Noel et al. (2001)**	**Weber et al. (2005)**
No. of patients	58	13	65	45	29
Type of radiotherapy	Proton	Proton + photon	Fractionated proton + photon	Fractionated proton + photon	Proton
Prior surgical resection	55 patients underwent surgical resection	7 patients underwent partial or subtotal resection	59 patients underwent surgical resection	42 patients underwent complete/grossly incomplete resection	All patients underwent surgical resection
Mean tumour volume (cm3)	N/A	39.7	28 (1 – 125)	30 (3 – 124)	Chordoma GTV: 16.4 (1.8 – 48.1) PTV: 91.6 (12.7 – 229.1) Chondrosarcoma GTV: 15.2 (2.3 – 57.3) PTV: 112 (6.7 – 156.4) *Note: median values*
Mean dose (Gy/CGE)	70.7 ± 3.19 (64.8 – 79.2)	Median: 72 (63 – 95)	66.7 (60 – 70) [1.8 – 2.0 CGE per fraction, 5 days a week]	66.7 (60 – 70) [1.8 – 2.0 CGE per fraction, 5 days a week]	Chordoma 74 (67-74) Chondrosarcoma 68 (64-74)
Mean follow-up (months)	33.2 (7 – 75)	Median: 69.3 (14.6 – 123.4)	32 (4 – 71)	30.5 (2 – 56)	Median: 29 (6 – 68)
Local control (at time of analysis)	Overall 83% Chordoma 75% Chondrosarcoma 92%	54%	78.5%	Overall 82% Chordoma 83.4% Chondrosarcoma 82%	Chordoma 89% Chondrosarcoma 100%
Actuarial control	Chordoma 3-, 5-year: 67%, 59% Chondrosarcoma 3-, 5-year: 94%, 75%	3-, 5-year: 67.1%, 46.0%	2-, 3-year (all tumours): 88.4 ± 4.5%, 78.9 ± 6.0% 2-, 3-year chordomas: 90 ± 5%, 71 ± 8.7% 2-, 3-year chondrosarcomas: 85 ± 9.8%, 85 ± 9.8%	2-, 3- year (all tumours): 92.9%, 84.4% 2-, 3-year chordomas: 93.8%, 83.1% 2-, 3-year chondrosarcomas: 90%, 90%	Chordoma 3-year: 87.5% Chondrosarcoma 3-year: 100%
Survival	**Overall** 93% Chordoma 3-, 5-year: 87%, 79% Chondrosarcoma 3-, 5-year: 100%, 100%	**Overall** 3-, 5-year: 84.6%, 66.7% **Cause-specific** 3-, 5-year: 91.7%, 72.2% **Progression-free** 3-, 5-year:	**Overall** 87.7% 2-, 3-, 4-year (all tumours): 92 ± 3.6%, 89 ± 4.2%, 84 ± 6.5% 2-, 3-, 4-year chordomas:	**Overall** 89% 3-, 4-year (all tumours): 90.9%, 83.9% 3-, 4-year chordomas:	**Overall** 3-year: 93.8% Progression free 3-year: 90%

		61.5%, 42.2%	91 ± 4.5%, 88 ± 5.32%, 88 ± 5.2% 2-, 3-, 4-year chondrosarcomas: 94 ± 6.1%, 94 ± 6.1%, 75 ± 17.5%	91.2%, 91.2% 3-, 4-year chondrosarcomas: 90%, 60%	

Local control rates ranged from 54% to 100% for both tumours (chordomas and chondrosarcomas). Three-year actuarial local control rates were reported in all studies, ranging from 67% to 84%. Patients treated with proton therapy for chordomas achieved local control rates of 67% to 87% 3-years post-treatment. Meanwhile, patients with chondrosarcomas achieved 3-year local control rates ranging from 85% to 100% (Table 15). In contrast to other studies which achieved 3-year local control rates of approximately 80%, Igaki et al. (2004) reported sightly lower local control (67%) despite administration of comparable radiation dosage. It should be noted that the mean tumour volume (39.7 cm^3) of patients treated by Igaki et al. (2004) was substantially greater than in other studies (Table 15). Interestingly, a trend towards better local control was noted for patients with tumours < 30 mL preoperatively compared to those with larger tumours (Igaki et al. 2004), but this was not statistically significant.

c) Pituitary tumours

Table 16 summarises the local control and survival rates reported in the two studies for pituitary tumours. Ronson et al. (2006) demonstrated 100% radiographic local control of adenomas at the median follow-up of 47 months. This remarkable control rate was attributed to the high dose administered (54 Gy; 1.8 to 2.0 Gy fractions) which is approximately 10% to 20% higher than doses reported in historic studies with fractionated photon therapy. Complete regression of tumour size was shown in a larger percentage of tumours that were less than 2cm compared to those ≥ 2cm in size (33.4% vs 4.8%, p = 0.047). Ronson et al. (2006) reported crude biochemical control rates of 8% and 40% hormonal normalisation. The actuarial rate of hormonal normalisation was 22.8% ± 0.2% at 5-years.

Table 16: Local tumour control and survival (pituitary tumours)

	Fitzek et al. (2006)	**Ronson et al. (2006)**
Tumours type	Craniopharyngiomas	Pituitary adenomas
No. of patients	15	47
Type of radiotherapy	Proton + photon	Proton
Prior surgical resection	Several patients underwent subtotal/gross total resections	42 patients underwent transphenoidal resection/craniotomy
Mean tumour volume (cm3)	N/A	8.09 ± 8.95 (1 – 36)
Mean dose (Gy/CGE)	Median: 56.9 (53.4 – 67.5)	Minimal GTV dose: 48.93 ± 2.56 (42 – 54)
Median follow-up (months)	186 (122 – 212)	47 (6 – 139)
Local control (at time of analysis)	87%	100%
Actuarial control	5-, 10-year: 93%, 85%	N/A
Survival	**Actuarial** 5-, 10-year: 93%, 72%	**Overall** 100%

Fitzek et al. (2006) achieved local control rates of 87% for craniopharyngiomas, which is comparable with results from previous studies utilising conservative surgery followed by photon radiotherapy (Fitzek et al. 2006).

d) Nasopharyngeal tumours

The two studies included for the treatment of nasopharyngeal tumours reported markedly differing results with regards to local control and survival (Table 17). However this was expected due to the differing biology between these tumours. Pommier et al. (2006) reported 5-year local control rate of 94% and 5-year survival rate of 77%, in comparison Lin et al. (1999) achieved 2-year local control rate of 50% and 2-year survival rate of 50%. It should be noted that the patient cohort of Lin et al. (1999) consisted of high-risk, recurrent nasopharyngeal carcinomas where conventional photon radiotherapy has failed to achieve control. Interestingly, the high local control rate achieved by Pommier et al. (2006) did not translate to improved survival rates compared with historical controls (Pommier et al. 2006).

Table 17: Local tumour control and survival (nasopharyngeal tumours)

	Lin et al. (1999)	**Pommier et al. (2006)**
Tumour type	Nasopharyngeal carcinoma	Adenoid cystic carcinoma
No. of patients	16	23
Type of radiotherapy	Proton	Proton + photon
Prior surgical resection	No prior surgical resection. Patients underwent prior photon radiotherapy	12 patients underwent surgical resection
Mean tumour volume (cm3)	N/A	N/A
Mean dose (Gy/CGE)	62.8 (59.4 – 68.4)	Median: 75.9 (70.0 – 76.8)
Mean follow-up (months)	23.7 (4 – 47)	Median: 64
Local control (at time of analysis)	N/A	93.9%
Actuarial control	2-year: 50%	5-, 8-year: 93%, 82%
Survival	**Actuarial** 2-year: 50% **Disease-free** 2-year: 50%	**Overall** 78.3% **Actuarial** 5-, 8-year: 77%, 59% **Disease-free** 5-, 8-year: 56%, 31%

At the end of the study by Lin et al. (1999), 7/8 (87.5%) patients with optimal DVHs[4] were alive, compared to 2/8 (25%) of patients with suboptimal DVHs. DVH analyses revealed that optimal patients achieved 2-year actuarial survival rates of 83% compared to 17% in suboptimal patients ($p = 0.006$). Interestingly, Lin et al. (1999) concluded that adequate tumour coverage, not total dose, was the most significant variable affecting local control and survival (as determined by DVH and multiple regression analyses) (Lin et al. 1999).

Univariate exploratory analyses by Pommier et al. (2006) revealed that change in vision at presentation ($p = 0.01$) and optic nerve invasion ($p < 0.001$) were predictive

[4] Patients who received ≥ 90% of the prescribed dose to ≥ 90% of the target volume were classified as having 'optimal' DVHs. Patients that did not achieve either of the aforementioned were classified as having 'suboptimal' DVHs.

for local failure. In addition, univariate analysis of disease-free survival rates showed that patients aged ≤ 46-years ($p = 0.04$), change in vision at presentation ($p = 0.02$), pterygopalatine fossa involvement ($p = 0.02$) and sphenoidal and clivus involvement ($p = 0.02$) were predictive for decreased disease-free survival rates. Meanwhile, multivariate analysis revealed that sphenoidal and clival involvement was predictive for disease-free survival ($p = 0.01$). With regards to overall survival rates, univariate analysis showed that patients aged ≤ 46-years ($p = 0.01$), change in vision at presentation ($p < 0.001$), and sphenoidal and clival involvement ($p = 0.02$) were predictive of decreased overall survival rates. In multivariate analysis change in vision at presentation ($p = 0.02$) and sphenoidal and clival involvement ($p = 0.01$) were predictive for overall survival (Pommier et al. 2006).

e) Acoustic neuromas/vestibular schwannomas

The studies in acoustic neuromas reported remarkably consistent local control and survival rates (Table 18). The 2-year local control rates reported by Weber et al. (2003) and Harsh et al. (2002) was in accordance with the published long-term relapse rates of 0% to 5% after radiotherapy (Weber et al. 2003). Meanwhile, Bush et al. (2002) reported 100% local control when utilising fractionated proton therapy. The authors attributed this to the use of fractionated proton therapy which enabled the delivery of higher doses with lower incidences of radiation-induced toxicity.

Table 18: Local tumour control and survival (acoustic neuromas)

	Bush et al. (2002)	**Harsh et al. (2002)**	**Weber et al. (2003)**
No. of patients	30	68	88
Type of radiotherapy	Fractionated proton	Proton	Proton
Prior surgical resection	No	9 patients underwent surgical resection	15 patients underwent surgical resection
Mean tumour volume (cm3)	4.3 (0.2 – 29.5)	2.49 (0.3 – 12.7)	Median: 1.4 (0.1 – 15.9)
Mean dose (Gy/CGE)	Patients with useful hearing: 54 (30 fractions) Patients w/o useful hearing: 60 (30-33 fractions) [1.8 – 2.0 CGE daily]	Prescribed dose:12 Max dose: 17.1	Median max dose: 17.1 (13.3 – 20) Median min dose: 12 (4.3 – 20)
Mean follow-up (months)	34 (7 – 98)	34 (6 – 96)	Median: 38.7 (12 – 1.206)
Local control (at time of analysis)	100%	94%	94.3%
Actuarial control	N/A	2-, 5-year: 94%, 84%	2-, 5-year: 95.3% (90.9 – 99.9%), 93.6% (88.3 – 99.3%)
Survival	N/A	N/A	N/A

Cost Analysis

The study by Goitein and Jermann (2003) in Switzerland analysed the relative costs of proton and X-ray radiation therapy and concluded that the construction costs of a current two-gantry proton facility, complete with equipment, was estimated at €62,500,000 while a two-linac X-ray facility would cost €16,800,000. (One Euro = 1.67 Australian $ on 8/12/06.) The cost of operation of a proton therapy facility was found to be dominated by business costs (42%, primarily the cost of repaying the presumed loan for construction of the facility), personnel costs (28%) and the cost of servicing the equipment (21%). Meanwhile, the cost of operation for an X-ray facility was dominated by the personnel cost (51%) and the business cost (28%). The cost per fraction was estimated to be €1025 for proton therapy and €425 for X-ray therapy, which is a ratio of costs of 2.4 ± 0.35 (85% confidence). Goitein and Jermann suggested that they expect substantial opportunities for treatment cost reduction over the next 5 to 10 years. Based on a set criterion of assumptions[5], the authors estimated that the cost of proton and X-ray therapy can be reduced to €650 and €310 respectively, resulting in a ratio of costs of 2.1. If however the initial capital investments were ignored, which would mean that the operating costs need not repay the investment, the future costs for proton and X-ray therapy could be reduced to €370 and €230 respectively, for a cost-per-fraction ratio of 1.6. Overall, is it likely that proton beam therapy would continue to be more expensive compared to X-ray therapy; despite future assumptions of cost reductions (Goitein and Jermann 2003). The question is whether the greater cost of proton beam therapy is clinically worthwhile.

Meanwhile, another economic evaluation of proton therapy (Lundkvist et al. 2005) that was limited to four types of cancers (left-sided breast cancer, prostate cancer, head and neck cancer and childhood medulloblastoma) reported that despite extensive published literature on proton therapy for these cancers, the information about the clinical effects of proton therapy relative to conventional radiotherapy is very limited. Overall, the authors concluded that proton therapy was cost-effective only if the appropriate risk groups were chosen. Large uncertainties necessitated the use of various assumptions; the author stated that the average cost per QALY gained for the four types of cancer assessed was approximately €10,130. Therefore if the value of a QALY was set to €55,000, the total yearly net benefit of treating 925 cancer patients with the four types of cancer was approximately €20.8 million, in this case investment in a proton facility may be cost-effective (Lundkvist et al. 2005). However the author cautioned that results of this study should be interpreted carefully due to the numerous assumptions utilised in this study.

[5] Reduction in equipment cost, nominal time per fraction, equipment service rate, and MD + PhD + dosimetrist effort (Table 6, Goitein and Jermann 2003).

Ethical Considerations

Informed Consent

Clinicians have an ethical obligation to inform patients on the current understanding of the effectiveness of proton beam therapy for tumour control and to ensure that the patient understands the risks associated with this treatment modality. It is imperative that the patient is aware that the clinical studies conducted so far are case series and the lack of comparative studies does not allow clinicians to determine objectively and confidently if proton therapy is significantly better or safer compared to conventional radiotherapy. At best, only modelling studies have shown substantial dose-sparing of normal tissue when comparing proton treatment plans to conventional photon treatment plans. Patients should be informed in advance that during treatment it is necessary for the head and neck to be immobilised to ensure accurate proton beam targeting, similar to conventional photon radiotherapy.

Access Issues

Proton beam therapy is a complicated and technologically advanced treatment and therefore can only be performed in well-equipped medical institutions under the supervision of trained radiation oncologists, medical physicists and dosimetrists. Therefore this treatment will only be available in major cities with adequate infrastructure and funding to purchase/maintain the equipment necessary for proton beam therapy.

Training and Accreditation

Training

The administration of proton beam therapy appears to be similar to conventional radiotherapy. Medical specialists would need to familiarise themselves with the treatment planning software and the operation of the proton beam gantries. Details regarding formal training for proton beam therapy were not retrieved in this search.

Clinical Guidelines

There are currently no clinical practice guidelines that include proton beam therapy in Australia and New Zealand. If proton beam therapy is approved by the TGA, clinical guidelines will need to be developed.

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology. Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.
A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search Strategy Used for Report

The sources utilised in this assessment are listed in Table 19. The medical literature was searched with the search terms outlined in Table 20 to identify relevant studies up to November 2006. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

Table 19: Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University of Adelaide library
Australian Medical Index	University of Adelaide library
CINAHL	University of Adelaide library
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Databese, the NHS Economic Evaluation Database	University of Adelaide library
Current Contents	University of Adelaide library
Embase	Personal subscription
Pre-Medline and Medline	University of Adelaide library
PyscINFO	Personal subscription
RACS electronic library	Personal subscription
Internet	

Blue Cross and Blue Shield Association's Technology Evaluation Center	http://www.bcbs.com/tec/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca
Current Controlled Trials metaRegister	http://www.controlled-trials.com/
EuroScan	http://www.euroscan.bham.ac.uk/
Health Technology Assessment International	http://www.htai.org/
International Network for agencies for Health Technology Assessment	http://www.inahta.org
Medicines and Healthcare products Regulatory Agency (UK)	http://www.mhra.gov.uk/
US Food and Drug Administration, Center for Devices and Radiological Health	http://www.fda.gov/cdrh/index.html
US Food and Drug Administration, Manufacturer and User Facility Device Experience Database	http://www.fda.gov/cdrh/maude.html
UK National Research Register	http://www.nrr.nhs.uk/
Websites of specialty organisations	Dependent on technology assessed

Table 20: Search terms utilised

Search terms
MeSH Ionising radiation; radiotherapy; neoplasm; proton; radiation oncology; therapeutic radiology; radiation therapy; medical oncology; protons/therapeutic use; radiation Injuries/prevention and control. **Text words** proton beam therapy; proton therapy; proton radiation; radiotherapy; proton irradiation; heavy ions/therapeutic use; radiotherapy, high energy; ions/therapeutic use; protons/therapeutic use; particle accelerators. **Limits** English, human

Availability and Level of Evidence

A total of 24 peer reviewed case series (level IV intervention evidence) reported safety and efficacy outcomes on the use of proton beam therapy for the treatment of patients with various head and neck tumours. In addition, two economic studies were retrieved for assessment in this report. Four comparative treatment planning (modelling) studies were included in this assessment to supplement the evidence from case series due to the lack on comparative studies available on this technology. The profiles of the included case series studies are summarised in Appendix B.

Sources of Further Information

No ongoing or future clinical trials assessing the safety and efficacy of proton beam therapy for head and neck cancers were located within the Current-Controlled Trials or the UK National Research Register database.

Conclusions

From a theoretical perspective, proton beam therapy has been explored for patients suffering from tumour growth in locations adjacent to critical anatomical structures. The procedure involves the construction of a 3D treatment plan utilising specialised software which is then relayed to the proton beam accelerator (synchrotron) where the protons will be delivered into the targeted tumour. Patients are immobilised utilising custom-made moulds to ensure accurate delivery of the radiation to the target site. The procedure is complicated and involves the use of high-tech equipment requiring input from several medical and scientific specialists. At the time of writing, over 39,000 patients have received proton therapy either alone or in conjunction with conventional radiotherapy (Levin et al. 2005).

Existing comparators for proton beam therapy include external radiation therapy (IMRT etc.), internal radiation therapy (brachytherapy) and systemic radiation therapy. External radiation therapy often uses a photon energy source, such as X-rays and gamma rays. It is commonly utilised to treat various solid tumours and can be applied intraoperatively if required. Brachytherapy involves the implantation of a radiation source within the tumour to induce cell death while systemic radiation therapy involves the injection or ingestion of radioactive materials. The key disadvantage of these treatment modalities is the irradiation of healthy tissue surrounding the tumour due to the dose-distribution characteristics of conventional radiotherapy. Proton therapy could potentially be a preferable alternative to these therapies as the dose-characteristics for protons are more desirable compared to photons (refer to Figure 1).

The studies included for assessment in this Horizon Scanning report were predominantly relatively small case series, with limitations in generalising the results (level IV intervention evidence). Outcome measures reported in studies include local control and survival rates, actuarial control and survival rates were calculated based on the Kaplan-Meier methodology. Complications were graded based on the LENT/SOMA scale as a measure of the severity of radiation-toxicity/side effects. Several treatment-planning studies were included that modelled the potential advantages of proton therapy to provide perspective when assessing the case series studies.

The prevalence of the radiation-induced side effects in the short and long term varied quite widely across studies and appears to be within the range expected for conventional photon therapy. Several studies which utilised proton therapy exclusively suggested that protons are capable of reducing radiation-toxicity. However, the lack of consistency across the included studies and the lack of direct comparative studies severely limit the conclusiveness of these results. Ronson (2006)

concluded that even with proton therapy it was still not possible to prevent visual morbidity in patients with tumours close to the optic chiasm.

The regimen for proton beam therapy may impact on toxicity. For example it would appear that toxicity increased when proton and photon therapy were combined (pituitary insufficiency - Noel 2001, 2003 and Weber 2005 and endocrinological complications – Fitzek, 2006). In one study by (Bush 2002) there was a suggestion that fractionated proton therapy might reduce the risk of facial neuropathies that were apparent in two other studies with unfractionated proton therapy. However the rate of hearing preservation was low in the fractionated study and the dose applied may have been higher than necessary.

Modelling studies (Lee et al. 2005, Lin et al. 2000, Miralbell et al. 2002, Miralbell et al. 1997, St.Clair et al. 2004) included within this report all concluded that proton therapy should result in substantial dose-sparing to adjacent critical structures which should translate to lower toxicity, however this has yet to be shown consistently in clinical studies.

The reported local control and survival rates for patients treated with proton beam therapy were largely unconvincing due to the large variations in results. Studies on meningiomas reported improved control and survival rates when proton radiation was administered (Wenkel et al. 2000, Weber et al. 2004, Noël et al. 2002), however a clear dose-response relationship was not defined due to conflicting results. Local control and survival rates appeared to be substantially better for patients with pituitary tumours (Ronson et al. 2006, Fitzek et al. 2006) however the outcomes for other head and neck tumours were largely inconclusive. Based on current evidence, it is difficult to state if proton beam therapy results in improved local tumour control and/or survival rates.

The cost-effectiveness studies on proton beam therapy revealed that proton beam therapy will continue to be more expensive compared to conventional X-ray/photon therapy despite future assumptions of cost reductions (Goitein and Jermann 2003). This is predominantly related to substantial capital costs, and the costs of operating the synchrotron.

There are a substantial number of studies of proton beam therapy for the treatment of neoplasms involving, or adjacent to, cranial structures. However, they varied in treatment methodology, only included small numbers of patients, did not use a concurrent control and used different methodologies for capturing adverse event information. Hence the results are largely inconclusive and further investigations are required to establish if proton beam therapy offers the safety advantages purported by numerous model/treatment-planning studies. Such studies should determine the optimal dosing regimen for each type of tumour including whether it should be used in combination with proton therapy and in what form (e.g. unfractionated). In addition, long-term comparative studies are required to determine if proton therapy results in increased local control rates and survival rates compared to conventional radiotherapy.

Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§among non-consecutive patients with a defined clinical presentation††	A prospective cohort study ***	A prospective cohort study ***	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§among non-consecutive patients with a defined clinical presentation††	All or none§§§	All or none§§§	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial† Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognosis factors amongst unrelated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study with concurrent controls: Historical control study Two or more single arm study‡ Interrupted time series without a parallel control group	Diagnostic case-control study††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ⌗	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Tablenotes

[*] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

[§] Definitions of these study designs are provided on pages 7 – 8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

[†] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C).

[‡] Comparing single arm studies i.e. case series from two studies.

[**] The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies.* Available at: www.msac.gov.au

[§§] The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews, *BMC Medical Research Methodology*, 2003, 3: 25.

[††] Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-controlled studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

[‡‡] Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

[***] At study inception the cohort is either non-diseased or all at the same stage of the disease.

[§§§] All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come deom the disappearance of small-pox after large-scale vaccination.

[†††] If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot be feasibly captures within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and dales reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; (Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

Appendix B: Profile of Studies

Study	Location	Study design	Study population	Study details	Outcomes assessed	Length of follow-up
Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H. (1995)	Massachusetts, United States	Case series Level IV interventional evidence Fractionated proton and photon radiotherapy	18 pediatric patients with case of skull or cervical spine chordomas	All patients had undergone surgical resection Surgical resection was incomplete in all cases 8 patients underwent second surgery to reduce tumour size before irradiation	Treatment-related side effects, survival rates, disease-free survival.	Median: 72 months
Bush DA, McAllister CJ, Loredo LN, Johnson WD, Slater JM, Slater JD. (2002)	California, United States	Case series Level IV interventional evidence Fractionated proton radiotherapy	30 adults with acoustic neuromas	8 patients had undergone surgical resection.	Treatment-related side-effects, hearing preservation, local control, disease regression	Mean: 34 months
Fitzek MM, Linggood RM, Adams J, Munzenrider JE. (2006)	Massachusetts, United States	Case series Level IV interventional evidence Proton and photon radiotherapy	10 adults and 5 children with craniopharyngiomas	9 patients had previous radiotherapy after subtotal resection or biopsy All patients had undergone surgical resection or biopsy.	Treatment-related side-effects, local control, survival	Median: 186 months
Gudjonsson O, Nyberg G, Pellettieri L, Montelius A, Grusell E, Dahlgren C, Isacsson U, Lilja A, Glimelius B. (1999)	Uppsala, Sweden	Case series Level IV interventional evidence Stereotactic proton radiotherapy	19 adult patients with inextirpable skull base meningiomas	15 patients had undergone incomplete surgical resection. No patients had undergone previous systemic chemotherapy, embolisation of tumour feeding arteries or irradiation.	Treatment-related side-effects, local control	Mean: 36 months
Harsh GR, Thornton AF, Chapman PH, Bussiere MR, Rabinov JD, Loeffler JS. (2002)	Massachusetts, United States	Case series Level IV interventional evidence Proton radiotherapy	68 adults with vestibular schwannomas	Patients only selected if disease progression was evidence by tumour enlargement or clinical deterioration. Patients with tumour volumes	Treatment-related side-effects, local control, clinical status	Mean: 34 months

				>15 cm^3 excluded		
Hug EB, DeVries A, Thornton AF, Munzenrider JE, Pardo FS, Hedley-Whyte ET, Bussiere MR, Ojemann R. (2000)	Massachusetts, Unites States	Case series Level IV interventional evidence Proton and photon radiotherapy	31 adults with atypical and malignant meningiomas	Atypical 15 patients Malignant 16 patients Three malignant patients had prior external radiotherapy 8 patients (26%) underwent gross total resection 21 patients (68%) underwent subtotal resection	Treatment-related side-effects, local control, distant metastasis, survival	Mean: 59 months
Hug EB, Loredo LN, Slater JD, DeVries A, Grove RI, Schaefer RA, Rosenberg AE, Slater JM (1999)	California, United States Massachusetts, United States	Case series Level IV interventional evidence Proton radiotherapy	58 patients with skull base tumours (33 for chordoma, 25 for chondro-sarcoma)	40/58 patients had undergone 1 surgical resection; 15/58 patients had undergone 2-6 surgical resections; 3/58 had undergone biopsy sample only	Local tumour control, treatment-related side effects, survival rates, disease-free survival, gross tumour volume and brainstem involvement.	Mean: 32.2 months
Hug EB, Muenter MW, Archambeau JO, DeVries A, Liwnicz B, Loredo LN, Grove RI, Slater JD. (2002b)	California, United States	Case series Level IV interventional evidence Conformal fractionated proton therapy	27 pediatric patients with progressive or recurrent low-grade astrocytoma	23 patient had undergone surgical resection or biopsy 12 patients (44%) underwent radiation for primary disease, 15 (56%) patients for recurrent disease	Treatment-related side effects,local control, survival, recurrence-free survival. Univariate and multivariate analysis for prognostic factors.	Mean: 39.6 months
Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. (2002a)	California, United States	Case series Level IV interventional evidence Fractionated proton/proton and photon radiotherapy	29 pediatric patients with mesenchymal neoplasms invading skull base	Benign 9 patients Malignant 20 patients All patients had either undergone surgical resection or biopsy 13 patients underwent proton radiotherapy alone	Treatment-related side effects, local control, survival.	Mean: 40 months

				16 patients received a combination of proton and photon radiotherapy		
Igaki H, Tokuue K, Okumura T, Sugahara, S, Kagei K, Hata M, Ohara K, Hashimoto T, Tsuboi K, Takano S, Matsumura A, Akine A (2004)	Ibaraki, Japan Tomobe, Japan	Case series Level IV interventional evidence Proton and photon radiotherapy	13 patients with skull base chordoma	None of the patients had received radical surgery. 7/13 underwent tumour removal surgery before proton beam therapy.	Treatment-related side effects, cause-specific, overall and disease-free survival rates, local control rates.	Median: 69.3 months
Lin R, Slater JD, Yonemoto LT, Grove RI, Teichman SL, Watt DK, Slater JM (1999)	California, United States	Case series Level IV interventional evidence Repeat proton therapy	16 patients with nasopharyngeal carcinoma	15/16 patients had been treated initially with conventional radiation therapy; 1/16 had undergone surgical resection and postoperative radiation therapy. Chemotherapy was previously administered to 12/16 patients.	Treatment-related side effects, overall survival, local control and disease-free survival	Mean: 23.7 months
McAllister B, Archambeau JO, Nguyen MC, Slater JD, Loredo L, Schulte R, Alvarez O, Bedros AA, Kaleita T, Moyers M, Miller D, Slater JM. (1997)	California, United States	Case series Level IV interventional evidence Fractionated proton/photon and proton boost radiotherapy	28 pediatric patients with cranial tumours	Retrospective analyses of 28 patients treated between August 1991 and December 1994	Treatment-related side-effects, local control.	Median: 25 months
Noel G, Habrand J-L, Jauffret E, de Crevoisier R, Dederke S, Mammar H, Haie-Meder C, Pontvert D, Hasboun D, Ferrand R, Boisserie G, Beaudre A, Gaboriaud G, Guedea F, Petriz L, Mazeron J-J (2003)	Orsay cedex, France	Case series Level IV interventional evidence Fractionated proton and photon radiotherapy	67 patients with skull base or cervical spine chordoma or chondrosarcoma (2 were excluded from the analysis)	9/65 has undergone complete surgical resection; 50/65 had undergone incomplete surgical resection; 6/65 had undergone a biopsy alone as the last surgery.	Treatment-related side effects, overall survival, local control.	Median: 29 months

Noël G, Habrand JL, Helfre S, Mammar H, Kalifa C, Ferrand R, Beaudre A, Gaboriaud G, Mazeron JJ. (2003a)	Orsay cedex, France.	Case series Level IV interventional evidence Fractionated proton radiotherapy	17 pediatric patients with intracranial neoplasms	15 patients (88%) had undergone surgical resection: 4 complete, 11 grossly incomplete 2 patients had biopsy (12%)	Treatment-related side effects, local control.	Mean: 27 months
Noël G, Habrand JL, Mammar H, Haie-Meder C, Pontvert D, Dederke S, Ferrand R, Neaudre A, Gaboriaud G, Boisserie G, Mazeron JJ. (2002)	Orsay cedex, France	Case series Level IV interventional evidence Proton and photon radiotherapy	17 adult patients with intracranial meningiomas	All patients had undergone surgical resection. 12 benign and 5 atypical/ malignant meningiomas 16 patients had proton and photon radiotherapy 1 patient had proton radiotherapy only	Treatment-related side-effects, local control, clinical symptoms, survival	Mean: 36 months
Noel G, Habrand J-L, Mammar H, Pontvert D, Haie-Meder C, Hasboun D, Moisson P, Ferrand R, Beaudre A, Boisserie G, Gaboriaud G, Mazal A, Kerody K, Schlienger M, Mazeron J-J (2001)	Orsay cedex, France	Case series Level IV interventional evidence Fractionated proton and photon radiotherapy	45 patients with chordoma or chondrosarcoma of the skull base	4/47 had undergone complete surgical resection; 38/47 had undergone grossly incomplete surgical resection; 3/47 had undergone a biopsy only as last surgery.	Treatment-related side effects, overall survival, local control.	Median: 29 months
Pommier P, Liebsch NJ, Deschler DG, Lin DT, McIntyre JF, Barker FG, Adams JA, Lopes VV, Varvares M, Loeffler JS, Chan AW (2006)	Massachusetts, United States	Case series Level IV interventional evidence Combined proton and photon therapy	23 patients with skull base adenoid cystic carcinoma	3/23 patients had undergone gross total resection with positive margins; 9/23 has received partial resection; 11/23 had undergone biopsy alone. No patient received concurrent chemotherapy; 1/23 patients received induction chemotherapy	Treatment-related side effects, local and regional control, distant metastasis, survival rates, salvage treatment, visual, neurologic and endocrine outcomes.	Median: 62 months
Ronson BB, Schulte RW, Han KP, Loredo LN, Slater JM, Slater JD. (2006)	California, United States	Case series Level IV interventional evidence Proton radiotherapy	47 adults with pituitary adenomas	42 patients had undergone surgical resection 5 patients had undergone primary	Treatment-related side-effects, radiographic response, endocrinological response,	Median: 47 months

				radiation 4 patients underwent additional surgery after proton radiotherapy.	subjective response	
Weber DC, Chan AW, Bussiere MR, Harsh GR, Ancukiewicz M, Barker II FG, Thornton AT, Martuza RL, Nadol JB, Chapman PH, Loeffler JS. (2003)	Massachusetts, United States	Case series Level IV interventional evidence Proton radiotherapy	88 adults with vestibular schwannomas	One patient was previously treated with proton radiotherapy for functional pituitary adenoma	Treatment-related side-effects, tumour control, tumour response, hearing preservation , facial neuropathy	Median: 38.7 months
Weber DC, Lomax AJ, Rutz HP, Stadelmann O, Egger E, Timmermann B, Pedroni ES, Verwey J, Miralbell R, Goitein G. (2004)	Geneva, Switzerland	Case series Level IV interventional evidence Proton radiotherapy	16 adults with intracranial meningiomas	13 patients had undergone surgical resection	Treatment-related side-effects, radiological response, local control, progression -free survival , overall survival	Median: 34.1 months
Weber DC, Rutz HP, Pedroni ES, Bolsi A, Timmermann B, Verwey J, Lomax A, Goitein G (2005)	Villigen, Switzerland Geneva, Switzerland	Case series Level IV interventional evidence Proton radiotherapy	29 patients with skull base chordomas and low-grade chondrosarcomas	13/29 underwent radiotherapy after the first resection; 16/29 underwent radiotherapy at relapse, all after second surgery. No patient underwent biopsy only.	Treatment-related side effects, overall survival, progression -free survival, complicatio n-free survival, local control	Median:29 months
Wenkel E, Thornton AF, Finkelstein D, Adams J, Lyons S, De La Monte S, Ojeman RG, Munzenrider JE. (2000)	Erlangen, Germany	Case series Level IV interventional evidence Fractionated proton and photon radiotherapy	46 adult patients with meningiomas	All patients had recurrent, biopsied or subtotally resected benign meningiomas 45 patients received a combination of proton and photon radiotherapy 1 patient had proton radiotherapy only	Treatment-related side-effects, local control, overall survival, survival without severe toxicity	Mean: 73 months
Vernimmen FJ, Harris JK, Wilson JA, Melvill R, Smit BJ, Slabbert JP. (2001)	Cape Town, South Africa	Case series Level IV interventional evidence Stereotactic proton (SRT) and hypofractiona	27 adult patients with intracranial meningiomas	15 patients (65%) had undergone surgical resection or biopsy. 18 patients (78%) had hypofractionate	Treatment-related side-effects, radiologic response/local control, clinical stability	Mean: 31 (SRT) to 40 (HSRT) months

		ted proton radiotherapy (HSRT)		d stereotactic radiotherapy 5 patients (22%) had stereotactic radiation therapy		

Appendix C: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
  http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
  http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI)
  http://www.dsi.dk/engelsk.html

FINLAND

- Finnish Office for Health Technology Assessment (FINOHTA)
  http://finohta.stakes.fi/FI/index.htm

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)
  http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA
  http://www.dimdi.de/dynamic/en/

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
  http://www.kunnskapssenteret.no/

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)
  http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment
  http://www.cmt.liu.se/

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

UNITED KINGDOM

- NHS Quality Improvement Scotland
  http://www.nhshealthquality.org

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)
  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.your.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)
  http://www.bcbs.com/tec/index.html

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