

Childhood Brain Tumours: Proton Beam Therapy

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Abstract

There is a long tradition for multidisciplinary therapy which includes surgery, chemotherapy and radiotherapy in the treatment of paediatric malignancies. In most childhood brain tumours radiotherapy is a necessity for the achievement of local control. However, radiation treatment may also lead to serious late side effects that may affect the quality of life of the children who become long time survivors.

The dosimetric advantages of proton beams make them very attractive for paediatric radiotherapy.

There are three main advantages of using protons instead of photons:

1. Protons reduce late side effects by sparing normal tissue,
2. Because of the reduced side effects, it might be possible to escalate the radiation dose resulting in better tumour control and
3. Protons reduce the risk of secondary malignancy

The advantage of protons over photons has been demonstrated in several treatment planning studies, but there are no randomized

controlled studies proving the superiority of protons. Nevertheless, a large number of hospital based modern proton facilities are currently under construction and in the close future protons will be available for a larger group of cancer patients, especially for children. This chapter describes the basic principles of proton radiotherapy and provides a review of the literature on paediatric brain tumours irradiation with special emphasis on the value of proton radiotherapy.

Introduction

Long Term Outcome in Childhood Malignancies

The incidence of malignancies in children under 15 years in the developed countries is 140 per million. The most common are leukemias, brain tumours and lymphomas. The survival rates are about 80 % after 5 years for the whole group of paediatric cancers, ranging from over 90 % for Hodgkin's lymphoma and retinoblastoma to 60 % for AML and cPNET (Kaatsch 2010). These survival rates are very much in contrast to the survival rates in the 1960s where the 5 year overall survival rate for all paediatric cancer patients was only 30 % (Robison et al. 2009). The increase in survival is a result of improvements in diagnostic methods and therapies such as surgery, radiation therapy, chemotherapy and supportive care, and it is especially due to the introduction of a multi-disciplinary approach which now characterizes paediatric oncology.

Although the survival improvement is a success, it appears that cure comes at a high price as survivors are at a high risk for chronic morbidity such as cardiovascular, pulmonary, musculoskeletal, endocrine diseases or heavy neurocognitive impairment. Brain tumours are the second most common childhood cancers and survivors of childhood brain cancer have a high risk for functional and cognitive impairments. These patients often present with multiple morbidities such as seizures, auditory or visual and neurocognitive

disturbances or endocrine disorders (Oeffinger et al. 2006). On top of this, these patients have a considerably increased risk for secondary radiation induced cancer. As seen in the studies of the Japanese atomic bomb survivors, children have a higher sensitivity for radiation induced cancer than adults. The lifelong risk of having a radiation induced cancer is age dependent, and varies between children and adults by a factor of 10. Scatter radiation inside the treated patient is also more important in the small body of a child than in a large body of an adult. Some childhood malignancies also have genetical susceptibilities that make them more likely to develop a radiation induced cancer (Hall 2006).

However, by combining radiotherapy with chemotherapy it has become possible to reduce the radiation dose in some patient groups. This has been shown in randomised studies, especially for low risk medulloblastoma where the total dose to the craniospinal axis in some patients could be reduced when RT is combined with chemotherapy. In addition, chemotherapy may be used to postpone RT in small infants. Since the brain in infants less than 3 years old is especially vulnerable to radiation it is of utmost importance, whenever possible, to delay RT until after this age. In intracranial low risk germinoma, chemotherapy has replaced the craniospinal irradiation and radiation is only needed for the periventricular and initial tumour volumes.

Finally, prophylactic brain irradiation is now most often omitted after chemotherapy for childhood leukemia. These changes in treatment policy will lead to a reduction in the long term morbidity after childhood cancer therapy.

Modern Radiotherapy

The present literature on radiation related morbidity following therapy for childhood brain cancer is based on the use of traditional photon therapy. Use of photon radiotherapy inevitably leads to unintended exposure of the surrounding normal tissue. Until recently two to four photon fields were usually used to achieve an acceptable homogeneous dose to the tumour volume. As a

result of these beam arrangements large volumes of normal brain received a dose which potentially leads to radiation induced morbidity. It has been the goal of the technological development in modern radiotherapy to reduce the radiation dose to the normal tissue.

Accurate patient alignments by use of imaging of the patients in the treatment position at the accelerator immediately prior to each treatment session represent a major step forward in radiation therapy. Image guided radiation therapy (IGRT) is based on either mega-voltage X-rays delivered by the accelerator or by kilo-voltage systems that are mounted on the accelerator. Both technologies allow for planar and volumetric imaging. Most sophisticated is the cone-beam CT which allows acquisition of CT images which are matched to the treatment planning scans. From these matched images, errors in positioning can be determined and the patient can be accurately repositioned.

Another technological development has been to conform the dose distribution more precisely to the tumour volume. Intensity modulated radiotherapy (IMRT) is a technique which uses advanced treatment planning algorithms and powerful computers. The use of multiple beams shaped by a multi-leaf collimator enables dose distributions conforming to the shape of the target with a steep dose fall-off outside the target. By volumetric arc therapy (VMAT), the radiation is delivered during one or two perpendicular gantry rotations around the patient. Novel technologies are now being developed with the specific purpose to deliver IMRT under IGRT guidance. The tomotherapy machine is a compact LINAC integrated with a MV single-slice CT scanner which treats the patient slice-by-slice with simultaneous imaging of the treated volume.

IMRT is useful in the therapy of a number of childhood brain tumours. As an example, it has become possible to spare the inner ear in the therapy of posterior fossa medulloblastoma. However, by IMRT or VMAT the radiation dose is being re-distributed from critical normal tissue to less critical normal tissue or over a larger volume with less dose and the total body dose is increased because of leakage radiation by the accelerator equipment. Modelling studies

have suggested an increased risk for secondary malignancies when IMRT is used (Hall 2006).

Proton Radiotherapy

William Bragg discovered the deposition of ionization density at the end of the path of alpha particles already in 1905. Protons are charged particles produced by removing an electron from a hydrogen atom. They deposit almost all their energy in a very narrow spot, the Bragg Peak, and there is only a small exit dose. Because of their mass, their penetration in depth can be controlled. They have thus a finite range in the body. This physical characteristic can be used to spare normal tissue beyond the tumour and to keep the irradiated volume and thus late side effects low.

In 1954, the first patient was treated with proton irradiation of the pituitary gland at Berkeley University. Until recently, proton units were mainly operated by physical laboratories that were conducting physical particle research but allowed radiation oncologist clinics to use their accelerators with dedicated time slots for patients. Technical development offering lighter and more comfortable machines has increased the availability of proton therapy for the radiation community in the last years. Although these treatment facilities have a high cost and despite the fact that protons are not the usual standard of care in the therapy of a large number of tumour types, the number of hospital based proton centers under planning or under construction worldwide is increasing considerably. Thirty-five proton treatment units exist today, of which seven have an energy that only permits the treatment of ocular lesions. Nineteen other units are in a planning or construction phase. So far, more than 96,000 patients have been treated with protons worldwide (PTCOG 2012).

The unique dose distribution characteristics of protons allowing a high dose at the end of their path with virtually no exit dose make them particularly attractive in the field of paediatric radiotherapy. The total dose to the body is lower for protons than for photons and might lessen the risk for induction of secondary cancers (Fig. 8.1).

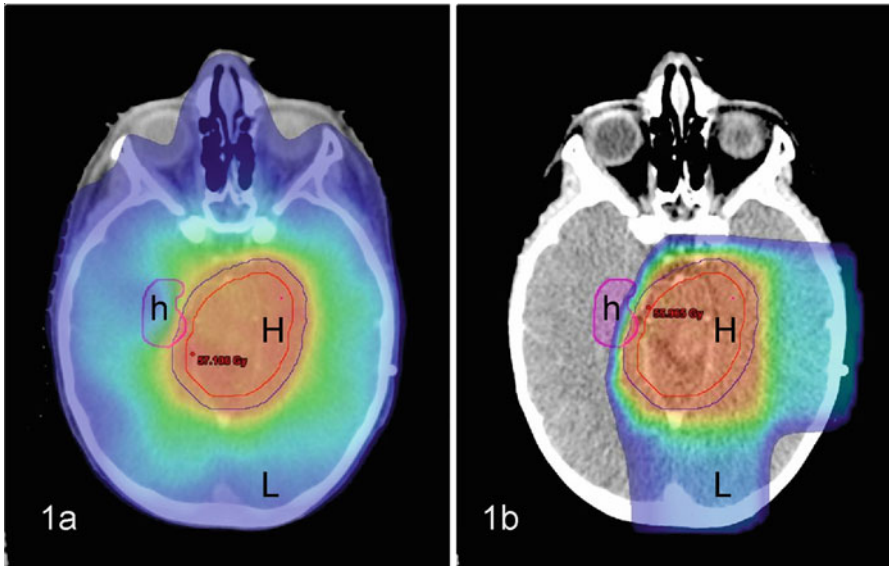


Fig. 8.1 Treatment planning study for a 3 year old child with a glioma. (a) Shows a VMAT photon plan and (b) a two field proton plan for a treatment with 54 Gy. (The threshold dose of the dose colorwash was set to 7 Gy). The low dose area

L is spread out over a much larger volume with the VMAT plan, the high dose area *H* is nearly identical for the two techniques and highly conformal to the target. The right hippocampus *h* can be better spared by the proton plan

Although photons and protons differ with respect to the physical dose distribution, they are almost identical in regards to the radiobiological effects. Protons have a very discrete increased radiobiological effectiveness (RBE) with respect to photons. In general, the dose of 1 Gy in protons is equivalent to 1.1 Gy in photons.

The high precision of proton beams is a challenge in treatment delivery. Proton radiation plans are less robust than photon radiation plans. Minor changes in patient anatomy or set up errors can increase or decrease the beam range and dose delivered to the patient and can thus lead to an increase or decrease of dose in the target and the organs at risks. Image guided techniques and firm immobilization are therefore of utmost importance in proton therapy.

As stated above proton treatment can be especially attractive in paediatric radiotherapy as long time survivors are not at risk for developing functional impairments and secondary cancers. However, there is a lack of statistical evidence to demonstrate the clinical superiority of proton treatment. Some studies have shown that local control is comparable to photon treatment, but

there are as yet no published studies on late morbidity after proton therapy (Brada et al. 2009). Some caution is also advisable, since the risk of secondary cancer might be higher than theoretically estimated for proton treatment because of neutron contamination with some proton delivery systems. There are no randomized controlled trials comparing the therapies in children and it is controversial whether conduction of such trials would be possible or desirable. Right now there are not enough proton facilities worldwide to meet the needs for treatment of paediatric patients therefore it is not realistic to expect that all children needing radiotherapy will be treated with protons. Accordingly, a case selection is necessary. It must be emphasized that protons are mainly superior to photons when patients are treated for cure. In case of palliative radiotherapy there is no or very little advantage of protons.

As large randomized controlled face-to-face trials comparing modern photon and proton radiotherapy are not expected to be conducted, it is important that all information on children treated on routine basis are collected in databases and evaluated. It is therefore desirable that all

children treated with modern treatment modalities such as photon IMRT or proton radiotherapy are included in large multi-institutional databases for registration of local control, survival and late morbidity outcomes.

The following review will focus mainly on childhood brain tumours with a good prognosis, when proton therapy is expected to have an important impact on the long term outcome compared with modern photon treatment.

Photon Radiotherapy for Common Childhood Brain Tumours

Medulloblastoma

Primitive neuroectodermal tumours (PNET) arise from the neural crest. PNET tumours of the posterior fossa of the brain are referred to as medulloblastoma.

Due to their location adjacent to the fourth ventricle they often cause increased intracranial pressure at the time of diagnosis. They are considered as grade IV tumours in the WHO classification and have an aggressive growth not only locally but also by their potential to disseminate in the whole subarachnoid space.

Radiation therapy to the complete cerebrospinal axis combined with systemic therapy has dramatically improved survival and today medulloblastoma patients have a 5 year survival rate of 60–80 % depending on their risk profile.

Treatment for medulloblastoma includes surgical resection, radiotherapy and chemotherapy. The surgery needs to be as radical as possible. Standard risk patients have no or only residuals following surgery and no dissemination to the cerebrospinal fluid (CSF) or along the subarachnoid space. High risk patients have macroscopic residual tumour following surgery or spread of tumour cells to the CSF. Radiotherapy consists of irradiation of the complete cerebrospinal axis and a boost in the posterior fossa. Chemotherapy has allowed reduction of the dose to the craniospinal axis in standard risk patients and the delay of radiotherapy in small infants. A routine prescription for standard risk patients is 23.4 Gy

to the craniospinal axis combined with a boost in the posterior fossa to a total dose of 54–55 Gy. High risk patients need a radiation dose to the craniospinal axis of 36 Gy followed by a boost in the posterior fossa to a total dose of 55 Gy. Concomitant single agent chemotherapy is administered along with the radiotherapy and multidrug chemotherapy is continued for several cycles after completion of radiotherapy for all medulloblastoma patients. Newer protocols and studies are aiming to confine the boost volume to the tumour bed with a small margin instead of irradiating the whole posterior fossa.

Traditional irradiation of the craniospinal axis is conducted with photons. The technique consists of two lateral fields to include the whole brain and the upper cervical spine combined with posterior fields to cover the rest of the subarachnoid space until the sacral roots. Often two to three posterior fields have to be applied depending on the length of the spinal cord. All the fields have to be perfectly matched and it has to be assured that field junctions between the fields are neither under- or overdosed. Although only the spinal cord is the desired target to treat, the beam will exit through the organs anterior to the spinal cord, thus resulting in a considerable dose to the vertebral bodies, the thyroid gland, the heart, the gastrointestinal tract, the lungs, the kidneys and the female reproductive tract, resulting in possible side effects to multiple organs from irradiation. With modern photon based IMRT techniques doses to organs anterior to the craniospinal axis like the mediastinum, the thyroid gland or the heart as well as structures anterior to the posterior fossa like the cochleae or the pituitary gland can be spared to some degree.

Electron irradiation of the spinal axis has been proposed and is practised in some institutions. It has the advantage that with the rapid fall off of dose at depth, tissues anterior to the spinal cord can be better spared. But matching with cranial photon fields and resulting dosimetric uncertainties make electrons difficult to use. Because of insufficient range of the electrons this technique may lead to underdosage of deeply located parts of the spinal subarachnoid space.

Nowadays prospective clinical studies often stratify patients according to immunohistochemical

and histological risk factors, and patients may be allocated to treatments designed according to the risk factors, but the principle of irradiating the whole subarachnoid space and boosting the tumour bed remains for the moment unchanged. Pattern of failure studies have shown that cerebral recurrences often occur in the posterior fossa, the subventricular area and the frontal area and it has been speculated whether the whole brain irradiation could be replaced with subtotal irradiation of the brain which includes these areas (Miralbell et al. 1997a, b).

Radiation remains an integral part of the therapy of medulloblastoma, but the risk for late morbidity for these patients is high because of the large volumes needing irradiation.

Low Grade Glioma

Low grade glioma originate from the glial cells. These tumours present a variety of different histologies and localisations in the brain. They often grow along the midline structures of the brain like the optical pathways, the hypothalamus and the brainstem and can also be found in the supratentorial hemispheres and the cerebellum. Long term survival is favourable in patients treated with macroradical resection. Radical resection can often be achieved in tumours of the supratentorial hemispheres, but more rarely in the cerebellum and in the midline regions where even a biopsy carries a risk of severe morbidity.

Radiotherapy is used for patients with progressing tumours where radical surgery is not possible. The timing of radiotherapy is controversial. Immediate postoperative radiotherapy in the case of residual disease has shown to increase the progression free survival, but not the overall survival. Therefore, radiotherapy is in general deferred in case of asymptomatic patients with slowly progressing low grade glioma. Radiotherapy is advised in the case of symptoms or progressing tumour at the time of recurrence. Trials are investigating the use of chemotherapy at progression of low grade glioma with the primary purpose of deferring radiotherapy as long as possible. Radiotherapy is usually applied with conformal

techniques with localized irradiation of the lesion and an appropriate margin for microscopic disease. The dose given is usually 45–54 Gy in 25–30 fractions depending on the site of the lesion. Small lesions have been successfully treated by some centers with stereotactic radiosurgery or fractionated stereotactic radiotherapy with favourable local control and morbidity (Kortmann et al. 2003). The overall survival of children with low grade glioma treated with radiotherapy is in the range of 80 % at 10 and 20 years after treatment.

Ependymoma

Ependymoma arise from the neuroepithelial linings of the ventricles. They are graded into grade II ependymoma and grade III anaplastic ependymoma. Two thirds of the tumours are located in the posterior fossa and one third in the hemispheres. It is mainly a neoplasm of children and adolescents, but one third of the patients are small infants (MacDonald and Yock 2010).

The standard treatment for cerebral ependymoma consists in gross tumour resection followed by radiation therapy. Radical surgery is an important prognostic factor and improves survival. If the surgery was not radical, a second look operation is often recommended. Postoperative chemotherapy may be considered in case of residual tumour (MacDonald and Yock 2010; Massimino et al. 2006).

Postoperative radiotherapy consists of involved field irradiation of the tumour bed with an appropriate margin to a total dose of 54 Gy. Radiotherapy yields a local control of up to 80 % if the initial surgery was radical (MacDonald and Yock 2010).

Less than 10 % of cerebral ependymoma disseminate into the subarachnoid space or the CSF. The pattern of failure is mainly locally, and postoperative craniospinal radiotherapy has been abandoned as a standard treatment for non disseminated tumours. In cases with CSF seeding the postoperative radiotherapy should include radiotherapy to the whole craniospinal axis with 36 Gy and a local boost to the spinal metastases and the initial tumour site.

Postoperative chemotherapy may defer radiotherapy in infants younger than 3 years old. Studies on young infants have conflicting results. There are reports on long term survival in infants treated by chemotherapy without radiotherapy. On the other hand several studies have shown that the progression free survival is impaired if radiotherapy is delayed to more than 1 year after surgery (MacDonald and Yock 2010; Koshy et al. 2011).

Craniopharyngioma

Craniopharyngioma are benign tumours arising from embryonic tissue in the pituitary region and often affect the functions of the optic chiasm, the hypothalamus and the pituitary gland. They often contain a mixture of cystic components and solid components.

The primary therapy is surgery, but as the lesions are situated in the area described, in close proximity to important risk organs, radical resection is often not possible. Postoperative radiotherapy is not needed in case of total tumour resection, but salvage radiotherapy is often used in case of progression after primary surgery. The overall survival is good, in most series approximately 80 % at 20 years after diagnosis.

Radiotherapy needs to be applied with a dose of at least 50 Gy (Fitzek et al. 2006). Although this tumour is often curable using combined treatment modalities, the patients often suffer from side effects related to therapy.

Intracranial Germinoma

Intracranial germ cell tumours are rare tumours that arise in the region of the third ventricle. Histologically, they are divided – like germ cell tumours in other locations – into pure germinoma and non-germinomatous germ cell tumours. In this section intracranial pure germ cell tumours will be described. These germ cell tumours may occur in children and in adolescents and have an excellent prognosis. Surgery may be omitted unless a histological confirmation of the diagnosis in addition to serum markers and MRI-scans is

needed. These tumours may be cured with radiotherapy alone. Previously, radiotherapy of pure intracranial germ cell tumours included the whole craniospinal axis with a boost in the tumour region. Nowadays, the therapy consists of combined chemo- and radiotherapy where the later is restricted to the periventricular volume and a boost to the tumour volume.

Morbidity After Radiotherapy for Childhood Brain Tumours

In radiation therapy it is important to distinguish between acute, temporary toxicities like headache, nausea or fatigue starting during the course of radiotherapy and late complications. Acute side effects are often due to edema and are usually treated with steroids and disappear in less than 3 months after the treatment. Late toxicity is defined as toxicity appearing later than 3 months after the treatment, these side effects usually do not resolve and may become permanent. Neurocognitive impairments, neuroendocrine deficits, hearing loss, impaired vision, increased risk for vascular insult and secondary cancer are examples of late reactions caused by irradiation of the brain. Impaired thyroid gland-, cardiac- and pulmonary function, growth retardation and infertility may be late manifestations of irradiation of the craniospinal axis. The development of these morbidities is dose and often also volume dependent.

Neurocognitive Problems After Radiotherapy

Varying degrees of neurocognitive changes after cerebral irradiation unfortunately are a frequent occurrence and often result in reduced quality of life. Survivors have a lower chance of getting employed and of getting married (Fossati et al. 2009). The brain tumour itself and the surgical procedure may lead to intellectual deficits. This may be further worsened however by structural changes caused by radiation therapy. Endocrine disturbances and ototoxicity may attribute to the neurocognitive problems as well. Neurocognitive

decline is most pronounced after whole brain irradiation. The mechanism involved is mostly white matter loss, but vascular factors and glial cell atrophy may be responsible as well (Fossati et al. 2009).

Neurocognitive disturbances are more pronounced after irradiation of children than in adolescents or adults. Neurocognitive impairment is dose dependent and reduction of the whole brain irradiation dose from 36 to 23.4 Gy in standard risk medulloblastoma patients has resulted in less neurocognitive decline (Fossati et al. 2009).

The neurocognitive function has been correlated to the dose delivered to the whole brain, supratentorial brain, and the temporal lobes. Regarding the dose to the supratentorial brain it was shown in a study of childhood ependymoma that the risk of neurocognitive loss was related not only to the irradiation of the high dose volume (> 40 Gy), but also the low dose volume (< 20 Gy) and even the very low dose volume (< 5 Gy). This has to be considered when treating these patients with IMRT because the very low dose and low dose volume will be increased with IMRT (Merchant et al. 2005). Unfortunately the supratentorial brain and temporal lobes, as well as the subventricular and hippocampal areas may often not be spared in the therapy of midline and supratentorial tumours. However, the dose to the brain outside the target should be kept at a minimum.

Neuroendocrine Problems After Radiotherapy

Endocrine effects occur as a consequence of irradiation of the hypothalamic-pituitary axis. Growth hormone deficiency may be caused by irradiation of the hypothalamic region and has an impact not only on growth, but also on metabolism, cardiovascular function and neurocognitive function. The threshold dose for development of neuroendocrine dysfunction is low; when doses > 16 Gy are given to the hypothalamus the patient may develop growth hormone deficiency. The higher the dose to the hypothalamus, the higher is the risk for growth hormone deficiency and the earlier it may appear (Merchant et al. 2011). This condition can be treated by growth

hormone substitution. Accordingly it is important that children who have received radiotherapy to the hypothalamic region are screened regularly (Fossati et al. 2009).

Irradiation of the pituitary gland will often result in dysfunction of the gonadotrophic axis. This may result in precocious puberty which together with growth hormone deficiency and irradiation of the vertebral bodies during craniospinal irradiation may lead to growth retardation. Patients should also be screened for adrenal cortical hormone deficiency and thyroid hormone deficiency due to a hypopituitarism.

Vascular Problems After Radiotherapy

It has been demonstrated that children treated for brain tumours have a higher risk of vasculopathy like Moyamoya disease and strokes and also for developing vascular malformations and aneurysms. In the childhood cancer survivor study cohort it has been shown that the relative risk of developing stroke after irradiation for childhood brain cancer was 7 % higher for patients than for their siblings, 25 years after radiotherapy. There was proposed a dose effect, with the risk for stroke increasing at doses above 30 Gy and the risk being highest at doses above 50 Gy. Endocrine changes can also attribute to this. Vascular changes after radiotherapy are more often seen in children with neurofibromatosis NF1. Venooclusive disease and Moyamoya vasculopathy may already develop in the first years after radiotherapy. Mineralizing microangiopathy can already be seen at doses as low as 15 Gy. Some adult survivors are also at increased risk of developing migraine attacks several years after treatment (Morris et al. 2009).

Auditive Problems After Radiotherapy

Ototoxicity results from irradiation of the cochlear region and is a sensorineuronal hearing loss. It is dose dependent and the threshold dose

has been estimated at 35 Gy (Moeller et al. 2011). Hearing loss therefore often occurs if tumours are located in the posterior fossa, as it is the case for medulloblastoma or ependymoma. The risk is increased by addition of chemotherapy such as cisplatin which is often given with radiotherapy in the treatment of medulloblastoma. New generations of protocols allowing restriction of the irradiated volume to the tumor bed instead of the whole posterior fossa will most likely have an impact on the risk of hearing loss. With modern photon based IMRT techniques the inner ears can often be spared.

Visual Problems After Radiotherapy

Reduced vision due to development of cataract may occur after irradiation of the lens at low doses of 7 Gy. In young children the frontal sinus is not well developed and therefore the cribriform plate is often located at the same level as the lens and the lens may receive some dose during radiation treatment of medulloblastoma. In pattern of failure studies, recurrences appeared at the cribriform plate because of shielding of the lens (Miralbell et al. 1997a, b). However, as cataract is relatively easily treatable, the dose coverage to the cribriform plate should not be compromised. Vision loss due to irradiation of the chiasm and the optical nerves is rare, as the dose of 54 Gy customarily employed for irradiation of childhood brain tumours is generally tolerated by the optic apparatus.

Secondary Cancer After Radiotherapy

Cancer secondary to irradiation is a concept founded mainly on radiobiological models as well as the experience of following the Japanese atomic bomb survivors. The field is filled with uncertainties and conflicting results.

Carcinogenesis is derived partly from the primary irradiation of the radiation field. This risk will probably be reduced in proton treatment as less radiation is necessary to achieve the same coverage of the target. But carcinogenesis is also

induced by secondary radiation. In photon treatment secondary radiation is due to leakage from the accelerator head and multileaf-collimator. This stray irradiation is difficult to estimate and is generally not reported by treatment planning systems. With conformal radiotherapy techniques the tumour is irradiated through few portals with a homogenous dose and secondary cancers are expected to arise in the high dose volumes along with the treatment fields. In modern IMRT the high dose volume is reduced at the expense of increased medium and low dose volumes. It is speculated if IMRT techniques increase the risk of secondary cancer induction (Hall 2006).

Among children followed in the childhood cancer survivor study, medulloblastoma patients had the highest risk for death from secondary cancer in comparison to other childhood malignancies. It was concluded that increased risk for secondary cancer was due to the craniospinal irradiation which leads to secondary neoplasms in the brain as well as in the body (Armstrong et al. 2009).

Toxicities After Radiotherapy of the Craniospinal Axis

Irradiation of the entire spinal cord as in therapy for medulloblastoma leads to a considerable dose to organs anterior to the spinal cord resulting in acute as well as late toxicity. As acute toxicity the children often experience nausea which may be reduced with modern antiemetic therapy. The patients may also present with moderate mucositis. Transient haematological toxicity is also often present and haematological parameters need to be followed during treatment and at follow up.

Radiation induced cardiac diseases have been described especially after the treatment of mediastinal targets in Hodgkin's disease. They often develop several decades after the radiation therapy. The risk for cardiac morbidity in patients with Hodgkin's disease is even further increased by the use of anthracycline chemotherapy. Cardiac toxicity after craniospinal radiotherapy is less well studied. In treatment planning studies it has

been shown that the dose to the heart can be reduced by modern IMRT photon technique. Studies from the childhood cancer survivor study cohort show that patients with Hodgkins lymphoma or nephroblastoma are at the highest risk of cardiac mortality and that medulloblastoma patients even after a long period of follow up and treated with conventional photon treatment do not have an increased risk for cardiac mortality. However this cohort has not yet reached a plateau for late toxicity and cardiac toxicity might still arise at a later time in the craniospinal group (Armstrong et al. 2009).

Asymptomatic restrictive lung disease has been described in medulloblastoma patients and is attributed to radiotherapy not because of a high dose nor volume treated, but because of a reduced chest volume due to the reduced growth of the spine (Fossati et al. 2009).

Height and especially sitting height is impaired in medulloblastoma patients after craniospinal radiotherapy. This is due to both neuroendocrinological dysfunction and irradiation of the vertebral bodies. The lumbar spine is often more affected than the thoracic region and the upper cervical region seems to be least affected. The threshold dose for growth retardation seems to be approximately 25 Gy (Fossati et al. 2009).

Ovarian function may suffer after craniospinal irradiation and also after chemotherapy regimens containing especially alkylating agents (Fossati et al. 2009). Preservation of ovarian tissue is therefore advisable before radiotherapy. Likewise in boys sperm conservation is advisable prior to radiotherapy.

Proton Radiotherapy for Common Childhood Brain Tumours

Proton treatments, although already available for several decades have in the past mainly been used for the treatment of ocular melanoma or of skull base tumours. In the last decade proton treatment has gained much more interest in radiation oncology and many treatment planning studies for different tumour histologies and localisations have demonstrated that proton treatment is superior to

photon treatment for sparing organs at risk that are not a part of the target region and makes it feasible to decrease the total body dose to the patient necessary to deliver the desired dose in the target.

Proton Radiotherapy for Medulloblastoma

In dose planning studies proton treatment has been shown to be important for decreasing the risk of late toxicities that can develop after craniospinal irradiation with a boost to the posterior fossa. When considering the different components of the treatment, target coverage is generally as good as with photon treatment. The technique for the neuraxis is often the same as with conventional photon treatment, lateral fields for the whole brain part, posterior fields for the spinal cord and often lateral fields for the boost to the posterior fossa.

Considering the whole brain part of the irradiation no normal brain tissue can be spared as the whole brain is the target. It was shown that with two posterior oblique proton fields the lens can be spared more efficiently without compromising coverage of the cribriform plate (Cochran et al. 2008).

Considering the irradiation of the spine, the target is essentially the subarachnoid space. The vertebral bodies are usually included to avoid asymmetrical growth. One treatment planning study showed that the dose to the vertebral body could be reduced to 6 Gy with protons a dose that is considered negligible for growth problems (Miralbell et al. 1997a, b). It is controversial if all the vertebral body has to be included into the target to avoid asymmetric growth. The organs in front of the spinal cord are not considered as targets but cannot be avoided with photon techniques unless modern IMRT techniques are used. Several treatment planning studies have shown that with proton treatment the dose to the heart and lungs is negligible and that the total body dose to the patient is reduced in comparison to modern photon techniques (Lee et al. 2005; St. Clair et al. 2004; Brodin et al. 2011; Miralbell et al. 1997a, b; Yoon et al. 2011). Also the ovaries can be spared (Fig. 8.2).

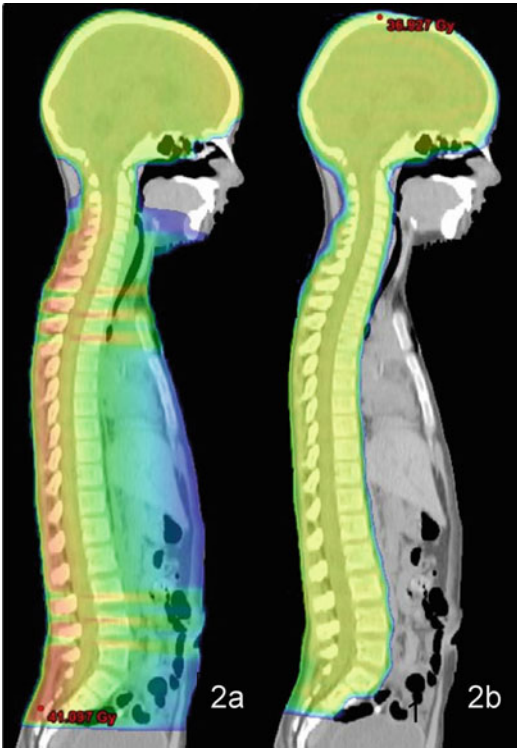


Fig. 8.2 Shows a treatment planning study for a 9 year old boy with a medulloblastoma for a treatment of the craniospinal axis with 35 Gy, (the threshold dose of the colour wash was set to 15 Gy). (a) Shows a photon plan and (b) shows a proton plan. The dose anterior to the spinal cord is neglectable in the proton plan, whereas in the photon plan a larger low dose area is found anterior to the spine

The boost irradiation to the posterior fossa increases the dose to organs at risk near the posterior fossa like the inner ear and the hippocampus, more distantly also to the pituitary gland, the temporal lobes and parts of the supratentorial brain. With 3 D conformal photon treatment all these structures receive considerable doses by the boost treatment. With intensity modulating techniques the dose to critical structures can be decreased to acceptable levels. With proton treatment the dose to the organs at distance in the supratentorial brain becomes negligible, the dose to the inner ear is reduced substantially and the total dose to the brain is diminished in comparison to modern photon techniques. As the supratentorial brain and the temporal lobes are not receiving as much from the boost dose in protons as in photon treat-

ment, neurocognitive models have shown that the expected decline in intelligence after irradiation for medulloblastoma might be slower after proton radiotherapy than after photon radiotherapy (Merchant et al. 2008).

A clinical study that followed patients treated for medulloblastoma with proton therapy for ototoxicity showed that high grade ototoxicity was found only in 5 % of the patients at 1 year after treatment (Moeller et al. 2011).

Several treatment planning studies have tried to assess the risk for secondary cancer after irradiation of medulloblastoma patients with different techniques. However, it has to be emphasized that several uncertainties have to be accounted for when estimating the risk of radiation induced secondary cancer. Proton therapy decreases the risk of secondary cancer induction because of a lower total body dose to the patient. In proton treatment secondary radiation is due to neutron contamination, which can be higher with passive modulated treatment delivery techniques than with pencil beam scanning techniques. However, the pencil beam scanning techniques are more sophisticated and more challenging and most of the proton centers still employ the passive modulated technique (Hall 2006). Neutrons are important for carcinogenesis, but the amount of neutrons produced by proton treatments is again difficult to estimate and cannot be calculated by a treatment planning system. In general treatment planning studies show that the risk of developing secondary cancer is substantially reduced by protons also when secondary stray irradiation by neutrons is taken into account (Table 8.1).

Although the risk of secondary cancer can be substantially reduced by proton irradiation it will take several decades until this will be demonstrated in the clinical setting.

Proton Radiotherapy for Low Grade Glioma

Low grade glioma requires focal radiation therapy in the area of the brain where the tumour is situated. When the tumour is localised in the optical pathways, the optical nerves or the chiasm can

Table 8.1 Showing several doseplanning studies for development of secondary cancer in medulloblastoma and comparing proton and photon irradiation

Protons (%)	3 D Photons (%)	IMRT/VMAT/Tomo (%)	Endpoint	Reference
7	45	56	2ndary cancer Lifetime risk Dose 23.4 Gy	Brodin et al. (2011)
9	56	71	2ndary cancer Lifetime risk Dose 36 Gy	Brodin et al. (2011)
0.05	0.71	0.43	2ndary cancer Yearly incidence after radiotherapy	Miralbell et al. (2002)
4.4–5.1	54.8	31.4	2ndary cancer Lifelong risk	Newhauser et al. (2009)

be either part of the target volume or very close to it. Similarly, the hypothalamus and the pituitary gland are in close relationship with these structures. Additionally the medial parts of the temporal lobes and sometimes the hippocampal zone as well can be close to the target. When the tumour is localised in the supratentorial hemispheres, sparing of the contralateral hemisphere is very important, a feat that can be difficult to achieve with modern photon IMRT techniques as the volume irradiated with low doses is substantially increased. When the tumour is localised in the cerebellum, the inner ears, the brain stem as well as the hippocampal zones might be near the target volume.

Although stereotactic photon radiotherapy methods spare normal tissue effectively when the target is small, a treatment planning study showed that protons could spare the normal brain better than stereotactic treatment delivered by linacs or gamma knife and that this effect became more pronounced with larger or more irregular shaped lesions (Verhey et al. 1998).

One series of 27 children treated for low grade glioma with protons had comparable local control and survival data compared to photon data and no recurrence was found at the field margins or outside the high dose region. No serious late effects apart from one case of Moyamoya vascular disease in a child with neurofibromatosis were noted after a median follow up of 3.3 years (Hug et al. 2002).

In a treatment planning study of optical pathway low grade glioma comparing irradiation with protons and photons it was shown in a neurocognitive model that the differences in dose to the structures important for neurocognitive function was only small but that it was still expected that this would be clinically significant (Merchant et al. 2008).

Proton Radiotherapy for Ependymoma

Radiotherapy for childhood ependymoma usually consists in focal irradiation to the posterior fossa carrying a risk for late toxicities concerning the auditory, neurocognitive and endocrine function and a risk of vascular disease and secondary malignancies.

A cohort of 17 ependymoma patients were treated with localised radiotherapy with protons. Tumours were located both infra- as supratentorially. The outcome data after a median follow up of 26 months were excellent, the proton treatment did not impair local control or survival. Subtotally resected patients had a worse outcome than radically resected, as expected. No major toxicity was seen in the patients so far at follow up (MacDonald et al. 2008).

A treatment planning study of an ependymoma case with a neurocognitive model analysing the dose to the neurocognitive structures showed that

these structures could be spared better by protons than by photons (Merchant et al. 2008). That could also be confirmed in a second treatment planning study that analysed doses to the same structures (MacDonald et al. 2008). This is noteworthy as the patients are often very young children and neurocognitive late effects can be expected to be worsened when treatment is done at a younger age. In the two studies it was also demonstrated that the dose to the hypothalamus can be decreased significantly by protons in comparison to conventional photons or photon IMRT. The same was true for the dose to the inner ear (MacDonald et al. 2008).

Proton Radiotherapy for Craniopharyngioma

Craniopharyngioma are usually situated in the midbrain area and treated if indicated with local irradiation in this area. This can lead to toxicities from the optical apparatus, the endocrine system, the vascular system and the neurocognitive functions. Two studies have reported outcome and toxicity data of children treated with protons for craniopharyngioma. The outcome data are good and in the same range as for comparative photon data, demonstrating that local control is not impaired by more conformal therapy. In one study, five irradiated children also finished high school, and three of them went to college, all were living independently at follow up. These children did not experience any serious side effects from the radiation treatment after a median follow up of 13 years (Fitzek et al. 2006). In another study three children out of 12 long time survivors experienced serious side effects at a mean follow up of 60 months. One child had developed hypopituitarism, one child an ischemic episode and one child a meningioma. This child had also received photon radiotherapy at an earlier time in the same location (Luu et al. 2006).

A treatment planning study with a neurocognitive model analysed doses to the neurocognitive structures in craniopharyngioma patients with protons and photons. The difference in dose to

these structures was small but was assumed to be clinically significant (Merchant et al. 2008).

Another treatment planning study in craniopharyngioma patients has shown that the dose to the central vessels could be reduced with protons in comparison to photon IMRT therapy (Boehling et al. 2012).

Craniopharyngioma poses a particular challenge to radiotherapy because the cysts can alter their volume during the several weeks of irradiation. An increase in the size of the cysts especially during the beginning of the treatment has been described, sometimes necessitating an aspiration of the cysts. Studies have demonstrated that regular interfractional scanning of the target volume is necessary to assess the size of the cystical components during treatment and that adaptive replanning often has to be performed. Assessment of the cyst size is critically important as target coverage is very precise with proton therapy (Winkfield et al. 2009).

Proton Radiotherapy for Intracranial Germinoma

As these tumours have an excellent prognosis, the long term survivors are at risk for developing long term sequelae that can be mainly neurocognitive and endocrine as the periventricular area and the tumour is irradiated.

The early outcome data for 22 children treated with proton therapy for germ cell tumours after a median follow up of 28 months showed that the local control was excellent, as expected. One patient had a peritoneal failure attributed to a ventriculoperitoneal shunt. As late complications only growth hormone and thyroid hormone deficiency have been noted. The authors also made a treatment planning study of a periventricular irradiation case comparing protons with intensity modulating photon irradiation. The dose to the temporal lobes and to the whole brain was significantly reduced by proton treatment, although the paraventricular hippocampal zone could not be spared. It was noted that the ocular lenses received

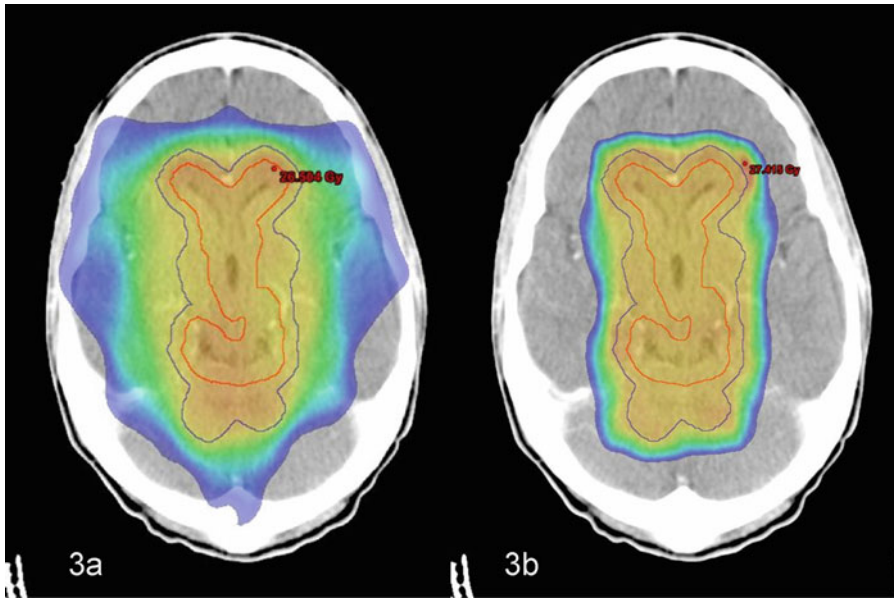


Fig. 8.3 Shows a treatment planning study for a 17 year old adolescent with a cranial germinoma for a treatment with 26 Gy in the ventricular area. (The threshold dose for the colorwash was set to 15 Gy). (a) Shows a six field

IMRT plan. (b) Shows a three field proton plan. The proton plan is highly conformal and the lateral temporal lobes are better spared from low and intermediate dose

radiation doses that could induce a cataract with the photon plan. The lenses could be completely spared by the protons (MacDonald et al. 2011) (Fig. 8.3).

Conclusion

Radiotherapy is an important part in the multidisciplinary treatment of childhood brain tumours. For some tumours chemotherapy has permitted a decrease in the radiation dose or volume necessary for achieving local control. However, in most curable childhood brain tumours radiotherapy cannot be omitted.

With modern radiotherapy techniques doses to organs at risk outside the target volume can be efficiently spared by using intensity modulating photon techniques. The disadvantage of these very efficient techniques is a redistribution of the radiation dose to a larger low dose region and an increase of the total body dose distant to the target, which might lead to an increase in secondary cancer in the future.

Proton radiotherapy has been shown in both dose planning studies as well as in forthcoming

clinical studies that organs at risks are efficiently spared by the favourable dose depth characteristics that allow for sparing organs beyond the target. In addition, organs that are relatively close to the target can be better spared than with any photon technique and dose to organs further away can become negligible, simultaneously the total dose to the body is decreased and thus the risk for developing a secondary cancer can be reduced at the same time.

This makes protons especially interesting for the use in paediatric malignancies and it is to be hoped that more proton facilities will soon be available so that children with curable diseases necessitating radiotherapy will have an easy access to proton radiotherapy.

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