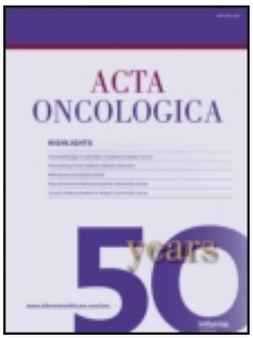

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ORIGINAL ARTICLE

The potential of proton beam therapy in paediatric cancer

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Abstract
A group of Swedish oncologists and hospital physicists have estimated the number of patients in Sweden suitable for proton beam therapy. The estimations have been based on current statistics of tumour incidence, number of patients potentially eligible for radiation treatment, scientific support from clinical trials and model dose planning studies and knowledge of the dose-response relations of different tumours and normal tissues. It is estimated that in paediatric cancers, proton beams are of potential importance in 80–100 children annually in Sweden. About 20 of the patients have medulloblastoma. The main purpose is to reduce late sequelae, but these are also increased chances to avoid myelosupression during e.g. concomitant chemo-radiation and to further intensify the chemotherapy.

Some 300 children contract malignancies annually in Sweden [1]. The percentage shares of the 12 most common forms of cancer in children (aged under 15) in the Nordic countries during the period 1985–1994 are: leukaemias 30%, lymphoma 11%, central nervous system (CNS) tumours 28%, sympatic nervous system tumours 6%, retinoblastoma 3%, kidney tumours 6%, liver tumours 1%, skeletal tumours 3%, soft tissue tumours 6%, germinal cell tumours 3%, carcinomas 2% and miscellaneous tumours 0.5% [2]. It is noteworthy that leukaemias comprise about 1/3 of paediatric cancers while solid tumours represent the other 2/3, of which about 50% are brain tumours. Roughly 20% of children's brain tumours are medulloblastomas (primitive neuroectodermal tumour (PNET) in the posterior fossa). The incidence of paediatric cancer is increasing slightly in Sweden [3], primarily due to an increasing incidence of brain tumours [4].

Survival after treatment of paediatric cancer has improved considerably all over the world during the past 40 years [5–8]. In the Nordic countries, the chance of surviving after treatment for paediatric cancer is around 70% after 12 years [6]. Excess late mortality, from recurrence of the primary disease, second cancer and other causes, is seen, however [8,9]. Chemotherapy is the most common treatment for paediatric cancer and has also led to dramatic improvements in survival. Surgery is an important treatment for solid tumours in children, as with adults. The aim of surgery is to radically remove the tumour without functional or cosmetic loss. In order to achieve this goal, chemotherapy often precedes surgery.

Radiotherapy for paediatric cancer

Radiotherapy also has an established role in the treatment of paediatric cancer. Cranio-spinal radiotherapy for medulloblastoma in children was already described at the end of the 1940s, by Sir Ralston Paterson [10]. In a review published in the mid-1990s, Taylor stated that 40–50% of paediatric cancer patients underwent radiotherapy [11]. Radiotherapy can be administered either as the sole treatment, e.g. for retinoblastoma, but more commonly after chemotherapy or surgery, e.g. in cases of medulloblastoma, soft tissue sarcoma and advanced stages of Wilms' tumour. It may be administered prophylactically, e.g. for some types of leukemia and lymphoma, as whole-body irradiation before stem cell transplantation or as palliation for local symptoms due to metastasis. When radiotherapy is

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administered after chemotherapy and/or surgery, the remaining tumour mass is usually small, so it may be assumed that tumour hypoxia is a relatively smaller problem in children than in connection with radiotherapy of tumours in adults. Since children more often contract radiation-sensitive tumours than do adults, the total radiation dose given children is usually lower than that administered to adults [12].

Primitive neuroectodermal tumour (PNET) of the central nervous system is the most common malignant brain tumour in children. The vast majority of these tumours is situated in the posterior cranial fossa and are, as previously mentioned, classified as medulloblastomas. In contrast to most other types of brain tumour, medulloblastoma is characterized by a relatively high rate of subarachnoidal metastasis (10–30%) at the time of diagnosis [13,14]. Metastasis outside the central nervous system (CNS) is very rare ($<5\%$), but may occur late during the course of the disease. Age at onset, remaining tumour after surgery and metastasis at diagnosis are known prognostic factors, on the basis of which patients are classified as standard- or high-risk. Surgery, radiotherapy (to the cranio-spinal region with a boost to the tumour area) and chemotherapy constitute the current standard combined treatment for adults and children aged over 3–4 years old [14]. Today, three-dimensional conformal radiotherapy (3D-CRT) up to a dose of 23–35 Gy to the cranio-spinal region with a boost to the posterior fossa, and a total dose of 55 Gy, is standard radiotherapy for medulloblastoma [15]. The usual dose per fraction is 1.6–1.8 Gy. There is, however, interest in evaluating the effect of hyperfractionated radiotherapy, as for example in the ongoing randomized SIOP (International Society of Paediatric Oncology) study in Europe, PNET 4.

Side effects of radiotherapy for paediatric cancer

The effects of ionizing radiation on growing tissue were noted already at the beginning of the twentieth century [16]. Shortly after the introduction of radiotherapy for paediatric cancer, irreversible sequelae after radiotherapy were observed in growing children [17,18]. During the mid-seventies, reductions in sitting and standing height, correlated to age and dose, were reported in long-term survivors who had undergone irradiation of the spinal column for medulloblastoma [19]. The current level of knowledge is more extensive and includes sequelae after irradiation of the CNS, kidneys [20,21], endocrine glands, e.g. pituitary [22,23] and thyroid [24,25], heart [26–28], and gonads [29,30]. The neuropsychological side effects of irradiation of the brain for CNS tumours in children of various ages and with varying doses have been especially thoroughly studied [31–34]. Hearing impairment, with subsequent effects on learning and language development, is another serious sequela [35–37].

Treatment-induced secondary malignancy in long-term survivors of successfully treated paediatric cancer is another very serious and specific side effect [38–40]. A recently published study reports more than 20% annual relative risk of contracting a secondary solid tumour 25 years after successful treatment of Hodgkin's lymphoma [41]. Age at radiotherapy, radiation dose, the anatomic area irradiated, organ-specific radiation sensitivity, hereditary factors and the irradiated volume are factors which may affect the risk of developing secondary cancer [42–46].

Clinical experience of proton beam therapy

Just as with adults, proton beam therapy (PBT) is mainly used to treat children with tumours for which dose escalation within the tumour area is desirable without an accompanying increase in the integral doses. The PBT treatment of 18 children aged 4–18 years with posterior fossa and cervical spine chordomas has been reported from Massachusetts General Hospital and Harvard Medical School. Actuarial survival was 68% after five years, and disease-free survival 63% after a follow-up time of 72 months. The long-term side effects were described as "acceptable" [47]. In a later paper from Boston, concerning 29 children aged 1–19 years old with mesenchymal posterior fossa tumours treated with PBT, a substantial degree of local tumour control and survival was reported [48]. Another article from Boston reports on seven children treated with PBT for optic nerve glioma [49]. There is also a report, from the same centre, of an additional 27 children, aged 2–18 years, treated with PBT for low-grade glioma. Local tumour control was found in 21 of 27 subjects and the treatment was considered to be "generally well tolerated" after a follow-up time of 3.3 years [50]. PBT has also been successfully used for children with base of skull tumours [48]. In a series of 17 children with CNS tumours, treated with up to 69 CGE at the Centre de Protontherapie d'Orsay, local and systemic control have been seen in 15 patients [51]. The follow-up is median 27 months. Another report describes PBT treatment of a four-year-old boy with a paraspinal neuroblastoma; good dose homogeneity and dose minimization to critical organs such as the liver, kidneys and spinal cord were reported [52]. Finally, there is a report from Loma Linda on three children with medulloblastoma treated with craniospinal irradiation with protons. The authors describe a substan-

tially reduced dose to the cochlea, vertebral bodies and virtually no exit dose through thorax, abdomen and pelvis and also no clinical significant lymphocyte count reduction during the treatment, thereby creating conditions for reduced late side-effects and also reduced acute side-effects [53].

Model studies

In the light of the above-mentioned side effects, not least the risk of subsequent onset of secondary malignancy, it is appealing to study PBT and compare it to three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). Wambersie and co-workers [54] saw clear dose distribution advantages for childhood brain tumours at different sites. In a Swedish study published in 1997, Isacsson and co-workers showed the advantages of PBT, compared to 3D-CRT, in the boost treatment of Ewing's sarcoma [55]. A model study comparing PBT and 3D-CRT for irradiation of the posterior fossa in nine children revealed that PBT yielded lower radiation doses to normal tissue, thus decreasing the risk of hearing impairment as a sequela [56]. PBT has also compared favourably with 3D-CRT in model studies of optic nerve glioma in children [57]. A model study of children with parameningeal embryonal rhabdomyosarcoma and medulloblastoma has highlighted the possibility of reducing the incidence of radiation-induced secondary paediatric cancers by administering PBT instead of photon therapy [58]. This conclusion was also drawn in a study exploring various treatment techniques for retinoblastomas [59].

In summary, the studies mentioned above have demonstrated substantial advantages to PBT, compared to 3D-CRT, when it comes to lowering the risk of serious sequelae of radiotherapy in children, since the dose to normal tissue is minimized with PBT [60]. There is no information about model studies, clinical studies or the use of light ions in the treatment of paediatric malignancies, although an early investigation from Heidelberg estimated the potential benefits of charged particles (carbon ions) for tumours of the retroperitioneal region [61].

Assessment of the number of PBT cases

Some 120 children, about 40% of the children with malignancies in Sweden, are given radiotherapy at some point during the course of their illness [62]. PBT can be estimated to be better than 3D-CRT in 80–100 of these cases. Of these, about 20 patients have medulloblastoma. The advantages primarily consist of a reduction of serious sequelae, but also a possibility of escalating the dose to radiation-resistant tumours such as glioma, and to deliver chemotherapy with less risk of myelosuppression.

Cost-benefit calculations

Due to potentially reduced long-term toxicity of using PBT rather than 3D-CRT or IMRT, the use of protons for the treatment of a 5 year old patient with medulloblastoma was cost-saving in a model study [63].

Need for research

The need for clinical research concerning PBT treatment of children has recently been summarized by Taylor [64] and Yock and Tarbell [60]. Clinical research with long-term follow-up is then needed to study whether proton therapy is more beneficial, especially when it comes to late side effects, than 3D-CRT or other techniques currently in use. Studies concerning acute side effects, e.g. bone marrow toxicity, would also be valuable since a potential decrease in these effects might enable an intensification of treatment, for instance, with chemotherapy [54].

Summary assessment

An estimated 80–100 children with malignancy would be primarily eligible for PBT annually in Sweden, if PBT equipment were available. There are substantial advantages to PBT, compared to photon therapy, in terms of increased local tumour regression and an essential reduction in sequelae.

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