Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2008)
7, 9–18

doi: 10.1017/S1460396907006218

Original Article

What are the potential benefits and limitations of particle therapy in the treatment of paediatric malignancies?

P. Hardy[1], P. Bridge[2]

[1]*Department of Radiotherapy, Derbyshire Royal Infirmary, London Road, Derby, UK,* [2]*Faculty of Health and Wellbeing, Collegiate Crescent Campus, Sheffield Hallam University, Sheffield, UK*

Abstract

The reduction in dose received by normal tissue is essential in radiotherapy to reduce the chance of late side-effects. This is especially true in paediatric radiotherapy as any late-effects can seriously impair the future quality of life experienced by the treated child.

Particle therapy uses high-energy particles to deliver a surgically precise beam of energy to a pre-determined position in the body. Common side-effects associated with conventional radiotherapy (CRT) are considerably reduced, often virtually eliminated, owing to the reduction in dose received by neighbouring healthy tissues, improving future quality of life. The superior accuracy of particles also means the dose can be escalated improving control rates.

Clinical trials, reviews and planning studies have been reviewed to assess the benefits and limitations offered by particle therapy in paediatric treatments. The reduced integral dose and improved conformity is clearly highlighted throughout these studies, demonstrating the potential advantages available with particles when treating paediatric patients.

The data suggest that the advantages experienced with particle therapy result in a significant reduction in the side-effects experienced and therefore an improvement in quality of life when compared with conventional therapy. Owing to the reduction of subsequent sequelae, paediatric patients need to be considered when designing and constructing a particle centre in the UK.

Keywords

Paediatric malignancy; particle therapy; protons; radiation side effects

INTRODUCTION

Although cancer is rare in childhood, approximately 1,400 children still contract malignancies annually in the UK.[1] Leukaemias comprise about one-third of these paediatric cancers, with solid tumours representing the remainder, of which approximately 50% are brain tumours.[2] Survival after treatment of paediatric cancer has improved considerably throughout the world over the last few decades and with current therapies around two-thirds of children treated can expect to become long-term survivors.[3] In the 1940s and 1950s, children surviving cancer was

Correspondence to: Paul Hardy, Department of Radiotherapy, Derbyshire Royal Infirmary, London Road, Derby, DE1 2QY, UK. E-mail: Paulhardy@hotmail.co.uk

rare, but new methods of implementing therapies by combining different treatment modalities (surgery, chemotherapy and radiotherapy) were discovered in the 1960s and greater numbers of patients experienced sustained remission and cures as a direct result of these new approaches.[4]

As a result of these modern methods, a substantial and rapidly rising population of individuals, who have been cured of childhood malignancy now exists. Consequently, it is estimated that 1 in 1,000 of the adult population in the UK, is currently a survivor of childhood cancer[1] and these individuals can expect to survive for many years, even decades, from the time they were treated. Unfortunately though, these long-term survivors face considerable, mainly uncharacterised risks to their future health and well-being as a direct result of their treatment and disease, which they must cope with for the rest of their lives.[4]

Although survival rates have improved considerably throughout the world over the past 40 years[5] and the majority of children with cancer are cured,[2] the benefits of treatment must always be balanced against the possible acute and late side-effects, which can be devastating and have been well documented.[6–9] The potential complications associated with radiotherapy in particular, can be a considerable burden not only to the child treated, but also to family and friends, and the society in general. These problems can also seriously impair future quality of life and pose a financial burden on the health service. It has been estimated that two-thirds of childhood cancer survivors suffer at least one acute or late-effect of their treatment, and about one-third experience severe or life-threatening difficulties.[9] These late-effects are also more critical with younger children, as these children are more susceptible to radiation damage.[10] Unfortunately many of these side-effects are related to irradiation of structures that are not part of the intended treatment volume, but which are in close proximity to the target.

A major aim of paediatric radiotherapy is to maintain or improve the excellent cure rates highlighted above, while minimising the dose to these neighbouring structures, reducing subsequent treatment sequelae. Treatment of paediatric malignancies using particle beams provides a unique opportunity to reduce significantly the acute and long-term complications that are experienced with conventional radiotherapy (CRT). Particle beam therapy (PBT), offers a high degree of conformity to target volumes, with particles entering the body at a low uniform dose, enabling the oncologist to calculate the exact depth at which the energy is deposited. This helps keep the integral dose to healthy tissues low, providing a maximum homogeneous dose to the target volume, while eliminating any exit dose. This in turn leads to substantial normal tissue sparing, minimising the risk of radiation-induced secondary malignancies and late-effects occurring, reducing subsequent morbidity. With the reduction of damage to normal tissue the dose to the tumour can be escalated, helping to further increase the probability of cure.

This literature review aims to examine the potential limitations and benefits of particle therapy in the treatment of paediatric malignancies, with added emphasis on how this treatment modality may restrict the side-effects of therapy. It also aims to ensure that the paediatric population are considered when designing and building a particle centre in the UK and that paediatric malignancies are eventually treated in such a centre.

METHODS

A systematic review of the literature was carried out through a search of the CINAHL, MEDLINE, and ScienceDirect databases. The keywords are paediatric, proton therapy, ion therapy, carbon therapy, PBT, and hadron therapy. Papers were selected on the basis of their relevance to the topic. All the articles were available in English, and any articles that appeared to have vested interests were identified. Articles presented in the form of case studies were included if they added any significant information.

THE PHYSICAL PRINCIPLES OF X-RAYS AND PARTICLES

Particles offer considerable advantages over X-rays regarding the sparing of normal tissues.

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

This is due to the physical characteristics of the particle beam when compared with an X-ray beam. X-rays are highly penetrating electromagnetic waves which deliver dose throughout any volume of tissue irradiated.[11] This means that X-rays will always deliver substantial unnecessary dose both proximally and distally to the tumour volume. Furthermore, the depth at which the maximum dose of X-ray radiation is delivered (Dmax) ranges from as little as 0.5 cm, to a maximum of 3 cm, depending on the energy utilised. Tumours are often located deeper than these ranges and as X-ray beams decay exponentially throughout the body, a higher dose is invariably delivered to the healthy tissue anterior to the tumour,[12] while the tumour is treated in the region of the beam where the energy deposition is falling off. This can be overcome with the use of beams from multiple angles which centre on the tumour, allowing the dose to accumulate within the tumour volume. However, since the beam travels throughout the entire thickness of the body, all normal tissue from the beam entrance to its exit will be affected, increasing the total or integral dose.

The absorbed dose of a particle beam, however, increases very gradually with increasing depth and then suddenly rises to a peak at the end of the particle range, which is known as the Bragg Peak (Dmax).[12] The particle beam can be directed and spread out to create an area of uniform dose, ensuring that the Bragg Peak effect occurs precisely within the tumour volume, something that cannot be achieved using X-rays. As particles have little side scatter, and their range is energy-dependant[12] the dose received by the surrounding healthy tissue is much less than that received by the tumour. This means that the dose beyond the Bragg Peak is essentially zero, which allows for the sparing of the healthy tissue around and beyond the tumour volume. In contrast to an X-ray beam, a single particle beam can be shaped to deliver a homogenous dose of radiation to an irregular 3D volume.[13] The improved dose distribution obtained when using particles has been found to reduce the integral dose by more than 50% in many treatments,[14] reducing the likelihood of secondary radiation-induced malignancies occurring later in life.[15]

The exit dose experienced when using CRT and intensity-modulated radiotherapy (IMRT) can restrict the use of certain angles as the beam frequently exits through critical structures distal to the target, causing unnecessary damage. These critical structures can also restrict the total dose delivered when using CRT and IMRT as the tolerance dose of these structures may be less than the dose required for tumour control, compromising the treatment. Simpler beam arrangements are possible in PBT owing to the absence of any dose exiting through distal critical structures (owing to the Bragg Peak effect) allowing for increased dose in these situations, improving the probability of cure.

CURRENT ROLE OF PARTICLE THERAPY IN PAEDIATRICS

Particles are currently used in many centres around the world to treat various malignancies in both adult and paediatric population and each centre has the capability to treat several thousand patients a year. Approximately 55,000 patients have been treated with particle therapy since its introduction in 1954.[16]

Paediatric malignancies currently treated include medulloblastoma, craniospinal ependymoma (boost), pineal tumours, astrocytoma, retinoblastoma and orbital rhabdomyosarcoma. The centre at Loma Linda University is also exploring the use of particles to treat non-cancerous paediatric diseases such as intractable childhood epilepsy.[17]

There is currently only one, short range, 62 MeV facility in the UK (Clatterbridge) which only treats adult patients with tumours of the eye. Over 1,400 patients have received proton therapy at Clatterbridge with an excellent local control rate of 98%.[18] A higher energy facility is required in the UK to treat deeper situated cancers and to transfer these exceptional control rates to other cancer sites. If the British Government fails to invest in a higher energy facility, informed parents may take their children abroad to receive the best possible treatment available. Jones suggests that these referrals abroad would have a

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

severe and detrimental effect on UK oncology treatments.

Glimelius et al. (2005) estimated that approximately 120 out of 330 new paediatric cancer cases a year benefit from particle therapy in Sweden.[19] With 1,400 new cases a year in the UK, extrapolation of these figures would mean approximately 500 children a year would benefit from a particle therapy centre in the UK.

CLINICAL ADVANTAGES OF PARTICLES FOR PAEDIATRIC MALIGNANCY TREATMENT

The avoidance of even moderate amounts of healthy critical structures is extremely important in the treatment of paediatric patients and combined with the fact that 50% of solid paediatric tumours occur in the brain, an increased need for improved conformity and reduced integral dose becomes even more essential in these treatment areas. Head and neck tumours are frequently situated near dose limiting critical structures, making it difficult to deliver a curative dose of CRT. Because of this, cranial irradiation can cause many late sequelae to the irradiated child such as losing hearing ability and sight, interfering with intellectual development, leading to obesity, increasing the chance of secondary malignancies occurring and affecting the child's physical growth. These late-effects of cranial irradiation are caused by a number of critical factors including total radiation dose, dose per fraction, volume of tissue irradiated, age of patient at treatment, the anatomic area irradiated and the combination of radiotherapy with other treatment modalities, that is chemotherapy and radiotherapy.[20]

Modern 3D treatment techniques such as IMRT and PBT have helped improve dose conformity to the treatment site and numerous dosimetric studies have been performed, comparing the dose distribution of PBT with CRT and IMRT in paediatric malignancies. The fact that many long-term effects of treatment appear to be related to dose and volume of tissue treated warrants the need for this research into less damaging treatment techniques that provide at least similar cure rates.

It has been found that the predominant long-term effect of moderate to high-dose cranial radiotherapy is reduced intellectual capacity.[21] A recent report found that children exposed to 18–24 Gy of cranial irradiation were three to seven times more likely than the national average to be unemployed later in life,[22] highlighting the damaging late-effects of irradiation. It has also been found that brain tumour survivors who are irradiated at a younger age are more vulnerable to cognitive dysfunction before radiotherapy.[23] A review of 22 studies of childhood brain tumour sufferers, treated with radiotherapy, found that those treated at a younger age had a 14-point larger deficit in IQ when compared with children treated at an older age.[23]

The reduction of dose to healthy tissues is critical in this area and Lin et al. (2000) compared the normal tissue dose-sparing capabilities of proton radiotherapy with photon therapy in the treatment of the posterior fossa.[24] With identical coverage of the target volume, doses to 50% and 10% of the temporal lobe volume were limited to 2% and 67% when using protons, compared with 56% and 100% with 3D conformal photons, respectively. This demonstrates that particle therapy allows for escalation of tumour dose while reducing dose to non-target tissue, potentially decreasing the chance of severe late-effects, including cognitive dysfunction, while increasing the chances of survival. Another common option available to children suffering from brain cancer is open surgery, but this treatment method can prove extremely daunting to a young child and can also pose a considerable risk to the patient. In these instances, particle therapy offers an excellent alternative.

Treatment of rhabdomyosarcoma, the most common primary orbital malignancy in children and the most common childhood soft-tissue sarcoma,[2] also presents its own distinct problems. During radiotherapy of this particular malignancy the exit dose needs to avoid both the ipsilateral and contra lateral critical structures. Ninety percent of children treated for rhabdomyosarcoma fortunately survive,[25] but the long-term side-effects such as cataracts, orbital hypoplasia, conjunctivitis, keratopathy, corneal ulcers, exophthalmia, vitreous haemorrhage and hypopituitarism, caused by

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

irradiation of developing neighbouring structures can be severe. A recent study on the long-term effects of orbital radiation on paediatric patients found that all patients in the cohort experienced soft-tissue changes and 50% of patients developed bone changes that resulted in visible facial asymmetry.[26]

Yock et al. (2005) conducted a study on seven patients aged between five and eight, comparing PBT with CRT in orbital rhabdomyosarcoma.[27] These patients were treated with PBT, and retrospective photon plans were created, to compare the dose distribution differences between the treatments. This study concluded that PBT provides excellent dose distribution to the tumour while sparing healthy tissue. All the structures evaluated in this study received lower doses from the PBT treatment plans and a dramatic benefit to sparing the contra lateral structures was recorded. The reduced incidence of late-effects of PBT are also highlighted in this study. Follow-ups were conducted on the patients and it was found that none of the patients suffered from side-effects of the treatment, and none of the patients required hormone replacement from scattered dose received by the hypothalamic/pituitary axis (a commonly experienced side-effect after CRT).

Studies on medulloblastoma, one of the most common paediatric CNS tumours,[27–30] have found that particles deliver superior target dose coverage and sparing of healthy tissues, when compared with both IMRT and CRT. Advances in the treatment of this particular malignancy, which was once considered incurable, have led to an increase in survival of children with this disease.[28] With this improvement in long-term survival of children suffering from this disease, there is increased concern regarding late side-effects. Dramatic differences were highlighted throughout these studies in most of the critical structures examined.[28–30] By comparing the dose volume histograms (DVH), it was found that the use of particles in the treatment of medulloblastoma could reduce the dose to 50% of the pituitary volume from 84.5% with CRT to 26.7% and 0.5% with IMRT and protons, respectively,[28] significantly reducing the probability of late-effects occurring.

With neuroendocrine dysfunction, such as growth hormone deficiency (GHD), being a common dose and site-related sequelae following irradiation of the brain,[9] reduction of unnecessary dose to glands such as the pituitary (which can result in reduced height), becomes essential. GHD is reported as the most common endocrinopathy following cranial irradiation.[9] Livesey et al. (1990) supports this stating that out of a total of 144 paediatric patients treated with conventional cranial radiotherapy, 140 had evidence of GHD.[30] Treatment of this group of patients with growth hormone substitutes fortunately results in near normalisation of stature, but the annual cost of GHD has been estimated at a massive £9,170 per patient.[31] The use of particles in this treatment would not only reduce the need for continuous use of growth hormone substitutes, but would also drastically reduce on-going health care costs.

Medulloblastoma treatments also require irradiation of the whole of the spinal cord as the disease has a propensity to metastasise via the cerebrospinal fluid.[2] This brings a substantial amount of healthy tissue along the spinal axis into the treatment field. This method places other vital structures at risk including the thyroid. Ionising radiation that penetrates the thyroid causes nodule development which can lead to thyroid cancer later in life.[32] St Clair et al. (2004) concluded that the risk of thyroid cancer was 16 times the expected risk in their cohort of paediatric patients treated with CRT.[28] By reducing the amount of radiation received by the thyroid, PBT can reduce the subsequent risk of thyroid cancer occurring. Studies have found that the volume of thyroid receiving 10 Gy can be reduced from 100%, when using CRT, to only 7% with PBT.[33] This reduction in dose to the thyroid would have remarkable effects on the child's future quality of life, not only reducing the risk of secondary malignancy but also minimising the chance of hypothyroidism occurring from 33% to >1%.[30] Raney et al. (2000) support these findings by stating that 8% of patients receiving CRT require hormone replacement later in life.[34]

Recent research has also concluded that particle therapy is much quicker and less complicated

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

than IMRT in the treatment of medulloblastoma.[28] The spinal IMRT technique in this particular study required the use of seven isocentric beams, which were chosen to avoid critical structures, compared with the simpler single beam arrangement used in the particle treatment. The use of multiple beams during IMRT not only increases the complexity and time taken for treatment, but also increases the integral dose,[35] escalating the chances of secondary malignancies and long-term sequelae.

Research into the treatment of medulloblastoma and rhabdomyosarcoma has found that the use of particle beams reduced the expected incidence of radiation-induced secondary malignancies by a factor of >2 in rhabdomyosarcoma treatments and by a factor of 8–15 when compared with either IMRT or CRT.[15] The author of this particular study concluded that this potential reduction in secondary cancers when using particles represents a significant case in favour of the use of PBT for most radiotherapy treatments in paediatric oncology.

Exposure of the paediatric chest to ionising radiation is also common in many types of radiotherapy treatments including craniospinal, mantle, chest, mediastinum and lung fields. These treatments often expose the lungs, kidneys, liver, heart and developing breast tissue to significantly high doses of ionising radiation. These non-target organs are then at increased risk of late sequelae developing as a direct result of treatment, including secondary malignancies. Treatment of medulloblastoma and Hodgkin's disease in particular delivers a significant exit dose to the developing breast tissue of female paediatric patients and is accountable for an increased risk of breast cancer. It has been shown that girls treated for Hodgkin's disease between the ages of 10 and 16 face a significantly increased risk of breast cancer later in life.[36]

At present most patients with Hodgkin's disease are cured,[37] but are at increased risk of late sequelae as a result of the treatment. It has been estimated that children treated for this malignancy are 22 times more likely to develop a secondary cancer than the general population.[38] In 2002, Ng et al. studied a large population of patients ($n > 1{,}000$) with Hodgkin's disease and found that the risk of death from late complications was greater after 14 years than the risk of death from the initial disease.[39] Studies have found that the use of particle therapy in this particular malignancy can eliminate any exit dose, substantially reducing subsequent morbidity.[40,41]

Irradiation of the heart in CRT is also often unavoidable in paediatric mantle, chest and spinal radiation fields. Hull et al. (2003) estimates that 16% of children who receive chest or spinal irradiation would have considerable cardiovascular morbidity within 20 years of treatment owing to the asymmetric growth of the irradiated heart.[42] Similar late-effects are noted in the lungs of children treated with these fields, with radiation being associated with chronic cough, exercise related dyspnoea, and secondary lung cancer.[2] Miralbell et al. (1997) found that paediatric patients receiving spinal irradiation were 4.3 times more likely to have restrictive lung disease as a consequence of treatment, despite only a small portion of the lung being in the treatment field.[29]

It has been found that in the treatment of chest, mantle and spinal fields, particles can not only completely eliminate any unnecessary dose to the heart, lungs and breast tissue, but can also help avoid the liver and kidneys.[13,29,33,37] Kirsch et al. (2005) found that due to the rapid dose fall-off experienced with particles, the same biological dose could be delivered to the target as conventional RT while reducing the dose outside the target volume, when treating Hodgkin's disease,[37] minimising the risk of severe late-effects occurring.

Radiation therapy to the abdomen, pelvis and spine may also significantly affect either the ovaries or the testes. Particles, again, have the ability to eradicate any scattered dose received by these organs.[33] It has been found that PBT can reduce the volume of ovary receiving 10 Gy from 86% when using CRT, to 0% with PBT, in the treatment of pelvic sarcomas.[33] The use of particles in this situation would help preserve the future fertility of patients undergoing this treatment.

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

In their paper of 2001, Neglia et al. report on 116 survivors of childhood malignancies from the childhood cancer survivor study cohort who developed subsequent malignant and benign tumours of the CNS.[8] The researchers arrived at three main conclusions. First, the single most significant risk factor for the development of a further CNS tumour in survivors of childhood malignancies is exposure to therapeutic radiation. Second, after adjustment for radiation dose, neither initial tumour diagnosis nor chemotherapy was related with the risk of CNS tumours. And finally, the higher risk of subsequent glioma in children irradiated at a very young age (before 5), may reflect greater susceptibility of the developing brain to radiation.[8]

POTENTIAL DISADVANTAGES

If particle therapy is so good then why isn't it available in the UK? The main disadvantage with particle therapy is the initial expensive cost of the equipment and the subsequent increased on-going operating, maintenance and personnel costs. The recently completed MD Anderson centre in America cost 120 million pounds.[43] The initial cost is reflected in the individual treatment and Goitein and Jermann (2006) calculated the cost of a complex intensity-modulated proton treatment at 2.4 times the cost of an IMRT plan.[16] However, when discussing the cost of particle therapy the initial and running costs must be weighed against the improved health gain and reduced late-effects and morbidity. The superior dose distribution experienced with particle therapy would undoubtedly reduce long-term toxicity and prevent late side-effects occurring, especially in paediatric malignancies. This in turn would help to reduce the need for long-term drug use, (growth hormone replacement for patients receiving irradiation of the pituitary gland), or extensive follow-up and screening (mammography for female patients treated for Hodgkin's disease). Combining these facts with the simpler beam arrangements available makes the use of particles even more attractive. Jones (2006) estimated that a single UK particle centre should recoup its own initial running costs within 6 years if it is able to treat 2,500 patients by its third year of operation.[18]

Orecchia et al. (1998) estimated the cost per patient of proton therapy to be approximately £4,200 compared with £2,000 for CRT £12,500 for an intensive course of chemotherapy and £4,500 for conformal radiotherapy.[44] Considering PBT is still relatively new, and the costs of new technologies have a tendency to decrease, the price for this highly effective treatment seems extremely appealing. However, a full cost benefit analysis, weighing the initial and subsequent running costs of a particle therapy centre against the potential savings is beyond the scope of this paper but would provide a valuable future contribution to the evidence base.

The particle therapy centre also has the drawback of its reliance on a single accelerator. This accelerator injects the particles into a synchrotron and particles are then further accelerated by the synchrotron before being extracted and delivered to the different treatment rooms. This reliance on one accelerator means that if the accelerator breaks down then the whole department comes to a stand still. This could prove very distressing for paediatric patients and their families who may have travelled long distances to receive their treatment.

Another disadvantage of PBT when treating paediatric patients is the intimidating size of the gantry. An isocentric rotating gantry is required for PBT which consists of a huge rotating cylindrical structure containing the beam-bending magnets. These structures can be massive; weighing over 100 tonnes for protons and 200 tonnes for ions[18] and these massive gantries can prove very distressing for small children.

The main reason for acute and late-effects from PBT is non-conformity of treatment dose which places a great deal of pressure on the physicist to ensure maximum accuracy when planning the treatment and the radiotherapist when positioning the patient. The results of treatments do show, however, that this is achievable.

DISCUSSION

Many of the studies mentioned above did not actually treat patients with particle therapy

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

but are quantitative planning studies that have used generated particle plans. The resulting plans and DVH have then been analysed and compared with the IMRT and CRT plans and the doses received by amount of normal tissue spared by photon therapy was then calculated. This method means that follow-up of the patients in these studies is impossible and long-term follow-up of patients is essential to assess the actual value of PBT. The studies that did actually use PBT were small scale, and retrospective, limiting the results of the studies. Long-term follow-up from larger studies into particle therapy is required to confirm and record the expected reduction in late sequelae. Whether phase III studies that directly compare particles with conventional therapies are possible, however, remains very doubtful as this may be seen by some as unethical. Clinicians and patients are already aware of the dose advantages associated with PBT and may therefore refuse to allow their patients to participate in this type of study. For accurate assessments to be made, prospective studies will need to be performed on a large patient populations, with long-term follow-ups helping to evaluate the expected improvement in quality of life.

Measuring this quality of life, however, can prove difficult, especially in the paediatric population. One such example of this is a T-cell lymphoma survivor with severe restrictive lung disease and moderate cardiomyopathy who described her health as 'great'.[9] The use of quality-adjusted life years (QALY) may prove a more appropriate method to asses the cost-effectiveness of the differing treatment techniques.

The building of a national centre would mean children travelling long distances from all over the country to be treated at a single centre. These children would therefore need to be accompanied by parents or carers. This would result in missed schooling for the children and absence from work for their carers. Although this may be difficult in the short-term, the eventual reduction in side-effects and the subsequent decrease in future hospital visits, would far outweigh this temporary problem. This situation is nevertheless, more attractive than the scenario painted by Jones (2006), who suggests that between 5,000 and 12,000 patients will demand treatment abroad within the next decade if the UK does not develop a PBT centre. This situation would undoubtedly have a catastrophic effect on British oncology.[18]

Clinical results from countries using particles are very impressive and consistently highlight the reduced side-effects experienced as a result of the improved dose distributions. Combining this with the fact that the United States, Japan, China and many parts of Europe are investing billions of dollars in the expansion of particle facilities emphasises the significant benefits of this treatment technique and the need for development of particle beam facilities within the UK.[18]

The treatment of childhood malignancies alone, however, could not possibly justify the construction of a particle therapy centre but the paediatric population must be considered in the eventual design of a national centre. Waiting areas and treatment rooms should be built with children in mind and staff with knowledge of children's needs should be employed.

CONCLUSION

All of the above studies conclude that the dose distribution and resultant sparing of healthy tissue realised with PBT is far superior to that of CRT. These studies have also demonstrated substantial advantages in PBT, when compared with CRT and IMRT, not only because PBT offers a significant prospect of tumour control but also in the reduction in the probability of serious late-effects occurring, since the dose received by normal tissue is minimised. PBT has also been shown to be quicker and less complicated that CRT and IMRT. Reductions in side-effects in a population of patients with a high probability of cure and a lengthy life expectancy will not only substantially improve the individuals future quality of life, but will also help reduce the accumulative cost of treating each patient.

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

Clinical research with long-term follow-up, is however necessary to assess the real value of particles in paediatric tumour treatment and to evaluate whether the benefit in the related long-term side-effects persist. For many children suffering from cancer, particle therapy has the potential to limit the late-effects of radiotherapy, including the risk of second malignancies, and therefore offers a valuable advantage and increased long-term hope for the children and their families.

The development of a PBT centre should therefore include paediatric patients with the construction of child friendly waiting areas and treatment rooms, and the employment of staff who are comfortable working with children and their families. Accommodation should also be made available to the patients and immediate family to reduce their expenses and ease their worries.

References

1. Taylor RE. Paediatric oncology. In: Bomford CK, Kunkler IH (eds). Walter and Miller's Textbook of Radiotherapy, 6th edition. Edinburgh: Churchill Livingstone, 2003, pp. 583– 596.
2. Souhami R, Tobias J. Cancer and its Management, 5th edition. Oxford: Blackwell Publishing 2005, pp. 405–425.
3. Magnani C, Aareleid J, Viscomi S, Pastore G, Berrino F. Variation in survival of children with central nervous system (CNS) malignancies diagnosed in Europe between 1978 and 1992: the EUROCARE study. Eur J Cancer 2001; 37:711–721.
4. University of Minnesota Cancer Center. Last accessed on 14th November 2006 at URL http://www.cancer.umn.edu
5. Bjork-Eriksson T, Glimelius B. The potential of proton beam therapy in paediatric cancer. Acta Oncol 2005; 44:871–875.
6. American Cancer Society, 2007. Last accessed on 4th May 2007 at URL http://www.cancer.org/downloads/STT/Cancer_Statistics_Combined_2007.ppt#257, 2, US Mortality, 2004.
7. Halperin EC. Particle therapy and treatment of cancer. Lancet Oncol 2006; 7:676–685.
8. Neglia JP, Friedman DL, Yasui Y. et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. J Natl Cancer Inst 2001; 93 (8):618–629.
9. Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: Foundations for providing risk-based health care for survivors. CA Cancer J Clin 2004; 54:208–236.
10. Kiltie AE, Lashford LS, Gattamaneni HR. Survival and late effects in medulloblastoma patients treated with craniospinal irradiation under three years old. Med Pediatr Oncol 1997; 28:348–354.
11. Metz J. Reduced normal tissue toxicity with proton therapy. University of Pennsylvania: Abramson Cancer Center, 2006.
12. Loeffler JS, Smith AR, Suit HD. The potential role of proton beams in radiation oncology. J Clin Oncol 1997; 24:686–695.
13. Hug EB, Nevinny-Stikel M, Fuss M, Miller DW, Schaefer RA, Slater JD. Conformal proton radiation treatment for retroperitoneal neuroblastoma: introduction of a novel technique. Med Pediatr Oncol 2001; 37:36–41.
14. Jones B, Burnet NG. Radiotherapy for the future. Br Med J 2005; 330:979–980.
15. Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumours. Int J Radiat Oncol Biol Phys 2002; 54:824–829.
16. Goitein M, Jermann M. The relative costs of proton and photon therapy. Clin Oncol 2003; 15:S37–S50.
17. Slater JD. Clinical applications of proton radiation treatment at Loma Linda University: review of a fifteen-year experience. Technol Cancer Res Treat 2006; 5 (2):81–89.
18. Jones B. The case for particle therapy. Br J Radiol 2006; 79:24–31.
19. Glimelius B, Ask A, Bjelkengren G et al. Number of patients potentially eligible for proton therapy. Acta Oncol 2005; 44:836–849.
20. Halperin EC, Constine LS, Tarbell NJ et al. Paediatric Radiation Oncology, 3rd edition. Philadelphia: Lipincott Williams & Wilkins, 1999, pp. 1–586.
21. Kirsch DG, Tarbell NJ. Conformal radiation therapy for childhood CNS tumours. Oncologist 2004; 9:442–450.
22. Mulhern RK, Palmer SL. Neurocognitive late effects in paediatric cancer. Curr Probl Cancer 2003; 27:177–197.
23. Mulhern RK, Hancock J, Fairclough D, Kun L. Neuropsychological status of children treated for brain tumours: a critical review and integrative analysis. Med Paediatr Oncol 1992; 20:181–191.
24. Lin R, Hug EB, Schaefer RA, Miller DW, Slater JM, Slater JD. Conformal proton radiation therapy of the posterior fossa: a study comparing protons with three-dimensional planned photons in limiting dose to auditory structures. Int J Radiat Oncol Biol Phys 2000; 48:1219–1226.
25. Hug EB, Adams J, Fitzek M, De Vries A, Munzenrider JE. Fractionated, three-dimensional, planning-assisted Proton-radiation therapy for orbital rhabdomyosarcoma: a novel

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press

technique. Int J Radiat Oncol Biol Phys 2000; 47 (4): 979–984.

26. Guyuron B, Dagys A, Orth D. Long-term effects of orbital irradiation. Head Neck Surg 1987; 10:85–87.
27. Yock T, Schneider R, Friedmann A, Adams J, Fullerton B, Tarbell N. Proton radiotherapy for orbital rhabdomyosarcoma: clinical outcome and a dosimetric comparison with photons. Int J Radiat Oncol Biol Phys 2005; 63:1161–1168.
28. St Clair WH, Adams JA, Bues M. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a paediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 2004; 58:727–734.
29. Miralbell R, Lomax A, Russo M. Potential role of proton therapy in the treatment of paediatric medulloblastoma/primitive neuro-ectodermal tumours: spinal theca irradiation. Int J Radiat Oncol Biol Phys 1997; 38 (4):805–811.
30. Livesey EA, Hindmarsh PC, Brook CG, Whitton AC, Bloom HJ, Tobias JS, Godlee JN, Britton J. Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 1990; 61:622–625.
31. Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. Cancer 2005; 103:793–801.
32. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991; 325:599–605.
33. Lee CT, Bilton SD, Famiglietti RM et al. Treatment planning with protons for paediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? Int J Radiat Oncol Biol Phys 2005; 63 (2):362–372.
34. Raney RB, Anderson JR, Kollath J. Late effects of therapy in 94 patients with localized rhabdomyosarcoma of the orbit: report from the intergroup rhabdomyosarcoma study (IRS)-III, 1984–1991. Med Paediatr Oncol 2000:417.
35. Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of paediatric base of skull tumours. Int J Radiat Oncol Biol Phys 2002; 52:1017–1024.
36. Bhatia S, Yasui Y, Robinson LL. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects study Group. J Clin Oncol 2003; 21:4386–4394.
37. Van Leeuwen FE, Travis IB. Second cancers. In: DeVita VT, Hellman S, Rosenberg SA (eds). Cancer: Principles and Practice of Oncology. 6th edition. Philadelphia: Lippincott Williams & Wilkins, 2001, pp. 2939–2964.
38. Donaldson S. Lessons from our children. Int J Radiat Oncol Biol Phys 1993; 26:739–749.
39. Ng AK, Bernardo MP, Weller E. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 2002; 20:2101–2108.
40. Kirsch DG, Ebb DH, Hernandez AH, Tarbell NJ. Proton radiotherapy for Hodgkin's disease in the sacrum. Lancet Oncol 2005; 6:532–533.
41. Suit HD. Protons to replace photons in external beam radiation therapy? Clin Oncol 2003; 15:29–31.
42. Hull MC, Morris CG, Pepine CJ. Valvular dysfunction and carotid, sublevel, and coronary artery disease of Hodgkin lymphoma treated with radiation therapy. JAMA 2003; 290:2831–2837.
43. Sisterton J. Proton Therapy Co-operative Oncology Group Newsletter. Boston: Massachusetts General Hospital, 2001.
44. Orecchia R, Zurlo A, Loasses A, et al. Particle beam therapy (hadrontherapy): Basis for interest and clinical experience. Eur J Cancer 1998; 34 (4):459–468.

https://doi.org/10.1017/S1460396907006218 Published online by Cambridge University Press