ELSEVIER

European Journal of Cancer 40 (2004) 2091–2105

European Journal of Cancer

www.ejconline.com

Paediatric Update

New technology for radiotherapy in paediatric oncology

Frank Saran *

Department of Radiotherapy and Department of Paediatric Oncology, Royal Marsden Hospital NHS Trust, Downs Road, Sutton, Surrey, SM2 5PT, UK

Received 15 August 2003; received in revised form 26 November 2003; accepted 3 December 2003
Available online 4 August 2004

1. Introduction

Before the era of chemotherapy, surgery and radiotherapy were the mainstays for children with malignant tumours, but in many instances yielded only a moderate overall chance of survival. With the introduction of systemic chemotherapy in the second half of the last century, significant improvements in outcome were achieved. Cure rates continually increased and are today unprecedented [1]. At the same time there has been a growing number of reports of late morbidity associated with radiotherapy using simple, large-field parallel pairs of orthovoltage or ^{60}Co beams. Based on prospective clinical trials, this finding has led either to a graduated reduction in irradiation or the replacement of radiotherapy by chemotherapy. By the end of last century it had become apparent that to avoid radiotherapy for certain tumours (e.g. medulloblastoma) might be detrimental, and that the use of limited low-dose radiotherapy might improve outcomes in certain high-risk groups (e.g. neuroblastoma) [2–4].

Radiotherapy has undergone rapid changes in recent years, with numerous developments aimed at improving efficacy. Many of these have been translated into clinical practice in the last 10 years or so. In combination, these changes seek to deliver clinical benefits, with a potential therapeutic gain from improved tumour control, reduced toxicity or both (i.e. improving the therapeutic ratio). This substantial shift in the therapeutic ratio in favour of radiotherapy has fostered its revival as a treatment concept for many solid tumours of childhood among national and international oncology groups. Radiotherapy techniques continue to evolve, with attempts to minimise the volume of normal tissue irradiated to a dose associated with a specified toxicity. The aim is to maintain adequate and homogeneous coverage of the planning target volume (PTV) of a tumour, while minimising the dose to nearby normal tissues. In children, because radiotherapy must be given during growth and development, it is particularly important to minimise all potential long-term, radiation-induced effects. Late sequelae of radiation in children include, among others, impaired cognitive development, altered physical appearance and organ dysfunction leading to impaired quality of life and the risk of second malignant neoplasms (SMNs). These outcomes are in addition to the complications induced by the tumour itself or by other treatments that may contribute to late morbidity and mortality. The incidence and severity of late complications are frequently multifactorial and require careful evaluation in the individual patient [5–14].

Therefore, the two major directions of research that have influenced paediatric radiotherapy over the last 10–20 years have been to restrict maximally the radiation to the target and to enhance the definition of the target volume using improved and new methods of imaging. New machines and the power of computed planning systems spawned by the revolution in information technology have begun to deliver success with therapies that were first attempted over 40 years ago [15]. This technological progress has allowed clinicians to come closer to their goal of maximally conforming high doses of radiation to the target (conformal radiotherapy; CRT), thus sparing normal tissues from unwanted dosages and potentially reducing the late sequelae. The latest imaging techniques can also visu-

* Tel.: +44-208-661-3826; fax: +44-208-661-3470.
E-mail address: frank.saran@rmh.nthames.nhs.uk (F. Saran).

doi:10.1016/j.ejca.2003.12.028

alise normal tissues and tumours with improved anatomical definition, as well as providing new functional and biological ways of defining the target in the first instance (multimodality imaging) [16]. The delivery of advanced radiotherapy is a complex process and the overall quality depends upon the 'weakest link', which may vary between institutions.

Progress includes not only technical advances, but also the improved pretreatment assessment and preparation of children with the help of experienced play therapists. Particularly in patients who are only just able to comply with the stringent requirements of radiotherapy planning and delivery, such a contribution is invaluable. It reduces the need to give radiotherapy under either sedation or general anaesthesia (GA), so providing the child with greater control over the treatment itself and adding greater flexibility to accommodate the needs and commitments of parents.

Progress has occurred in every aspect of radiotherapy, from patient selection, immobilisation and target definition to planning, verification and delivery. The use of twice-daily fractionation (hyperfractionation) may improve outcome in patients with rapidly proliferating tumours; this possibility is currently being explored in primitive neuroectodermal tumours [17–19] and in neuroblastoma [2], with evidence of a reduction in late sequelae such as thyroid dysfunction [20,21]. The use of charged particles, e.g. protons, instead of photons offers a further possibility of sparing the normal tissues beyond the high-dose field [22–24].

The implementation of standardised protocols and central reviews by the large co-operative groups (Socuét'e Internationale D'Oncologie Pédiatrique (SIOP) and Childrens Oncology Group (COG)) has ensured minimum standards, improved outcome and set an example for adult oncology. Online quality assurance should promote uniformity of practice and technique, even before the start of treatment. This approach will provide a prospectively gathered database of clinical information and patterns of failure and toxicity to guide future improvements. Incorporating complete, three-dimensional dose–volume data may eventually allow the production of detailed dose–response information for both normal tissues and tumours [25,26]. The United States of America (USA) has had a central database, QARC (Quality Assurance Review Centre) for many years, with which paediatric groups are closely involved [27].

In the paediatric setting, radiotherapy planning and treatment must specifically consider children of all ages, some of whom will require treatment under GA. Some of the new and complex techniques may therefore not be practical for infants and small children, but others, such as intensity-modulated radiotherapy (IMRT), may actually streamline treatment by improving the use of resources and reducing daily treatment times. IMRT is a CRT technique that employs a non-uniform dose delivery and provides treatment possibilities in the form of critical-organ avoidance and dose escalation not previously achievable for complex target volumes.

The personal selection in this article will, I hope, highlight some of the technical advances in external-beam radiotherapy that have either recently been introduced or are likely to affect paediatric oncology in the near future. In selected cases, additional benefits may also derive from the integration of other improvements in radiotherapy into the multimodal management of children, e.g. intraoperative radiotherapy, brachytherapy, hyperthermia or targeted radiotherapy such as ^{131}I mIBG, but these are beyond the scope of this review.

2. Set-up and patient immobilisation

The patient set-up, i.e. their position and immobilisation for radiotherapy, is individually chosen for comfort, as well as for technical factors, such as the optimal access of treatment beams to the target tissue. The degree of immobilisation required varies according to treatment intent, tumour site and technique used. It needs to be both accurate and precise to provide reproducible positioning of the patient. Day-to-day variation should be measured in the department for the different techniques to ensure adequate dose coverage and the appropriate selection of individual safety margins around the clinical target volume (CTV) [28].

The most precise immobilisation techniques are routinely used with curative intent in paediatric neuro-oncology, or in patients with locally recurrent disease following previous exposure to high-dose radiotherapy, using methods of rigid immobilisation, e.g. for stereotactic radiosurgery (SRS) (single fraction) or stereotactic CRT (SCRT) (multiple fractions) [29–33]. Many technical solutions have been found for this problem, including a rigid relocatable frame with an individualised mouth plate and headrest, as well as frameless techniques (Fig. 1) [28,34,35]. These methods can achieve a mean day-to-day reproducibility in the range of a little as 1–2 mm [34,36] compared with the 4–5 mm variability associated with commercial thermoplastic masks. For children unsuited to a frame-based system (e.g. having insufficient teeth or requiring GA), some centres have adapted the rigid frame by using bony landmarks (nasal bridge or external auditory canal) instead of a mouth plate to aid fixation. The Royal Marsden and St Jude Children's Hospital have developed an alternative using a modified shell-based system with an individually shaped, vacuum-moulded bag of polystyrene beads, which has a reproducibility similar to that of a frame-

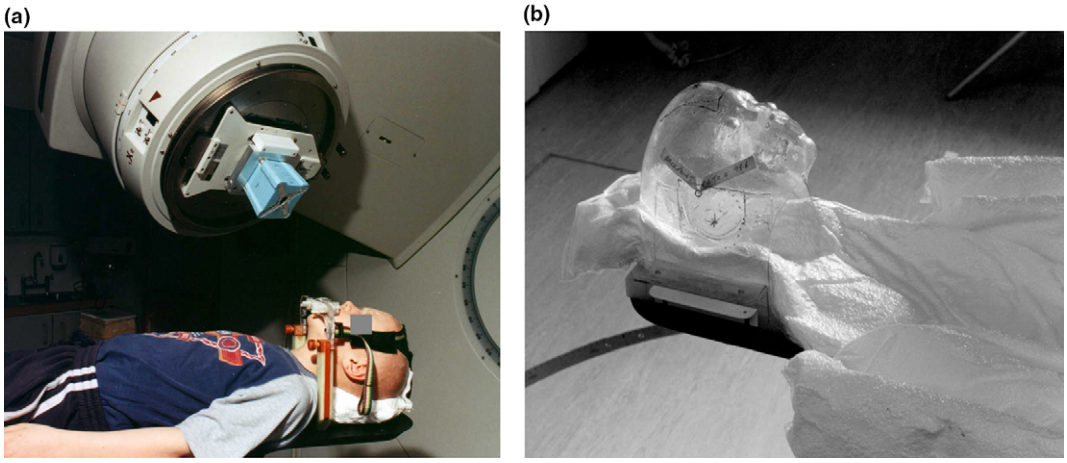


Fig. 1. Two methods of immobilisation used for conformal radiotherapy. (a) A lightweight paediatric frame-based system with an individualised mouthbite and a customised headrest. The rigid frame is fixed to the treatment couch of a linear accelerator and used for stereotactically guided conformal radiotherapy (SCRT). The mean day-to-day reproducibility using this type of system is approximately 1.0–1.5 mm. (b) A customised thermoplastic shell and moulded bag of polystyrene beads (VacFix®). The VacFix® bag is individually shaped and then hardened by vacuum to immobilise the head and upper body. The mean day-to-day reproducibility using such a system is approximately 1.5–2.5 mm.

based system [28,34]. If a single high-dose fraction of radiotherapy is to be delivered (SRS), a rigid frame is usually pinned to the skull under local anaesthesia, eliminating any movement.

Stereotactic immobilisation techniques have also been used for head-and-neck radiotherapy because of the many radiosensitive tissues in the radiotherapy volume [37]. The use of whole-body stereotactic frames for extracranial tumours is less developed, but may have technical advantages for young children and for targets close to the spinal cord [38,39].

For thoracic tumours, the active breathing control device is a further development entering clinical practice for selected tumours. It controls the delivery of radiation during a standardised breath hold and minimises the amount of lung and heart exposed within the high-dose irradiation volume. As this device requires a measure of active compliance it may only be usable in some children, but it has already been used for selected lung, breast and abdominal tumours in adults [40].

3. Radiotherapy verification

Advances in verification include electronic portal imaging devices (EPID) fixed to the treatment machine. These allow an image of a treatment field on the linear accelerator to be taken and compared using bony landmarks to reference images from the planning computer or simulator. Enhanced imaging quality (e.g. amorphous silicon imagers) and computerised measurements have significantly enhanced the quality of treatment verification. Any new immobilisation system is only validated as being superior if the set-up has been prospectively measured and analysed for a particular patient and group of patients treated with that system [28].

Therapy machines are now being developed with an integrated orthovoltage source plus a detector mounted on the linear accelerator at 90° to the treatment head and EPID. After the patient has been positioned for treatment, the device rotates around them to produce a high-resolution, soft tissue computerised tomography (CT) scan that provides a regular, three-dimensional check of the patient's internal and bony anatomy for image-guided or 'adaptive' radiotherapy [41]. Online corrections can be made before each fraction to reduce even further the geometric uncertainties of daily treatment delivery. Reductions in the CTV/PTV margins for selected tumours may be possible, with a concomitant reduction in the amount of normal tissue exposed to high-dose irradiation.

4. Imaging for radiotherapy planning

Optimum visualisation of the tumour volume and its surrounding anatomical structures is essential for any local cancer treatment. Soon after their introduction, CT scanners were adapted for radiotherapy planning to visualise internal structures and to provide the required electron-density data to planning computer systems for accurate dose calculation [42]. Despite the advent of magnetic resonance imaging (MRI), CT still forms the basis of modern, computer-assisted, planned three-dimensional CRT.

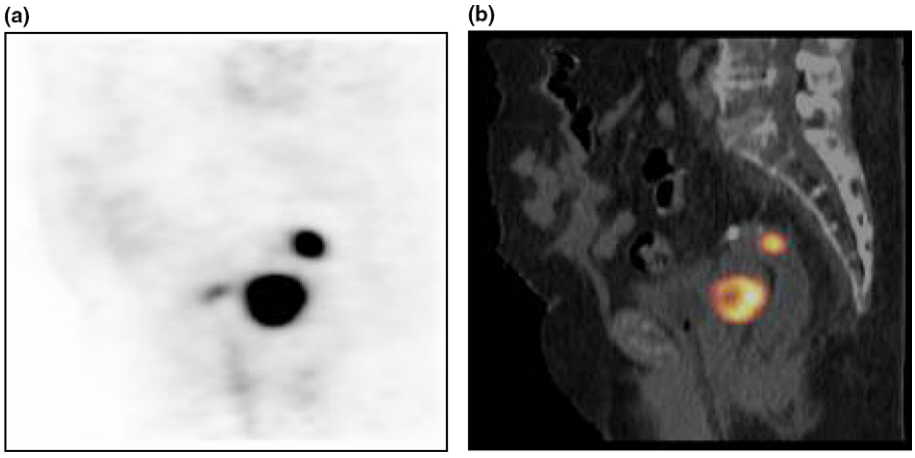


Fig. 2. Sagittal images from a combined or hybrid computerised tomographic/position emission tomographic (CT/PET) scanner. (a) A PET scan showing marked [^{18}F]-fluorodeoxyglucose (FDG) uptake in a verified cervical tumour and a pre-sacral focus consistent with a metastatic deposit. The concomitant CT scan did not demonstrate a pathologically enlarged lymph node in this location. (b) This image demonstrates a fused CT and PET image that localises the presacral uptake from the PET scan onto the CT scan indicating metastatic spread to a regional lymph node. Such methods of combining anatomical details with biological tumour information are likely to improve staging accuracy and aid target definition for radiotherapy planning in the future. (With the kind permission of CTI Molecular Imaging.)

In routine practice, conventional imaging is used to define the gross tumour volume (GTV). Depending on the tumour type and its biological behaviour, an individual margin is added to account for potential microscopic spread, so defining the CTV. A further margin is then added to provide the PTV. This last margin incorporates internal organ movement and the uncertainties of daily repositioning, and is the volume that should be encompassed by 95% isodose of the prescribed dose [43,44]. The rigid immobilisation techniques that have been discussed earlier allow for a prospective reduction in this margin, thus exposing less normal tissue to high-dose irradiation.

Precise data for quantifying the margin from GTV to CTV are lacking for many sites and are based on knowledge from pathological specimens, patterns of recurrence, past clinical trials and empirical experience only. However, new functional imaging modalities and scan-fusion technology may begin to change this in the future by using biological information in conjunction with traditional anatomy [16,45]. Clinical position emission tomography (PET) scanning has evolved rapidly over the last decade to provide functional tumour information and, compared with conventional staging, has changed the way of selecting patients for radiotherapy, as well as helping in target definition in, for example, Hodgkin's disease [46,47]. Clinicians have begun to integrate information from these new imaging tools into radiotherapy planning (multimodality imaging). Examples include fusing a PET scan on to the planning CT scan for adult lung cancer to define the PTV and critical structures [48,49] or PET fused with CT/MRI planning scans for head-and-neck cancer [50]. However, prospective trials to validate patient-derived benefits are awaited.

Using commercially available software programs, the anatomical detail of helical CT can be amalgamated with the functional information of PET with a high degree of accuracy for sites such as the brain. However, this technique is relatively inaccurate for other anatomical regions, owing to changes in the patient's position and movement artefacts between scans. Some of these problems have been solved by the introduction of combined or hybrid CT/PET scanners; these can perform both a CT and PET scan with the patient in the same anatomical position at a single visit (Fig. 2).

CT/MRI fusion has been most successfully used for radiotherapy planning in neuro-oncology. Other regions of the body, such as the pelvis or chest, produce problems of temporal and spatial correlation from MRI distortion and the movement of internal organs during respiration, peristalsis and heart beating [51,52]. Some of these technical problems may be overcome by using an open, low-field MRI that reduces the distortion to only 1–2 mm for all regions of the body [53], as well as by faster imaging sequences.

Attempts have been made to utilise information from single-photon emission computerised tomography (SPECT) [54], PET [55] and magnetic resonance spectra (MRS) [56,57] to improve the target volume definition for gliomas. Results have demonstrated a mismatch between anatomical and metabolic information for high-grade gliomas [56], but also the possibility of reducing the clinical target volume for the irradiation of low-grade gliomas using MRS [57]. Lastly, brain map-

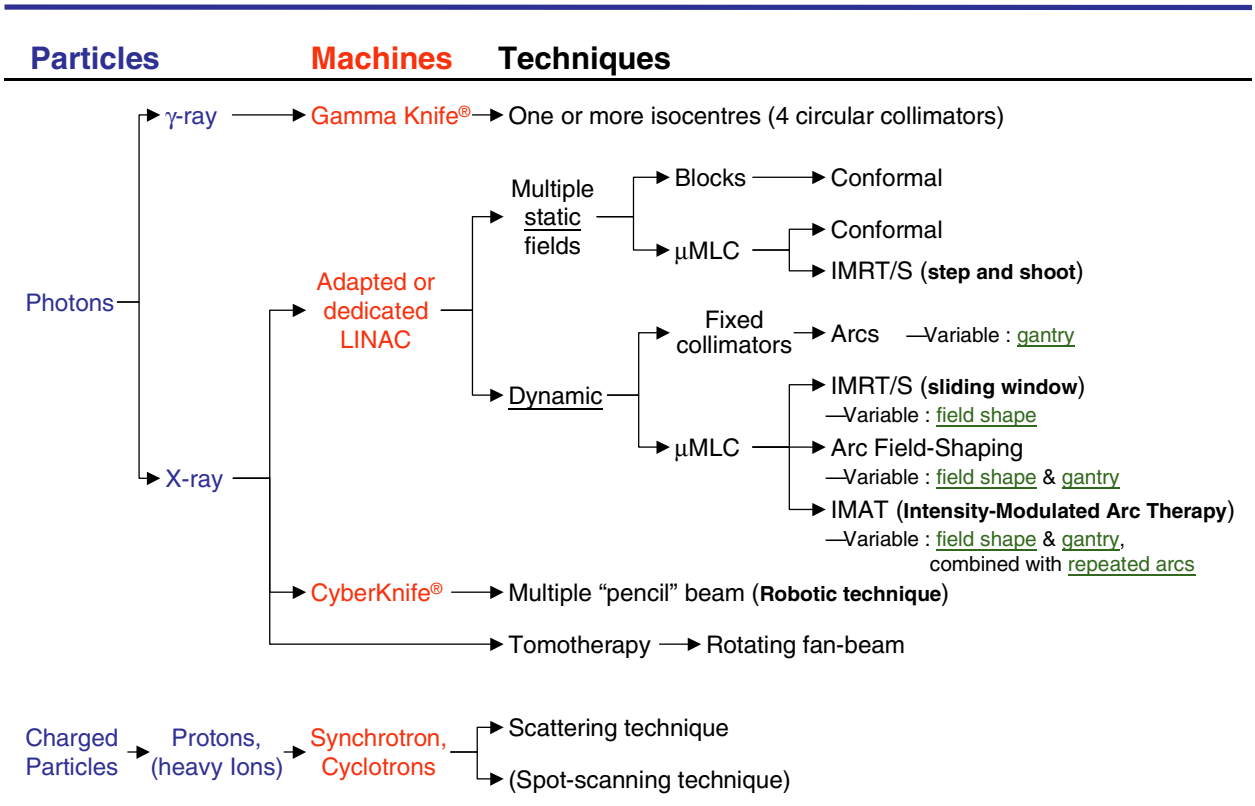
ping using functional MRI may allow the selective avoidance of regions of the brain, so reducing the risk of specific functional impairment after radiotherapy as well as surgery [58,59].

5. Radiotherapy planning and delivery

Newer techniques of radiotherapy involve the maximum conformation of high-dose radiation to the target with sparing of normal tissue. Table 1 summarises some of the particles, machines and delivery techniques currently in use or development (Table 1). These techniques include three-dimensional conformal radiotherapy using fixed beams, SCRT (or SRS) and intensity-modulated radiotherapy. Radiotherapy is usually delivered with the machine gantry fixed, but techniques that move the gantry during treatment (arc therapy) have also been combined with other developments (intensity-modulated arc therapy; IMAT). All such techniques have in common improved patient immobilisation, target localisation and treatment delivery, with some variation in the method used. More complex radiation techniques aim to augment the conformity of the dose delivered to the PTV, but this increase in complexity may also increase the volume of normal tissue receiving low or very low doses of radiation. These lower doses have to be taken into account when comparing and assessing different plans and choosing the final treatment plan. Compared with the effects of conventional two- or three-dimensional coplanar treatments, the increase in tissues receiving even low doses may be enough to increase the risk of SMNs (e.g. thyroid, salivary, brain and skin cancers) [60–62] or impair growth.

Rival plans from different techniques can be evaluated and compared in terms of the physical dose distribution within the target and relevant normal tissues, for which a tumour control probability (TCP) and toxicity (normal tissue complication probability; NTCP) may be estimated [63–65]. Although the concept of the therapeutic ratio (i.e. TCP/NTCP) is frequently used to compare or develop new treatment protocols, its clinical relevance remains limited as such concepts are, at present, only partially validated for adult tumour systems. The assumed level of tolerance to radiotherapy of a certain tissue is usually set at an agreed level for a given

Table 1
Conformal radiotherapy techniques



Particles, machines and treatment techniques currently used or being developed for conformal radiotherapy demonstrating the variety of options available for radiosurgery or stereotactic-guided conformal radiotherapy. (With the kind permission of Stefano Gianolini, Royal Marsden Hospital, Sutton UK.) LINAC, linear accelerator; IMRT, intensity-modulated radiotheraphy; μMLC, μ-multileaf collimator.

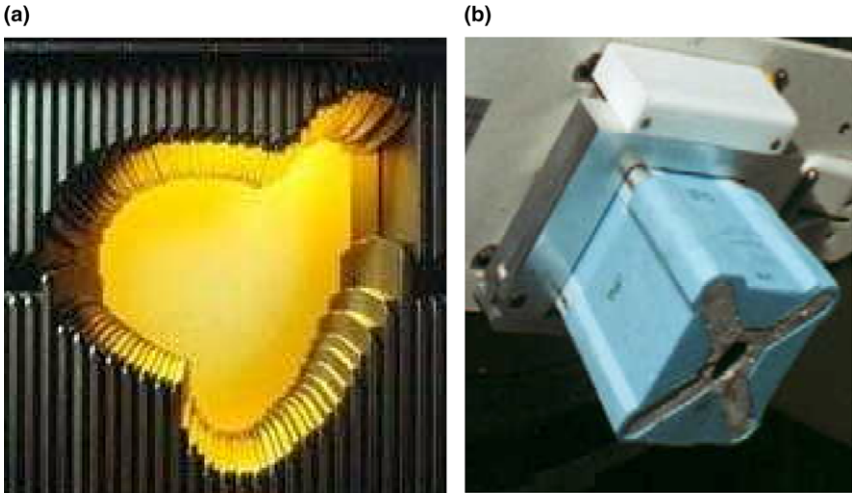


Fig. 3. Examples of field-shaping methods for Conformal Radiotherapy (CRT). (a) Varian® Multi-leaf collimator (MLC) integrated into a linear accelerator showing how the shape of a treatment field may be conformed to the target volume by computer controlled movement of each pair of leaves. For "dynamic" intensity-modulated radiotherapy (IMRT), the distance between each pair of leaves can be varied with the beam continuously switched on. (b) A customised conformal lead alloy block derived from the Beams Eye View facility of a 3D planning computer system. As each field of the treatment plan is treated in turn, the individualised customised block relating to it is attached to the treatment machine.

clinical setting. It is a complex function and depends on the volume irradiated, total dose delivered, dose per fraction, radiation energy and overall treatment time. The risk of experiencing a predefined toxicity is an overall probability and not predictive for any one patient. The development of late toxicity can be difficult to estimate as it is multifactorial and depends on factors such as age, comorbidity, genetic susceptibility, tumour-related damage, surgery and chemotherapy, as well as the use of radiotherapy. Newer radiation techniques may have technical advantages, but aim in principle to improve current practice by reducing acute and/or late toxicity for a preselected antitumour dose or allowing dose escalation with equivalent toxicity based on a predefined normal tissue/organ dose. Early results suggest that hypothalamic endocrine deficits related to radiotherapy, for example, are dose–volume dependent and thus would benefit from CRT [66].

Increased complexity of planning and delivery of radical radiotherapy is appropriate for some tumour sites to optimise the therapeutic ratio for radical treatments (the balance between treatment toxicity and clinical benefit). This approach may also be appropriate in selected palliative settings. There has been a stepped development in radiotherapy from a conventional parallel pair based on bony landmarks to multiple fields and three-dimensional CRT using stereotaxy. Different beam arrangements are usually evaluated using modern, three-dimensional planning software before a final plan is selected. This plan may involve beams entering the patient in a single plane (coplanar) or exploit all three dimensions (non-coplanar). Unnecessary portions of each beam are shielded so that the shape of each beam conforms to the shape of the target in each 'beam's eye view' direction. This shielding is accomplished with a customised shielding block physically fitted on to the linear accelerator for each field or by using automated, computer-controlled metal leaves (multileaf collimators; MLC) incorporated into its head (Fig. 3).

Radiotherapy planning studies have been used to demonstrate the physical benefits of three-dimensional CRT (improved target definition, target coverage and the avoidance of critical structures) for adult tumours [67] and other childhood tumours, such as sarcomas [68,69]. Clinical benefits are generally inferred from these planning studies and non-randomised clinical studies [70,71]. However, randomised evidence quantifying the clinical benefits of CRT does exist for adult prostate cancer. Studies have demonstrated reductions in acute and late toxicity [72,73], as well as improved local biochemical control [74,75] and have provided evidence of a 'proof of principle'.

6. Stereotactic radiotherapy

Stereotaxy refers to the use of a fiducial system of relocation in three-dimensional space and was originally developed for neurosurgery and has been adapted for radiotherapy [76,77] to exploit the benefits of precise patient repositioning and improved immobilisation. The largest experience with stereotactic radiotherapy has been gained in the fields of neuro-oncology and head-and-neck cancer.

SCRT using CT/MRI fusion has been used in paediatric neuro-oncology for well-demarcated, slow-growing tumours, such as low-grade gliomas and craniopharyngiomas [29,30]. In this context, the CT

scan provides not only data on electron density for dosimetry, but also other information such as details of the extent of the calcification associated with craniopharyngioma or improved visualisation of the bony extent of a meningioma not visible on MRI [78]. The fused CT and MRI scans have to be interpreted in the context of all previous imaging and if required in collaboration with the neuroradiologist and neurosurgeon. A prerequisite for successful management is therefore a well-established and comprehensive multidisciplinary team unhampered by interdisciplinary rivalry.

The ideal way of delivering a homogeneous dose to non-spherical lesions with the optimum sparing of normal tissue is through multiple fixed fields conforming to the shape of the lesion [79]. This is achieved by shaped shielding with the MLC, with the mini-MLC using narrower leaves (<1 cm), or through individually shaped lead-alloy shielding blocks [80,81] (Fig. 3). For childhood tumours of the central nervous system (CNS) measuring 3–6 cm in diameter, representing the majority of cases, the optimum sparing of normal brain is achieved with four to six conformal, non-coplanar fixed fields [82]. SCRT is feasible in younger children, even under GA [34,83]. Nevertheless, the beam arrangements have to be carefully chosen to avoid radiation, particularly to organs susceptible to radiation-induced SMNs at low doses, such as the thyroid gland [84].

Recent reports of SCRT in children with low-grade glioma, intracranial germ-cell tumours and craniopharyngioma using smaller than conventionally prescribed safety margins [30–32,85–87] are encouraging. No increased risk of tumour recurrence directly adjacent to the high-dose regions suggestive of geographical misses was reported. Tumour control has been within historical experience, as, for example, demonstrated in low-grade gliomas treated at St. Jude's, Heidelberg and the Royal Marsden Hospital with fractionated CRT [30–32]. Follow-up is generally still short and some relevant endpoints have not been reached, but current data suggest a reduction in late morbidity related to the use of CRT [88]. The Boston group reported their results for conservative surgery and SCRT for childhood craniopharyngioma using a programme of prospective neurocognitive and memory assessment before and following radiotherapy [89]. The St. Jude's experience also suggests less toxicity with this approach compared with initial aggressive surgery alone [90]. Management of craniopharyngiomas by conservative surgery and SCRT remains controversial, but prospective outcome data of this quality are likely to make it appear superior to attempted macroscopic resection in the majority of patients, given the excellent long-term rates of control [90–94].

SCRT and SRS have also been used for head-and-neck cancer, particularly for re-irradiation and for IMRT of, for example, nasopharyngeal carcinoma, a tumour occasionally seen in adolescents [95,96]. The advantages of such an approach are minimising the volume of tissue re-irradiated and avoiding critical structures in close proximity to the PTV, such as the major and minor salivary glands.

SRS is used to deliver a single ablative fraction of radiation akin to surgical ablation, but without the damage and risks that surgical access may entail. A single fraction avoids the inconvenience of fractionated radiotherapy over many weeks, but lacks the benefit of fractionation to minimise late toxicity.

SRS can be delivered either with a conventional linear accelerator using either an arc or a fixed-field technique or via a dedicated radiotherapy unit using 201-fixed cobalt (^{60}Co) sources (Gammaknife®). The Gammaknife® produces an equally rapid fall-off in dose away from the target as a linear accelerator [97,98]. For technical reasons, the Gammaknife® and linear accelerator–SRS are usually restricted to tumours of 3–3.5 cm at a 'safe' distance from known sensitive organs at risk such as the optic chiasm, significantly limiting their use in children. Treating morphologically complex tumours larger than 3.5 cm with Gammaknife®-based SRS or a linear accelerator-based arc technique leads to dose inhomogeneity and undesirable 'hot spots' of at least up to twice the prescribed dose within the target and potentially within the surrounding normal tissues. Therefore, in children and adolescents, particularly for curative procedures, SCRT is preferable to SRS, given the benefits of normal tissue-sparing derived from fractionation.

SRS has a place in selected cases where standard fractionated radiotherapy has failed [33,99–102]. The use of SRS in children should remain restricted to experienced centres as the radiosurgical ablation of intact nerve fibres, e.g. hypothalamus, mesial temporal lobes or limbic pathways, either within or in close proximity to the target, affects memory and neurocognitive outcomes, and requires careful planning and treatment delivery [89].

Benign conditions such as arteriovenous malformations (AVM) have also been treated successfully with SRS. The late effects of this ablative form of radiotherapy on the vasculature are specifically utilised to obliterate the malformation and are used as a surrogate endpoint of treatment success [103,104]. It remains uncertain if this technique reduces the incidence of AVM-associated bleeding in the long-term [105].

7. Intensity-modulated radiotherapy (IMRT)

Radiation beams usually have a uniform intensity or fluence across the field. In the past, simple methods of modifying radiation intensity have been used (e.g.

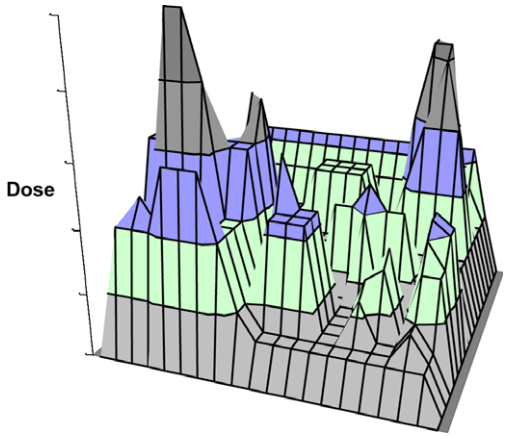


Fig. 4. IMRT fluence profile. The figure shows an example of an intensity modulated radiotherapy (IMRT) fluence profile for a single field demonstrating the dose variation across the beam. Along the path of irradiation, the peaks of higher radiation intensity correspond to tumour-containing areas and troughs to normal tissue or critical structures.

wedges or compensating filters). IMRT involves the production of a non-uniform beam intensity across a field (Fig. 4) using advanced planning, verification and delivery techniques. The non-uniform intensity is summated in three-dimensions for all the treatment fields and permits the creation of concavities in the high-dose distribution. IMRT can therefore produce more conformal dose distributions than before for irregular targets that contain concavities. This approach spares critical structures lying within the concavities or in close proximity to the target (conformal avoidance). The benefits include adequate target coverage and the possibility of dose escalation, whilst keeping critical structures within predetermined dose levels (Fig. 5). IMRT can also create inhomogeneous dose distributions that place a 'hot spot' in regions at higher risk of tumour recurrence, so providing the ability to deliver a concomitant boost [106], as well as to avoid radiosensitive tissues (dose painting).

The complex planning peculiar to IMRT (inverse planning) requires the treating clinician to stipulate the desired dose and volume constraints for the target and critical structures. The planning computer then attempts to meet these by generating fluence profiles for a predefined field arrangement. These fluence profiles are then recalculated in an iterative manner until an 'opti-

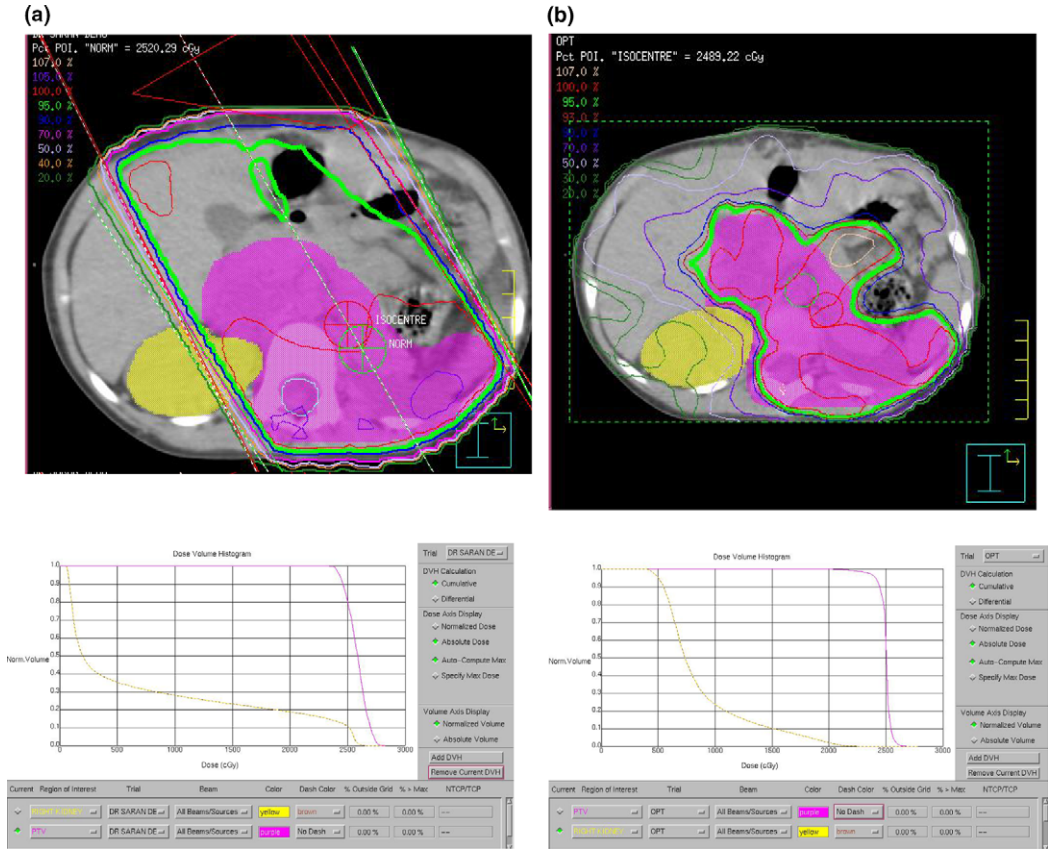


Fig. 5. Improved organ avoidance by IMRT compared with conventional beam arrangements. (a) The conventional plan for a patient with a stage III left-sided Wilms' tumour with extension in the IVC and hepatic veins exposes the remaining right-sided kidney to a significant radiotherapy dose above 17 Gy. The plan provides adequate coverage of the planning target volume (PTV) with a dose prescription of 25.2 Gy. (b) An optimised IMRT plan using a five-field step and shoot technique. The IMRT solution significantly reduces the kidney tissue receiving critically high doses at the expense of an increase in the isodoses below 8 Gy. Additionally, the plan provides more homogenous and conformal dose coverage for the PTV.

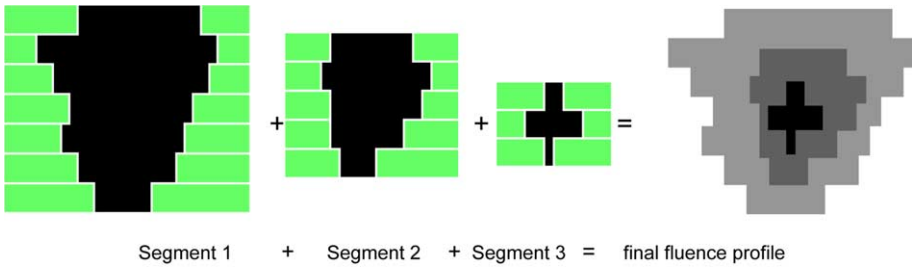


Fig. 6. Step and shoot IMRT delivery. For each segment, each leaf of the multi-leaf collimator (represented by the horizontal bars) is moved under computer control to shape the treatment aperture. Each segment is treated in turn with the sum creating the final fluence profile for that field. The darker areas in the final fluence profile represent a higher dose.

mised' solution is reached, with the desired balance of target coverage and organ-at-risk avoidance. The optimum number of fields, their directions and the planning objectives applicable to most tumours at a particular site is termed a 'class' solution. Class solutions are under development for many tumour sites and, in the future, this optimisation and search for the best solution may also be computer automated [107].

Currently, there are several different methods of generating a field's fluence profile to deliver an optimised IMRT plan. They include, for example, the manufacture of a three-dimensional metal compensator or different ways of using MLC leaves under computer control, e.g. step and shoot (Fig. 6). For further details of how these are delivered and for which tumours, we refer the reader to reviews of the different techniques in current use and development [108,109] and a consensus document from the IMRT Collaborative Working Group [110].

At present, clinical data on outcomes are sparse, but data showing the potential clinical gains for adult cancers are emerging [111–113]. Planning studies have shown clear physical advantages for avoiding the spinal cord and parotid in head-and-neck cancers [114] and early clinical outcome studies on xerostomia have corroborated this finding [112,113,115]. Early data also suggest that an planned intensity-modulated boost to the posterior fossa may reduce grade 3 and 4 ototoxicity in children with standard-risk medulloblastoma treated by radiotherapy and cisplatin-based adjuvant chemotherapy when compared with conventional parallel pairs [116]. The ototoxicity of the combined treatment can be as high as 32% [117]. Similar sparing can be achieved with CRT, and the conclusion drawn from the retrospective small series has been criticised for the unusually high ototoxicity in the standard group treated with conventional parallel pairs, imbalances between the two treatment groups and PTV underdosage [118,119].

IMRT is in a period of rapid evolution as more reliable and efficient methods are introduced and tested. The machinery is becoming less work-intensive and expensive, with off-the-shelf hardware and software now available. However, many issues of quality assurance still need to be resolved and IMRT requires specific expertise. For some tumours, detailed knowledge on target-volume definition is lacking, as are internationally agreed dose–volume constraints for organs at risk, limiting the safe use of IMRT. In part, this knowledge may be gained by the integration of new methods of imaging into the planning process. Even so, IMRT utilises novel planning and delivery techniques that require careful refinement, validation and evaluation, especially with regard to children, before widespread implementation.

8. Proton therapy

Significant efforts have been devoted to the development of proton therapy for clinical use. Protons are particles that can deposit their energy at a set depth into tissue with virtually no exit of dose beyond the PTV. Compared with conformal photon plans, this has clear technical advantages in terms of reducing the volume of normal tissue irradiated, which is particularly relevant for young children [24]. Examples of tumours treated in this manner include low-grade tumours of the optic pathway, medulloblastoma, meningioma neuroblastoma, and it is established as the 'treatment of choice' for ocular melanoma [22,23,120–126] (Fig. 7). There is an already well-established indication for proton therapy in inoperable or recurrent chordoma and low-grade chondrosarcoma of the base of skull [127]. As a dedicated cyclotron is essential for the production of high-energy protons, cost and limited availability currently prevent the widespread use of proton therapy. At present, the evidence of benefit for proton-based therapy of base-of-skull chordoma and low-grade chondrosarcoma is strong enough to persuade the notoriously cash-strapped British National Health Service to fund comprehensively such treatment at the French proton facility in Orsay [128]. Proton treatment is approximately 2.4 times more expensive than conventional photons [129]. Its potential to spare normal tissue, and thus its ability to reduce treatment-related complications including second malignancies, while having equal if not improved local control compared with a conventional

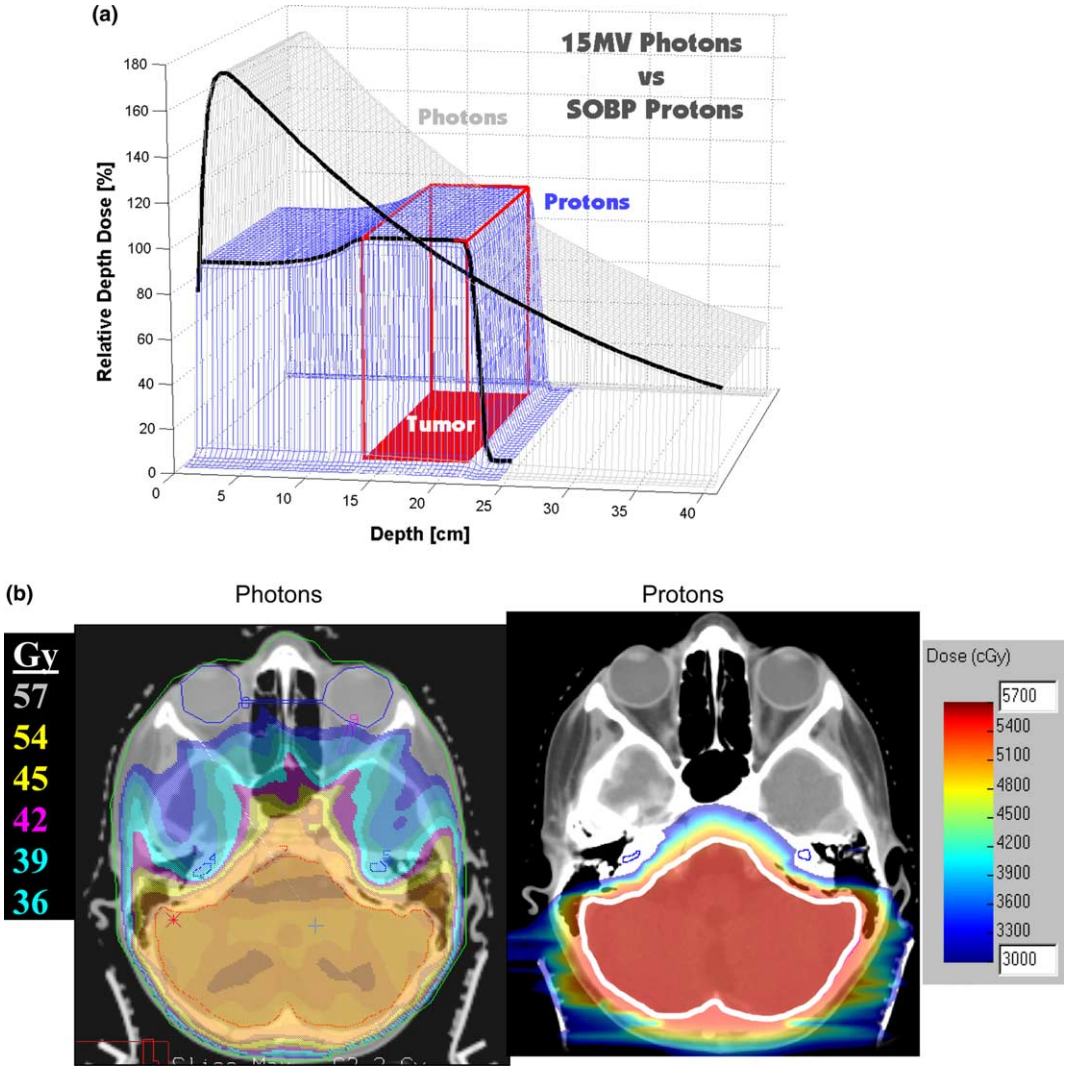


Fig. 7. Comparison of the depth dose characteristics of photons and protons. (a) The graph demonstrates the differences of dose distribution with increasing depth of tissue for a photon and a proton beam. For this deep-seated tumour, there is minimal radiation dose deposited beyond the defined planning target volume compared with a single photon beam. (b) Dose distribution for a posterior fossa volume for a child with a primitive neuroectodermal tumour (PNET) of the posterior fossa (medulloblastoma). A proton plan significantly reduces the dose outside the PTV even compared with a conformal intensity-modulated photon plan, particularly to the temporal lobes and hypothalamus, thus potentially reducing radiotherapy-associated late sequelae. (With the kind permission of Nancy Tarbell, MGH, Boston, MA, USA.)

photon treatment will make a case for powerful public demand, particularly in the United States [130–132]. Theoretical modelling for prostate cancer suggests that intensity-modulated proton therapy, a further increase in complexity combining proton treatment with non-uniform beam intensities, may lead to significant improvements in complication-free tumour control [133–135]. If this prediction should hold true in clinical practice, it will rapidly widen the indications for this modality. This assumption is underpinned by the approved expansion of proton facilities in the United States, with multi-billion dollar investments over the next 5–10 years providing the means of setting-up prospective clinical trials on a large-scale [136]. This visionary development is likely to set an example for Europe to follow and could lead to a replacement of photon therapy in many indications for curative radiotherapy, both in adult and paediatric practice, by the time I retire. Yet proton therapy is not a treatment free of morbidity, as demonstrated by recently published case reports, and should therefore not be seen as a panacea for paediatric radiotherapy [137,138].

9. Summary and future perspectives

The major research directions in paediatric radiotherapy have been related to CRT (including SCRT, SRS and IMRT) and multimodality imaging (MRI, MRS, PET, SPECT etc.) to improve target definition. Most recent technical advances in radiotherapy are not easily testable in the paediatric setting, as relevant clin-

ical endpoints are multifactorial and difficult to measure. Evidence from prospective, randomised studies exists for certain advances such as the value of three-dimensional CRT to reduce acute and late toxicity and improve tumour control, as demonstrated in prostate cancer in adults. Although these results are not directly applicable to the paediatric setting, they represent an important 'proof of principle'. As for new chemotherapeutic drugs, vigorous, prospective academic testing must be pursued to prove and quantify the benefits of modern radiotherapy planning and delivery techniques compared with current standards, rather than relying on simplistic, selected physical dose distributions or radiobiological models with all their limitations [139–141]. Techniques such as IMRT have opened up new avenues of critical organ avoidance, dose escalation and concomitant boosting, aiming to reduce acute and late morbidity, while offering the potential to improve local tumour control. However, given the rapid changes in technology, it may not be possible, or even appropriate, to perform prospective, randomised, controlled trials for every technical advance in radiotherapy or for each tumour site. Small patient numbers and the lack of appropriate measurement tools for specified endpoints in growing children, such as vision or quality of life, further hamper the collection of evidence-based data. Only limited information can be derived from comparison with historical series, as significant changes will have occurred over time in staging, imaging, surgery, pathology and chemotherapy, making such comparisons difficult and academically unsatisfactory. In particular, many reports of radiation-associated late sequelae in children and adolescents are rendered obsolete by the 'standard of care' in modern radiotherapy. Therefore, guidance by the large paediatric oncology groups (COG, SIOP) is required to inform and steer best practice in paediatric radiotherapy. However, progress in paediatric radiation oncology will not be achieved by the improvement of a single step, but by the continuous improvement of the whole pathway.

Finally, clinicians, particularly paediatric oncologists, should not be deterred from carefully incorporating 'modern' radiotherapy into paediatric protocols. To do so acknowledges the significant contribution radiotherapy can make in achieving locoregional control and long-term cure. In this respect, radiotherapy in paediatric oncology has a bright future.

Acknowledgements

The author thank Dr. R. Soomal for his helpful discussions during the preparation of the manuscript and his support with the literature research.

References

1. Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst* 1999, **91**(12), 1051–1058.
2. Kushner BH, Wolden S, LaQuaglia MP, Kramer K, Verbel D, Heller G, *et al*. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. *J Clin Oncol* 2001, **19**(11), 2821–2828.
3. Wolden SL, Gollamudi SV, Kushner BH, LaQuaglia M, Kramer K, Rosen N, *et al*. Local control with multimodality therapy for stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000, **46**(4), 969–974.
4. Bouffet E, Bernard JL, Frappaz D, Gentet JC, Roche H, Tron P, *et al*. M4 protocol for cerebellar medulloblastoma: supratentorial radiotherapy may not be avoided. *Int J Radiat Oncol Biol Phys* 1992, **24**(1), 79–85.
5. Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *J Clin Oncol* 2001, **19**(15), 3470–3476.
6. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. *J Clin Oncol* 1998, **16**(5), 1723–1728.
7. Hogeboom CJ, Grosser SC, Guthrie KA, Thomas PR, D'Angio GJ, Breslow NE. Stature loss following treatment for Wilms tumor. *Med Pediatr Oncol* 2001, **36**(2), 295–304.
8. Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, *et al*. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med* 1993, **328**(2), 87–94.
9. Eiser C, Jenney ME. Measuring symptomatic benefit and quality of life in paediatric oncology. *Br J Cancer* 1996, **73**(11), 1313–1316.
10. Walter AW, Hancock ML, Pui CH, Hudson MM, Ochs JS, Rivera GK, *et al*. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St. Jude Children's Research Hospital. *J Clin Oncol* 1998, **16**(12), 3761–3767.
11. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, *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.
12. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit Jr ME, Ruccione K, *et al*. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol* 2001, **19**(13), 3163–3172.
13. DeVile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. *Arch Dis Child* 1996, **75**(2), 108–114.
14. Kao GD, Goldwein JW, Schultz DJ, Radcliffe J, Sutton L, Lange B. The impact of perioperative factors on subsequent intelligence quotient deficits in children treated for medulloblastoma/posterior fossa primitive neuroectodermal tumors. *Cancer* 1994, **74**(3), 965–971.
15. Proimos BS. Beam-shapers oriented by gravity in rotational therapy. *Radiology* 1966, **87**(5), 928–932, passim.
16. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, *et al*. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *Int J Radiat Oncol Biol Phys* 2000, **47**(3), 551–560.
17. Gandola L, Cefalo G, Massimino M, Navarria P, Spreafico F, Pignoli E, *et al*. Hyperfractionated accelerated radiotherapy (HART) after intensive postoperative sequential chemotherapy

for metastatic medulloblastoma. International Society of Paediatric Oncology SIOP XXXIV Annual Meeting. *Med Pediatr Oncol* 2002, **39**(4), 248.
18. Allen JC, Donahue B, DaRosso R, Nirenberg A. Hyperfractionated craniospinal radiotherapy and adjuvant chemotherapy for children with newly diagnosed medulloblastoma and other primitive neuroectodermal tumors. *Int J Radiat Oncol Biol Phys* 1996, **36**(5), 1155–1161.
19. Prados MD, Edwards MS, Chang SM, Russo C, Davis R, Rabbitt J, *et al*. Hyperfractionated craniospinal radiation therapy for primitive neuroectodermal tumors: results of a phase II study. *Int J Radiat Oncol Biol Phys* 1999, **43**(2), 279–285.
20. Ricardi U, Corrias A, Einaudi S, Genitori L, Sandri A, di Montezemolo LC, *et al*. Thyroid dysfunction as a late effect in childhood medulloblastoma: a comparison of hyperfractionated versus conventionally fractionated craniospinal radiotherapy. *Int J Radiat Oncol Biol Phys* 2001, **50**(5), 1287–1294.
21. Corrias A, Einaudi S, Ricardi U, Sandri A, Besenzon L, Altare F, *et al*. Thyroid diseases in patients treated during pre-puberty for medulloblastoma with different radiotherapic protocols. *J Endocrinol Invest* 2001, **24**(6), 387–392.
22. Hug EB, Nevinny-Stickel 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**(1), 36–41.
23. 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**(4), 1219–1226.
24. Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study. *Radiother Oncol* 2003, **68**(1), 1–14.
25. Lee SW, Fraass BA, Marsh LH, Herbort K, Gebarski SS, Martel MK, *et al*. Patterns of failure following high-dose 3-D conformal radiotherapy for high-grade astrocytomas: a quantitative dosimetric study. *Int J Radiat Oncol Biol Phys* 1999, **43**(1), 79–88.
26. Pai HH, Thornton A, Katznelson L, Finkelstein DM, Adams JA, Fullerton BC, *et al*. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2001, **49**(4), 1079–1092.
27. Halperin EC, Laurie F, Fitzgerald TJ. An evaluation of the relationship between the quality of prophylactic cranial radiotherapy in childhood acute leukemia and institutional experience: a Quality Assurance Review Center-Pediatric Oncology Group study. *Int J Radiat Oncol Biol Phys* 2002, **53**(4), 1001–1004.
28. Zhu Y, Stovall Jr J, Butler L, Ji Q, Gaber MW, Samant S, *et al*. Comparison of two immobilization techniques using portal film and digitally reconstructed radiographs for pediatric patients with brain tumors. *Int J Radiat Oncol Biol Phys* 2000, **48**(4), 1233–1240.
29. Tarbell NJ, Barnes P, Scott RM, Goumnerova L, Pomeroy SL, Black PM, *et al*. Advances in radiation therapy for craniopharyngiomas. *Pediatr Neurosurg* 1994, **21**(Suppl 1), 101–107.
30. Saran FH, Baumert BG, Khoo VS, Adams EJ, Garre ML, Warrington AP, *et al*. Stereotactically guided conformal radiotherapy for progressive low-grade gliomas of childhood. *Int J Radiat Oncol Biol Phys* 2002, **53**(1), 43–51.
31. Merchant TE, Zhu Y, Thompson SJ, Sontag MR, Heideman RL, Kun LE. Preliminary results from a phase II trail of conformal radiation therapy for pediatric patients with localised low-grade astrocytoma and ependymoma. *Int J Radiat Oncol Biol Phys* 2002, **52**(2), 325–332.
32. Debus J, Kocagoncu KO, Hoss A, Wenz F, Wannenmacher M. Fractionated stereotactic radiotherapy (FSRT) for optic glioma. *Int J Radiat Oncol Biol Phys* 1999, **44**(2), 243–248.
33. Stafford SL, Pollock BE, Foote RL, Gorman DA, Nelson DF, Schomberg PJ. Stereotactic radiosurgery for recurrent ependymoma. *Cancer* 2000, **88**(4), 870–875.
34. Adams EJ, Suter BL, Warrington AP, Black P, Saran F, Brada M. Design and implementation of a system for treating paediatric patients with stereotactically-guided conformal radiotherapy. *Radiother Oncol* 2001, **60**(3), 289–297.
35. Ryken TC, Meeks SL, Pennington EC, Hitchon P, Traynelis V, Mayr NA, *et al*. Initial clinical experience with frameless stereotactic radiosurgery: analysis of accuracy and feasibility. *Int J Radiat Oncol Biol Phys* 2001, **51**(4), 1152–1158.
36. Karger CP, Jakel O, Debus J, Kuhn S, Hartmann GH. Three-dimensional accuracy and interfractional reproducibility of patient fixation and positioning using a stereotactic head mask system. *Int J Radiat Oncol Biol Phys* 2001, **49**(5), 1493–1504.
37. Chou RH, Wilder RB, Wong MS, Forster KM. Recent advances in radiotherapy for head and neck cancers. *Ear Nose Throat J* 2001, **80**(10), 704–707, 711–714, 716 passim.
38. Lohr F, Debus J, Frank C, Herfarth K, Pastyr O, Rhein B, *et al*. Noninvasive patient fixation for extracranial stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 1999, **45**(2), 521–527.
39. Wulf J, Hadinger U, Oppitz U, Olshausen B, Flentje M. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. *Radiother Oncol* 2000, **57**(2), 225–236.
40. Wong JW, Sharpe MB, Jaffray DA, Kini VR, Robertson JM, Stromberg JS, *et al*. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Radiat Oncol Biol Phys* 1999, **44**(4), 911–919.
41. Jaffray DA, Siewerdsen JH, Wong JW, Martinez AA. Flat-panel cone-beam computed tomography for image-guided radiation therapy. *Int J Radiat Oncol Biol Phys* 2002, **53**(5), 1337–1349.
42. Dobbs HJ, Parker RP, Hodson NJ, Hobday P, Husband JE. The use of CT in radiotherapy treatment planning. *Radiother Oncol* 1983, **1**(2), 133–141.
43. International Commission on Radiation Units and Measurements. ICRU Report 50. Prescribing, recording and reporting photon beam therapy: Bethesda MD ICRU; 1993.
44. International Commission on Radiation Units and Measurements. ICRU Report 62. Prescribing, recording and reporting photon beam therapy (Supplement to ICRU Report 50): Bethesda MD ICRU; 1999.
45. Rosenman J. Incorporating functional imaging information into radiation treatment. *Semin Radiat Oncol* 2001, **11**(1), 83–92.
46. Partridge S, Timothy A, O'Doherty MJ, Hain SF, Rankin S, Mikhaeel G. 2-Fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretreatment staging of Hodgkin's disease: influence on patient management in a single institution. *Ann Oncol* 2000, **11**(10), 1273–1279.
47. Spaepen K, Stroobants S, Dupont P, Thomas J, Vandenberghe P, Balzarini J, *et al*. Can positron emission tomography with [(18)F]-fluorodeoxyglucose after first-line treatment distinguish Hodgkin's disease patients who need additional therapy from others in whom additional therapy would mean avoidable toxicity? *Br J Haematol* 2001, **115**(2), 272–278.
48. Mah K, Caldwell CB, Ung YC, Danjoux CE, Balogh JM, Ganguli SN, *et al*. The impact of (18)FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 2002, **52**(2), 339–350.
49. Erdi YE, Rosenzweig K, Erdi AK, Macapinlac HA, Hu YC, Braban LE, *et al*. Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). *Radiother Oncol* 2002, **62**(1), 51–60.
50. Nishioka T, Shiga T, Shirato H, Tsukamoto E, Tsuchiya K, Kato T, *et al*. Image fusion between 18FDG-PET and MRI/CT for

radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. *Int J Radiat Oncol Biol Phys* 2002, **53**(4), 1051–1057.
51. Khoo VS, Dearnaley DP, Finnigan DJ, Padhani A, Tanner SF, Leach MO. Magnetic resonance imaging (MRI): considerations and applications in radiotherapy treatment planning. *Radiother Oncol* 1997, **42**(1), 1–15.
52. Khoo VS. MRI – "magic radiotherapy imaging" for treatment planning. *Br J Radiol* 2000, **73**(867), 229–233.
53. Krempien RC, Schubert K, Zierhut D, Steckner MC, Treiber M, Harms W, *et al*. Open low-field magnetic resonance imaging in radiation therapy treatment planning. *Int J Radiat Oncol Biol Phys* 2002, **53**(5), 1350–1360.
54. Grosu AL, Weber W, Feldmann HJ, Wuttke B, Bartenstein P, Gross MW, *et al*. First experience with I-123-alpha-methyl-tyrosine spect in the 3-D radiation treatment planning of brain gliomas. *Int J Radiat Oncol Biol Phys* 2000, **47**(2), 517–526.
55. Nuutinen J, Sonninen P, Lehikoinen P, Sutinen E, Valavaara R, Eronen E, *et al*. Radiotherapy treatment planning and long-term follow-up with [(11)C]methionine PET in patients with low-grade astrocytoma. *Int J Radiat Oncol Biol Phys* 2000, **48**(1), 43–52.
56. Pirzkall A, McKnight TR, Graves EE, Carol MP, Sneed PK, Wara WW, *et al*. MR-spectroscopy guided target delineation for high-grade gliomas. *Int J Radiat Oncol Biol Phys* 2001, **50**(4), 915–928.
57. Pirzkall A, Nelson SJ, McKnight TR, Takahashi MM, Li X, Graves EE, *et al*. Metabolic imaging of low-grade gliomas with three-dimensional magnetic resonance spectroscopy. *Int J Radiat Oncol Biol Phys* 2002, **53**(5), 1254–1264.
58. Hamilton RJ, Sweeney PJ, Pelizzari CA, Yetkin FZ, Holman BL, Garada B, *et al*. Functional imaging in treatment planning of brain lesions. *Int J Radiat Oncol Biol Phys* 1997, **37**(1), 181–188.
59. Fried I. Magnetic resonance imaging and epilepsy: neurosurgical decision making. *Magn Reson Imaging* 1995, **13**(8), 1163–1170.
60. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, *et al*. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995, **141**(3), 259–277.
61. Modan B, Chetrit A, Alfandary E, Tamir A, Lusky A, Wolf M, *et al*. Increased risk of salivary gland tumors after low-dose irradiation. *Laryngoscope* 1998, **108**(7), 1095–1097.
62. Shore RE, Moseson M, Xue X, Tse Y, Harley N, Pasternack BS. Skin cancer after X-ray treatment for scalp ringworm. *Radiat Res* 2002, **157**(4), 410–418.
63. Kutcher GJ, Burman C, Brewster L, Goitein M, Mohan R. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. *Int J Radiat Oncol Biol Phys* 1991, **21**(1), 137–146.
64. Lyman JT, Wolbarst AB. Optimization of radiation therapy, III: a method of assessing complication probabilities from dose-volume histograms. *Int J Radiat Oncol Biol Phys* 1987, **13**(1), 103–109.
65. Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys* 1991, **21**(1), 123–135.
66. Merchant TE, Goloubeva O, Pritchard DL, Gaber MW, Xiong X, Danish RK, *et al*. Radiation dose-volume effects on growth hormone secretion. *Int J Radiat Oncol Biol Phys* 2002, **52**(5), 1264–1270.
67. Emami B, Purdy JA, Simpson JR, Harms W, Gerber R, Wippold JF. 3-D conformal radiotherapy in head and neck cancer. The Washington University experience. *Front Radiat Ther Oncol* 1996, **29**, 207–220.
68. Michalski JM, Sur RK, Harms WB, Purdy JA. Three dimensional conformal radiation therapy in pediatric parameningeal rhabdomyosarcomas. *Int J Radiat Oncol Biol Phys* 1995, **33**(5), 985–991.
69. Merchant TE. Conformal therapy for pediatric sarcomas. *Semin Radiat Oncol* 1997, **7**(3), 236–245.
70. Hazuka MB, Martel MK, Marsh L, Lichter AS, Wolf GT. Preservation of parotid function after external beam irradiation in head and neck cancer patients: a feasibility study using 3-dimensional treatment planning. *Int J Radiat Oncol Biol Phys* 1993, **27**(3), 731–737.
71. Sandler HM, McLaughlin PW, Ten Haken RK, Addison H, Forman J, Lichter A. Three dimensional conformal radiotherapy for the treatment of prostate cancer: low risk of chronic rectal morbidity observed in a large series of patients. *Int J Radiat Oncol Biol Phys* 1995, **33**(4), 797–801.
72. Koper PC, Stroom JC, van Putten WL, Korevaar GA, Heijmen BJ, Wijnmaalen A, *et al*. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. *Int J Radiat Oncol Biol Phys* 1999, **43**(4), 727–734.
73. Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, *et al*. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999, **353**(9149), 267–272.
74. Dearnaley DP, Hall E, Jackson C, Lawrence D, Huddart R, Eeles R, *et al*. Phase III trial of dose escalation using conformal radiotherapy in prostate cancer: side effects and PSA control. *Br J Cancer* 2001, **85**(Suppl 1), 15.
75. Dearnaley DP. Radiotherapy and combined modality approaches in localised prostate cancer. *Eur J Cancer* 2001, **37**(Suppl 7), S137–S145.
76. Graham JD, Warrington AP, Gill SS, Brada M. A non-invasive, relocatable stereotactic frame for fractionated radiotherapy and multiple imaging. *Radiother Oncol* 1991, **21**(1), 60–62.
77. Schlegel W, Pastyr O, Bortfeld T, Gademann G, Menke M, Maier-Borst W. Stereotactically guided fractionated radiotherapy: technical aspects. *Radiother Oncol* 1993, **29**(2), 197–204.
78. Khoo VS, Adams EJ, Saran F, Bedford JL, Perks JR, Warrington AP, *et al*. A Comparison of clinical target volumes determined by CT and MRI for the radiotherapy planning of base of skull meningiomas. *Int J Radiat Oncol Biol Phys* 2000, **46**(5), 1309–1317.
79. Laing RW, Bentley RE, Nahum AE, Warrington AP, Brada M. Stereotactic radiotherapy of irregular targets: a comparison between static conformal beams and non-coplanar arcs. *Radiother Oncol* 1993, **28**(3), 241–246.
80. Shiu AS, Kooy HM, Ewton JR, Tung SS, Wong J, Antes K, *et al*. Comparison of miniature multileaf collimation (MMLC) with circular collimation for stereotactic treatment. *Int J Radiat Oncol Biol Phys* 1997, **37**(3), 679–688.
81. Adams EJ, Cosgrove VP, Shepherd SF, Warrington AP, Bedford JL, Mubata CD, *et al*. Comparison of a multi-leaf collimator with conformal blocks for the delivery of stereotactically guided conformal radiotherapy. *Radiother Oncol* 1999, **51**(3), 205–209.
82. Perks JR, Jalali R, Cosgrove VP, Adams EJ, Shepherd SF, Warrington AP, *et al*. Optimization of stereotactically-guided conformal treatment planning of sellar and parasellar tumors, based on normal brain dose volume histograms. *Int J Radiat Oncol Biol Phys* 1999, **45**(2), 507–513.
83. Jalali R, Brada M, Perks JR, Warrington AP, Traish D, Burchell L, *et al*. Stereotactic conformal radiotherapy for pituitary adenomas: technique and preliminary experience. *Clin Endocrinol (Oxf)* 2000, **52**(6), 695–702.
84. Shepherd SF, Childs PJ, Graham JD, Warrington AP, Brada M. Whole body doses from linear accelerator-based stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 1997, **38**(3), 657–665.
85. Zissiadis Y, Dutton S, Kieran M, Goumnerova L, Scott RM, Kooy HM, *et al*. Stereotactic radiotherapy for pediatric intracranial germ cell tumors. *Int J Radiat Oncol Biol Phys* 2001, **51**(1), 108–112.
86. Selch MT, DeSalles AA, Wade M, Lee SP, Solberg TD, Wallace RE, *et al*. Initial clinical results of stereotactic radiotherapy for the treatment of craniopharyngiomas. *Technol Cancer Res Treat* 2002, **1**(1), 51–59.

87. Schulz-Ertner D, Frank C, Herfarth KK, Rhein B, Wannenmacher M, Debus J. Fractionated stereotactic radiotherapy for craniopharyngiomas. *Int J Radiat Oncol Biol Phys* 2002, **54**(4), 1114–1120.
88. Loeffler JS, Kooy HM, Tarbell NJ. The emergence of conformal radiotherapy: special implications for pediatric neuro-oncology. *Int J Radiat Oncol Biol Phys* 1999, **44**(2), 237–238.
89. Carpentieri SC, Waber DP, Scott RM, Goumnerova LC, Kieran MW, Cohen LE, *et al*. Memory deficits among children with craniopharyngiomas. *Neurosurgery* 2001, **49**(5), 1053–1057, discussion 1057–1058.
90. Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, *et al*. Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. *Int J Radiat Oncol Biol Phys* 2002, **53**(3), 533–542.
91. Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, *et al*. Craniopharyngioma – a long-term results following limited surgery and radiotherapy. *Radiother Oncol* 1993, **26**(1), 1–10.
92. Brada M, Thomas DG. Craniopharyngioma revisited. *Int J Radiat Oncol Biol Phys* 1993, **27**(2), 471–475.
93. Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, *et al*. The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. *Int J Radiat Oncol Biol Phys* 1999, **44**(2), 255–263.
94. Hetelekidis S, Barnes PD, Tao ML, Fischer EG, Schneider L, Scott RM, *et al*. 20-year experience in childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys* 1993, **27**(2), 189–195.
95. Pai PC, Chuang CC, Wei KC, Tsang NM, Tseng CK, Chang CN. Stereotactic radiosurgery for locally recurrent nasopharyngeal carcinoma. *Head Neck* 2002, **24**(8), 748–753.
96. Ahn YC, Kim DY, Huh SJ, Baek CH, Park K. Fractionated stereotactic radiation therapy for locally recurrent nasopharynx cancer: report of three cases. *Head Neck* 1999, **21**(4), 338–345.
97. Phillips MH, Stelzer KJ, Griffin TW, Mayberg MR, Winn HR. Stereotactic radiosurgery: a review and comparison of methods. *J Clin Oncol* 1994, **12**(5), 1085–1099.
98. Verhey LJ, Smith V, Serago CF. Comparison of radiosurgery treatment modalities based on physical dose distributions. *Int J Radiat Oncol Biol Phys* 1998, **40**(2), 497–505.
99. Hodgson DC, Goumnerova LC, Loeffler JS, Dutton S, Black PM, Alexander 3rd E, *et al*. Radiosurgery in the management of pediatric brain tumors. *Int J Radiat Oncol Biol Phys* 2001, **50**(4), 929–935.
100. Chiou SM, Lunsford LD, Niranjan A, Kondziolka D, Flickinger JC. Stereotactic radiosurgery of residual or recurrent craniopharyngioma, after surgery, with or without radiation therapy. *Neuro-oncology* 2001, **3**(3), 159–166.
101. Hadjipanayis CG, Kondziolka D, Gardner P, Niranjan A, Dagam S, Flickinger JC, *et al*. Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary. *J Neurosurg* 2002, **97**(1), 56–64.
102. Milker-Zabel S, Zabel A, Thilmann C, Zuna I, Hoess A, Wannenmacher M, *et al*. Results of three-dimensional stereotactically-guided radiotherapy in recurrent medulloblastoma. *J Neurooncol* 2002, **60**(3), 227–233.
103. Smyth MD, Sneed PK, Ciricillo SF, Edwards MS, Wara WM, Larson DA, *et al*. Stereotactic radiosurgery for pediatric intracranial arteriovenous malformations: the University of California at San Francisco experience. *J Neurosurg* 2002, **97**(1), 48–55.
104. Levy EI, Niranjan A, Thompson TP, Scarrow AM, Kondziolka D, Flickinger JC, *et al*. Radiosurgery for childhood intracranial arteriovenous malformations. *Neurosurgery* 2000, **47**(4), 834–841, discussion 841–842.
105. Brada M, Kitchen N. How effective is radiosurgery for arteriovenous malformations? *J Neurol Neurosurg Psychiatry* 2000, **68**(5), 548–549.
106. Butler EB, Teh BS, Grant WH, Uhl 3rd BM, Kuppersmith RB, Chiu JK, *et al*. Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 1999, **45**(1), 21–32.
107. Rowbottom CG, Nutting CM, Webb S. Beam-orientation optimization of intensity-modulated radiotherapy: clinical application to parotid gland tumours. *Radiother Oncol* 2001, **59**(2), 169–177.
108. Nutting C, Dearnaley DP, Webb S. Intensity modulated radiation therapy: a clinical review. *Br J Radiol* 2000, **73**(869), 459–469.
109. Webb S. Advances in three-dimensional conformal radiation therapy physics with intensity modulation. *Lancet Oncol* 2000, **1**(1), 30–36.
110. Intensity-modulated radiotherapy: current status and issues of interest. *Int J Radiat Oncol Biol Phys* 2001, **51**(4), 880–914.
111. Zelefsky MJ, Fuks Z, Hunt M, Yamada Y, Marion C, Ling CC, *et al*. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002, **53**(5), 1111–1116.
112. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001, **50**(3), 695–704.
113. Eisbruch A. Intensity-modulated radiotherapy of head-and-neck cancer: encouraging early results. *Int J Radiat Oncol Biol Phys* 2002, **53**(1), 1–3.
114. Eisbruch A, Foote RL, O'Sullivan B, Beitler JJ, Vikram B. Intensity-modulated radiation therapy for head and neck cancer: emphasis on the selection and delineation of the targets. *Semin Radiat Oncol* 2002, **12**(3), 238–249.
115. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, *et al*. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002, **53**(1), 12–22.
116. Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, *et al*. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. *Int J Radiat Oncol Biol Phys* 2002, **52**(3), 599–605.
117. Packer RJ, Goldwein J, Nicholson HS, Vezina LG, Allen JC, Ris MD, *et al*. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. *J Clin Oncol* 1999, **17**(7), 2127–2136.
118. Fukunaga-Johnson N, Sandler HM, Marsh R, Martel MK. The use of 3D conformal radiotherapy (3D CRT) to spare the cochlea in patients with medulloblastoma. *Int J Radiat Oncol Biol Phys* 1998, **41**(1), 77–82.
119. Soomal R, Saran F, Brada M. In regard to Huang et al.: intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. *Int J Radiat Oncol Biol Phys* 2002, **52**, 599–605, *Int J Radiat Oncol Biol Phys* 2003, **55**(3), 853; author reply 853–854.
120. Fuss M, Hug EB, Schaefer RA, Nevinny-Stickel M, Miller DW, Slater JM, *et al*. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. *Int J Radiat Oncol Biol Phys* 1999, **45**(5), 1117–1126.
121. Miralbell R, Lomax A, Russo M. Potential role of proton therapy in the treatment of pediatric medulloblastoma/primitive neuroectodermal tumors: spinal theca irradiation. *Int J Radiat Oncol Biol Phys* 1997, **38**(4), 805–811.
122. Noel G, Habrand JL, Mammar H, Haie-Meder C, Pontvert D, Dederke S, *et al*. Highly conformal therapy using proton component in the management of meningiomas. Preliminary experience of the Centre de Protontherapie d'Orsay. *Strahlenther Onkol* 2002, **178**(9), 480–485.

123. Vernimmen FJ, Harris JK, Wilson JA, Melvill R, Smit BJ, Slabbert JP. Stereotactic proton beam therapy of skull base meningiomas. *Int J Radiat Oncol Biol Phys* 2001, **49**(1), 99–105.
124. Egger E, Schalenbourg A, Zografos L, Bercher L, Boehringer T, Chamot L, *et al*. Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma. *Int J Radiat Oncol Biol Phys* 2001, **51**(1), 138–147.
125. Courdi A, Caujolle JP, Grange JD, Diallo-Rosier L, Sahel J, Bacin F, *et al*. Results of proton therapy of uveal melanomas treated in Nice. *Int J Radiat Oncol Biol Phys* 1999, **45**(1), 5–11.
126. Habrand JL, Schlienger P, Schwartz L, Pontvert D, Lenir-Cohen-Solal C, Helfre S, *et al*. Clinical applications of proton therapy. *Bull Cancer Radiother* 1996, **83**(Suppl), 207s–211s.
127. Proton therapy for base of skull chordoma: a report for the Royal College of Radiologists. The Proton Therapy Working Party. *Clin Oncol (R Coll Radiol)* 2000, **12**(2), 75–79.
128. Taylor RE. Obtaining funding for proton therapy at Orsay, France. *Clin Oncol (R Coll Radiol)* 2000, **12**(2), 73–74.
129. Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. *Clin Oncol (R Coll Radiol)* 2003, **15**(1), S37–S50.
130. Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of pediatric base of skull tumors. *Int J Radiat Oncol Biol Phys* 2002, **52**(4), 1017–1024.
131. 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 tumors. *Int J Radiat Oncol Biol Phys* 2002, **54**(3), 824–829.
132. Noel G, Habrand JL, Helfre S, Mammar H, Kalifa C, Ferrand R, *et al*. Proton beam therapy in the management of central nervous system tumors in childhood: the preliminary experience of the Centre de Protontherapie d'Orsay. *Med Pediatr Oncol* 2003, **40**(5), 309–315.
133. Yeboah C, Sandison GA. Optimized treatment planning for prostate cancer comparing IMPT, VHEET and 15 MV IMXT. *Phys Med Biol* 2002, **47**(13), 2247–2261.
134. Lomax AJ, Boehringer T, Coray A, Egger E, Goitein G, Grossmann M, *et al*. Intensity modulated proton therapy: a clinical example. *Med Phys* 2001, **28**(3), 317–324.
135. Lomax AJ, Goitein M, Adams J. Intensity modulation in radiotherapy: photons versus protons in the paranasal sinus. *Radiother Oncol* 2003, **66**(1), 11–18.
136. Sisterson J. In: *Proton therapy co-opeartive oncology group newsletter*. Boston, Massachusetts General Hospital, 2001.
137. Bowyer J, Natha S, Marsh I, Foy P. Visual complications of proton beam therapy for clival chordoma. *Eye* 2003, **17**(3), 318–323.
138. Santoni R, Liebsch N, Finkelstein DM, Hug E, Hanssens P, Goitein M, *et al*. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. *Int J Radiat Oncol Biol Phys* 1998, **41**(1), 59–68.
139. Amols HI, Ling CC. EUD but not QED. *Int J Radiat Oncol Biol Phys* 2002, **52**(1), 1–2.
140. Wu Q, Mohan R, Niemierko A, Schmidt-Ullrich R. Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose. *Int J Radiat Oncol Biol Phys* 2002, **52**(1), 224–235.
141. Halperin EC. Overpriced technology in radiation oncology. *Int J Radiat Oncol Biol Phys* 2000, **48**(4), 917–918.