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Overview

Clinical and Practical Considerations for the Use of Intensity-modulated Radiotherapy and Image Guidance in Neuro-oncology

N.G. Burnet [*] [†], R. Jena [*] [†], K.E. Burton [‡], G.S.J. Tudor [*] [†] [§], J.E. Scaife [*] [†], F. Harris [‡], S.J. Jefferies [*] [‡]

[*] *University of Cambridge Department of Oncology, Cambridge Biomedical Campus, Addenbrooke's Hospital, Cambridge, UK*
[†] *Cancer Research UK VoxTox Research Group, University of Cambridge Department of Oncology, Addenbrooke's Hospital, Cambridge, UK*
[‡] *Oncology Centre, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*
[§] *Medical Physics Department, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

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Abstract

Intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy offer significant opportunities to improve outcomes for our patients, although they are not yet as widely used as they might be. IMRT allows better target coverage and lower organ at risk doses than conformal therapy. It also allows inhomogeneous dose plans to be developed, where these can provide benefit, either to dose escalate the tumour or reduce dose to adjacent or overlapping organs at risk. Image guidance adds precision and the possibility of careful reduction in planning target volume margins. The technologies can be valuable both for patients with highly malignant tumours, such as glioblastoma, and those with less malignant or benign tumours. In glioblastoma, temozolomide chemotherapy and surgical developments have improved survival, and developments in radiotherapy techniques should also be used to optimise outcome. Target volume delineation, including calculation of the planning target volume margin is critical. Clear definitions of the gross tumour and clinical target volumes are essential, following established guidelines. Normal tissue volume delineation is also essential for IMRT. The planning organ at risk volume has become a valuable tool to manipulate dose away from organs at risk to avoid toxicities. This is distinct from 'optimising volumes' used to drive the computer optimiser during planning. Hard data on central nervous system (CNS) normal tissue tolerance is surprisingly slight, reflecting the clinical imperative to avoid serious complications in neurological tissues. The effect of chemotherapy on radiotherapy tolerance in the CNS remains obscure, and more needs to be done to develop the knowledge base. IMRT provides better conformation of the high dose treatment to the shape of the target, and reduces the dose to normal tissue structures. Image guidance improves the accuracy of dose delivery, which is particularly important where steep dose gradients are present. These technologies should be regarded as the state-of-the-art for our CNS patients.

Key words: CNS; GBM; IGRT; IMRT; NTVD; PTV

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

Author for correspondence: N.G. Burnet, University of Cambridge Department of Oncology, Cambridge Biomedical Campus, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK.
E-mail address: ngb21@cam.ac.uk (N.G. Burnet).

Introduction

An overarching principle of radiation oncology is the successful delivery of a prescribed dose to a defined target, while minimising the dose to surrounding normal tissues. Dose correlates well with outcomes for both tumour response and normal tissue effects, and therefore behaves as an effective biomarker, within the limits of our current knowledge.

This concept has been appreciated since the earliest days of radiotherapy, and underpinned the change from

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orthovoltage to megavoltage treatment machines [1]. It also applies to improvements in dose distributions achieved using modern technologies, first conformal radiotherapy (CRT) and, more recently, intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). The value of these modern technologies in general, especially in reducing toxicity, is supported by an increasing evidence base [2–13]. This overview addresses the clinical and practical considerations for the use of IMRT and IGRT in the context of central nervous system (CNS) tumours. Developments in stereotactic radiosurgery are highly relevant to the CNS [14], but are not covered here.

The success of radiotherapy in ablating a tumour depends on the total dose, which is limited by the tolerance of the surrounding normal tissues. IMRT allows a reduction in the normal tissue dose by more effectively conforming the high dose volume to the shape of the target. In turn, this reduces toxicity, for a given level of tumour dose, and within the CNS, reduction of toxicity is the major consideration. However, IMRT also allows better target coverage, especially for tumours with complex, irregular shapes, ensuring delivery of the intended dose. For a few tumours (e.g. chordoma not suitable for proton beam therapy (PBT)) IMRT may allow dose escalation, with the expectation of a higher probability of tumour control [15]. This is possible because of the steep dose gradients that can be produced using rotational IMRT [16–18]. IMRT has also been used to dose escalate and accelerate treatment of patients with glioblastoma (GBM) (see below) [19,20], although the value of these strategies is unproven.

All such approaches are contingent on the dose being delivered accurately, which makes IMRT less forgiving of set-up inaccuracies. Thus, the full benefits of IMRT can only be obtained with the use of accurate targeting using IGRT. The combination of IG-IMRT allows radiotherapy to be given to some patients who were previously considered impossible to treat [12,21]. In one study, 5% of patients (including some with CNS tumours) were considered untreatable without access to IG-IMRT, and all of the (few) CNS cases were considered to have benefitted substantially from integrated IG-IMRT [21].

IMRT planning is often quicker than CRT, but the contouring of multiple normal tissue structures takes longer for clinicians. IMRT is often faster to deliver than CRT [21,22]. These factors have implications for clinical workflow, which are largely advantageous.

For GBM, the addition of temozolomide chemotherapy has improved not only the median survival, but also the proportion of patients surviving long-term (over 4 years) [23], and this advantage has translated into routine clinical practice [24,25]. There is every reason to suppose that the addition of new targeted agents will further improve this [26,27]. Radiotherapy retreatment for distant intracranial relapse might also become more important [28]. Surgical improvements, especially using fluorescence-guided resection, have improved the volume of tumour being removed safely, the macroscopic complete resection rate [25,29] and, apparently, survival [25,30]. In this context of incremental improvement in other modalities, it is essential that we should expect to provide the best possible radiotherapy for all the patients who might benefit.

IMRT implementation has been relatively slow in the UK [31] and it seems that IGRT is not being used with all IMRT cases [32]. CNS cases may not have been prioritised for IG- and IMRT. However, evidence of clinical value through improved dose plans provides an opportunity to improve outcomes for patients with all tumour types, from benign (meningioma, pituitary adenoma) to highly malignant (GBM). These technologies should now be regarded as the state-of-the-art for many of the tumours we treat [33].

General Considerations of IMRT for Central Nervous System Tumours

The principles of the application of IMRT for CNS tumours are shown in Table 1. In all sites studied, including the CNS, IMRT achieves better conformation of high dose volume to the shape of the target planning target volume (PTV), particularly for irregular and concave targets [34–37]. In one study of radiotherapy for GBM, IMRT always improved conformality, in some cases only a little, but in some by as much as 8% in the $V_{95\%}$ coverage [38]. Organs at risk also typically receive a lower dose [34,35,39,40].

The issue of more normal tissue receiving a low dose remains a clinical concern. However, the trade-off is that less normal tissue receives a high dose, and in general it appears that this is better for the patient. Moreover, there is evidence that IMRT actually reduces the integral dose (i.e. total energy deposited) compared with CRT, by up to 7–10% [35]. The use of IGRT can reduce margins, which may also lead to a reduced integral dose [41]. To reduce the integral dose still further requires techniques such as PBT.

Although the overall effect is to lower doses to critical normal tissues, careful attention must be paid to where the lower doses fall, and there have been unexpected consequences from the low dose 'bath'. For example, patients in the IMRT arm of the PARSPORT trial experienced more fatigue, thought to be due, at least in part, to dose received by the brainstem and cerebellum [11,42]. This also emphasises the need for careful evaluation of newer techniques.

Table 1
Situations in which intensity-modulated radiotherapy (IMRT) can be advantageous

To achieve target dose homogeneity
Large tumours
Tumours with complex shape
Tumours around which body contour changes rapidly
To avoid field junctions
To achieve target dose inhomogeneity
Graduated dose plan, replacing two phase treatment
Simultaneous integrated boost (for dose escalation)
For stereotactic radiosurgery (on a standard linac)
Conformal avoidance
To avoid critical organs at risk
For retreatment
Steep dose gradients
For dose escalation close to dose-limiting organs at risk

Hard evidence of the value of IMRT is typically based on data from tumour sites that are both more common and have toxicities that are easier to quantify than those in the CNS, such as the breast and prostate. This type of data provides proof-of-principle that better dose plans translate into better outcomes, as noted above, and it should encourage the use of IMRT, and complimentary image guidance, to minimise dose to normal tissue structures wherever possible. Formal clinical trials of dose sparing of every structure would be unwarranted [43].

The Value of IMRT for Central Nervous System Tumours

The better conformation of dose to the target means that IMRT is ideally suited to treating targets with a complex shape (Table 2). This includes meningiomas of the skull base, but also other tumours, including some gliomas (Figure 1). For gliomas close to the orbit, i.e. those situated especially in the temporal pole or anterior inferior frontal lobe, adequate coverage of the target is difficult to achieve without violating normal tissue dose constraints (Figure 2). At least as important is the concept of using IMRT to achieve improvement in target dose homogeneity. This can be challenging for larger tumours, such as gliomas, where the patient contour changes in all three dimensions (Figures 1–3).

The capability to produce dose plans with variable dose, developed using the computer optimiser according to the specific planning requirements, allows for graduated dose plans and simultaneous integrated boosts (Figures 3 and 4).

Dose escalation has been made possible by IMRT. This is applicable to relatively few tumour types and locations within the CNS because of the dose limitations imposed by normal tissues, but meningioma (Figure 5) and chordoma (Figure 6) provide examples. Dose escalation for grade II and III meningioma is being tested in clinical trials [37] and IMRT will help to minimise toxicities. For chordoma, where the dose required to control 50% of tumours (TD_{50}) is 65 Gy [44], dose escalation is needed if cure is to be attempted. For chordoma patients who are not suitable for treatment abroad with PBT, IG-IMRT offers a possible solution for modest dose escalation, for example to 70 Gy (Figure 6) [12,15,21].

Table 2
Tumours that may benefit from intensity-modulated radiotherapy (IMRT)

Definitely treat with IMRT
Skull base meningioma
Optic nerve meningioma
Glomus tumour
Temporal lobe glioma
Chordoma with metal (or otherwise not suitable for protons)
Graduated dose (replacing two phase) plans
Simultaneous (synchronous) integrated boost (e.g. glioma)
Other tumours with complex shapes
Retreatments
Prefer to treat with IMRT
Medulloblastoma – craniospinal axis and posterior fossa boost phases
Ependymoma
Pituitary adenoma and craniopharyngioma (in adults)

Dose Escalation for Glioblastoma

Dose escalation has been tested in small single institution phase I/II studies. Cohort-based dose escalation to 66–81 Gy using IMRT with concurrent (and adjuvant) temozolomide chemotherapy was studied in 38 patients [20]. Significant neurotoxicity occurred with doses of 78 Gy or more, but not in those patients receiving 75 Gy or less. This is a rather higher than standard dose, as discussed below. Overall survival was 20.1 months, with long-term survival at 4 and 5 years similar to conventional treatment [23], which the authors felt was promising. The study also suggested that methionine positron emission tomography (PET) was useful in defining areas at high risk of recurrence, and might have application for tissue volume delineation.

A study of 24 patients with GBM delivered hypofractionated IMRT with (conventional concurrent and adjuvant) temozolomide [19]. Graduated doses were delivered, such that the surgical cavity and T1 abnormality plus a small (5 mm) margin received 60 Gy in 10 fractions, whereas a larger volume (T2 abnormality plus 5 mm) received 30 Gy (in 10 fractions). Median survival was 16.6 months (cf. 14.6 months [45]). Although no late neurological toxicities greater than grade 2 were observed, 22 of 24 had to re-start steroids. Six patients had a reoperation (at a median of 10.3 months) and in two the pathological specimen showed 100% necrosis. The authors concluded that the treatment was safe and the outcomes comparable with standard practice.

Clearly, schedules such as these are interesting as potential developments. However, they can only be regarded as experimental and would require full phase III evaluation before changing practice.

Efforts to achieve dose escalation without excess toxicity have included the use of ion beam radiotherapy. Early efforts to use proton boost dose escalation were not successful [46]. In the current Cleopatra study in Heidelberg [47], patients will receive temozolomide chemoradiotherapy up to a dose of 50 Gy. The standard arm then uses a proton (PBT) boost of 10 Gy equivalent (Gy E) in five fractions, whereas the experimental arm delivers an additional 18 Gy E in six fractions using carbon ions. The temozolomide will be given continuously during the boost in both arms. The study aims to capitalise on the higher relative biological effectiveness of the carbon ions in the Bragg peak, together with the virtually absent exit dose beyond.

The study excludes patients if they have had complete tumour resection, so the timing of the postoperative scan

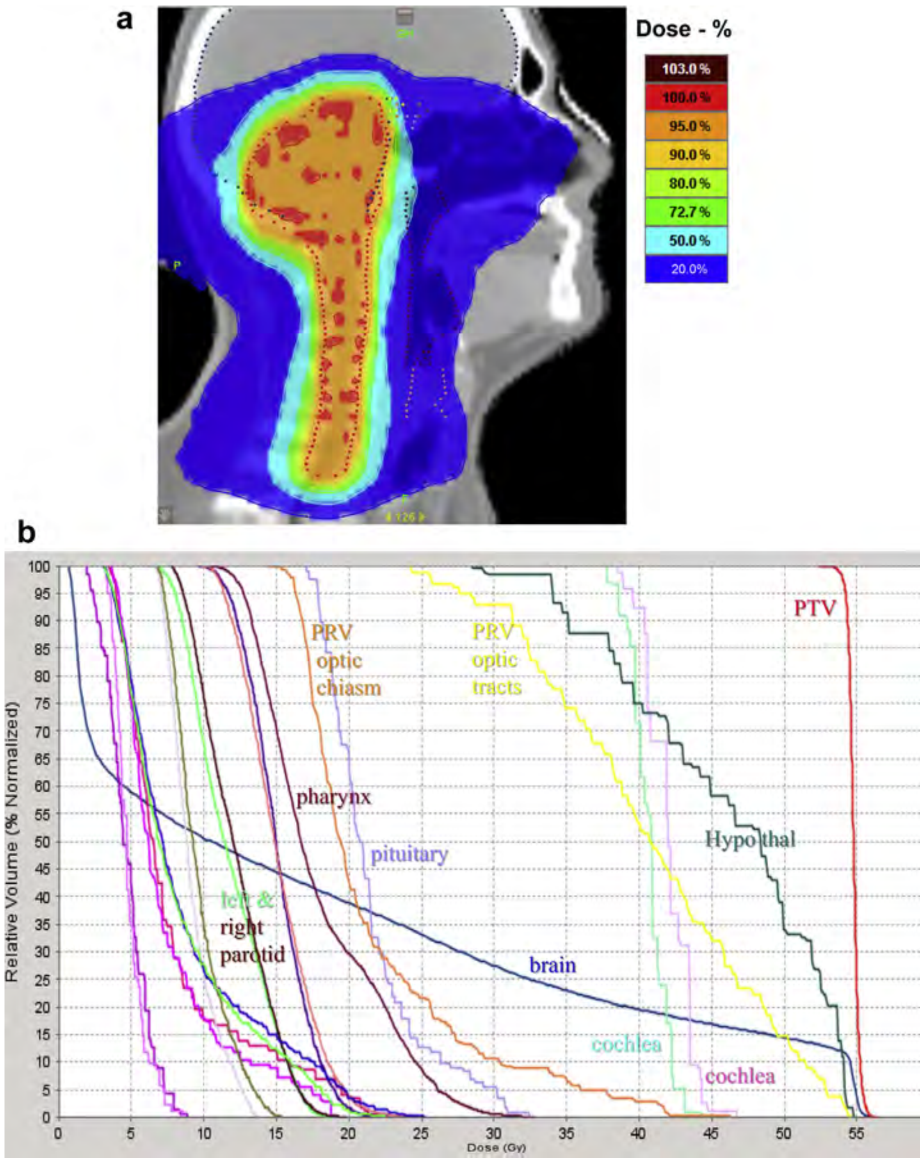

Fig 1. Para-sagittal dose distribution (a) and dose–volume histogram (b) for a very extensive low grade glioma centred on the upper cervical cord, extending up into the brain stem and down through the whole of the cervical cord. Dose 55 Gy in 33 fractions. Mean parotid gland doses were 11.5 and 12 Gy. Contours shown: red – planning target volume (PTV); brain – mid blue; pharynx – purple; larynx – pink; contours of the optic chiasm, optic tracts and hypothalamus can just be seen anterior to the PTV superiorly.

for that decision point is critical. This is an interesting concept for patients who have residual tumour after surgery. It is the first hadron therapy randomised controlled trial in glioma being conducted in the era of modern imaging and contemporary surgical techniques. Although the treatment will be accessible to limited numbers of patients, we await the results with interest.

Reducing the Dose to Critical Structures

The use of IMRT to reduce the dose to critical structures is also a key indication. IMRT allows the planner to specify dose limits for organs at risk, in effect choosing where dose is ‘allowed’. IMRT is particularly helpful when the PTV overlaps a critical planning organ at risk volume (PRV) (see below), requiring a different dose in the overlap region, because the computer optimiser can be used to provide a solution that is almost impossible to achieve using CRT. This is a tremendously powerful technique for reducing toxicity in many tumour types (Figures 1–3 and 5–7). The use of multi-criteria optimisation, once available in routine practice, will refine the results of organ at risk sparing by allowing the user to explore the Pareto–optimum boundary [48].

By sparing high dose to healthy normal brain and with a reduced dose to other organs at risk, IMRT may also facilitate hypofractionated regimens, the use of chemotherapy [36], or both.

Craniospinal irradiation merits special consideration (Figure 7). IMRT leads to a reduction of dose to organs

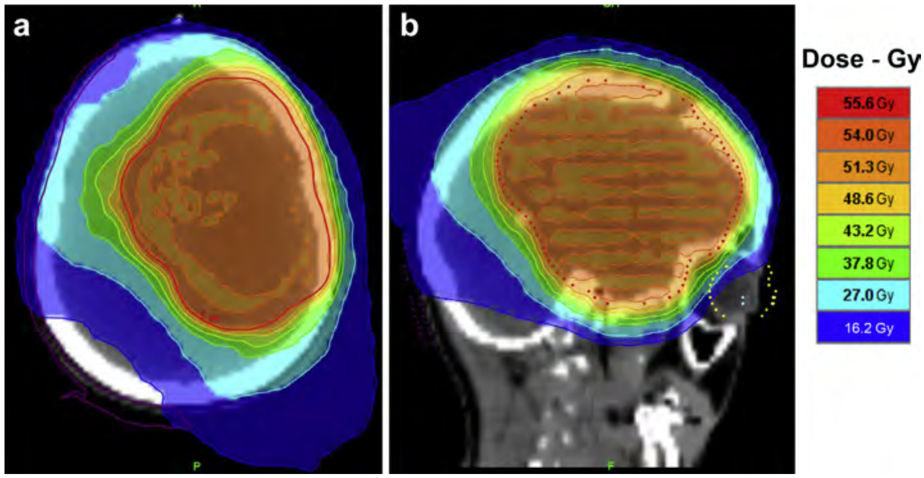

Fig 2. Axial (a) and para-sagittal (b) planes showing a treatment plan for a grade II glioma with a focus of grade III disease, to deliver 54 Gy in 30 fractions. Excellent homogeneity is seen, including above and behind the orbit. The orbital contents are substantially spared; the lacrimal gland mean dose was 24 Gy. The TomoTherapy 'thread effect' can be seen in the 100% isodose in (b). Contours shown: red – planning target volume (PTV); yellow – globe of the eye; light blue – lens.

at risk [39,40], while also ensuring better dose homogeneity. With TomoTherapy, junctions are completely avoided, thus completely eliminating one potential source of error.

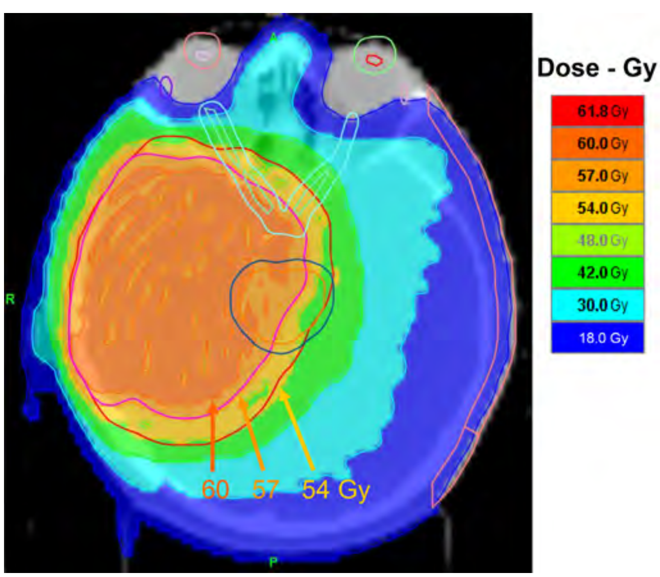

Fig 3. Axial plane showing treatment plan for a glioblastoma to deliver 54 and 60 Gy in 30 fractions, using a graduated dose plan. Homogeneity is excellent. The optic pathway and brain stem, both with surrounding planning organ at risk volumes (PRVs), lie within the 60 Gy planning target volume (PTV), which has not been modified to reduce dose to these structures. See text for further discussion. Dose–volume histogram (DVH) analysis shows that no 'hot spots' are found within these structures. Contours shown: red – 54 Gy PTV; pink – 60 Gy PTV; brown and mid blue – brain stem and its PRV; pale blue – optic pathway and its PRV; light pink and purple – lacrimal glands; the orbit and lenses are shown; the scalp on the contralateral side is contoured in mid-pink, to help to redistribute dose away from the skin. The 60, 57 (i.e. 95% of 60) and 54 Gy isodoses are arrowed in their own colours. 54 Gy is used in the graduated dose plan as the equivalent to 50 Gy from the first phase of a 'conventional' two phase plan.

Planning Volumes and Their Use for IMRT Plan Solutions

Target Volumes and Target Volume Delineation

The definition of target volumes for IMRT planning uses the ICRU definitions and guidelines [49,50]. The gross tumour volume (GTV) is the starting point. Although this is classically defined as tumour that can be imaged, for GBM it may be more pragmatic to use a definition of imageable

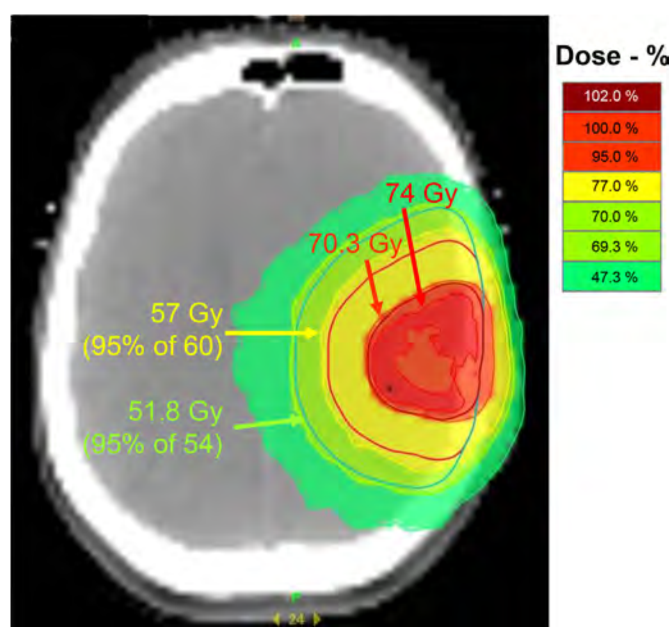

Fig 4. Axial plane plan for simultaneous integrated boost for a small, dose escalated glioblastoma. Three target volumes have been contoured, to deliver graduated doses from 54 to 60 Gy and finally 74 Gy, in 30 fractions (blue, red, dark red). The 74, 70.3 (95% of 74), 57 (95% of 60) and 51.8 Gy (95% of 54 Gy) isodoses are arrowed.

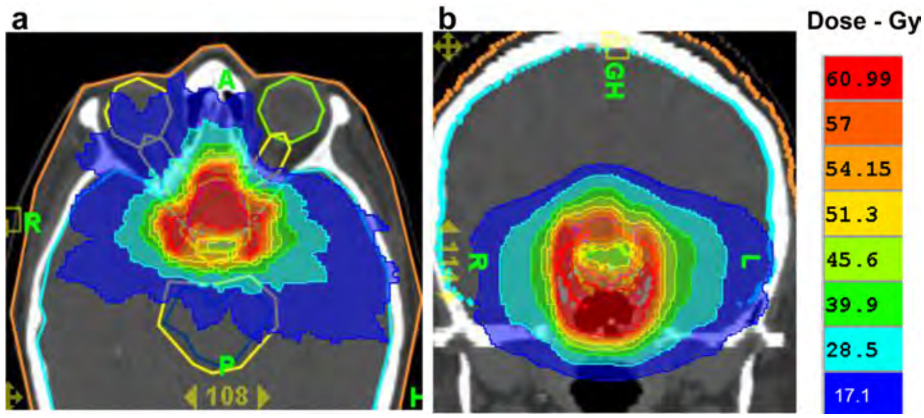

Fig 5. Axial (a) and coronal (b) planes of intensity-modulated radiotherapy (IMRT) plan designed to achieve dose escalation to 60 Gy in 30 fractions for a recurrent meningioma, with origin on the planum sphenoidale. This plan would also provide an excellent solution if a conventional dose (such as 50 Gy in 30 fractions) was intended. The optic pathway and brain stem structures have been expanded into planning organ at risk volumes.

tumour plus postoperative cavity. The postoperative volume should be used for planning, as volume changes after surgery can be substantial [33,51], particularly using a fluorescence-guided approach where gross total removal may be achieved [29]. Specific radiotherapy planning magnetic resonance imaging is necessary for GBM, as early tumour recurrence is common. For glioma and meningioma, newer imaging approaches have great potential to lead to improved target volume delineation and greater individualisation, including the potential to graduate dose according to tumour burden [52].

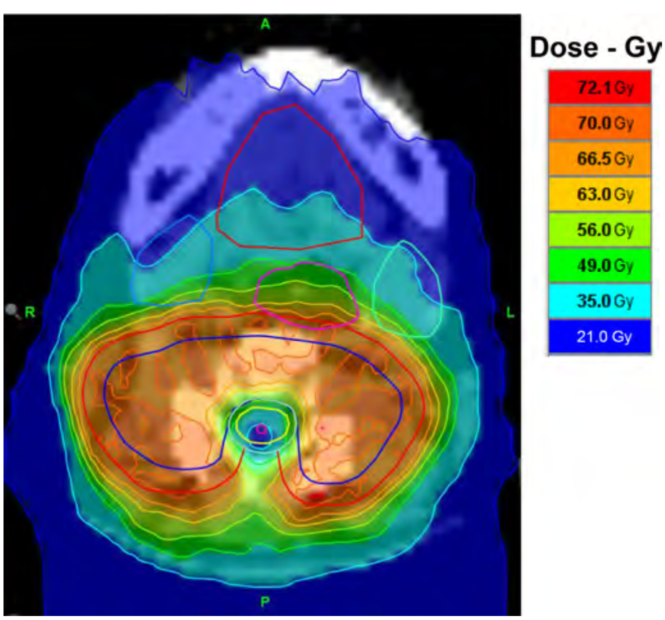

Fig 6. Axial plane plan for post-operative RT for cervical chordoma. The prescription was 70 Gy in 39 fractions. Contours on this slice are: royal blue – CTV; red (plus overlying pale blue) – PTV – PRV cord; the full PTV is not shown (for clarity); yellow – spinal cord; pink – centre of cord; pale blue – PRV cord; oral cavity – red; pharynx – pink; submandibular glands – 2 shades of blue. The CTV to PTV margin was 5 mm; cord PRV margin 2 mm.

The clinical target volume (CTV) is defined as the volume containing the demonstrable GTV and/or subclinical disease. By definition, the CTV contains tumour that cannot be seen or imaged, but which needs to be treated. A development in ICRU 83 [50] is the concept that the CTV contains subclinical disease with a certain probability. No consensus currently exists as to what probability this should be, but a figure of 90–95% seems reasonable. Unfortunately, the CTV is based on historical population data, and does not include individualisation, except at anatomical boundaries.

The fact that anatomical boundaries can alter the extent to which tumours can spread is important in considering how the CTV is 'grown', and shows that simple isotropic growing is not necessarily sufficient to generate the final CTV, but may simply create a volume that can be used as a guide for further editing. This process of editing is harder to define than an isotropic margin, embodied within a protocol, and varies between individuals. It is also time-consuming. Computer-based applications to undertake this editing would be welcome.

The PTV is a geometrical concept used for treatment planning, defined to select appropriate beam sizes and arrangements to ensure that the prescribed dose is actually delivered to the CTV [49,50,53]. It needs to encompass all sources of geometric error that actually result in a displacement between the true position of the target and the location of the treated volume. However, positional errors that have been corrected as part of online or offline IGRT will no longer be present when the treatment is delivered, and should not be included in the CTV–PTV margin.

The most common margin recipe, often referred to as the 'van Herk recipe', gives the PTV margin as $2.5\Sigma + 0.7\sigma$, where Σ and σ are the standard deviations of the systematic and random errors, respectively [53,54]. It provides for coverage of the CTV with 95% of prescription dose and 90% certainty [54]. Although this is an approximation to the full expression for margin calculation, it applies well to PTV margin calculations required for CNS radiotherapy. The formula shows that systematic errors have a much (three times) greater impact than random errors, and so their elimination is a priority.

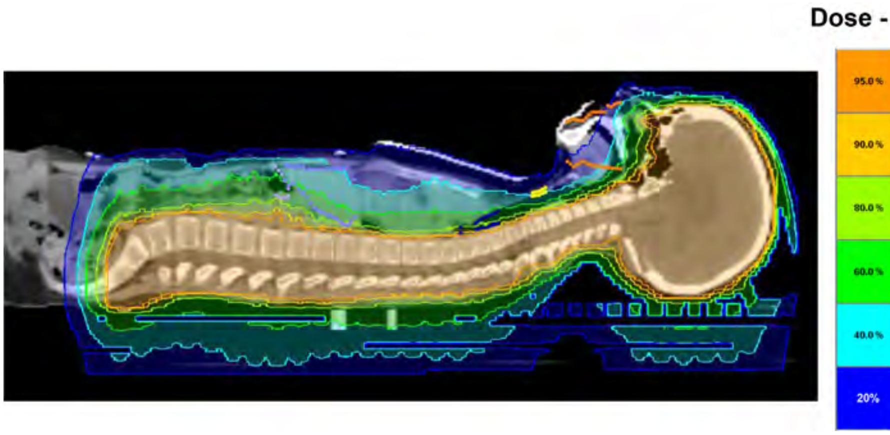

Fig 7. Craniospinal axis intensity-modulated radiotherapy (IMRT) plan sagittal plane with TomoTherapy [83]. As well as achieving excellent dose homogeneity and reduced dose to organs at risk in the trunk, compared with conventional planning [39,40], there are no field junctions with this plan. This last feature is unique to TomoTherapy because of its specific treatment delivery method.

Normal Tissue Volumes and Normal Tissue Volume Delineation (NTVD)

Multiple normal tissue structures have to be contoured for IMRT planning, to monitor and control the dose to these structures. Some, although not all, of these structures would routinely be contoured for conformal therapy in order to achieve the same control over dose, albeit using a forward planned approach rather than an inverse planned objective function computational strategy.

As well as contouring structures themselves, additional structures may be required around these. For the classic serial architecture structures of the optic pathway, brainstem and spinal cord, a PRV is recommended. The PRV is useful in two situations. The first is where dose escalation to the target is desired, where the target dose will exceed the nominal tolerance dose of the relevant structure. The second consideration is to be able to avoid hotspots within the critical normal tissue structure, which can incur the penalty of ‘double trouble’ [55], a disproportionately higher risk of damage as the result of a larger dose per fraction as well as a higher total dose from the hotspot.

For the spinal cord, contouring of the spinal canal can represent a PRV. However, typically this produces a larger PRV margin than would be needed, so for challenging clinical cases where this margin is critical, it is worth imaging with magnetic resonance imaging to define the position of the spinal cord itself as the starting point.

Typically, creating a real PRV around a parallel tissue architecture structure may be confusing or occasionally dangerous. In general, if this is carried out for tissues in CNS cases, the PRV dose volume histogram will often have the same mean dose but a shallower slope. Hypothetically this could have a different biological effect, and at the present time is not recommended (Figure 8).

The PRV margin is analogous to the expansion PTV margin. However, the region of high dose threatening the organ at risk is typically from only one direction, and mathematically this permits use of a smaller margin than the PTV [56]. When the threat is unidirectional, a margin of $1.3\Sigma + 0.5\sigma$ may be appropriate. Larger margins are needed if the threat is from more than one direction, or they can be used to increase the confidence level above 90%.

A second type of structure often required for IMRT is a ring structure, or a set of ring structures, around both the target and critical normal tissues. These structures can be used to drive the optimiser appropriately. Different treatment planning systems function slightly differently and the approach to ring structures may be different between them, much like linguistic variation in dialects. Such ring structures may appear similar to PRVs, but are, in fact, quite distinct both in size and function. These structures are better called ‘optimising’ volumes or structures.

ICRU Report 83

ICRU Report 83 is specifically dedicated to IMRT, and contains several useful recommendations. The report emphasises the need for very clear nomenclature for different targets, both GTV and CTV. We would strongly endorse this, and it will be a more important consideration as computerised methods for data mining develop.

ICRU 83 mentions the potential use of some additional parameters relating to dose. Of these, the equivalent uniform dose [57,58] has proven clinical value [59] and can now be reported in a number of treatment planning systems. It reduces an inhomogeneous dose distribution to an equivalent homogeneous (uniform) dose, allowing description by a single dose parameter, which can be a useful comparator.

A key concept for IMRT presented in ICRU 83 relates to overlap between target (PTV) and normal tissue structures (organs at risk). Where such organs at risk are potentially dose-limiting, it is important not to edit the PTV, but rather to create a structure of ‘PTV–PRV’ (Figure 6). This can then be used by the optimiser, with the help of the human planner, to develop the best possible solution for coverage of the PTV without violating the constraints set for the PRV. It renders plan evaluation more straightforward as the DVH

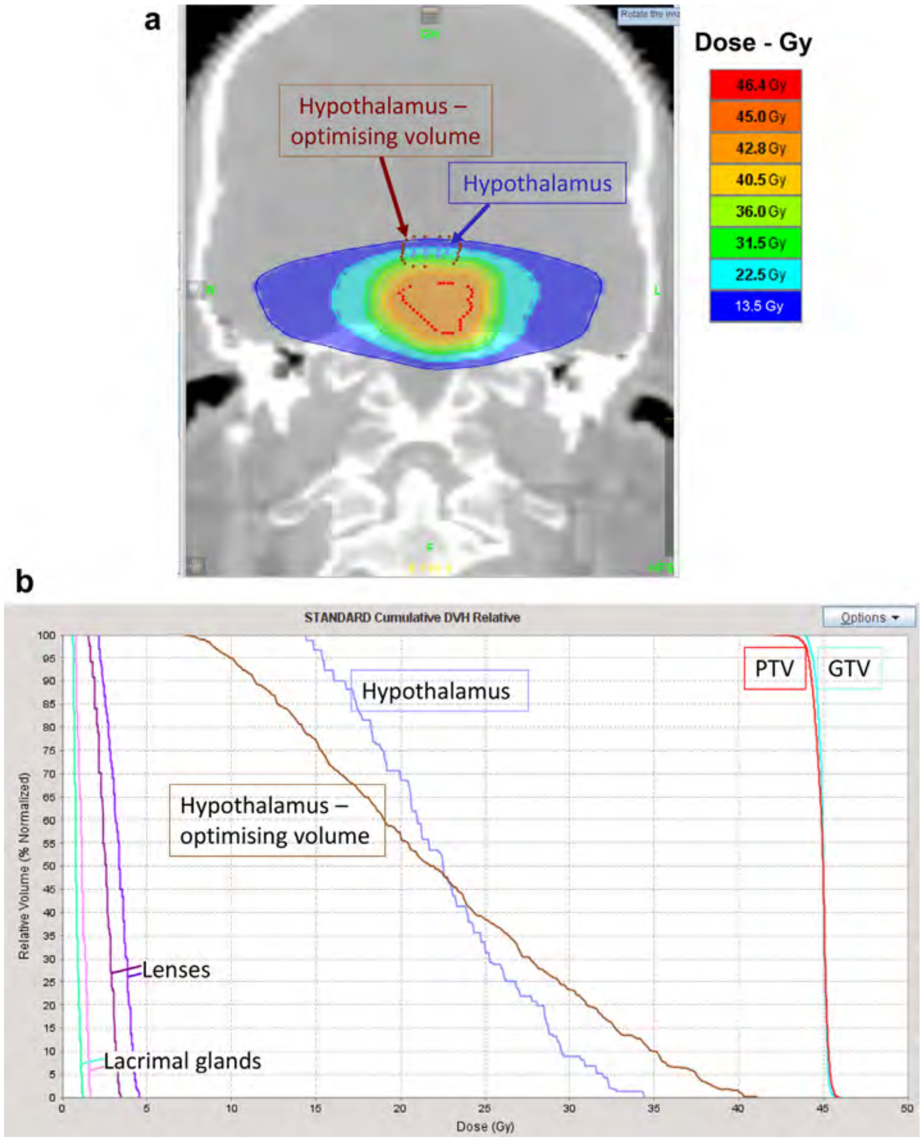

Fig 8. Coronal section of a plan (a) to treat a pituitary adenoma to 45 Gy in 25 fractions. The 95% isodose is the highest seen in this plane. The hypothalamus (blue-purple) has been contoured and then expanded into an 'optimising volume', *not* a planning organ at risk volume (PRV). It is important to distinguish the two types of expanded volume, and a PRV would not be useful for a small parallel structure such as this. If this expanded volume were to be regarded as a PRV, then the biological effects might be completely misinterpreted, as shown in (b), as there may be *major* biological differences between the two dose–volume histograms (DVHs).

for the target volume 'PTV–PRV' should have the familiar 'square' shape, allowing confirmation of coverage at least in that part of the target. An essential component of planning is the determination of a clear set of priorities.

Normal Tissue Tolerance

In the CNS, normal tissue tolerance is particularly pertinent as critical structures such as the optic nerves, chiasm, retina and brainstem are often in close proximity to the target.

When assessing risk, the overall disease prognosis is important: an acceptable risk depends on whether the tumour is benign and the patient has a near normal life expectancy (such as pituitary adenoma) or is highly malignant with a demonstrated dose response and a high probability of fatality, such as GBM. As survival from GBM increases, after chemotherapy and surgical developments, the same risk may become less acceptable. The results of the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) trials [60,61] looking at radio- and chemotherapy in anaplastic (grade III) oligodendroglioma patients have shown a marked increase in survival for those with 1p19q chromosomal codeletion. As further biomarkers become available, and those in use acquire increasing clinical relevance [62], it may be that dose constraints for radiotherapy have to be tailored to tumour subtype.

The excellent QUANTEC report [63–67] suggests that Emami's original estimate for fractionated partial brain

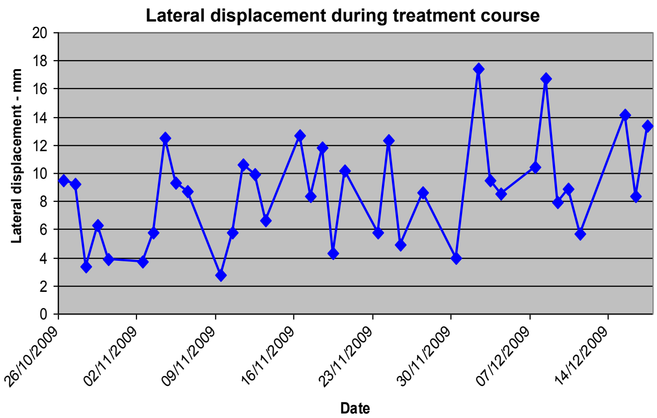

Fig 9. Plot of daily positional correction movements required in the lateral dimension in a patient with a spinal chordoma at T12. The target volume was wrapped round the spinal cord and a dose of 70 Gy in 39 fractions was given [12]. The mean displacement was 8.4 mm; although this would have been largely corrected by an offline approach, there was drift during the course. In addition there was substantial daily set-up discrepancies, evidenced by the jagged nature of the graph, which could only be corrected by daily online imaging.

radiotherapy (5% risk at 5 years for one-third brain, 60 Gy) is overly conservative [68]. More recent data suggest that that the 5% risk at 5 years for partial brain radiotherapy, using 2 Gy fractionation, is 72 Gy (range 60–84) [63]. The authors note that in some scenarios an incidence of 1–5% radiation necrosis at 5 years would be unacceptably high. A more realistic estimate for standard fractionation seems to be a 5% and 10% risk of symptomatic radiation necrosis at a Biologically Equivalent Dose (BED) of 120 Gy (range 100–140 Gy) and 150 Gy (range 140–170 Gy), respectively [corresponding to a dose of 72 Gy (range 60–84 Gy) and 90 Gy (range 84–102 Gy) in 2 Gy fractions]. The brain is especially sensitive to fraction sizes >2 Gy and, surprisingly, twice daily radiotherapy. Interestingly, the report uses and recommends an estimate of the alpha:beta ratio for normal brain of 2.9 Gy [63,69], rather than the more traditional 2.0 Gy figure.

For the brainstem, the whole of the brainstem can receive 54 Gy with minimal risk of long-term neurotoxicity [64]. Smaller volumes (1–10 ml) can receive 59 Gy with fractions ≤2 Gy with minimal risk of toxicity. This risk to the brainstem elevates markedly at doses >64 Gy.

The risk of optic nerve and optic chiasm injury was also probably overestimated by the Emami data [65]. The QUANTEC estimate is of negligible risk at 50 Gy. For doses less than 55 Gy in fractions of less than 2 Gy, the incidence of radiation injury is very low. The risk between 55 and 60 Gy is said to be 3–7% at 5 years, with most cases occurring at the higher end of the dose range (i.e. 59 Gy) and the risk rises markedly for doses over 60 Gy.

An important consideration today is whether the addition of chemotherapy such as temozolomide leads to a change in tolerance of the normal brain, brain stem and optic pathway. It is clear that some drugs, for example methotrexate, seriously affect the risk of CNS radiation damage, but the effects of other agents, including temozolomide, are unclear. The QUANTEC reviews [63,65] acknowledge that there are insufficient data on chemotherapy and newer targeted biological agents, so that both radiation necrosis and cognitive function outcomes need to be systematically evaluated.

At the current time there are only two case reports of GBM patients who developed optic neuropathy after concomitant chemoradiotherapy. One was treated with temozolomide and bevacizumab [70]. In this case there was damage of the optic pathway as a secondary consequence of tumour growth and the relationship to the chemoradiation remains doubtful. In the other [71], a damaging effect of temozolomide on the optic nerves/chiasm is conceivable, although the effect may have been strengthened by concurrent use of hypericin (from self-medicated St. John's wort). It would seem that limiting the optic pathway to 55 Gy in ≤2 Gy fractions would confer negligible risk to patients receiving chemoradiation for GBM. In some GBM cases it may be reasonable to limit the optic pathway to this dose, whereas in other GBM cases, such as where the CTV lies close to the optic pathway, a full 60 Gy dose may be more appropriate, accompanied by counselling on the attendant risk.

Image Guidance for IMRT for Central Nervous System Tumours

Whatever form of IGRT is used, effective immobilisation remains essential, whether with a shell or relocatable frame system [72–74]. IGRT can be used for two complimentary purposes to enhance outcome. First, it can be used to increase the precision of treatment delivery; second it can be used to reduce the PTV margin, with consequent reduction of dose to tissues surrounding the target. In the prostate, cohort studies have shown that use of IGRT can lead to an improvement in biochemical tumour control in high-risk patients, with reduced urinary toxicity [75]. However, caution is also required. In a seminal paper on IGRT, Engels *et al.* [76] showed a worse biochemical failure rate using IGRT, in effect as a result of such over-reduction of the PTV margin. The same considerations apply to CNS tumours. Image guidance is all the more important where steep dose gradients are present (Figure 6).

IGRT allows correction of both systematic (treatment preparation) and random (treatment delivery) errors [53,73], so that targeting can be more accurate [73], providing greater security of target coverage and reducing dose to surrounding normal tissues [8,77].

Online IGRT refers to the process by which the error (discrepancy) in the current placement of the patient is corrected immediately, before treatment commences (Figure 9). Efficient integration of the IGRT system with the linac is essential for efficient workflow [21]. In principle, it is possible to fully correct all observed translational errors, both systematic and random. It therefore has the power to eliminate set-up error in its traditional form, albeit partially replacing it with smaller errors inherent in the IGRT process, such as matching error, couch position error and intra-fractional movement.

Offline IGRT uses the images obtained from usually the first three or five treatment fractions, to inform the position of future fractions. This results in a considerable reduction in the systematic component of set-up error, but has no impact on the random component. It is, however, faster, because imaging, image matching and positional correction are not carried out on subsequent fractions.

Optimisation of imaging protocols is essential in order to provide access to IGRT for as many patients as possible. This includes the frequency of imaging, the quality of imaging, the specific purpose for which it is required and the time taken to image and correct the patient's position [21,78].

Although much of the set-up error can be eliminated from the CTV–PTV margin by daily online IGRT, it is replaced to some extent by uncertainty in the IGRT process itself, such as uncertainty in the registration of the image guidance localisation images with the planning images. Furthermore, as the traditionally dominant components of set-up error are reduced in magnitude, the remaining errors, although small, become more important to consider [79].

Rotational errors should be considered, as they may not be correctable by the form of IGRT chosen. The shape of the CTV becomes important in determining the impact of such rotational errors: a purely spherical target, as approximated in some stereotactic radiosurgery treatments, will exhibit no sensitivity to a rotational error, provided the centre of mass is correctly positioned. Conversely, a highly irregular target, such as a skull base meningioma, will need the impact of rotational variation to be accounted for properly, which may require a larger PTV margin.

In practice, the direct visualisation of the target is almost always not possible using currently available IGRT, and the skull is typically used as a surrogate. Although motion of intracranial targets with respect to the skull is non-zero, it is small, at less than 1 mm [80–82]. It should be included in the calculation of the PTV margin.

Conclusions

IMRT provides better conformation of the high dose treatment to the shape of the target, and reduces dose to normal tissue structures. Image guidance improves the accuracy of dose delivery, which is all the more important where steep dose gradients are present. Thus, the combined technologies of image guidance and IMRT provide the opportunity to enhance the outcomes for our CNS patients in a number of ways. Analysis of the results of formal IMRT studies, in terms of survival, patterns of failure and neurocognitive function, will help shape our understanding of how to refine the future use of IMRT and IGRT in our patients.

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