Clinical Oncology 26 (2014) 395–406

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

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*

Received 25 March 2014; accepted 4 April 2014

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.

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

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).

0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2014.04.024

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