Clinical Oncology xxx (2014) 1–13

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Imaging and Target Volume Delineation in Glioma

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Received 2 April 2014; accepted 11 April 2014

Abstract

Here we review current practices in target volume delineation for radical radiotherapy planning for gliomas. Current radiotherapy planning margins for glioma are informed by historic data of recurrence patterns using radiological imaging or post-mortem studies. Radiotherapy planning for World Health Organization grade II–IV gliomas currently relies predominantly on T1-weighted contrast-enhanced magnetic resonance imaging (MRI) and T2/fluid-attenuated inversion recovery sequences to identify the gross tumour volume (GTV). Isotropic margins are added empirically for each tumour type, usually without any patient-specific individualisation. We discuss novel imaging techniques that have the potential to influence radiotherapy planning, by improving definition of the tumour extent and its routes of invasion, thus modifying the GTV and allowing anisotropic expansion to a clinical target volume better reflecting areas at risk of recurrence. Identifying the relationships of tumour boundaries to important white matter pathways and eloquent areas of cerebral cortex could lead to reduced normal tissue complications. Novel magnetic resonance approaches to identify tumour extent and invasion include: (i) diffusion-weighted magnetic resonance metrics; (ii) diffusion tensor imaging; and (iii) positron emission tomography, using radiolabelled amino acids methyl-11C-L-methionine and 18F-fluoroethyltyrosine. Novel imaging techniques may also have a role together with clinical characteristics and molecular genetic markers in predicting response to therapy. Most significant among these techniques is dynamic contrast-enhanced MRI, which uses dynamic acquisition of images after injection of intravenous contrast. A number of studies have identified changes in diffusion and microvascular characteristics occurring during the early stages of radiotherapy as powerful predictive biomarkers of outcome.

Key words: Amino acid PET; glioma; imaging biomarkers; molecular resonance imaging; radiotherapy planning; target volume delineation

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

High-grade [World Health Organization (WHO) grade III and IV] gliomas comprise most malignant primary central nervous system tumours in adults; most are glioblastoma (GBM, WHO grade IV astrocytoma). Low-grade gliomas are much less common in adults and most are WHO grade II gliomas. In 2010, the age-adjusted incidence of primary central nervous system and intracranial tumours was 12 per 100 000 population in England [1]. By tumour type, over the period 2006–2010 in England, 34% were astrocytomas (95% of these high grade, 80% GBM), 3% oligodendrogliomas, 2% ependymomas and 6% other (unspecified) gliomas [1]. This overview focuses on WHO grade II–IV astrocytic, oligodendroglial and oligoastrocytic tumours. It does not cover WHO grade I gliomas, which are rare in adults, ependymomas and other rare gliomas.

Radiotherapy has a major role in the management of WHO grade II–IV gliomas. The current standard of care for newly diagnosed GBM in patients of good performance status and aged up to 70 years is maximal safe surgical debulking, followed by adjuvant radiotherapy to a dose of 60 Gy in 30 fractions, with concurrent and adjuvant temozolomide chemotherapy [2,3]. For WHO grade III gliomas, the standard of care is maximal safe surgical debulking and radiotherapy, which in the case of tumours with 1p and 19q chromosomal deletion is supplemented with procarbazine,

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2014.04.026

Please cite this article in press as: Whitfield GA, et al., Imaging and Target Volume Delineation in Glioma, Clinical Oncology (2014), http://dx.doi.org/10.1016/j.clon.2014.04.026

lomustine and vincristine (PCV) chemotherapy either before or after the radiotherapy [4,5]. In recent and ongoing trials in WHO grade III glioma, the radiotherapy dose has usually been 59.4 Gy in 33 fractions [4–6]. For WHO grade II gliomas, when radiotherapy is given, doses of 50.4–54 Gy in 1.8 Gy fractions are standard, as higher doses do not improve progression-free or overall survival [7,8]. Early postoperative radiotherapy of 54 Gy in 30 fractions has a progression-free survival benefit and a benefit in seizure control compared with the same radiotherapy given on tumour progression, but not an overall survival benefit [9]. More recent trials are addressing the role of initial chemotherapy instead of radiotherapy, the role of chemoradiotherapy and the effect of 1p/19q chromosomal deletion on outcomes, but at present observation, surgery, radiotherapy and chemotherapy all have a place in the initial management of grade II gliomas, depending on the patient's age and symptoms, the histological type, evidence of 1p/19q deletion, the size and the location of the tumour [10]. Here we review current practices in target volume delineation for radical radiotherapy planning for gliomas. We discuss current magnetic resonance imaging (MRI) techniques and developments in imaging that might influence future radiotherapy for gliomas.

Current Practices in Radiotherapy Planning for Gliomas

Imaging for Radical Radiotherapy Planning

Radical radiotherapy planning should use both an MRI and planning computed tomography for tumour delineation and dosimetry. Computed tomography is acquired with the patient supine in a custom-made immobilisation shell; it typically uses 3 mm slice spacing and is acquired post-contrast. The planning MRI is acquired without the immobilisation device. For high-grade gliomas, the most helpful MRI sequence is the T1-weighted post-gadolinium (T1 gd) sequence. If there is also a low-grade component, a T2-weighted or preferably a fluid-attenuated inversion recovery (FLAIR) sequence should also be obtained. For low-grade gliomas, only the FLAIR (or T2-weighted) sequence is needed; however, a T1 contrast-enhanced scan may also be obtained to exclude new contrast enhancement indicative of high-grade transformation. The MRI may be acquired as axial slices or as a three-dimensional volumetric MRI reconstructed into axial slices. The MRI is co-registered with the planning computed tomography and both are accessible as one combined imaging data set on the radiotherapy planning software.

Target Volume Delineation for World Health Organization Grade IV Gliomas

A standard approach to target volume delineation for WHO grade IV gliomas is to define the gross tumour volume (GTV) as the surgical cavity, plus areas of enhancement on the T1 gd MRI, which represents residual macroscopic disease. The presurgical scans, early postoperative MRI and operation note may all help in interpreting the appearances. Treatment-related contrast enhancement usually does not appear for 3–4 days after surgery and therefore post-operative MRI within the first 24–48 h helps to assess the presence of residual tumour.

The clinical target volume (CTV) is obtained by applying a uniform (isotropic) expansion to the GTV, most often of 2.0–2.5 cm, to include the highest density of microscopic disease. The CTV should be carefully edited, taking into account anatomical boundaries to tumour spread, such as the skull, tentorium and falx, but bearing in mind that tumour may spread around such boundaries, e.g. via the corpus callosum to the contralateral hemisphere, or via the cerebral peduncles to the brainstem. The CTV to planning target volume (PTV) expansion depends on geometric uncertainties (particularly set-up variation), which may vary among radiotherapy departments; 5 mm is most often used.

However, there is no complete consensus on target volumes for WHO grade IV gliomas. Both the European Organisation for the Research and Treatment of Cancer (EORTC) and the US/Canadian Radiation Therapy Oncology Group (RTOG) guidelines (Table 1), developed for use in clinical trials, have been widely adopted. The EORTC method [3] is single phase. The GTV is the surgical cavity plus the T1 gd enhancing volume. The CTV is a 2.0–3.0 cm expansion of the GTV, without the intentional inclusion of peritumoural oedema. The CTV to PTV margin is typically 5 mm. The RTOG method [12] is two phase. In phase 1 the surgical cavity, T1 gd contrast enhancement and peritumoural oedema are treated with a 2.0–2.5 cm expansion to CTV. In phase 2, the surgical cavity plus T1 gd enhancing volume only with a 2 cm expansion to CTV are treated.

Current radiotherapy planning margins for high-grade glioma are informed by historic data on patterns of recurrence after radiotherapy on radiological imaging or at post-mortem, in which around 80–100% of recurrences occurred within 2 cm of the initial contrast-enhancing tumour [15–17]. As a result, whole brain radiotherapy with a boost to macroscopic disease was superseded by partial brain treatment. Although current margins may not include all microscopic disease, treating larger volumes, which limits the dose that can be given, will not necessarily increase survival for these radio-resistant tumours. Burger *et al.* [18] and Halperin *et al.* [19] identified glioma cells within the region of peritumoural oedema, but both also identified glioma cells beyond that. More recently, Farace *et al.* [20] showed that huge changes in oedema are observed between pre- and postoperative MRI, which may be a consequence of steroid treatment and changes in mass effect and does not support the deliberate inclusion of the T2 abnormality in the CTV. In the modern era of radiotherapy with temozolomide, Minniti *et al.* [21] analysed 105 patients with recurrent GBM treated to a CTV comprising enhancing tumour plus 2 cm. They also constructed theoretical plans, including peritumoural oedema with a 2 cm margin, and concluded that treating the smaller volumes (without intentional inclusion of oedema) reduced the brain volumes treated to a high dose without a significant increase in the

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