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How Histopathologic Tumor Extent and Patterns of Recurrence Data Inform the Development of Radiation Therapy Treatment Volumes in Solid Malignancies

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The ability to deliver highly conformal radiation therapy using intensity-modulated radiation therapy and particle therapy provides for new opportunities to improve patient outcomes by reducing treatment-related morbidities following radiation therapy. By reducing the volume of normal tissue exposed to radiation therapy (RT), while also allowing for the opportunity to escalate the dose of RT delivered to the tumor, use of conformal RT delivery should also provide the possibility of expanding the therapeutic index of radiotherapy. However, the ability to safely and confidently deliver conformal RT is largely dependent on our ability to clearly define the clinical target volume for radiation therapy, which requires an in-depth knowledge of histopathologic extent of different tumor types, as well as patterns of recurrence data. In this article, we provide a comprehensive review of the histopathologic and radiographic data that provide the basis for evidence-based guidelines for clinical tumor volume delineation.
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Introduction

The ability to effectively utilize radiation therapy (RT) depends critically on the availability of radiographic studies that can guide the delineation of the volumetric extent of disease. Advances in diagnostic imaging have allowed for improved delineation of the gross tumor extent, defined volumetrically as the gross tumor volume (GTV).Unfortunately, limitations still exist primarily in the inability to radiographically identify microscopic areas of disease that would not be identified with advanced imaging modalities. As a result, our knowledge of appropriate clinical tumor volume (CTV) margins has, in large, part been informed by surgical pathologic data as well as by analyzing patterns of recurrence and tumor spread. We aim to provide a comprehensive review of the current knowledge that informs modern day CTV margins for various solid malignancies.

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Central Nervous System

Malignant Tumors

Primary Malignant Brain Tumors

High-Grade Glioma. There are currently 2 methods utilized in the contouring of high-grade gliomas (HGG): a single phase vs a 2-phase scheme. For example, the EORTC promotes a single-phase scheme where the GTV encompasses the T1-enhancing tumor mass and the resection cavity with a wide 3 cm margin for the CTV. Recently published guidelines from ESTRO-ACROP recommend a single CTV composed of the resection cavity and areas of T1-enhancement with a 2 cm margin.[1] For secondary glioblastoma, they recommend the inclusion of areas of T2/FLAIR as well. In these single-phase schemes, the entire CTV receives the same dose with conventional fractionation. Others employ a 2-phase

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method, where CTV1 (T1-enhancing tumor and the resection cavity + area of T2 hyperintensity + 2 cm margin) is treated to an initial dose, followed subsequently by a boost to CTV2 (T1-enhancing tumor and resection cavity + 2 cm expansion).

Current recommendations of 2-3 cm margins on the CTV arise from patterns of failure analyses performed in the 1980s and 1990s, where autopsies of patients treated with HGG revealed that 80%-90% of recurrences were within 2 cm of the primary tumor site.[2-6] However, now some advocate smaller margins based on more recent patterns of failure analysis in the temozolomide era, whereby higher rates of recurrence occur within the highest radiation dose volume (72%-93%) despite a range of margin expansions (5 mm-3 cm) for both single-phase and 2-phase RT plans.[7-13] Furthermore, retrospective analyses suggest that margins of 5 mm-1 cm may not increase the risk of recurrence compared to a more generous conventional CTV expansion where CTV1 includes T2/FLAIR hyperintensity.[9,10,12] This is reflected in the American Brain Tumor Consortium (ABTC) recommendation of a 5 mm expansion margin on a 2-phase plan.

Another topic of controversy involves the inclusion of the T2 hyperintensity in CTV1 for 2-phase RT schemes. The basis for this practice comes from a study by Kelly et al[14] that correlated stereotactic biopsies with MRI-imaging findings in patients with low and HGG. They found that biopsies taken from the contrast-enhancing region consisted of bulk tumor, whereas those taken from T2-hyperintense regions contained individual tumor cells infiltrating and invading into normal brain parenchyma. However, infiltrating tumor cells were also found in some biopsied areas of the brain without radiographic abnormalities. Both single phase and 2-phase RT schemes appear to provide similar outcomes with low risks of failure outside of the treated volume with central and high dose volume recurrences being the most common site of failure. For a more thorough discussion of RT treatment fields for GBM, we refer the readers to the recently released ASTRO guidelines for GBM.[15,16]

Low-Grade Glioma. Contouring guidelines for low-grade gliomas (LGG) are similar to those of their high-grade counterparts, with the exception that LGG generally do not exhibit T1-contrast enhancement. Thus, the GTV should include the T1-contrast enhancing region (if present) and resection cavity and the area of T2-hyperintensity with a 1-2 cm expansion for the CTV to account for diffuse infiltration. These CTV margins are supported by patterns of failure analyses for LGG reporting nearly all RT failures occurred either within areas of radiographic abnormalities (eg, the GTV) or within the boost high dose RT fields (GTV + 0-3 cm margin).[17-21] Patterns of failure analysis in patients with LGG treated in the combined NCCTG/RTOG/ECOG trial comparing low-dose (50.4 Gy to GTV + 2 cm) and high-dose RT (50.4 Gy to CTV1 = GTV + 2 cm, with a 14.4 Gy boost to CTV2 = GTV + 1 cm) found that 92% of recurrences occurred within the RT volume.[22]

Most recent clinical trials involving RT for LGG have utilized a 2 cm margin expansion.[23,24] However, this 2 cm margin has generally been applied for 3-D conformal RT approaches that exhibit a penumbra of several millimeters, with the full prescribed dose only being achieved roughly 1.3-1.5 cm beyond the GTV. With a standard CNS planning target volume (PTV) of approximately 3 mm, the CTV component receiving full dose is actually only 1 cm beyond the GTV. Thus, for intensity-modulated RT (IMRT) and volumetric modulated arc therapy plans without a significant penumbra, a CTV expansion of only 1 cm may be appropriate for patients with LGG. This is supported by recent data from pediatric patients with LGG treated with fractionated stereotactic radiosurgery (SRS)[25] and IMRT[26] that showed nearly all failures occurred within the treatment volume for CTV expansions of 1 cm or less.

Paulino et al[26] retrospectively analyzed 39 pediatric patients with LGG treated with IMRT to 50.4 Gy with a CTV expansion of 0.5-1 cm. Failures occurred in 7 patients and were all localized within the high dose region of the IMRT field. Marcus et al[25] prospectively studied fractionated stereotactic radiotherapy with a minimal PTV expansion (no CTV, PTV = GTV + 2 mm) in 81 pediatric patients with LGG. With a mean dose of 52.2 Gy, the authors reported local progression in 6 patients, with all of the recurrences occurring within the primary tumor volume receiving the entire prescribed dose. These studies suggest that CTV margins for LGG may be safely reduced to 0.5-1 cm for pediatric patients; however, prospective studies in adults with LGG are needed to validate these findings.

Medulloblastoma. Due to the proclivity to spread throughout the CNS via dissemination into the CSF, the initial CTV for patients with medulloblastoma includes cranio-spinal irradiation (CSI: encompassing the whole brain and spinal cord down to the thecal sac, which is best identified on T2 weighted MRI). Particular attention to ensure adequate coverage of the cribriform plate is important during CSI to prevent subfrontal relapse.[27] RT is typically administered in a 2-stages, with the first stage consisting of CSI, followed by a boost to the primary tumor and any areas of gross metastatic disease.

Practice patterns differ with respect to the boost CTV to the primary tumor. Traditionally, the entire posterior fossa (PF) was boosted due to studies showing ~50%-70% of patients experience recurrence in the PF with lower doses of PF RT (less than ~50-53 Gy).[28-30] However, more recently, several retrospective studies have reported similar PF failure rates for patients receiving a boost to the primary tumor and resection bed only (involved-field boost) compared to complete PF boost,[31-33] with isolated PF recurrences being rare.

Merchant et al[34] reported results from a multi-institution prospective trial of reduced-dose CSI with involved field boost to the primary tumor in the PF for 86 patients with standard-risk medulloblastoma. The PF failure rate at 5 years was only 4.9%, comparable to that observed for similar patients treated with complete PF boost,[27,35,36] while dose to the temporal lobes, cochlea, and hypothalamus were significantly reduced. Reduced PF recurrence rates in contemporary studies are likely due to both improved RT techniques and optimized doses and incorporation of chemotherapy in the treatment of most patients. Most importantly, recently released results from a