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Review Article

The clinical target volume in lung, head-and-neck, and esophageal cancer: Lessons from pathological measurement and recurrence analysis

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ABSTRACT

Radiotherapy research has achieved remarkable progress in target volume definition. Advances in medical imaging facilitate more precise localization of the gross tumor volume, alongside a more detailed understanding of the geometric uncertainties associated with treatment delivery that has enabled robust safety margins to be customized to the specific treatment scenario at hand. By contrast, the clinical target volume, meant to encompass gross tumor, as well as, adjacent sub-clinical disease, has evolved very little. It is more often defined by clinician experience and institutional convention than on a patient-specific basis. This disparity arises from the inherent invisibility of sub-clinical disease in current medical imaging. Its incidence and expanse can only be ascertained via indirect means. This article reviews two such strategies: histopathological measurements on resection specimen and analyses of locoregional recurrences after radiotherapy.

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Introduction

Precise tumor localization is of utmost importance in the new era of high-precision radiotherapy (RT) delivered using photons or particles, and possibly even more so when adapting treatment during the course of irradiation. The creation of the target volume to be irradiated is a multi-step process. First, the radiation oncologist delineates the gross tumor volume (GTV; primary tumor and metastatic lymph nodes) visible on imaging (computed tomography, CT; magnetic resonance imaging, MRI; positron emission tomography, PET). It is known that most solid tumors exhibit microscopic tumor extension (ME) not manifest in clinical imaging. Thus the GTV is expanded by an empirically defined margin to the so-called clinical target volume (CTV), encompassing both macro- and microscopic tumor. Most treatment schedules are delivered throughout the course of several weeks. Therefore, another margin is added compensating for random and systematic setup errors occurring during treatment delivery, leading to the planning target volume that is to be irradiated (PTV).

In past years, RT-based research has focused on exact demarcation of the GTV with modern imaging techniques and on measurement-driven PTV definitions precisely compensating the setup uncertainties encountered [*e.g.* 1,2]. With these advances GTV and PTV can be tailored to individual patients. Incongruously, the CTV is still defined using non-individualized population-based empirical margins for all tumors of a given type in a given anatomical location. Moreover these margins are based on a few, mostly outdated studies, not utilizing modern pathological analysis techniques and unable to align and correlate findings with current medical imaging. This lack of knowledge may lead to excessive toxicity via overly generous margins, or to underestimation of the true extent of disease and likely recurrence. Modern RT delivery options stand to add another layer of complexity to this matter. Particle therapy, characterized by its steep dose fall-off distal to the Bragg peak, will offer less tolerance to underestimation of the target extent, while adaptive highly conformal strategies will need to consider the possibility of sub-clinical and gross disease evolving differently.

This review focuses on solid tumor types in which (adaptive) radio(chemo)therapy (using photons or particles) frequently is the only or the neoadjuvant treatment modality, and in which retrospective data on CTV have been published and can also be prospectively gathered. It covers series assessing the ME on a histopathological basis and publications on recurrence patterns. These two fields of study attempt to refine the CTV from opposing yet complementary viewpoints. The former directly probes the underlying pathology necessitating a CTV and is the best source of information for its design. The latter, more inclusive, approach can test the adequacy of CTV definition in clinical practice and also serves to evaluate its importance relative to other current concerns. The review concludes with a discussion including recommendations for future research.

Pathological measurement of microscopic tumor extension

This section describes the available literature covering measurements of ME in various solid tumors. Given its inherent invisibility in clinical imaging, ME can only be directly assessed in resection specimen. Aided by pathologists, researchers from the disciplines of surgery and radiooncology have hence performed investigations of this type in order to determine margin widths around the GTV, which encapsulate ME in a certain percentage of patients.

The general procedure of these investigations is fairly universal. Resection specimen undergo the standard histological processing yielding stained microscopic slides. Gross tumor is delineated either on these slides or on co-registered photographs of macroscopic thick slices taken after fixation. In either case delineation is usually performed without magnification. Conversely, ME is delineated under the microscope and identified as small tumor islets.

In order to be useful for RT planning, measurements on resection specimen must be translated to the *in-situ* tissue geometry. Depending on the tumor site this can represent an immense challenge, since deformations occur both upon removal of the tissue, as well as during the subsequent histological processing. A particular focus of this section will thus be to examine the way in which various groups have tried to ensure a geometric correspondence between the two states.

The following subsections discuss ME measurements around primary tumors originating in the lung, head-and-neck region, or esophagus. A summary of the spatial information contained in the reviewed literature is provided in Fig. 1. An overview of ME of nodal targets as well as other tumor entities can be found in a comprehensive review by Moghaddasi et al. [3].

Non-small cell lung cancer

There is a comparative wealth of histopathological studies concerned with non-small cell lung cancer (NSCLC) and its ME. Concentrating on the most modern research, a total of six analyses were available for this review. Most of them focus on the distribution of maximal ME, *i.e.*, the distance from the gross tumor edge to the farthest instance of ME detected in the whole specimen. Many studies investigate the influence of some property of the lesion on the extent of ME. Two of those were considered in more than one publication, namely the histological type and grade.

Kara et al. [4] analyzed 70 specimen obtained through various lung resection techniques. Their focus lay in examining tumor infiltration along the bronchial wall, in particular in the proximal direction. Fresh specimen were sectioned at predetermined distances from the gross tumor to yield transverse slices of the bronchus concerned. This allowed for quantification of the ME distance unencumbered by deformations suffered as a consequence of histological processing, albeit at a rather coarse resolution of 5 mm in most cases. Thirty-four specimen exhibited ME, with half of the observed instances directly abutting the gross tumor. Squamous cell carcinoma (SCC) had a higher likelihood than adenocarcinoma (ADC) of any ME being present, while in specimen positive for ME its extent was higher in ADC than SCC. The 86th and 93rd percentile of the inclusive ME distribution were located at 10 mm and 15 mm, respectively.

Giraud et al. [5] studied ME in 42 pneumonectomy and lobectomy specimen representing various stages of ADC and SCC. Tissue deformation was controlled by first gently inflating the specimen with the fixation agent and then selecting only those slides for analysis, which appeared well-insufflated (*i.e.* not exhibiting collapse of alveolar structures). The analysis revealed a significant difference in the extension distances for SCC and ADC, the respective mean measurements being 1.5 ± 2.4 mm and 2.7 ± 2.8 mm. The authors further report that the necessary margins required to encompass 95% of ME are 6 mm and 8 mm, respectively. These figures should be interpreted with caution, however, since this is one of the few studies reporting the ME measurements for each individual slide, not just the maximum value per patient. The quoted widths therefore apply to margins suitable to capture ME in a fraction of all histological slides. Without knowledge of how these slides are distributed among patients one cannot necessarily conclude that the suggested margins would cover all ME for said percentage of patients.