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REVIEW ARTICLE

Future Issues in Highly Conformal Radiotherapy for Head and Neck Cancer

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ABSTRACT

Improving the conformity of the radiation dose to targets in the head and neck promises reduced toxicity and, in some cases, potentially improved local-regional tumor control. Intensity-modulated radiotherapy (IMRT) is a method that allows highly conformal delivery of radiotherapy. In recent years, its use has spread rapidly in both academic and community radiation oncology facilities. The use of IMRT has raised multiple issues related to target definition, optimal treatment delivery methods, and the need to account for anatomic changes occurring during therapy. Some of these issues are reviewed in this article.

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INTRODUCTION

Since its first use in the mid 1990s, intensity-modulated radiotherapy (IMRT) has been widely applied to many types of malignancies, including squamous cell carcinoma of the head and neck. Using IMRT, high-dose areas can be conformed tightly to the targets, with steep dose fall-off immediately outside these regions.[1-8] In the head and neck, where tumors are very close to organs at risk (OARs), IMRT has the potential to ensure target coverage by the prescribed radiation dose while reducing radiation doses to OARs, thus potentially reducing treatment-related morbidity.[9-12] In a previous issue of this journal, Mendenhall et al[13] summarized current issues in IMRT of head and neck cancer. The purpose of this article is to examine future issues related to highly conformal planning for head and neck cancer.

TARGET DELINEATION

Technology has advanced such that we can treat irregularly shaped targets with highly conformal therapy. However, our knowledge of the exact extent of the tumors is still evolving. The incorporation of information obtained from computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) into delineation of primary tumors for highly conformal irradiation planning of head and neck cancer is a major area of ongoing research.

CT, MRI, and [^{18}F]Fluorodeoxyglucose-PET

At present, [^{18}F]fluorodeoxyglucose (FDG-PET) is the most common method used to obtain metabolic information about head and neck cancers. Although it is often helpful in detecting regional and distant disease, its ability to detail the local extent of gross tumor volumes (GTVs) is still investigational. Daisne et al[14] performed pretreatment CT, MRI, and FDG-PET on 29 patients with stage II to IV laryngeal and oropharyngeal cancers. Nine of these patients subsequently underwent total laryngectomy, and these specimens were compared with coregistered radiographic images. There was no difference between total CT and MR volumes, but GTVs obtained from FDG-PET were smaller than from these two methods, and surgical specimens were even smaller, indicating overestimation of GTVs with all three imaging modalities. However, when examined in detail, despite overestimating in most dimensions, all three imaging modalities actually underestimated the mucosal extent of disease, highlighting the importance of the physical examination in determining the mucosal extent of tumors for treatment planning purposes. Another study, from Emory University (Atlanta Georgia), did not have pathologic correlation, but imaged 40 patients with FDG-PET and CT.[15] In this report, the PET-GTV was smaller than the CT-GTV in 75% of patients, but larger in 18%. When the PET images were registered on the treatment plan constructed with only CT volumes, the PET-GTV was noted to be underdosed in 25% of patients.

It is possible that the difference in the results of these two studies can be attributed to different thresholds for determining PET positivity. Whereas

fixed thresholds commonly have been used, the group from the Universite Catholique de Louvain (Brussels, Belgium) has published work suggesting that the correct threshold depends on the signal-to-background ratio of each study, and typically is between 36% and 73%.[16,17] Currently, we are far from being able to delineate target volumes confidently with standard imaging modalities. Until we make progress in this area, our treatments may be precise but not necessarily accurate. We could both be underdosing gross tumor and overdosing normal tissues. No tracer can yet provide any information relevant to subclinical, microscopic tumor cells, which would help in delineating clinical target volumes requiring a moderate radiation dose to eliminate tumor residing within these targets.

Investigational PET Tracers

Although glucose metabolism measured by FDG-PET is the functional modality most often used to aid in target delineation, researchers are developing and testing new agents to image hypoxia, protein synthesis, DNA synthesis, and receptor expression. Hypoxia is a predictor for poor local control and the second-most developed area in PET imaging.[18-20] [^{18}F]misonidazole is a freely diffusible tracer that binds to intracellular molecules under oxygen concentration less than 10 mmHg such that 2 hours after injection, the tracer only remains in hypoxic viable cells. Static scans can identify areas of hypoxia, whereas dynamic scans can identify areas of poor blood flow.[21] Another compound, Cu-diacetyl-bis(N^4-methylthiosemicarbazone), is reduced in low oxygen conditions and is similarly trapped within viable hypoxic cells.[20] The correlation of uptake of these tracers and local control in head and neck cancer currently is being studied. Other types of tracers are being developed to image DNA synthesis through thymidine incorporation ([^{18}F]fluorothymidine), angiogenesis through $\alpha_v\beta_3$ receptor expression ([^{18}F]galacto-RGD), and epidermal growth factor receptor expression in the head and neck.[21-26] In addition to helping to define the tumor, some of these new PET tracers may yield additional useful information about tumor subvolumes that may not respond well to current therapies and should be targeted for intensification of treatment.

Dose Painting

In 2000, Ling et al[27] coined the terms dose painting and dose sculpting, referring to customizing radiation plans to deliver nonuniform doses to different subvolumes within tumors. Whereas dose uniformity traditionally has been favored, it is possible that a benefit may be gained from intensifying the doses in certain volumes within traditional anatomic borders. By incorporating metabolic, functional, and phenotypic biologic information into IMRT planning, we can achieve a so-called painting-by-numbers approach to delineate a boost volume of potentially more radioresistant areas of tumor, which may benefit from a higher dose. Theoretical planning studies have demonstrated this proof of principle using Cu-diacetyl-bis(N^4-methylthiosemicarbazone) and [^{18}F]misonidazole to increase the dose to hypoxic volumes within GTVs.[28,29] However, the clinical utility of these plans has not yet been examined. This issue seems to be much more complex than originally believed. For example, the hypoxic subvolumes within tumors change during the course of therapy,[30] reducing the potential utility of pretherapy planning of hypoxia-driven dose painting. It is possible that this utility is higher for imaging nearer the completion of therapy.[20] Using FDG-PET during therapy may be another method to evaluate tumor subvolumes that retain PET activity and might be less responsive to radiotherapy.[31] Whether boosting these subvolumes to a higher dose during the rest of the treatment course will overcome their perceived resistance is not yet known.

DOSE CONFORMALITY

The OARs in the head and neck include the spinal cord, brainstem, parotid glands, submandibular glands, oral cavity, and mandible. For nasopharynx cancer, the optic nerves, chiasm, and temporal lobes of the brain are also at risk. Exceeding the tolerances of these structures can lead to cord or brainstem dysfunction, xerostomia, osteoradionecrosis, blindness, or brain necrosis. Additional potential organs at risk are the swallowing structures (pharyngeal constrictors, glottic-supraglottic larynx, and esophagus).[32-34] Thus, for an IMRT plan for head and neck cancer, multiple avoidance structures as well as targets must be specified. To cover targets and avoid OARs, dose distributions ideally should be extremely conformal.

IMRT Planning

Linear-accelerator–based photon IMRT currently is the most common method to achieve high-dose conformality. Most commonly, five, seven, or nine equally spaced, nonopposing, coplanar beams are used to achieve dose distributions that cover targets while sparing OARs in close proximity. Plans using fewer beams may lose conformality of the target, whereas plans using many more beams may not achieve significant gain, although the time spent in treatment planning and delivery is increased.[35] Several groups have investigated optimizing beam arrangements to take into consideration the orientation of OARs in relation to targets, thereby allowing for intelligent design of beam angles for each patient, including noncoplanar beams.[36-40] In addition to the common dose and volume constraints currently used in the clinic for IMRT plan optimization, investigational tools include incorporation of biologic models of tumor control rates to improve the optimization process. These include the normal tissue complication probability, equivalent uniform dose, and tumor control probability models.[41,42]

Tomotherapy

Since the first patient was treated with helical tomotherapy in 2002, this technique has been increasingly used in clinical practice.[43] Whereas typical IMRT is delivered with a static patient and rotating linear-accelerator gantry, tomotherapy is delivered as a patient is moved through a rotating gantry, similar to a CT scan. Thus, instead of only a fixed number of five to nine beams used in standard IMRT, there are essentially an infinite number of beam angles and modulations possible. Several investigators have begun to compare dose distributions achieved in tomotherapy with standard five- or seven-field IMRT head and neck plans.[44-48] In general, target coverage is similar, with more uniform dose distributions and modestly improved normal tissue sparing, particularly of the parotid glands, at the expense of a higher tissue volume receiving low doses. However, it remains to be seen whether these numerical improvements in dose translate to improvements in treatment toxicity. In addition, it is possible that improved linear-accelerator–based IMRT, including the use of noncoplanar beams, may narrow the differences between the dose distributions produced by the two methods.

Proton Therapy

The vast majority of centers use photons, or high-energy x-rays, for their IMRT treatments. However, due to their inherent physical characteristics, protons are better able to concentrate dose inside targets and minimize dose to surrounding normal tissues. Most of the energy of a proton beam is deposited near the end of the beam path (the Bragg peak), the location of which is determined by the energy of the beam. Thus, the target can be included in the tissue volume receiving the high dose, whereas little is delivered before or after the beam passes through the target, and the integral dose delivered outside the targets is lower than that delivered using IMRT. This is expected to reduce the risk of secondary malignancies, which is especially important in pediatric cancer patients.[49] Using inverse planning, intensity-modulated proton therapy (IMPT) can further improve the therapeutic index of radiotherapy. Several groups, including the University of Florida (Gainesville, FL), Massachusetts General Hospital (Boston, MA), University Hospital Vienna (Vienna, Austria), and the Paul Scherrer Institute (Viligen, Switzerland), have published treatment planning comparisons of photon IMRT versus IMPT.[50-53] Using IMPT, mean doses to OARs (the parotid glands, in particular) have been reduced by as much as 50%. However, because IMPT has only been used for the last few years, long-term clinical treatment results are not yet available. The areas in the head and neck that likely could benefit from the added conformality achievable with protons are the paranasal sinuses and nasopharynx, given that they are often in close proximity to the optic nerves and chiasm, as well as brain. Retrospective reviews of three-dimensional conformal proton therapy from Massachusetts General Hospital and Loma Linda (Loma Linda, CA) suggest maintenance of local control rates with minimal toxicity, including preservation of vision in advanced sphenoid sinus cancers.[54-56] Currently, there are 25 operational proton facilities worldwide, with 10 more planned.[57] Five facilities are treating patients in the United States today. As more patients are treated with IMPT, we will be able to determine whether these dosimetric improvements lead to significant clinical gains.

Carbon Ion Therapy

In addition to protons, other particles have been used to treat head and neck cancers. Neutrons have found a niche in treatment of salivary gland tumors, after a small trial randomly assigning patients to photon or neutron radiotherapy demonstrated a survival benefit to neutron therapy.[58] Other ions, including helium, neon, and carbon, have been investigated during the last 50 years. Currently, carbon ion therapy shows the most promise. Compared with photons, carbon ions have the conformality advantage of protons, with the additional advantage of a greater relative biologic efficacy: a smaller dose of carbon ions is required to achieve the same biologic effect as a reference dose of photons. This is due to a higher linear energy transfer, which theoretically causes more irreparable DNA damage, is more effective on hypoxic cells, and is less subject to variation in radiosensitivity with the cell cycle. Currently, there are three centers worldwide that are able to treat with this modality. Two are hospital-based facilities in Japan: 1,800 patients have been treated at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, since 1994. The Hyogo Ion Beam Medical Center in Hyogo, Japan, is relatively new. In Germany, approximately 200 patients have been treated in the Gesellschaft fur Schwerionenforschung (Heavy Ion Research Center), in Darmstadt, since 1997.[59] Initial results in adenoid cystic carcinoma and locally advanced squamous cell carcinoma of the head and neck are promising and demonstrate excellent local control rates with low toxicities.[60,61] However, long-term results are not yet available.

REDUCTION OF MARGINS

In standard radiotherapy, the clinical target volume is the volume that should receive a prescribed dose of radiation based on the bulk of disease and likelihood of subclinical spread. A margin is added to the clinical target volume to create a planning target volume (PTV) to ensure complete coverage in the face of setup uncertainties (uncertainties in the position of the patient during each treatment relative to the position during the simulation CT scan, which was the basis for the treatment planning). In the head and neck, organ motion is minimal, so the goal of the PTV margin mainly is to account for daily setup variation.[62] Typically, the magnitude of the margin is 5 mm, which means that an extra 5-mm rind of normal tissue around the target receives the full dose. In a region with targets and OARs in close proximity, reducing this margin potentially can reduce treatment-related toxicity. Indeed, it has been estimated that each 1 mm of margin adds 1.3 Gy of dose to the parotid glands, which are particularly sensitive to low doses of radiation.[63] To reduce setup uncertainty, many groups have advocated daily imaging, with a position correction if the displacement from the original plan exceeds a threshold value. At the University of Michigan (Ann Arbor, MI), daily imaging and setup correction before each treatment fraction has reduced the setup error to a mean $\pm$ standard deviation of 1 ± 1 mm, enabling a reduction in PTV margins to 3 mm.

Another investigational method to reduce PTV margins is by modeling patient position through the course of radiotherapy. Multiple-instance geometry approximation is a technique that accounts for geometric uncertainties in treatment planning and dose calculation.[64] A computer-generated model of all treatment positions can be created so that one plan is derived by optimizing multiple positions concurrently. Using this method, the PTV margin theoretically could be eliminated, further improving normal tissue sparing.[65]

ANATOMIC CHANGES AND TREATMENT ADAPTATION DURING RADIOTHERAPY

Radiotherapy for head and neck cancer, whether used in the definitive or postoperative setting, typically spans 6 to 7 weeks. During this time, many anatomic changes can occur. Because dose distributions achieved using IMRT have such sharp gradients, and PTV safety margins are becoming smaller, it is especially important to understand the consequences of anatomic changes during therapy on the dose to both targets and normal tissues. In definitive cases, the primary tumor and/or nodes can shrink, whereas in postoperative cases, inflammation and edema can resolve. In addition, weight loss, a common consequence of acute treatment toxicity, can lead to muscle wasting and shifting of both normal tissue and tumor positions.

Barker et al[66] recently conducted a detailed study of such anatomic changes during radiotherapy for head and neck cancer. The primary tumors and nodes were noted to shrink at a median rate of 1.8% of the initial volume per treatment day, such that on the last day of treatment, the median overall volume loss was close to 70%.

The tumor center of mass changed as well: although the median displacement of the GTVs was small (3.3 mm), it varied widely and was 17.3 mm in one patient. The parotids moved medially during treatment such that the median displacement at the end of therapy was 3.1 mm (range, 0 to 9.9 mm), and the volume of the parotid glands decreased by a median of 28% by the end of treatment. These changes were highly correlated with patient weight loss and reflect significant changes in the position and size of both the gross tumor and OARs during therapy. Similar findings have recently been reported by additional investigators.[67-71]

Taken together, these studies indicate that the mean dose to the parotid glands increases during radiotherapy as they move medially toward high-dose regions. Given that parotid dose and resulting xerostomia have such a significant impact on quality of life, several replanning studies have been undertaken to specifically address parotid sparing. By replanning halfway through treatment, the volume of the parotids receiving 26 Gy or more was decreased by 15% to 20%.[68,70] Although objective salivary function tests and quality-of-life studies have not been performed to determine whether replanning results in clinical benefit, it seems that replanning at some point during treatment may be reasonable. However, it is unclear when and how often this should be performed. Daily replanning is not practical, considering the time and effort required to reoptimize and the repeated quality assurance required for each iteration. Because changes are very subtle from day to day, it may be more reasonable to replan once or twice during treatment. Strategies are being developed to deform treatment plans in near real time to account for differences in anatomy rather than replan the entire course of therapy.[72,73] This method closely approximates full IMRT replanning in a small fraction of the time required for full planning, and is likely to improve in the near future.

In summary, in the last 10 years, we have seen IMRT move from select academic centers to many community practices in the United States. Accurate delineation of the targets is an important area of investigation, with incorporation of biologic information to define specific areas for dose painting or deliver higher doses to subvolumes that may respond poorly to standard therapy. Target conformality is already excellent with linear-accelerator–based IMRT, but it may be improved with protons or carbon ions. In addition, given that OARs and targets are so intimately associated in the head and neck region, it is of utmost importance to minimize setup variability to reduce the amount of tissue receiving unnecessary radiation. Finally, we must determine which patients need replanning to improve tumor control or reduce toxicities, and develop an algorithm for adaptation that is practical and can be implemented easily in the clinic.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Head and neck cancers (HNCs) are clinically, pathologically, and biologically complex diseases arising in different sites of head and neck region [1]. Radiotherapy plays a key role in the management of HNCs, especially in locally advanced cases, either as definitive treatment or combined with surgery, chemotherapy, or both.Â Accelerated versus conventional radiotherapy with concomitant chemotherapy in locally advanced head and neck carcinomas: results of a phase III randomized trial. Int J Radiat Oncol Biol Phys 2008; 72:S31â€“S32. Cited Here | PubMed | CrossRef. 7 Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354:567â€“578. Cited Here | View Full Text | PubMed | CrossRef.