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Head and neck cancer

Target delineation in stereotactic body radiation therapy for recurrent head and neck cancer: A retrospective analysis of the impact of margins and automated PET-CT segmentation

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ABSTRACT

Background: Few guidelines exist on stereotactic body radiation therapy (SBRT) treatment planning for recurrent head and neck cancer. We assessed the impact of retrospectively adding margins/automated PET volumes to the gross tumor volume (GTV) in patients with post-SBRT recurrences.

Materials and methods: We reviewed 89 patients with recurrent head and neck cancer treated with SBRT using no margin around the GTV. GTVs were recontoured with 1–5 mm margins. PET-CT planned GTVs were also recontoured by adding PET-standardized uptake value $(SUV)_{3.5}$, $SUV_{4.5}$, $SUV_{40\%\ max}$, and signal/background ratio (SBR) to the original GTV. We deformably registered recontoured GTVs to post-SBRT scans and assessed fraction of recurrence volume (RV) falling within the GTV, the "RV-GTV overlap."

Results: With non-PET-CT planning, median RV-GTV overlap increased from 11.7% to 48.2% using 5 mm margins, and median GTV size increased by 41.8 cc (156%). With PET-CT planning, RV-GTV overlap increased from 45% to 93.6% using 5 mm margins, and GTV size increased by 34.8 cc (140%). Adding $SUV_{3.5}$ and SBR increased RV-GTV overlap from 45% to 73.3% and 73.6%, with GTV size increases of 0.8 (3%) and 3.1 cc (11%), respectively.

Conclusions: Recontouring increased recurrence coverage and also GTV size. Margins up to 5 mm may reduce failures but could possibly increase toxicities. Automated PET contours may reduce near-miss failures with smaller increases in GTV size.

Squamous cell carcinoma of the head and neck often presents at an advanced stage and is associated with high locoregional recurrence rates of 15–50% [1]. Most patients with recurrences are not surgical candidates, making salvage challenging. Re-irradiation is a strategy for recurrent, previously-irradiated cancers but has been limited by the observed toxicity reported in the literature [2–6]. Nevertheless, multiple studies have demonstrated the feasibility of re-irradiation with conventional techniques, reporting locoregional control rates from 20–65% [2–6]. Hypofractionated radiotherapy with stereotactic body radiation therapy (SBRT) has also been investigated. For many patients, the short treatment course is an invaluable feature of this treatment paradigm. Studies on SBRT for previously-irradiated, recurrent squamous cell carcinoma of the head and neck (rSCCHN) have demonstrated control rates comparable to conventional radiotherapy with acceptable treatment-related toxicities [7–11].

With the sharp dose fall-off and high dose per fraction of SBRT, accurate tumor delineation and treatment planning are essential to adequately cover tumors while avoiding excessive toxicity. In primary head and neck cancer, standard practice is to contour regions of lymphatic drainage and large margins around the gross tumor volume (GTV). For conventional hyperfractionated re-irradiation of rSCCHN, many institutions have used margins of 6–10 mm around the GTV [6]. However, there is no standard regarding the use of such margins for hypofractionated techniques such as SBRT for rSCCHN. Furthermore, the addition of margins has differed greatly between institutions studying this technique: Roh – 2-3 mm [7], Siddiqui – "slight" margin [8], Unger – 2-10 mm [10], Cengiz – none [11].

At our institution, SBRT for rSCCHN was first investigated in 2003 using doses of 12–36 Gy and fraction sizes from 3 to 6 Gy. We have typically contoured and treated the GTV with no margin

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(GTV = CTV = PTV) to avoid excessive toxicity from re-irradiation using increasing doses up to 44–50 Gy in 9–10 Gy fractions during our recent Phase I dose-escalation trial [9]. However, our recent patterns-of-failure analysis found that a fair proportion of failures after SBRT occurred near GTV borders. Furthermore, we also found that patients who had received PET-CT treatment planning had a reduced frequency of these failures [12]. We now consider whether addition of margins to the GTV could have prevented some of these recurrences, and if the addition of automated PET contours to the original GTV could have prevented recurrences in patients who failed SBRT despite receiving PET-CT treatment planning.

The purpose of this study was to evaluate possible tumor delineation guidelines by retrospectively altering target volumes. Using software capable of deformable registration, we added margins to the GTV and deformed recontoured GTVs to post-SBRT scans on which recurrences had been contoured, recording changes in both GTV size and coverage of these recurrences. For patients receiving PET-CT treatment planning, we also retrospectively added automated PET contours to the original GTV. Though PET-CT planning appears to be beneficial in reducing failures after SBRT for rSCCHN [12], there is no standard contouring method using PET information. At our institution, tumors were visually contoured. However, visual contouring of PET volumes can be associated with significant variability; simply adjusting the window level can dramatically change the apparent tumor volume [13]. We therefore investigated the impact of combining automated and visual PET contours.

Materials and methods

Study design and patient selection

We retrospectively analyzed patients with previously-irradiated, unresectable rSCCHN treated with CyberKnife™ (Accuray, Inc, Sunnyvale, CA) or Trilogy™ (Varian Medical Systems, Palo Alto, CA) SBRT from 2005 to 2009. The study was approved by the IRB. Data were de-identified to meet the Health Insurance Portability and Accountability Act guidelines. All patients had received prior radiation to the head and neck for primary disease and most had undergone prior surgery and/or chemotherapy. All primary tumors were confirmed to be squamous cell carcinoma. Biopsies of recurrences were not routinely performed if there was sufficient suspicion for recurrence based on imaging, history, and/or physical examination. Other inclusion criteria included age over 18 years and Karnofsky performance status (KPS) 50 or greater. Patients were excluded if they had received chemotherapy or radiation within 1 month prior to SBRT, if SBRT was adjuvant to definitive surgical salvage, or if they had no post-treatment PET-CT scans. Eighty-nine patients met these criteria. Of these, 39 (44%) had distant or regional metastases and were treated with palliative intent whereas 50 (56%) were treated with curative salvage intent, with no significant difference in prescribed dose.

Treatment planning and delivery

Treatment plans were created by contouring GTVs on a CT scan, integrated PET-CT scan (PET-CT planning), or CT with a rigidly-registered PET from a different date (PET-aided CT). Forty-five patients (51%) were planned using PET-CT whereas 44 patients (49%) were planned using non-PET-CT (CT–25, PET-aided CT–19). In addition, 25% of non-PET-CT planned and 15% of PET-CT planned patients also received an MRI. GTV delineation was based on visual inspection of the available imaging as well as findings on physical examination. The GTV was contoured with no margin and planning was performed using PTVs defined as GTV = CTV = PTV. The majority (around 75%) of contours were generated by a single radiation oncologist, with two other radiation oncologists contouring the others based on the same GTV = PTV protocol. SBRT was delivered in five equivalent fractions. Median prescription dose was 44 Gy, with most patients (91%) receiving median doses of 40–50 Gy. Median near-max dose was 55 Gy. Patients were treated to the 80% isodose line, which was designed to cover >90% of the target volume. Planning restriction volumes were generated around all organs at risk. Dose limits were based on results of our previously-published Phase I dose-escalation study and are described in our prior studies [9]. Dose volume histograms and phantom dose measurements were used to judge the acceptability of the treatment plan.

Skull or cervical spine tracking was used to localize lesions with a 1-mm spatial accuracy [14]. Before treatment, patients were immobilized and fitted with a personalized thermoplastic face-mask secured to the headrest. Near real-time digital x-rays or cone-beam CT images were used to verify target localization. Treatments lasted 30–120 min per fraction and were typically administered every other day. Following completion of the treatment course, patients were seen at 1 month, then every 3 months thereafter. All patients received a PET-CT, CT, or MRI between 1 and 3 months after treatment as part of their follow-up.

Assessment of patterns of failure

A detailed description of our assessment of patterns of failure following SBRT for rSCCHN can be found in our prior study [12]. Pre-treatment planning scans and GTVs were deformed to post-treatment follow-up scans with VelocityAI™ (Velocity Medical Systems, Atlanta, GA), which uses a modified B-spline deformable registration algorithm with a mean error of 1–2 mm for noise-free images [15,16]. Use of deformable registration to analyze patterns of failure has also been previously described in the setting of IMRT for primary SCCHN [17]. Failure was defined as initial disease progression or complete response/partial response/stable disease followed by progression, as described in previous patterns-of-failure analyses [12,18–20]. A trained radiologist interpreted each post-treatment PET-CT and made the determination of recurrent tumor volume based on anatomic features, contrast enhancement, and changes in PET FDG-avidity. Using the determinants of recurrence as specified by the radiologist, recurrences were contoured on post-treatment PET-CTs by one investigator in conjunction with the radiation oncologist who had contoured most of the original GTVs. Recurrent tumors were categorized: In-field (>75% inside GTV), Overlap (20–75% inside GTV), Marginal (<20% inside GTV but closest edge within 1 cm of GTV), or Regional/Distant (more than 1 cm from GTV). In-field, Overlap, and Marginal failures were considered local failures.

Recontouring GTVs

Supplementary Fig. 1 contains an outline of the recontouring process. For non-PET-CT planned patients, the original GTV was recontoured by adding uniform 1, 2, 3, 4, and 5 mm margins with VelocityAI™. For PET-CT planned patients, GTVs were recontoured with 1–5 mm margins and also by adding automated PET-based contours. Theoretically, the 1–5 mm margins represent retrospective GTV–CTV margins while the PET-based contours represent a retrospective alteration of the GTV itself. The automated PET-based contours were generated in VelocityAI™ using the following parameters: standardized uptake value (SUV) threshold 3.5 ($SUV_{3.5}$), SUV threshold 4.5 ($SUV_{4.5}$), SUV threshold 40 percent maximum intensity ($SUV_{40\%\ max}$), and signal/background ratio (SBR), as described by Simon et al. [21]. SBR volumes were generated using the Daisne et al. algorithm [22], using non-FDG-avid neck musculature as the background. A 2 cm region of interest box around the original GTV was used to set limits for automated