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Anisotropic Margin Expansions in 6 Anatomic Directions for Oropharyngeal Image Guided Radiation Therapy

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Abstract

Purpose—The purpose of this work was to determine the expansions in 6 anatomic directions that produced optimal margins considering nonrigid setup errors and tissue deformation for patients receiving image-guided radiation therapy (IGRT) of the oropharynx.

Methods and Materials—For 20 patients who had received IGRT to the head and neck, we deformably registered each patient's daily images acquired with a computed tomography (CT)-on-rails system to his or her planning CT. By use of the resulting vector fields, the positions of volume elements within the clinical target volume (CTV) (target voxels) or within a 1-cm shell surrounding the CTV (normal tissue voxels) on the planning CT were identified on each daily CT. We generated a total of 15,625 margins by dilating the CTV by 1, 2, 3, 4, or 5 mm in the posterior, anterior, lateral, medial, inferior, and superior directions. The optimal margins were those that minimized the relative volume of normal tissue voxels positioned within the margin while satisfying 1 of 4 geometric target coverage criteria and 1 of 3 population criteria.

Results—Each pair of geometric target coverage and population criteria resulted in a unique, anisotropic, optimal margin. The optimal margin expansions ranged in magnitude from 1 to 5 mm depending on the anatomic direction of the expansion and on the geometric target coverage and population criteria. Typically, the expansions were largest in the medial direction, were smallest in the lateral direction, and increased with the demand of the criteria. The anisotropic margin resulting from the optimal set of expansions always included less normal tissue than did any isotropic margin that satisfied the same pair of criteria.

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Conclusions—We demonstrated the potential of anisotropic margins to reduce normal tissue exposure without compromising target coverage in IGRT to the head and neck.

Introduction

During a typical course of fractionated radiation therapy, nonrigid setup errors and variations in patient anatomy change the shape and position of the target. This may compromise the treatment plan originally optimized according to a single-simulation computed tomography (CT) study. To ensure that adequate radiation is delivered to the tumor in the presence of these sources of uncertainty, the clinical target volume (CTV) is enlarged by a geometric margin during the treatment planning process to yield the planning target volume (PTV) (1). This margin represents a fundamental tradeoff in radiation therapy. Increasing the magnitude of the margin improves dosimetric target coverage, but it also compromises normal tissue sparing, escalating the risk of complications. Thus, the determination of this margin is a balancing act that warrants careful attention.

Recommendations regarding PTV margin expansions vary. Clinical margins for radiation therapy to the head and neck are typically isotropic and 3 to 5 mm in magnitude (2-6). Several Radiation Therapy Oncology Group protocols (0615, 0522, 0920, and 0619) require 5-mm margins unless daily image-guidance protocols or institution-specific margin studies are performed, in which case the margins may be as small as 3 mm (7).

Formulas to determine the magnitude of margins based on random and systematic positional uncertainties have been derived analytically (8, 9). However, these derivations assume rigid target motion and ignore the effects of nonrigid setup error and tissue deformation caused by tumor shrinkage and weight loss. Previous estimates of uncertainties used in conjunction with these formulas do not completely describe the effect of tissue deformation. Uncertainty estimates are made by comparing the position of the anatomy depicted in the planning CT with that in images acquired throughout treatment. The latter images may be acquired after daily patient alignment by the use of external positioning markers or, in the case of image guided radiation therapy (IGRT), internal anatomy. Measurement of the alignment between these images and the planning CT is limited to the rigid positioning of either the image as a whole or of a set of anatomic landmarks independently (2-5, 10-12). These measurements may be valid regarding the center of the target, but they do not adequately describe its periphery, which is at greater risk of being underirradiated.

The margin that is optimal when the daily variations of target shape and position are considered has not been established. The purpose of this work was to determine the expansions in 6 anatomic directions that produced optimal margins in the presence of tissue deformation for IGRT of patients with oropharyngeal cancer. “Optimal” was defined as minimizing the amount of normal tissue included within the margin while maintaining an adequate level of target coverage.

Methods and Materials

Patient population

Twenty patients receiving IGRT to the head and neck between January 2007 and December 2009 were randomly selected from a group being treated according to an adaptive radiation therapy protocol at our institution. The selection criteria for that protocol included stage III, IVa, or IVb head-and-neck disease according to the American Joint Committee on Cancer criteria. More information regarding the patients on this protocol is provided by Schwartz et al (13). For image-guided alignment, these patients underwent daily imaging before each treatment fraction with a CT-on-rails system in which a single couch was shared by a SmartGantry CT scanner (GE Healthcare, Waukesha, WI) and a 2100EX linear accelerator (Varian Medical Systems, Palo Alto, CA). The C2 vertebral body was the alignment target that determined the translation necessary for isocenter correction. Patient demographics are provided in Table 1.

Deformable image registration

The CT images acquired daily were registered to the patients' original planning CT by use of an in-house, intensity-based, deformable image registration algorithm. The implementation of this algorithm was described by Wang et al (14), who optimized the demons algorithm of Thirion (15) for improved accuracy and efficiency. Wang et al (14) found this algorithm reproduced mathematically deformed head-and-neck anatomy with a mean error of 0.02 cm (standard deviation = 0.06 cm), and that more than 99% of the errors were less than 0.2 cm. This accuracy justified the use of this algorithm for our application. Each registration resulted in a vector field that related the positions of corresponding anatomy in the 2 images.

Voxel tracking

By use of the vector fields from the image registration, the positions of volume elements within the CTV (target voxels) or within a 1-cm shell surrounding the CTV (normal tissue voxels) on the planning CT were identified on each daily CT. We selected the shell surrounding the CTV as an indicator of high-dose normal tissue damage because tissues near the target will likely receive the full prescription dose. This consistent description of normal tissue facilitated a direct comparison between patients. The use of organ-specific normal tissue sparing would have introduced additional confounding factors caused by interpatient variations in anatomy, tumor size and location, and the particular treatment plan.

Tracking the positions of voxels over the course of treatment via the daily CTs, an approach similar to that of Yan et al (16), provided a method to retrospectively determine the appropriateness of a PTV margin. The proportion of target voxels and normal tissue voxels that were positioned within a margin for at least a specified proportion of treatment fractions were considered the geometric target coverage provided by that margin and the normal tissue included within that margin, respectively (Fig. 1).

Margin dilation

For each of the 20 patients, we created anisotropic and isotropic PTV margins and evaluated the corresponding geometric target coverage and inclusion of normal tissue. The margins were created in MATLAB (MathWorks, Natick, MA) by morphologic dilation. This operation used ellipsoidal structuring elements described by a set of 6 radii to expand the CTV. These radii corresponded to margin expansions in the posterior, anterior, lateral, medial, inferior, and superior anatomic directions from the tumor volume. We validated our margin expansion method with a commercial treatment planning system (Pinnacle³, Philips Medical Systems, Andover, MA). The expansions had possible values of 1, 2, 3, 4, and 5 mm. The result of the dilation was 5^6 (or 15,625) possible structuring elements producing an equivalent number of unique, 3-dimensional PTV margins. Before dilation, the structuring elements were discretized into $0.68 \text{ mm} \times 0.68 \text{ mm} \times 2.5 \text{ mm}$ voxels to match the resolution of the CTs. The geometric extent of the structuring element in any direction was dependent on the interpolation between the nearest 3 of 6 radii defining the structuring element. As a result, distinct margins were produced even when the difference in the expansion magnitude along any individual radius was less than the dimension of a single voxel.

Evaluation of margins

Our goal was to identify the set of margin expansions that produced the PTV that included the minimum amount of normal tissue while maintaining adequate geometric target coverage over the required number of patients. The PTV margins were evaluated according to 4 geometric target coverage criteria and 3 population criteria. The geometric target coverage criteria were that (1) at least 90% of target voxels were within the PTV during at least 90% of treatment fractions ($\text{Vol}_{90\% \text{ Fx}} \geq 90\%$); (2) at least 90% of target voxels were within the PTV during at least 95% of treatment fractions ($\text{Vol}_{95\% \text{ Fx}} \geq 90\%$); (3) at least 95% of target voxels were within the PTV during at least 90% of treatment fractions ($\text{Vol}_{90\% \text{ Fx}} \geq 95\%$); and (4) at least 95% of target voxels were within the PTV during at least 95% of treatment fractions ($\text{Vol}_{95\% \text{ Fx}} \geq 95\%$). The 3 population criteria required these geometric target coverage criteria to be satisfied in at least 90%, 95%, or 100% of patients. Geometric target coverage and population criteria of less than 100% were considered because of the prohibitively large risk to normal tissue from margins of the magnitude necessary to guarantee complete target coverage to the entire population.

For each patient, the volumes of normal tissue within each margin for particular proportions of treatment fractions (eg, $\text{Vol}_{90\% \text{ Fx}}$) were determined. These values were normalized to those of each patient's 5-mm isotropic margin. These normalized values were averaged over the range of treatment fraction proportions to produce normal tissue averages specific to a particular patient and margin. For each pair of geometric target coverage and population criteria, the optimal margin was that which minimized the population median of these normal tissue averages.

Results

The margin expansions that resulted in the minimum amount of included normal tissue had magnitudes of 1 to 5 mm depending on the anatomic direction of the expansion and the

criteria evaluated. Each pair of geometric target coverage and population criteria resulted in a unique, anisotropic, optimal margin. Figure 2 depicts the proportion of patients satisfying the geometric target coverage criteria when isotropic margins were used. The optimal margins included less normal tissue than any of the isotropic margins that satisfied the same criteria. Plotting the large number of anisotropic margins in a similar way is not practical, and plotting only the optimal anisotropic margins is not pertinent because they are optimized to specific criteria.

Table 2 presents the margin expansions found to be optimal for each pair of geometric target coverage and population criteria. The margin expansions tended to be largest in the medial direction and smallest in the lateral and posterior directions. For a particular geometric target coverage criterion, the set of margin expansions increased with the proportion of the population required to satisfy the criterion. Overall, the Vol_{90%} F_X 90% criterion was satisfied by the smallest margin expansions, followed by Vol_{95%} F_X 90%, Vol_{90%} F_X 95%, and Vol_{95%} F_X 95%. This pattern held for all population criteria. Although the margin expansion along any individual direction may deviate from strict adherence to these trends, the geometry of the optimal margin did not depend exclusively on that single expansion, but rather on the set of margin expansions in each direction.

Table 2 also presents the population median values of the normal tissue averages used to determine the optimal margin expansions. These values were originally normalized to those of the 5-mm isotropic margin, and they illustrate the degree of normal tissue sparing achievable with smaller, anisotropic margins. The values in Table 2 increase, reflecting a decrease in normal tissue sparing, with the magnitude of the margin expansions and the demand of the geometric and population criteria. These normal tissue values can be compared with those for the isotropic margins in Table 3.

Discussion

The PTV margin expansions play an important role in the radiation therapy treatment planning process. Large margins increase the risk of normal tissue complications, and small margins may compromise disease control. In this work, we used a voxel-tracking method to score the geometric target coverage and normal tissue included within various margins. We found that the optimal margin for each pair of geometric target coverage and population criteria was unique and anisotropic. This suggests that conventional isotropic margins are suboptimal, including excess normal tissue without providing a benefit in terms of target coverage.

Our findings that the margin expansion magnitudes were largest in the medial direction and smallest in the lateral direction agree with the observations made by Barker et al (17), suggesting that weight loss, asymmetric tumor shrinkage, and variations in the local regional positioning of anatomy (11) may have contributed to the anisotropic margin expansions.

The magnitudes of the optimal margin expansions were similar to those of margins described previously with the use of global image registration techniques (3-5, 18) but smaller than those described with the use of supposedly more accurate local image

registration techniques (10-12). Global image registration techniques have been used to estimate the margins necessary for IGRT (with daily or less frequent imaging) and non-IGRT therapies. According to Den et al (3), 2- to 3-mm margins are appropriate when daily cone-beam CT is used, whereas 5-mm margins are necessary when it is not. Wang et al (4) published similar values (3 mm and 5-6 mm with and without IGRT, respectively). Similarly, Houghton et al (5) recommended 5-mm rather than 3-mm margins when daily IGRT was not incorporated. Humphreys et al (18) found that 3-mm and 5-mm margins covered 94% and 99% of setup errors, respectively, when image guidance was performed daily for the first week and weekly thereafter. These previous studies, however, were limited to rigid positional changes of the target.

Local registration techniques rigidly register subregions of the image independently, resulting in position-specific local margins. These techniques consider nonrigid anatomic changes between subregions, but they do not describe tissue deformation within each subregion. Using these techniques, Polat et al (10), Zhang et al (11), and van Kranen et al (12) demonstrated that 5- to 10-mm margins were required in the vicinity of several bony anatomy landmarks—margins greater than those from global registration techniques and also greater than the optimal margins we observed.

Chen et al (6) compared the patterns of disease failure between 3-mm and 5-mm isotropic PTV margins in more than 200 patients. They found no statistically significant difference with respect to 2-year rates of overall survival, distant metastasis-free survival, or local-regional control, suggesting that PTV margins can safely be reduced from 5 mm to 3 mm when daily IGRT is performed. Our work also suggests the margin expansions smaller than 5 mm or even 3 mm are sufficient depending on the desired geometric target coverage and population criteria (Fig. 2).

From the anisotropic margins in Table 2, it can be observed that the margin expansions for any particular direction do not increase monotonically as the geometric target coverage and population criteria become more strict. This is allowed because the margins expansions are not independent. The efficacy of each margin is evaluated according to the set of 6 simultaneous directional expansions. An increase in the margin magnitude in 1 direction may compensate for no change in, or even a decrease in, the margin magnitude in any orthogonal direction.

The margin strategies described here and in the cited literature are applied to a population of patients and may not result in the optimal margin for a particular individual. Although systematic and random uncertainties can be estimated for a particular patient after several treatment fractions, the patient-specific optimal margin, similar to the population margins derived here, can be fully reconstructed only after the course of treatment. The characteristics unique to each patient that govern their individual optimal margin remain unknown at the time of treatment planning, and a population-optimized approach remains appropriate for margin design.

The application of population margins requires the margins to be evaluated on a patient-by-patient basis. It is possible for the population-based anisotropic margin to encroach on an

organ at risk. It may be appropriate to trim or otherwise edit an anisotropic margin just as one would edit an isotropic margin. Intersecting target volumes and avoidance structures can occur when either current clinical standard margins or the anisotropic margins described here are used, and we do not believe that anisotropic margins are inherently more sensitive to this treatment planning challenge. Ultimately, the knowledge and experience of the responsible clinicians are required to assess the application of a population-based margin to a particular patient.

Our work focused on a relatively small, relatively homogenous patient population. Imprudent extrapolation of our work to patient populations that differ in disease type, treatment strategy, or both may lead to inappropriate application of the described anisotropic margins. However, some results, such as smaller lateral and larger medial margins required, may hold. Individuals interested in investigating the application of anisotropic margins in their own clinics should conduct an assessment of margins consistent with their institutional protocols and also recognize the approximations we have made to conduct this work.

One significant approximation was that this work evaluated margins from a purely geometric perspective and did not include dosimetric considerations. This served 2 purposes. The first was to ensure that our analysis was independent of treatment planning technique and dose distribution, which vary markedly between individuals and institutions. The second was to manage the large scale and complexity of the question at hand. To fully understand the clinical implications of anisotropic margins, dosimetric effects must be compared between many anisotropic and isotropic margins. Treatment plans need to be generated according to each margin, and the resulting dose must then be recalculated on the anatomy as depicted in the daily CT to account for the effect of tissue deformation. To perform this dosimetric workflow on the large number of patient-margin combinations described in this work (>300,000 combinations) was prohibitively intensive. Thus, we limited the scope of our work to a geometric approximation of target coverage.

We acknowledge that dosimetry is a more fundamental concern than geometry. Our geometric analysis will differ from a dosimetric analysis because of the characteristics of the dose distribution near the PTV. Voxels outside the PTV contribute nothing to the geometric target coverage. However, imperfect conformality of the dose distribution to the target means that voxels outside the PTV may still receive an adequate dose. Thus, the dosimetric target coverage is more tolerant than the geometric target coverage, and the necessary dosimetric margins may be smaller than our geometric margins. However, the dosimetric target coverage and the dose to normal tissue will depend on the particular treatment techniques and beam angle arrangements used.

Evaluation of the optimal dosimetric margin is outside the scope of this work. However, our optimal geometric margins illustrate direction-dependent uncertainties regarding target geometry that may be considered as a basis for future investigation to improve radiation therapy treatment plans.

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Summary

In image guided radiation therapy to the head and neck, isotropic margins are typically added to clinical target volumes to compensate for setup errors. This work used deformable image registration to evaluate the isotropic and anisotropic margins for a group of patients with oropharyngeal cancer treated with daily computed tomography-guided radiation therapy. The margins were evaluated according to the amount of normal tissue included within the margins and according to the geometric target coverage and population criteria.

Fig. 1.

Transaxial slice of clinical target volume with target voxels color-coded according to the proportion of treatment fractions during which they were positioned within a 1-mm (*above*) and a 5-mm (*below*) isotropic margin.

Fig. 2.
Proportion of patients satisfying geometric target coverage criteria according to isotropic margins.

Table 1

Patient statistics

Patient	Age (y)	Disease site	Initial target volume (cm ³)	Disease stage [*]
1	62	Base of tongue	119	T1 N2A
2	75	Base of tongue	129	T1 N2A
3	41	Tonsil	149	T2 N2B
4	53	Tonsil	234	T2A N2A
5	56	Base of tongue	130	T3 N2C
6	57	Base of tongue	136	T2 N1
7	58	Base of tongue	287	T4 N2B
8	50	Base of tongue	168	T2 N2B
9	49	Tonsil	215	T2 N2B
10	42	Base of tongue	175	T2 N2A
11	54	Base of tongue	140	T4 N0
12	62	Tonsil	203	T4A N0
13	56	Tonsil	141	T3 N2B
14	50	Base of tongue	155	T2 N2A
15	51	Tonsil	200	T3 N2B
16	50	Base of tongue	364	T3 N2A
17	38	Tonsil	117	T1 N2B
18	68	Tonsil	109	T2 N2B
19	69	Tonsil	140	T3 N1
20	44	Base of tongue	130	T2 N2B

* No patient had metastatic disease.

Table 2

Optimal margin expansions for geometric target coverage and population criteria

Geometric target coverage criterion	Patients satisfying geometric target coverage criterion	Margin expansions (mm)						Population median of average normalized normal tissue volume (%)
		Posterior	Anterior	Lateral	Medial	Inferior	Superior	
Vol _{90%} Fx 90%	18 (90%)	3	2	1	1	2	1	36.5
	19 (95%)	1	3	1	3	3	1	39.5
	20 (100%)	1	4	1	4	3	1	45.6
Vol _{95%} Fx 90%	18 (90%)	1	1	1	3	3	3	41.2
	19 (95%)	1	2	1	4	2	2	45.6
	20 (100%)	1	3	1	5	3	2	52.5
Vol _{90%} Fx 95%	18 (90%)	2	3	1	4	2	3	52.6
	19 (95%)	1	4	1	5	3	2	56.5
	20 (100%)	2	3	1	5	4	3	62.5
Vol _{95%} Fx 95%	18 (90%)	1	3	1	4	4	4	62.5
	19 (95%)	1	5	2	5	5	2	69.8
	20 (100%)	3	5	1	5	5	2	73.0

Table 3

Relative amount of normal tissue included within isotropic margins

Isotropic margin expansion magnitude (mm)	Population median of average normalized normal tissue volume (%)
1	19.1
2	46.5
3	60.1
4	83.0
5	100.0