Intensity-Modulated Radiation Therapy for Head and Neck Cancer: Emphasis on the Selection and Delineation of the Targets

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The head and neck contain many critical, noninvolved structures in close vicinity to the targets. The tightly conformal doses produced by intensity-modulated radiation therapy (IMRT), and the lack of internal organ motion in the head and neck, provide the potential for organ sparing and improved tumor irradiation. Many studies of treatment planning for head and neck cancer have demonstrated the dosimetric superiority of IMRT over conventional techniques in these respects. The initial results of clinical studies demonstrate reduced xerostomia. They suggest an improvement in tumor control, which needs to be verified in larger studies and longer follow-up. Critical issues for successful outcome of head and neck IMRT are accurate selection of the neck lymph nodes that require adjuvant treatment, and accurate delineation on the planning computed tomography (CT) of the lymph-node bearing areas and subclinical disease adjoining the gross tumor. This review emphasizes these topics and provides some guidelines.

Head and neck cancer represent an attractive site for intensity-modulated radiation therapy (IMRT). The anatomy of the neck is complex, with many critical and radiation-sensitive organs in close proximity to the targets. Tight dose gradients around the targets, limiting the doses to the noninvolved tissue, are desirable and offer the potential for therapeutic gain. Noninvolved tissues in which sparing may offer tangible gains include the major and minor salivary glands dispersed within the oral cavity, the mandible, and the pharyngeal mucosa and musculature. In cases of nasopharyngeal and paranasal sinus cancer, critical normal tissues that may be partly spared using IMRT include the inner and middle ear, the temporomandibular joints, the temporal brain lobes, and the optic pathways.

In addition to noninvolved tissue sparing, IMRT offers a potential for improved tumor control by reducing the constraints on the tumor dose due to critical organ doses (eg, spinal cord or brain stem doses) that frequently limit tumor boost doses in conventional radiation therapy (RT). In addition, IMRT eliminates the need for posterior neck electron fields, commonly used in conventional RT, and their associated dose deficiencies. IMRT in the head and neck is more feasible than in other sites, because organ motion is practically absent. Patient setup uncertainties can be addressed by using adequate immobilization and by assessing the resulting setup variations.

A major potential pitfall of IMRT is the failure to select and delineate the targets accurately. This is especially relevant in head and neck cancer, in which a high risk of subclinical local and nodal disease exists, and adequate irradiation of the lymph nodes at risk is crucial for locoregional control and survival. For example, in standard three-field head and neck RT, the first echelon and the retropharyngeal nodes are treated routinely when the primary tumor is targeted. In contrast, these nodes will not be adequately irradiated by IMRT if they are not specified on the planning computed tomography (CT).

This review emphasizes issues in outlining potential subclinical disease near the primary tumor, the selection of neck nodal targets, and their delineation on the planning CT scan. The target selection guidelines in this review summarize a consensus reached by the authors at a panel addressing neck lymph nodal selection for head and neck cancer IMRT, held at the 43rd annual meeting of the American Society of Therapeutic Radiology and Oncology in San Francisco, November 2001.

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Patients and Methods

Patient selection

Head and neck IMRT is work intensive and lengthens treatment time. Not every patient is expected to benefit; those who would benefit most are patients with paranasal sinus cancer in which the targets are near the optic pathways, patients in whom standard RT fields encompass most of the salivary glands, and patients in whom standard techniques require a compromise in the tumor dose due to proximity of the tumor to the spinal cord or brain stem.

Imaging

The simulation contrast-enhanced CT is in most cases the only imaging modality required for the delineation of the targets. Magnetic resonance imaging (MRI) is limited by its sensitivity to artifacts, difficulty in interpretation, long examination time, and cost. A necessary adjunct to CT for tumors close to the base of the skull (ie, nasopharyngeal and paranasal sinus cancer), MRI provides better details of tumor extension and of the parapharyngeal and retropharyngeal spaces compared with CT.[1] Fluorodeoxyglucose positron emission tomography (FDG-PET) has recently been found to add significantly to the information gained from CT regarding tumor extent in lung cancer.[2] In contrast, series of head and neck cancer in which CT, MRI, and FDG-PET were obtained, and surgery was then performed to validate the primary tumor extent and lymph node involvement, reported a rather limited benefit of FDG-PET compared with CT/MRI.[3] This modality remains, for the time being, a research tool. In all cases, the findings of a careful clinical examination, including direct endoscopy under anesthesia, form the basis for assessing of the extent of the primary tumor.

ICRU Target Definitions in the Head and Neck

The gross target volumes (GTVs) consist of the primary tumor and of lymph nodes with apparent or suspected metastasis. The primary tumor GTV is defined using radiologic and clinical assessment. Lymph node GTVs include nodes with radiologic criteria of involvement: diameter >1 cm (in the case of the jugulodigastric nodes, >1.1-1.5 cm); smaller nodes with spherical rather than ellipsoidal shape; nodes containing inhomogeneities suggestive of necrotic centers; or a cluster of three or more borderline nodes.[4] The clinical target volume (CTV) surrounding the primary tumor consists of tissue perceived to contain microscopic, subclinical tumor extension. In addition to the primary tumor CTV, lymphatic CTVs consist of nodal areas that are at risk of metastatic disease but do not match the radiologic criteria of involved nodes.

Delineation of the Primary Tumor CTV

Factors used for assessing the extent of the CTV margins in each case include tumor site, size, stage, differentiation, and morphology (exophytic *vs* ulcerative, infiltrative *vs* pushing front). General suggestions are detailed as follows:

1. *Oral cavity cancer*
   - A. Floor of mouth: The CTV includes the genioglossus and geniohyoid muscles bilaterally, the sublingual and submandibular salivary glands ipsilaterally (bilaterally if midline tumor), the adjoining alveolar ridge and mandible, and the muscles at the root of the tongue.
   - B. Oral tongue: The CTV includes the intrinsic and extrinsic musculature of the tongue, the base of tongue, floor of mouth, the glossotonsillar sulcus, and the anterior tonsillar pillar.
   - C. Buccal mucosa: Due to lack of barriers to submucosal spread, the CTV extends cranially to include the buccal-gingival sulcus and infratemporal fossa, and caudally to include the buccal-gingival sulcus and submandibular salivary gland, anteriorly to behind the lip commissure and posteriorly to the retromolar trigone.
2. *Oropharyngeal cancer*
   - A. Tonsillar cancer: The CTV includes the adjacent buccal mucosa, palate, and base of tongue. In advanced cases, the mandibular bone, the ipsilateral pterygoid muscles, parapharyngeal space, and adjacent nasopharynx are included. When the posterior tonsillar pillars are involved, the CTV extends inferiorly to include the pharyngoepiglottic fold.

B. Base of tongue: The entire base of tongue, the vallecula, and generous portions of the oral tongue should be included in the CTV (at least 2-cm margins beyond the GTV). If the vallecula is involved, the suprahyoid epiglottic larynx is included.
C. Pharyngeal walls: Longitudinal mucosal spread, including skip lesions, may exist. The cranial extension of the CTV will therefore be through the nasopharynx and the caudal extension through the hypopharynx, including parapharyngeal space.
D. Soft palate cancer: The CTV includes the entire soft palate, the superior aspect of the tonsillar pillars and fossa, as well as the pterygopalatine fossa. In advanced lesions, the adjacent nasopharynx and pterygoid muscles are also included. If the pterygopalatine fossa is clinically involved, an assessment of the base of the skull using MRI is mandatory, and the CTV should encompass the foramina at the base of skull and the sphenoid sinus. In the case of minor salivary cancer (adenoid cystic carcinoma, high-grade acinic cell carcinoma), the course of the maxillary nerve to the fifth nerve ganglion in the cavernous sinus is included in the CTV, due to the risk of perineural spread. The same applies to other tumors involving the palatine nerve.

3. *Advanced laryngeal cancer*: The CTV includes the entire larynx, the pyriform sinuses, the vallecula, the paraglottic and preepiglottic spaces, and the entire thyroid cartilage. If tracheostomy was performed, the tracheostomy site is included in the CTV.
4. *Hypopharynx:* Submucosal longitudinal spread, often as skip lesions, is common. The CTV therefore includes the parapharyngeal tissue cranially through the nasopharynx and caudally 2 cm below the cricoid cartilage. The posterior pharyngeal wall and ipsilateral hemilarynx are included for pyriform sinus and lateral pharyngeal wall cancer. The ipsilateral thyroid lobe is included in cases of pyriform sinus cancer extending laterally.
5. *Paranasal sinuses*: The CTV depends on the sinuses involved and tumor extent. In general, the palate, alveolar ridge, nasal cavity, and the nasopharynx are included in the CTV in cases of maxillary sinus tumors, and the medial orbit in maxillary and ethmoid sinus cancers. The pterygopalatine fossa and infratemporal fossa, which are frequently at risk of subclinical disease, are included in the CTV. Superior lesions require extension of the CTV to the sphenoid sinus and foramen rotundum at the base of skull to accommodate potential involvement of the maxillary nerve. If MRI suggests neural involvement, the CTV should be extended to include the cavernous sinus. In lesions in the upper nasal cavity and ethmoid sinuses, the cribriform plate and a rim of the frontal lobe are included in the CTV. The anterior cranial fossa is included in cases with intracranial extension.
6. *Nasopharynx:* The CTV encompasses the base of skull, pterygoid plates, and superior parapharyngeal space (located lateral to the pharynx, and medial to the pterygoid muscles and the deep lobe of the parotid gland). The pterygoid muscles are encompassed in all but very early tumors. In the base of the skull, the sphenoid sinus and cavernous sinuses should be encompassed. The CTV is at least 7-8 cm wide to encompass the foramen ovale, carotid canal, and foramen spinosum that serve as potential routes for spread to the cavernous sinuses. Caudal to the primary tumor, the parapharyngeal space should be included in the CTV to approximately midtonsil level, while the retropharyngeal space is outlined as a part of the retropharyngeal lymph node CTV to the level of the hyoid bone. Posteriorly, the clivus is included, and anteriorly, the CTV includes the posterior third of the maxillary sinuses, the posterior ethmoid sinuses, and the posterior third of the nasal cavity. In cases of base of skull involvement, generous CTV margins may include the hypophysis, optic nerves, and chiasm. Limiting the dose received by these structures to 45-55 Gy (at daily fraction size <2 Gy) would be one of the objectives of planning. Figure 1A-D demonstrates the primary GTV and CTV of a case of nasopharyngeal cancer.

Selection and Delineation of the Lymphatic CTVs

Our knowledge of the pattern and risk of lymphatic drainage from different head and neck sites is based on the recently reviewed[5] classic

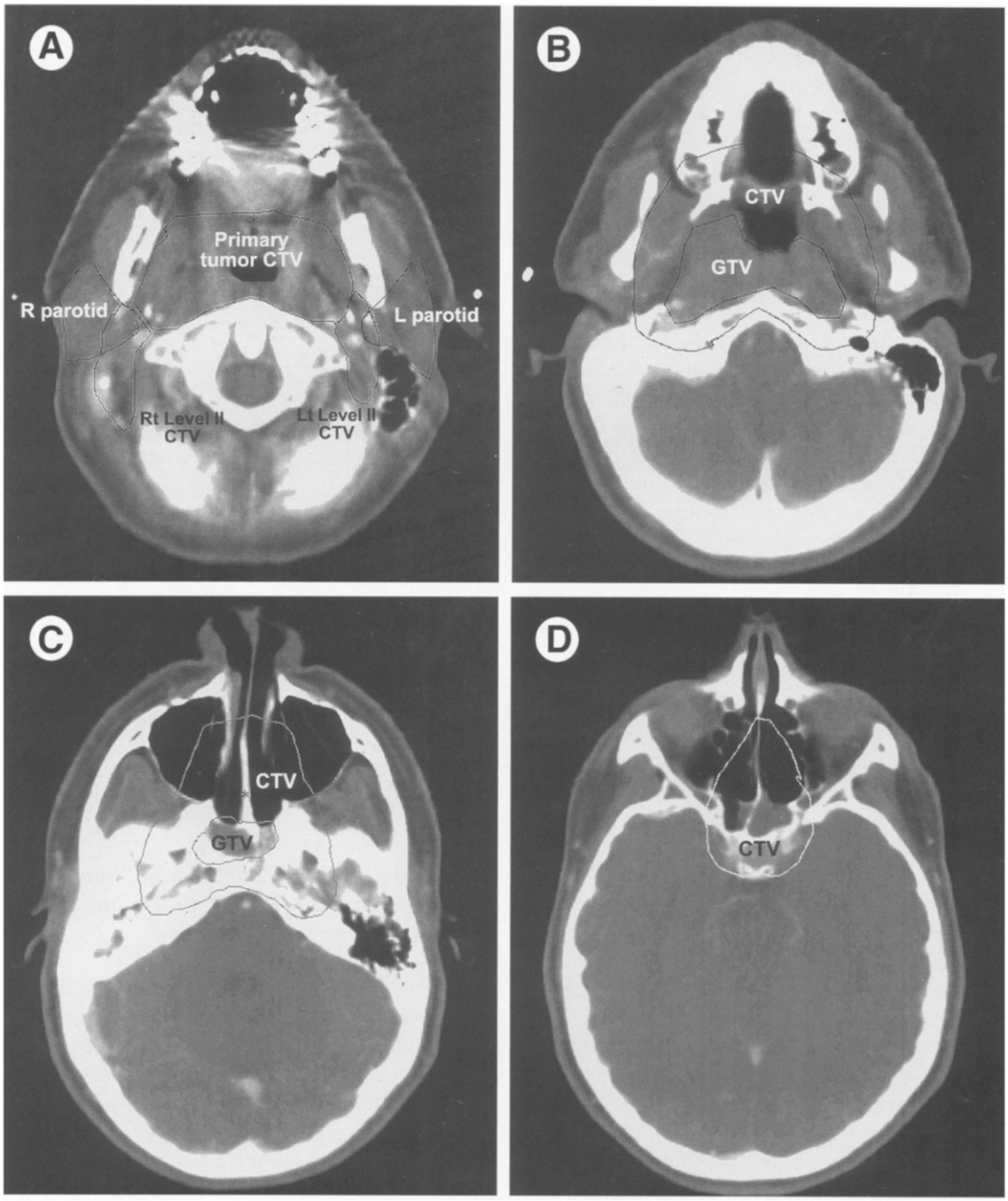


Figure 1. Delineation of the primary tumor GTV and CTV, and upper Level II CTVs, in a case of nasopharyngeal cancer, tumor stage T3. The GTV was delineated on MRI and the contours were registered with the planning CT. For treatment planning, the GTV and CTV were each expanded uniformly by 5 mm to yield the corresponding PTVs. (A) Caudal to the nasopharynx: The pharyngeal walls and parapharyngeal spaces constitute the primary tumor CTV. Level II CTVs are delineated to the base of skull bilaterally. (B-C) The clivus, foramina at the base of skull, pterygoid plates, posterior maxillary sinuses, and nasal cavity are encompassed by the CTV. (D) Cranial to the MRI-defined GTV, the sphenoid and cavernous sinuses are encompassed by the CTV.

anatomical work of Rouviere,[6] the assessment of the location and prevalence of clinical neck metastasis by Lindberg,[7] and the vast experience with elective neck dissections that provides information about microscopic metastases, reported by Byers et al[8] and Shah.[9] These studies have demonstrated that squamous cell carcinomas of the upper aerodigestive tract tend to metastasize to the neck in a predictable pattern, governed by the density and drainage of the lymphatics at each site, with increasing risk at each level if the adjoining proximal level is involved.

In order to provide the surgeons with a system that can be used to describe nodal groups removed at neck dissection, a simple anatomical neck division was proposed by surgeons from Memorial Sloan-Kettering and modified by Robbins et al.[10,11] In this classification, the neck is divided into 6 levels, with well-defined anatomical boundaries apparent during neck dissection. An imaging-based nodal classification, using CT or MRI-based criteria that correspond to the surgical anatomic landmarks, developed by prominent head and neck radiologists[12] is outlined as follows:

Level IA corresponds to the older "submental nodes" terminology. It lies anteriorly between the medial margins of the anterior bellies of the digastric muscles.

Level IB corresponds to the submandibular nodes. It lies lateral and anterior to the submandibular salivary gland, lateral to Level IA.

Level II corresponds to the upper jugular nodes. It extends from the skull base to the hyoid bone, posterior to the back of the submandibular gland, lateral to the carotid artery, and medial to the sternocleidomastoid muscle.

Level III corresponds to the midjugular nodes. It extends from the hyoid to the bottom of the cricoid cartilage, medial to the sternocleidomastoid muscle.

Level IV corresponds to the lower jugular nodes. It extends from the bottom of the cricoid to the head of the clavicle, lateral to the carotid artery, and anterior to the back of the sternocleidomastoid muscle.

Level V corresponds to the posterior triangle nodes. It lies posterior to the back of the sternocleidomastoid muscle and anterior to the anterior edge of the trapezius muscle.

Level VI corresponds to the paratracheal and pretracheal nodes that lie between the carotid arteries from the level of the bottom of the hyoid to the top of the manubrium.

The *retropharyngeal nodes* are bilateral structures not specified in the surgical levels terminology, because they are not routinely removed during neck dissection. They lie medial to the carotid arteries, from the base of skull through the hyoid bone.

In addition to these imaging-based, published criteria,[12] several recent, excellent articles have been published by radiation oncologists demonstrating how to outline the lymph node neck levels as CTVs on the planning CT scans[13-15] or axial MRI.[13] These publications are highly recommended to readers who contemplate performing head and neck IMRT.

An extensive review of the literature regarding the risk of metastases to each neck level has recently been published by Gregoire et al.[13] Our recommendations for the selection of neck levels as CTVs for adjuvant RT are detailed below. We assume that a 5% to 10% or higher risk justifies adjuvant therapy. The following factors affecting the risk of metastasis should be taken into account for each case: tumor stage, size, thickness (in oral cavity tumors), differentiation, keratinization status, lymphatic vessel invasion in the tumor specimen, and whether other neck levels are involved.

Selection of Neck Levels That Should Be Included in the CTV for Individual Primary Tumor Sites

For All Sites

1. For cases of lateralized cancer in which only the ipsilateral neck would ordinarily require therapy, contralateral neck treatment is always added when the ipsilateral neck involvement is greater than N1.
2. Level II neck nodes are the most frequent metastatic site for tumors in all mucosal sites. These nodes can be divided into the subdigastric (jugulodigastric) nodes, located below the level at which the posterior belly of the digastric muscle crosses the jugular vein (Fig 2A and B) and the more cranially located nodes below the base of skull ("junctional" nodes in Rouviere's terminology). The subdigastric nodes are the main nodes involved when con-

tralateral metastasis occurs, whereas the more cephalad nodes are at risk bilaterally in cases of nasopharyngeal cancer and in the neck side that contains other Level II-III metastasis.[15a]

3. Levels IB and IV are treated in all cases in the neck side with clinical involvement of Levels II or III.
4. Level V is treated in the neck side with involvement of Levels II-IV, in all cases.
5. The retropharyngeal nodes are treated bilaterally in all cases of oropharyngeal and hypopharyngeal cancer with clinical involvement of Levels II-IV (in cases of early lateralized oropharyngeal tumors with small N1 disease, treat ipsilaterally).
6. Level VI nodes are treated in all cases with clinical involvement of Level IV nodes.

Oral Cavity

Floor of mouth: Lateral tumors, stages T1-T2: ipsilateral Levels IA, IB, II, III, and contralateral Levels IA, IB, II. In the case of more advanced T stage, add ipsilateral Level IV and contralateral Level III.

Tongue: Tumor stage T1-T2, lateral lesions that do not involve the anterior third of the tongue: Ipsilateral Levels IA-IB and II-IV. For more advanced stages or anterior tongue involvement, add the same levels contralaterally.

Buccal mucosa and retromolar trigone: Levels IA-IB, II-III ipsilaterally.

Oropharynx

Tonsil: Stage T1-T2, N0-N1, no base of tongue/soft palate involvement: ipsilateral Levels II-IV. In larger tumors, or if the anterior tonsillar pillar is involved, add ipsilateral Level IB. Add contralateral Levels II-III if more advanced primary tumors, neck involvement greater than N1, or clinical evidence of base of tongue/palate involvement.[16]

Base of tongue: In all cases, Levels II-IV bilaterally. Add ipsilateral Level IB if the tumor extends to the true tongue, if stage T4, or if Level II nodes are involved.

Soft palate: Bilateral Levels II-III. Retropharyngeal nodes in locally advanced cases.

Larynx

Supraglottic larynx: Levels II-IV bilaterally. In the clinically negative neck, the upper lymph nodes included in Level II are the subdigastric nodes (situated beneath the level where the posterior belly of the digastric muscle crosses the jugular vein). In the clinically involved side of the neck, Level II is outlined to below the base of skull.

Glottic larynx: Stages T3-T4: It is reasonable to use similar guidelines for the supraglottic larynx. Stage T2: the risk of lymph node metastasis is borderline. It may be higher and may require adjuvant neck RT in stage T2B (reduced vocal cord mobility)[17]; in that case, treat like the supraglottic larynx.

Subglottic involvement, any tumor stage: Similar to supraglottic primaries; add Level VI bilaterally.

Hypopharynx

Pyriform sinuses and pharyngeal walls: Levels II-IV and retropharyngeal nodes bilaterally. Add Level VI if the pyriform sinus apex is involved, in advanced tumor stages, or if other neck levels are clinically involved.

Postcricoid area: Same as the pyriform sinuses; add Level VI in all cases.

Nasopharynx

Levels II-V and the retropharyngeal nodes bilaterally. Level II nodes are outlined bilaterally up to the base of skull. Level IB is included on the sides of the neck with Level II involvement.

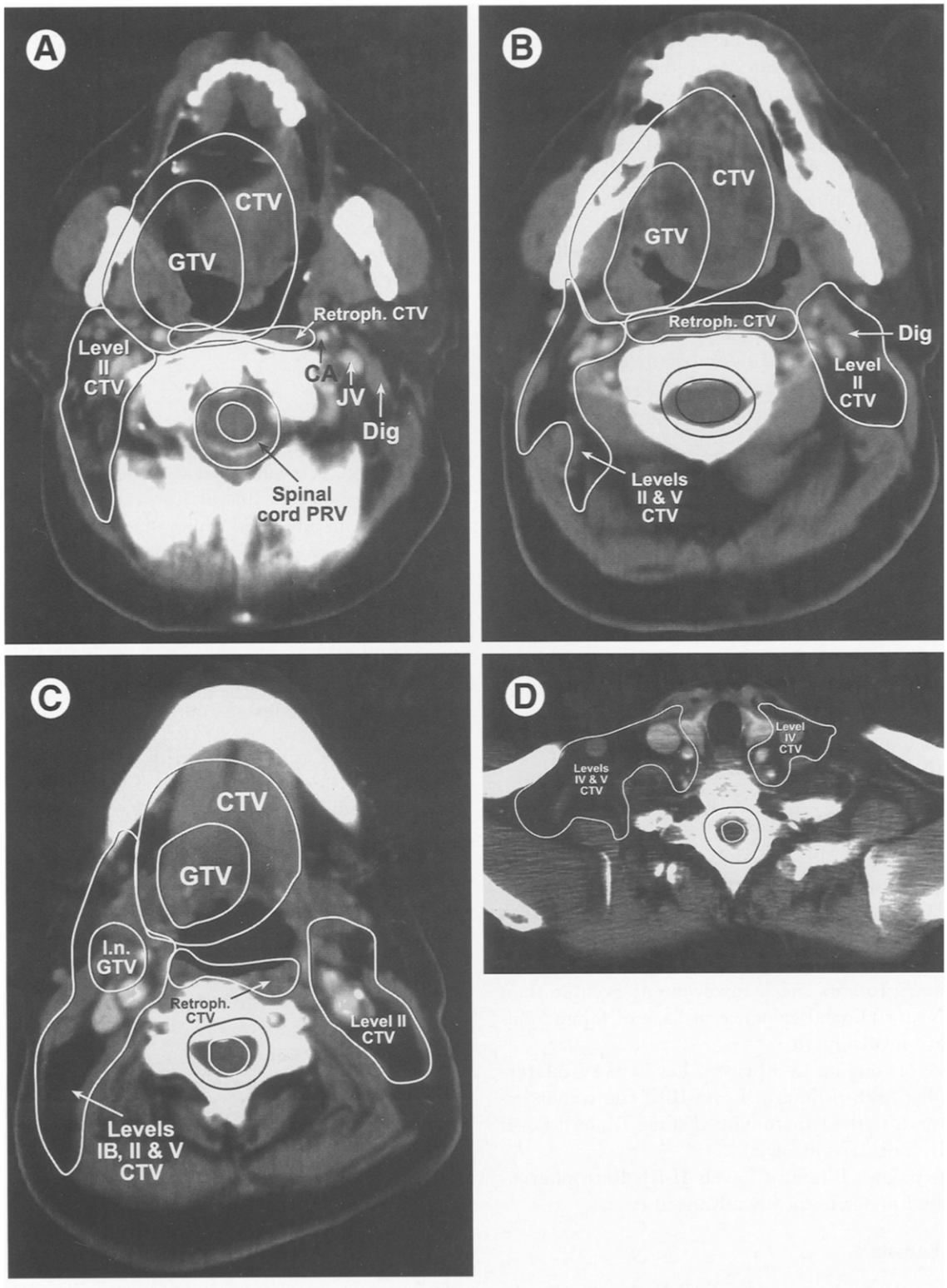
Paranasal Sinuses

For tumors confined to the ethmoid, sphenoid, or maxillary sinuses, no adjuvant RT of the neck is recommended; however, this is a controversial issue.[17a] In tumors that extend to neighboring sites with dense lymphatic drainage, such as the palate, oral cavity, oropharynx, nasopharynx, or nasal cavity, treat the neck levels according to the risk in these sites.

An example for delineating the GTVs and CTVs for a case of oropharyngeal cancer is shown in Figure 2. These targets were expanded uniformly by 5 mm to yield the corresponding planning tumor volumes (PTVs), for actual treatment planning. The reader is referred to detailed examples for outlining nodal neck CTVs.[13-15]

The Postoperative Case

The surgical specimens provide information that should be helpful in determining the neck levels


A
CTV
GTV
Retroph. CTV
Level II CTV
CA
JV
Dig
Spinal cord PRV
B
CTV
GTV
Retroph. CTV
Dig
Level II CTV
Levels II & V CTV
C
CTV
GTV
l.n. GTV
Retroph. CTV
Level II CTV
Levels IB, II & V CTV
D
Level IV CTV
Levels IV & V CTV

at risk. Neck dissection disrupts some anatomical landmarks used to define the borders between the levels. On the other hand, the surgical bed is apparent on the CT scan and should be encompassed entirely within the CTV. It is often impossible to distinguish between the primary tumor resection and the adjacent neck dissection bed, and they are encompassed within a unified CTV. Neck levels in which microscopic extracapsular lymph node extension is found are considered high-risk areas and assigned a higher dose (see below).

The PTVs

Once the CTVs are outlined on the axial CT images, a uniform expansion of the GTVs and the CTVs is performed to obtain the PTVs that accommodate setup uncertainties, typically by 3-5 mm. Doses are prescribed to the PTVs or to comparable "growth" areas in some planning systems. The extent of the target expansion to yield the PTVs depends on the setup errors, which are largely determined by the immobilization system. In general, thermoplastic masks with several rigid fixation points on the treatment table produce adequate immobilization, with displacement standard deviation of approximately 2 mm.[18] We recommend systems that immobilize the shoulders in addition to the head and neck, especially if the lower neck is included in the IMRT plans (several institutions perform IMRT only for targets in the head and high and mid-neck, and an anterior supraclavicular field is matched to the inferior edges of the IMRT beams).

Dose Prescription and Specification

The delivery of a single plan throughout the course of treatment provides better dose conformality compared with several consecutive plans that are common in standard RT for head and neck cancer.[19] When a single plan is prescribed, the gross tumor PTV receives both a higher total dose and a higher dose per fraction compared with the PTVs of the subclinical disease. Due to the differences in the daily fraction doses, a correction of the total dose to yield the biologically equivalent doses (BEDs) is required when the fraction dose is different from standard fractionation. An extensive discussion of this issue is provided by Mohan et al.[19] There are two general approaches to dose prescription. The first would be to prescribe a total dose delivering standard fraction doses to the gross disease PTV (eg, 70 Gy over 35 fractions), and doses delivering lower fraction doses to the subclinical disease PTVs: 63 Gy to the high-risk and 58.1 Gy to lower risk elective targets, which, over 35 fractions, would deliver fraction doses of 1.8 Gy and 1.66 Gy, yielding (normalized total doses [NTDs] of 60 Gy and 50 Gy, respectively. When used for advanced disease, this schedule is expected to be delivered concurrently with chemotherapy. The second strategy is to deliver a higher than standard fraction dose to the gross disease PTV, adjusting the total dose to yield an NTD near 70 Gy, and standard fraction doses to the elective targets PTVs. Such a strategy was adopted by the Radiation Therapy Oncology Group (RTOG) study of IMRT for oropharyngeal cancer (RTOG study H-0022). In this study, the gross disease PTV

Figure 2. Delineation of the GTVs and CTVs in a case of a stage T2N1 right tonsillar cancer extending clinically to the lateral base of the tongue. Neck levels at risk were judged to be ipsilateral Levels IB and II-V, contralateral Levels II-IV, and the retropharyngeal nodes bilaterally. (A) Cranial to the level in which the posterior belly of the digastric muscle crosses the jugular vein, Level II CTV is only delineated ipsilaterally. The retropharyngeal nodal CTV is delineated bilaterally. The primary tumor GTV and surrounding CTV are outlined. (B) Starting at the level in which the posterior belly of the digastric crosses the jugular vein, Level II is delineated contralaterally to encompass the contralateral subdigastric nodes. Ipsilaterally, both Levels II and V are encompassed within the lymphatic CTV. (C) At Level II, an enlarged lymph node is defined as a GTV. Ipsilaterally, Levels IB, II, and IV are encompassed within the lymphatic CTV. Contralaterally, only Level II is delineated within the CTV. (D) In the lower neck, Levels IV and V are encompassed within the lymphatic CTV. Contralaterally, only Level IV is included. All GTVs and CTVs were expanded uniformly by 5 mm to yield the corresponding PTVs. The spinal cord was also expanded by 5 mm to yield the planning organ volume (PRV). The prescribed doses were 66 Gy to the GTV-PTVs, 60 Gy to the ipsilateral CTV-PTV, and 54 Gy to the contralateral CTV-PTV and to the retropharyngeal nodal PTV, in 30 fractions. Abbreviations: CA, carotid artery; JV, jugular vein; Dig, posterior belly of the digastric muscle.

receives a total of 66 Gy in 30 fractions, 2.2 Gy/fraction. PTVs of high-risk subclinical disease PTV receive 60 Gy, and low-risk PTVs receive 54 Gy at 2.0 and 1.8 Gy/fraction, respectively. This results in the gross disease PTV receiving an NTD of 70 Gy over 6 weeks, which is expected to yield results similar to those achieved by an accelerated radiation course.[20] A more aggressive reported regimen delivers a total of 60 Gy in 25 fractions (2.4 Gy/fraction) to the gross disease and 50 Gy (2.0 Gy/fraction) to electively treated volumes, yielding an NTD of 66 Gy over 5 weeks.[21] A phase I dose escalation study is currently being conducted at the Medical College of Virginia, in which the fraction size and the total dose to the gross disease PTVs are escalated.[22]

Schemes delivering high-fraction doses to the gross tumor PTVs have been termed "simultaneous boosts."[19,21] It should be noted that they differ fundamentally from concomitant boost accelerated regimens, which deliver two daily fractions at an interval that allows sublethal damage repair of noninvolved tissue.[20] It is postulated that limiting the high-dose-treated volume to the target alone by IMRT may reduce the risk of late complications arising from large fraction doses. However, critical-normal tissues at risk in the head and neck (nerves, noninvolved mucosa, blood vessels, bone, etc) are embedded within the targets. Furthermore, typical IMRT plans contain relatively high target-dose heterogeneities that increase even further the daily dose delivered to these tissues. These schemes, therefore, should only be practiced within well-defined clinical trials.

Dose and dose-volume specifications are made to impose constraints on the DVHs of the targets, noninvolved tissue of interest, and nonspecified tissue outside the targets. RTOG protocol H-0022 specifies as the prescription dose the dose that encompasses at least 95% of the PTV. No more than 20% of the PTV can receive >110% and no more than 1% of the PTV can receive <93% of the prescribed dose. In order to limit hot spots outside the targets, the protocol specifies that no more than 1% of the tissue outside the PTVs can receive >110% of the prescribed dose. Dose constraints regarding most critical tissue are stated in terms of the maximal dose. Commonly applied constraints in the head and neck are maximal doses of 45 Gy to the spinal cord, 54 Gy to the brain stem, 70 Gy to the mandible, and 50-55 Gy to the optic pathway. These constraints were derived from standard irradiation, in which the organ at risk typically receives irradiation at a standard daily fraction dose for part of the therapy course and is then fully shielded. In contrast, IMRT delivers lower daily fraction doses to these organs throughout therapy. In most instances, therefore, these dose constraints are more conservative when applied to IMRT compared with standard RT. On the other hand, steep fall-off of doses near critical organs may increase the risk of inadvertent overdosage due to motion and setup uncertainties. This issue can be addressed by a uniform expansion of the critical organs, such as the spinal cord and optic nerves, by 3-5 mm, to yield the planning organ at risk volume (PRV), and a constraint for the dose to the expanded volume is then specified. Organs with parallel functional architecture require specification of the mean or partial organ dose, rather than a maximal dose. Examples include specification in RTOG protocol H-0022 of the maximal mean dose to the parotid salivary glands at 26 Gy, or limiting the dose to at least one half of the gland volume to <30 Gy, and the dose to two thirds of the larynx at <50 Gy.

The Optimization Process

The PTVs and noninvolved organs lie in close vicinity or overlap with each other. It is necessary to assign weighting factors (or penalty/importance factors) to each target and organ that determine the relative importance of fulfilling their dose specifications or constraints. These weighting factors are derived following an iterative, trial-and-error process that requires refinement for each patient to produce an optimal plan. These factors differ among the various optimization systems. Examples of penalty factors for head and neck cancer plans were provided by several authors.[23,24] It was noted that because normal structure doses are penalized during optimization only if they exceed the limits set by the user, the constraints need to be more stringent than the clinical criteria.[24] At the University of Michigan, the optimization system uses a cost function that strives to minimize the dose to some noninvolved structures, in addition to setting a maximal dose constraint, facilitating a reduction of the doses to these organs.[25] Also, with a combination of linear and high-power ob-

jective functions (in addition to the quadratic objective function used in most other systems), strict head and neck target-dose homogeneity can be achieved.[25]

In addition to the physical dose and dose-volume optimization criteria, several investigators examined the utility of biologic/clinical criteria as a basis for optimization in the head and neck, including the probability of uncomplicated tumor control,[26] tumor control probability (TCP) and normal tissue complication probability (NTCP),[27] and the equivalent uniform dose concept.[28] Work at the University of Michigan comparing various biologic factors and dose or dose-volume as bases for optimization found that the balancing of power and weights, rather than the specific cost function, is the determining factor for the optimization results.[29] Biologic cost functions may be superior to dose-based functions when the parameters of the biological models, derived from clinical dose-response and dose-complication data, are known with greater confidence. An example is the optimization of advanced paranasal sinus cancer plans, in which optic pathways NTCPs derived from patient dose-complication data were used for the critical organ cost function.[30]

Results

Several recent publications have demonstrated improved target doses and relative sparing of noninvolved tissue compared with conventional irradiation plans for head and neck cancer.[21-24,31,33-37] Clinical results of IMRT are still scant, but the number of reported studies is expected to rise rapidly in the near future. Several clinical studies assessed the utility of IMRT in parotid salivary gland sparing and in reducing xerostomia. When the doses and treated parotid gland volumes were correlated with the parotid salivary output following multisegmental IMRT, it was found that the large majority of the glands receiving a mean dose of more than 26 Gy did not produce measurable saliva and did not recover, whereas glands receiving lower mean doses produced variable salivary output that increased over time.[38] One year after RT, parotid glands receiving a moderate dose (mean dose, 17-26 Gy) recovered, on average, to the pre-RT salivary production levels. Analysis of a validated, patient-reported xerostomia questionnaire showed that xerostomia improved significantly over time, in tandem with the increase in saliva production.[39] Two years after radiation, xerostomia reported by patients receiving parotid-sparing bilateral neck radiation was only slightly worse than that in patients receiving unilateral neck RT. Factors found to be statistically significant predictors of patient-reported xerostomia included the mean dose to the major salivary glands and to the oral cavity, representing radiation received by the minor salivary glands. An improvement to mild or no xerosomia during the second year was also reported using the RTOG toxicity scale, following IMRT for nasopharyngeal cancer.[32] It is apparent from these and other studies[40] that the sparing of the salivary glands, made possible by IMRT, achieves tangible gains in the retention of the salivary production and in xerostomia symptoms. Additional potential functional gains include reported superior swallowing and speech measures following aggressive chemoirradiation with IMRT, compared with standard RT.[41]

Thus far, reports of tumor control and the pattern of recurrences are encouraging. Following IMRT of nasopharyngeal cancer, locoregional control rates of 85% to 100% have been reported in studies with limited patient numbers and follow-up periods.[21,32,42] The pattern of locoregional tumor recurrence at the University of Michigan was reported by Dawson et al.[43] Almost all recurrences occurred in-field, in high-risk volumes that had received the full prescribed dose. An update of this study includes 98 patients, mostly with oropharyngeal cancer, treated with primary (41 patients) or postoperative (57 patients) multisegmental IMRT. At a median follow-up of 40 months (range, 6-84 months), 15 locoregional failures (15%) occurred. Of these, 12 recurred in-field, and 3 were marginal recurrences in which less than 95% of the tissue volume harboring the recurrent tumor had received the prescribed dose. The cases with marginal recurrences included a patient with past history of neck surgery for oral cancer treated with RT for tumor recurrence. Tumor subsequently recurred in unpredicted lymph nodes and in subcutaneous tissue. This case highlights the unpredictability of the lymphatic drainage in patients with a past history of surgery, who, therefore, may not be suitable candidates for IMRT. Another patient who had oral cancer with multiple Level II-IV microscopic nodal metastasis had a marginal re-

currence in paratracheal nodes (Level VI), highlighting the risk at any neck level when adjoining levels are involved. A third patient with oropharyngeal cancer recurred marginally in ipsilateral retropharyngeal nodes. No patient recurred in the contralateral Level II near the base of skull, an area that had been spared in many patients, and no patient recurred in the spared parotid glands. Careful examination and reporting of the pattern of locoregional recurrence, by radiation oncologists treating head and neck cancer with IMRT, is essential to further understand and improve treatment.

Conclusions

Planning comparisons have shown significant improvements in noninvolved organ sparing and in target irradiation of head and neck cancer by IMRT compared with conventional techniques. However, clinical issues of adequate patient immobilization, accurate identification of the clinical disease, and, the most challenging task—accurate selection and delineation of subclinical potential disease requiring adjuvant irradiation—affect the outcome following IMRT. Knowledge of head and neck anatomy, and the risk and pattern of local spread and of metastasis to the neck, are essential for successful execution of head and neck cancer IMRT and should be studied by radiation oncologists contemplating its use. The recommendations for the selection and delineation of the targets, presented in this review, were intended to represent reasonable statements about the current state of knowledge from available studies, which are retrospective in nature. Assessing and reporting the sites of locoregional recurrences following IMRT, and their relation to the doses that had been delivered, will enhance our understanding of these issues and help improve future therapy.

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