International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer

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Received Nov 16, 2014, and in revised form Mar 24, 2015. Accepted for publication Mar 26, 2015.

Summary

Standardized, cross-sectional contouring guidelines are needed because of the increasing use of highly conformal radiation therapy techniques in esophageal and gastroesophageal junction cancer. Eight academic gastrointestinal radiation oncologists each generated contours for 3 representative cases; these were analyzed to generate a consensus atlas.

Purpose/Objective(s): Current guidelines for esophageal cancer contouring are derived from traditional 2-dimensional fields based on bony landmarks, and they do not provide sufficient anatomic detail to ensure consistent contouring for more conformal radiation therapy techniques such as intensity modulated radiation therapy (IMRT). Therefore, we convened an expert panel with the specific aim to derive contouring guidelines and generate an atlas for the clinical target volume (CTV) in esophageal or gastroesophageal junction (GEJ) cancer.

Methods and Materials: Eight expert academically based gastrointestinal radiation oncologists participated. Three sample cases were chosen: a GEJ cancer, a distal esophageal cancer, and a mid-upper esophageal cancer. Uniform computed tomographic (CT) simulation datasets and accompanying diagnostic positron emission tomographic/CT images were distributed to each expert, and the expert was instructed to generate gross tumor volume (GTV) and CTV contours for each case. All contours were aggregated and subjected to quantitative analysis to assess the degree of

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Presented in part at the 55th Annual Meeting of the American Society of Radiation Oncology, Atlanta, GA September 22-25, 2013.

Supported by U24CA81647 and U24 CA180803 from the National Cancer Institute.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Acknowledgment—The authors thank Cesar Della-Bianca and Stephen McNamara for their technical assistance on this project.

Int J Radiation Oncol Biol Phys, Vol. 92, No. 4, pp. 911–920, 2015
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2015.03.030

The panel also reached agreement on general guidelines and principles for contouring, depending on the location of the primary lesion within the esophagus.

concordance between experts and to generate draft consensus contours. The panel then refined these contours to generate the contouring atlas.
Results: The κ statistics indicated substantial agreement between panelists for each of the 3 test cases. A consensus CTV atlas was generated for the 3 test cases, each representing common anatomic presentations of esophageal cancer. The panel agreed on guidelines and principles to facilitate the generalizability of the atlas to individual cases.
Conclusions: This expert panel successfully reached agreement on contouring guidelines for esophageal and GEJ IMRT and generated a reference CTV atlas. This atlas will serve as a reference for IMRT contours for clinical practice and prospective trial design. Subsequent patterns of failure analyses of clinical datasets using these guidelines may require modification in the future.

Introduction

Radiation therapy (RT) has an important role in the treatment of esophageal and gastroesophageal junction (GEJ) cancer, in both the definitive and the preoperative settings. Definitive concurrent chemoradiation therapy can achieve long-term survival in a subset of patients (1). When used as preoperative therapy, chemoradiation improves the rates of margin-negative resection, pathologic complete response, and long-term survival (2). Traditionally, RT fields have been designed based on 2-dimensional planning, using esophagrams to identify the primary lesion and using simple geometric expansions and bony landmarks to shape radiation fields. To encompass subclinical disease extension and regional nodal spread, typical field borders were designated by 5-cm expansions proximally and distally beyond apparent tumor along the length of the esophagus, and 2 cm laterally, with these guidelines referring to distance to field or block edge (3, 4). In modern radiation therapy practice, treatment volumes are more commonly defined based on the International Commission on Radiation Units and Measurements definitions of clinical target volume (CTV) and planning target volume (PTV).

Intensity modulated radiation therapy (IMRT) and other highly conformal techniques, including volumetric arc therapy and proton therapy, represent an important advance in radiation therapy. These techniques allow for greater sparing of normal tissues, particularly the lungs and heart (5-8). However, highly conformal radiation techniques require the radiation oncologist to define target volumes with greater specificity, using computed tomography (CT)-derived images and anatomy. Although traditional guidelines for field design still govern contouring for IMRT in a broad sense, they are not likely to provide sufficient detail to ensure consistent delineation of target volumes between practitioners and patients.

Current prospective trials involving radiation therapy and esophageal cancer generally require 3-dimensional conformal RT and may allow the use of IMRT. However, no consensus reference contouring guidelines or atlas is available to guide target delineation for patients on these trials. A remedy for this gap in clinical practice is important because it has been demonstrated that variation in target volume delineation may have an impact on the outcome of therapy and can be improved with atlases that serve as teaching aids in gastrointestinal tract neoplasms (9, 10). To develop standardized contouring guidelines and to ensure adequacy of the CTV for ongoing and future clinical trials of radiation therapy for esophageal and GEJ cancers, we convened a panel of expert gastrointestinal radiation oncologists to generate a reference atlas for modern-day contouring. Because conformal techniques such as IMRT are also increasingly used in general practice to reduce radiation dose to organs at risk, such guidelines can serve as best-practice surrogates for the clinician treating patients outside of a clinical trial setting.

Materials and Methods

Expert panel and test case selection

An expert panel of academic radiation oncologists with expertise in gastrointestinal malignancies was convened, representing multiple National Cancer Institute–designated cancer centers throughout the United States. Because the esophagus spans different anatomic regions in the body, and regional nodal volumes can differ depending on the location of primary tumor, 3 sample cases were selected (see Appendix E1, available online at www.redjournal.org). Case 1 was a T3N0, Siewert II lesion spanning the GEJ; case 2 was a T3N1 lesion of the distal esophageal cancer without overt involvement of the GEJ; and case 3 was a T3N1 proximal esophageal lesion at and above the level of the carina. A simulation CT dataset from each case was distributed to each panelist and imported into his or her institutional treatment planning system. The panelists were instructed to contour each case assuming RT in a single course to 5040 cGy in 180-cGy fractions, with concurrent chemotherapy.

Because positron emission tomography (PET) imaging is now standard in the initial evaluation of esophageal cancer, and because fluorodeoxyglucose (FDG) avidity is a useful method to localize primary tumor and adenopathy on cross-sectional imaging, we distributed diagnostic PET-CT images for each test case to the panelists, along

with a clinical vignette on each case that provided other pertinent information such as esophagoduodenoscopy and endoscopic ultrasound findings. The primary tumors had SUV_{max} values of 12.6, 10.0, and 13.2, respectively.

Contour generation

The panelists were first instructed to contour the gross tumor volume (GTV) on each case, based on a free-breathing simulation CT, clinical information, and PET-CT images, so that the degree of consensus in GTV contouring could also be assessed.

The panelists were then instructed to use a reference GTV as the basis for their CTV to ensure that all panelists were using the same GTV to construct the CTV. Panelists were to define the CTV according to the basic instructions of the CALGB 80803 trial (see Appendix E2, available online at www.redjournal.org). These specified a 3 to 4 cm superior/inferior and 1- to 1.5-cm radial margin from GTV, inclusion of periesophageal nodes, mediastinal and supraclavicular nodes in proximal tumors, and celiac nodes in distal/GEJ tumors.

Statistical analysis

The panelists' contours were imported from DICOM files and merged onto a single scan for each test case, and imported into the Computational Environment for Radiotherapy Research (CERR) for statistical analysis. The κ statistics were calculated to characterize the level of agreement between physicians; a κ value of −1 represents complete disagreement, 0 represents agreement only at the level expected by chance, and 1 represents perfect agreement (11).

The Simultaneous Truth and Performance Level Estimation (STAPLE) algorithm, implemented in the CERR software, was used to generate preliminary consensus contours, as previously described (12). This algorithm considers a collection of contours and calculates a probabilistic estimate of the "true" contour (13). STAPLE contours with a 95% confidence level were used.

Based on review of the STAPLE contours and comparison of the submitted contours, the panel then discussed areas of significant variability or uncertainty and arrived at a set of contouring guidelines to accompany the reference atlas. To enhance their generalizability, the consensus contours were referenced to existing consensus radiographic definitions of nodal levels in the neck, thorax, and abdomen (Fig. 1) (14-16).

Results

GTV contours

The GTV and CTV contours were successfully obtained from the 8 panelists. Summary statistics on GTV and CTV contours are listed in Table 1. The κ statistics indicated substantial agreement among the panelists, with values of 0.651, 0.790, and 0.623 for cases 1, 2, and 3, respectively (κ values between 0.61 and 0.80 are considered "substantial" agreement).

CTV contours

The κ statistics again indicated substantial agreement in all 3 cases, with values of 0.683, 0.663, and 0.609 for cases 1, 2, and 3, respectively. STAPLE contours were generated for each case with volumes of 477, 569, and 442 cc, respectively.

These preliminary consensus contours were then reviewed and edited to smooth out the contours and resolve areas where, as a result of averaging, the algorithm had generated anatomically illogical contours (Fig. 2).

CTV contouring guidelines

Based on the high degree of agreement among the panelists' contours, the panel proceeded to establish the following guidelines for CTV contouring in esophageal cancer (Figs. 3-5).

Proximal border

The proximal border is a 3- to 4-cm margin above the proximal edge of the GTV, or 1 cm above any grossly involved periesophageal nodes, whichever is more cephalad. This margin should be oriented along the esophageal mucosa instead of being a simple geometric expansion. For very proximal tumors, the upper border should not extend above the level of the cricoid cartilage unless there is gross disease at that level.

Distal border

For proximal or midesophageal tumors, the distal border is a 3- to 4-cm margin below the proximal edge of the GTV, oriented along the esophageal mucosa. For distal esophageal or GEJ tumors, a 4-cm geometric margin distally for all cases would extend well below the GEJ and include unacceptably large volumes of stomach or other abdominal viscera when treating to 5040 cGy. Therefore, for this situation, at least a 2-cm margin along clinically uninvolved gastric mucosa was recommended. If treating to lower, preoperative-intent doses (≤4500 cGy), a 4-cm or greater gastric margin may be appropriate, particularly for tumors with significant gastric extension. Siewert III lesions, and lesions extending more than 5 cm into the stomach, fall outside the scope of this atlas and may be contoured using gastric cancer−specific guidelines.

Radial borders

In general, the CTV should include the GTV (including any grossly involved nodes) with at least a 1-cm margin in all directions. A 1-cm radial margin from the outer esophageal

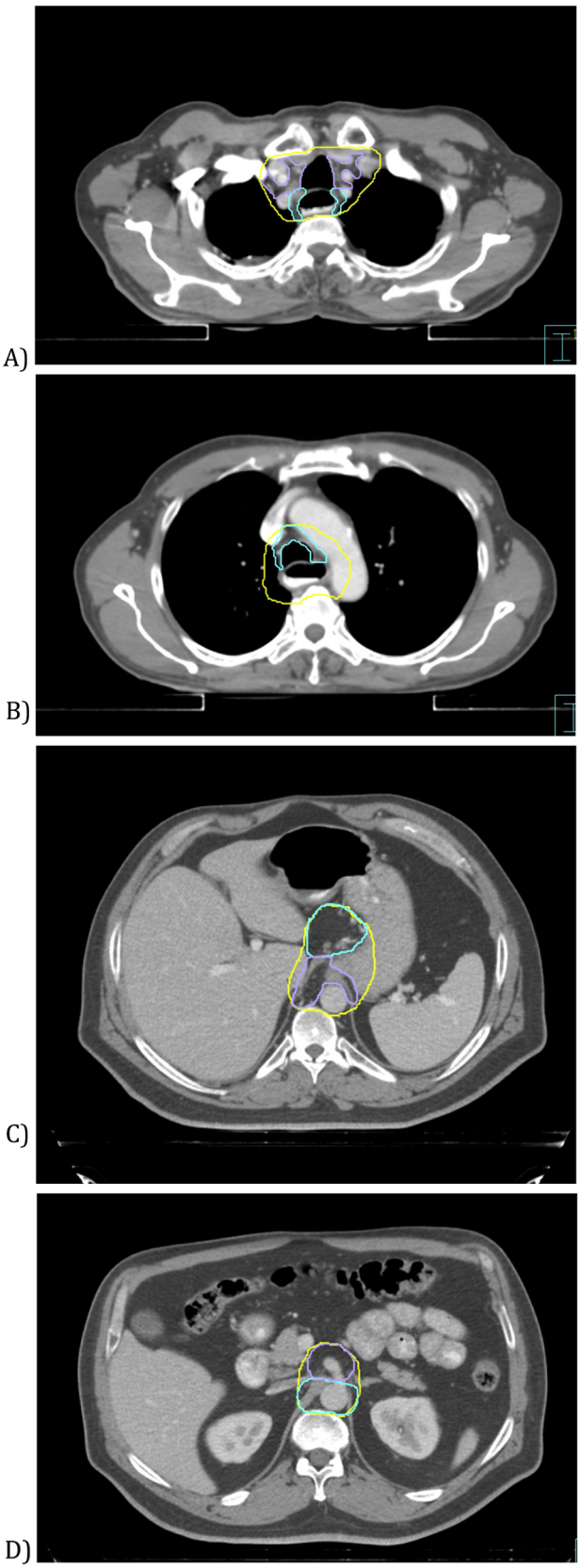

Fig. 1. Examples of consensus contours encompassing defined nodal regions. (A) Clinical target volume (CTV) contour (yellow) encompasses level 3 retrotracheal (blue) and level 2 upper paratracheal (purple) nodes. (B) CTV encompasses level 4 lower paratracheal (blue) and level 8 periesophageal nodes. (C) CTV encompasses lesser curvature/gastrohepatic ligament (blue) and paracardial (purple) nodes. (D) CTV encompasses para-aortic (blue) and celiac (purple) nodes. A color version of this figure is available at www.redjournal.org.

wall was recommended to encompass the periesophageal lymph nodes (level 8 in the International Association for the Study of Lung Cancer [IASLC] system). Unless the GTV was located at the esophagus/heart interface, it was recommended that the CTV expansion be limited to 0.5 cm into cardiac tissue (including pericardium), given the concern about excessive cardiac dose and the unlikelihood of microscopic extension into the myocardium in the absence of gross invasion. Similarly, the CTV expansion can be limited to 0.5 cm into uninvolved liver. Excluding the liver and heart from the CTV entirely is reasonable if robust motion management techniques, such as respiratory gating or an internal target volume approach, are used to minimize the possibility that a CTV border based on a static simulation scan is transgressed during radiation treatment as a result of tumor or organ motion. It was also recommended that the vertebral bodies be entirely excluded from the CTV in the absence of gross invasion.

Regional nodal volumes

For distal tumors involving or approaching the GEJ, the CTV should be extended inferiorly to the level of the origin of the celiac axis, to cover the celiac lymph nodes, which normally are located at the level of the T12 vertebral body. Typically, the celiac nodal CTV will be bounded by the lateral aspect of the vertebral body (usually T12) on the right, 0.5 to 1 cm beyond the lateral aspect of the aorta on the left, the vertebral body posteriorly, and the pancreatic body anteriorly. The kidneys should be excluded from the CTV.

In the upper abdomen, between the level of the GEJ and the celiac nodes, it was recommended that para-aortic and gastrohepatic ligament (often classified as lesser curvature or left gastric) nodes be included in the CTV. In this region, the liver will typically bound by the CTV on the right. On the left, the border will typically be the stomach. Anteriorly, the CTV typically includes the fatty space between the lesser curvature and the liver that contains the paracardial and gastrohepatic ligament nodes. The splenic hilar nodes are not considered regional nodes for esophageal cancer and do not need to be specifically included in the CTV, although they may be incidentally covered if the tumor extends significantly into the stomach. However, with Siewert type II GEJ tumors, given a higher risk of lymph node involvement, the panel agreed that inclusion of some or all nodes in the splenic hilum and greater curvature region can be at the discretion of the treating physician if lower doses are used, depending on the patient's clinical and pathologic features. For tumors above the level of the

Table 1 GTV and CTV structure measures

	GTV			CTV		
Structure measure (cc)	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3
Minimum volume	36.94	41.96	14.51	397.89	364.72	265.28
Maximum volume	106.18	68.28	67.20	563.21	712.12	496.65
Mean volume	73.54	54.13	53.16	467.67	489.89	384.21
Volume standard deviation	21.57	8.17	18.48	64.98	112.71	92.34
Intersection volume	27.10	34.05	12.13	219.15	178.45	110.50
Union volume	133.20	88.15	102.91	790.01	979.83	835.49
STAPLE volume	74.28	55.93	68.81	477.48	569.14	441.79
κ (scale of −1 to 1)	0.651	0.790	0.623	0.683	0.663	0.609

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; STAPLE = Simultaneous Truth and Performance Level Estimation.

carina, it was recommended that the bilateral supraclavicular nodal basins be included. The recommended borders of the supraclavicular nodes are analogous to level IV nodes in head and neck cancer (16), in which the cranial border is the level of the cricoid cartilage, and the anterior, posterior, and lateral borders correspond to the borders of the sternocleidomastoid muscles, with the inferior border extending into the thoracic inlet.

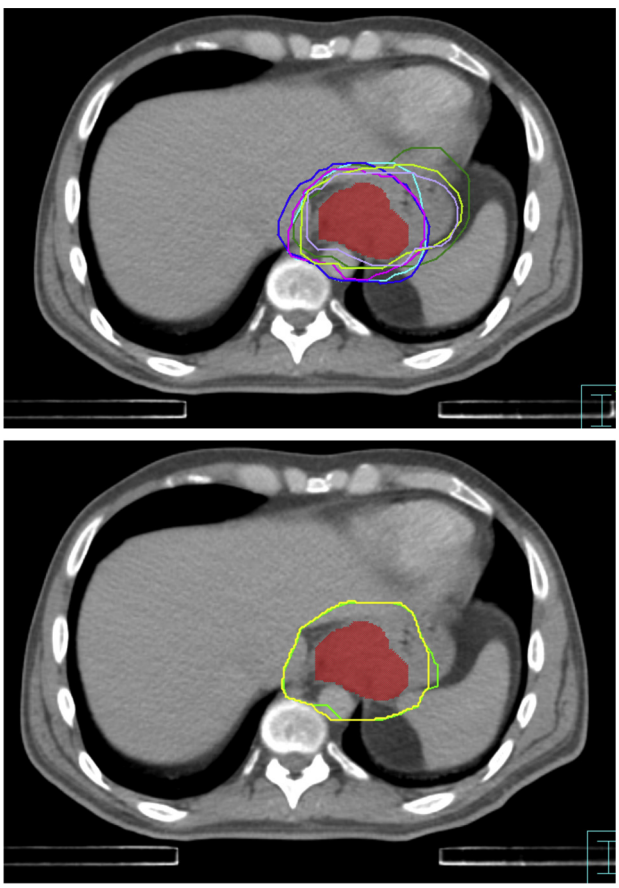

Fig. 2. Example of consensus contour generation. Above, superimposed panelists' contours relative to the reference gross tumor volume (red). Below, Simultaneous Truth and Performance Level Estimation consensus contour (green) and final consensus contour (yellow). A color version of this figure is available at www.redjournal.org.

A significant area of discrepancy exists regarding the extent to which mediastinal nodal stations should be explicitly included in the CTV. The seventh edition American Joint Commission on Cancer staging classification considers only nodes located in the paraesophageal region to be regional (17). Routine inclusion of all mediastinal node stations in the CTV will result in treatment volumes significantly larger than traditional fields based on 1- to 2-cm radial expansions from the esophagus, and result in significantly greater and potentially excessive radiation dose to the lungs. Therefore, for distal tumors in which the CTV extends superiorly to the mediastinum only to respect the 3- to 4-cm proximal margin on gross tumor, the panel did not consider it mandatory to deliberately include superior mediastinal nodal stations electively, other than would be encompassed by a 1-cm radial expansion of the esophagus.

For proximal tumors, in which the supraclavicular nodes are already at risk and lung dose is less of a limitation given the decreased craniocaudal extent of CTV into the thorax and the smaller relative volume of lung tissue at the apices, the panelists favored a more generous CTV to encompass mediastinal lymph nodes in addition to the periesophageal nodes. Above the carina, the CTV will therefore typically encompass the entire trachea and extend radially to encompass the lower and upper paratracheal nodal stations, which correspond to levels 2 and 4 in the IASLC staging map (15). Above the aortic arch, the anterior border of the CTV can be extended toward the sternum and clavicular heads to encompass the prevascular nodes (IASLC level 3) and create a smoother transition between the thoracic CTV and the supraclavicular nodal CTV. Above the level of the thoracic inlet, the trachea should be excluded from the CTV except insofar as the 1-cm radial margin on the normal esophagus requires it.

PTV guidelines

With respect to PTV delineation, the panel recommended expanding the CTV by 0.5 to 1 cm in all directions,

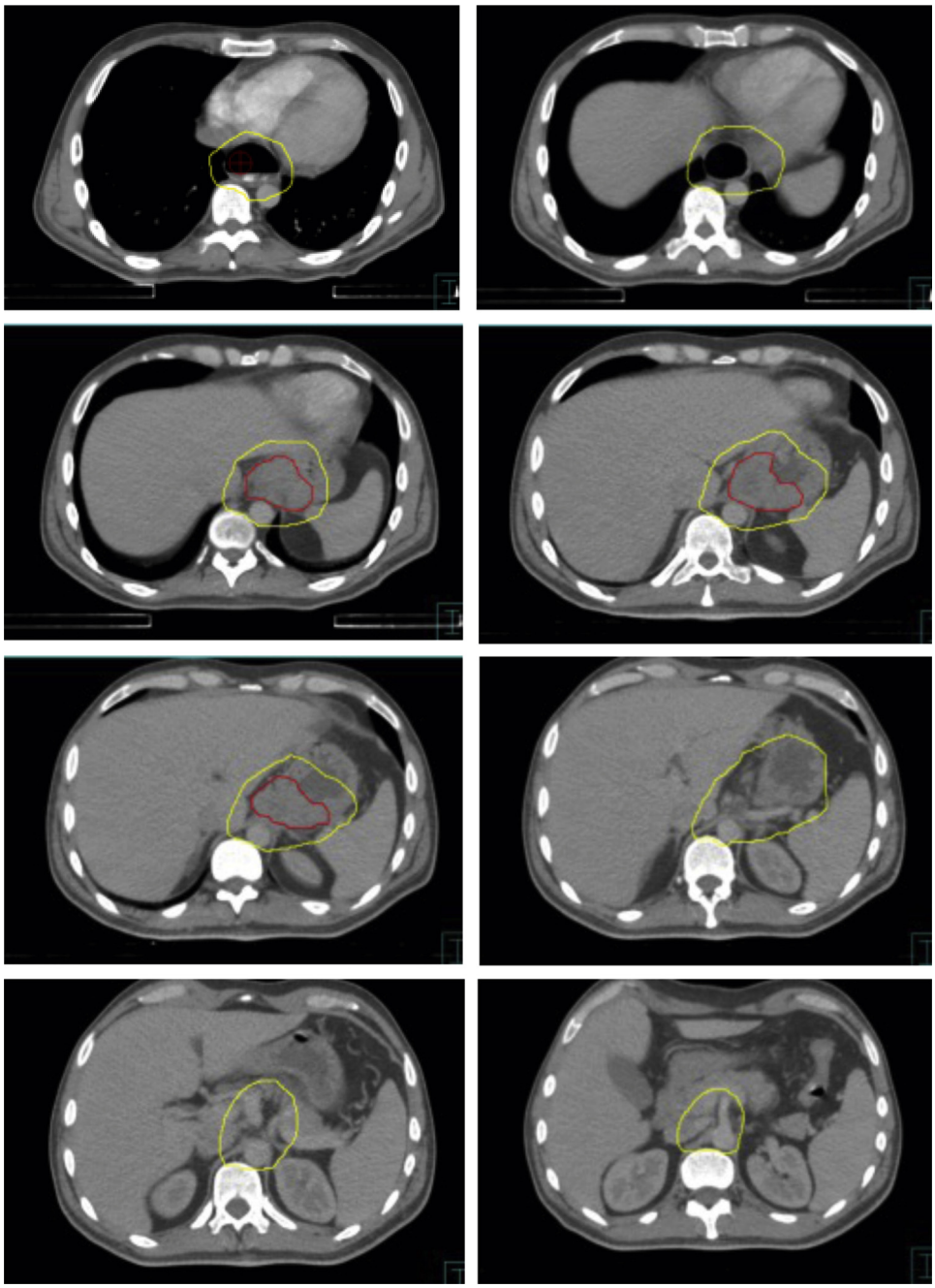

Fig. 3. Consensus contours for case 1: T3N0, Siewert II gastroesophageal junction cancer, gross tumor volume in red. A color version of this figure is available at www.redjournal.org.

depending on institutional guidelines and the frequency of portal imaging. For tumors involving the distal esophagus and GEJ, it is critical that respiratory motion be taken into account when highly conformal techniques such as IMRT are used. This should include, at a minimum, fluoroscopic or 4-dimensional CT imaging to estimate the degree of superior−inferior motion caused by respiration, which can then be incorporated into the PTV expansion. For situations where respiratory motion is observed to be in excess of 1 cm, the panel additionally recommends the use of techniques such as respiratory gating or abdominal compression. Variations in gastric filling may lead to significant intrafraction differences in the location of perigastric nodes, and dose to normal stomach. To mitigate this, most panelists recommended that patients receive nothing by mouth for 2 to 3 hours before simulation and each treatment. However, treating patients at a consistent interval after meals also appears to result in reproducible gastric positioning, and it may be more comfortable for some patients (18).

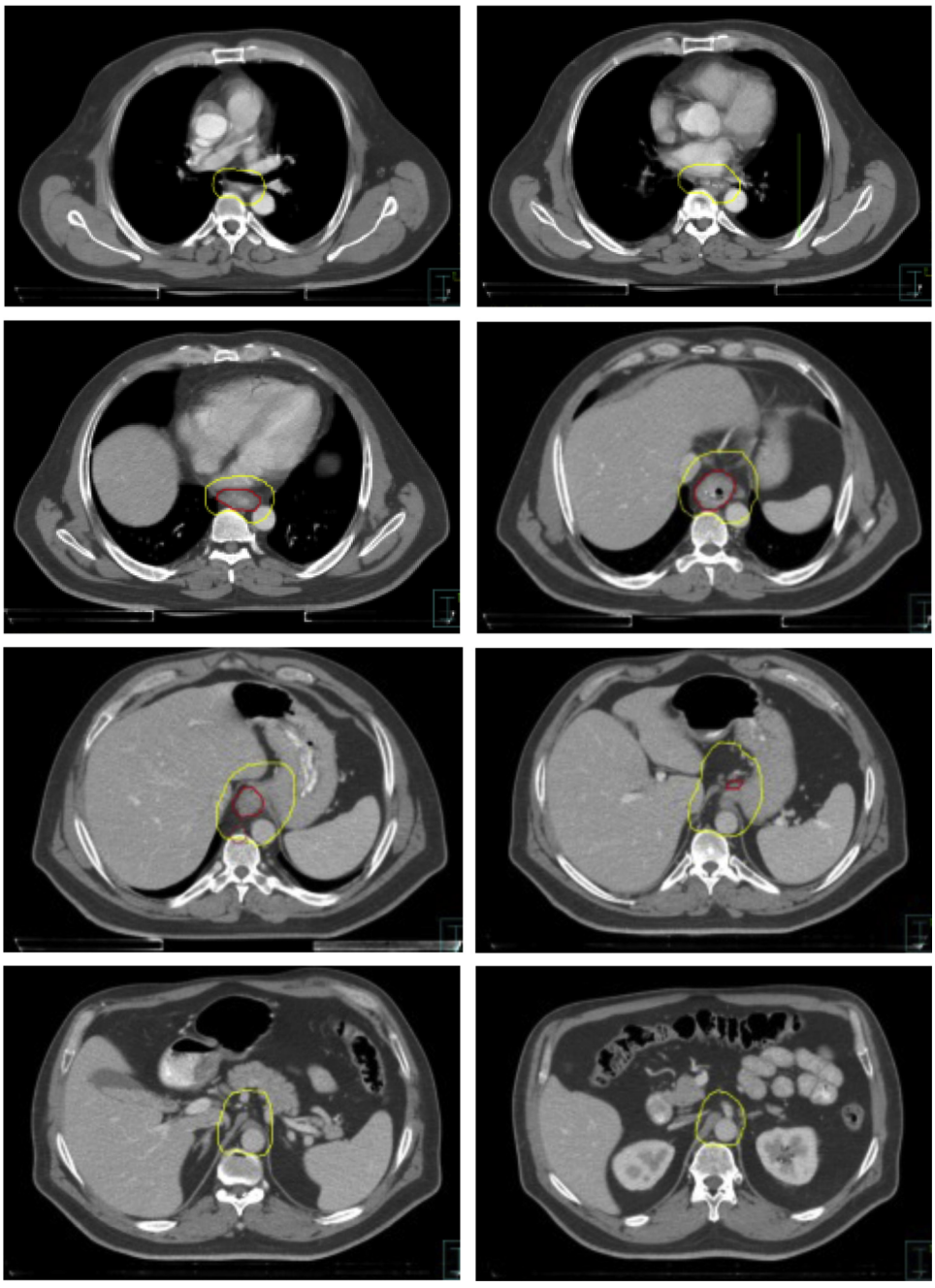

Fig. 4. Consensus contours for T3N1 distal esophageal cancer.

Discussion

Although IMRT and other highly conformal radiation therapy techniques provide greater target volume conformality, greater dose homogeneity, and increased ability to control dose to adjacent normal structures, they also place a greater responsibility on the radiation oncologist to appropriately delineate the GTV, CTV, and PTV at each axial level. Recent data indicate that patients with microscopic disease extending beyond the CTV margins have inferior outcomes, underscoring the importance of accurate CTV delineation (19). Existing guidelines have provided sufficient direction to design 2-dimensional fields and blocks, but they leave significant potential for uncertainty and variability when defining target volumes on cross-sectional imaging. This analysis indicates that expert gastrointestinal radiation oncologists can achieve a reasonable degree of consensus in contouring practice when starting from the same basic conditions (as outlined in CALGB 80803). Based on quantitative and qualitative analysis of each panelist's contours for each test case, a contouring atlas and consensus guidelines could be generated.

A significant limitation of our guidelines is that they are based on expert consensus, not directly on patient data

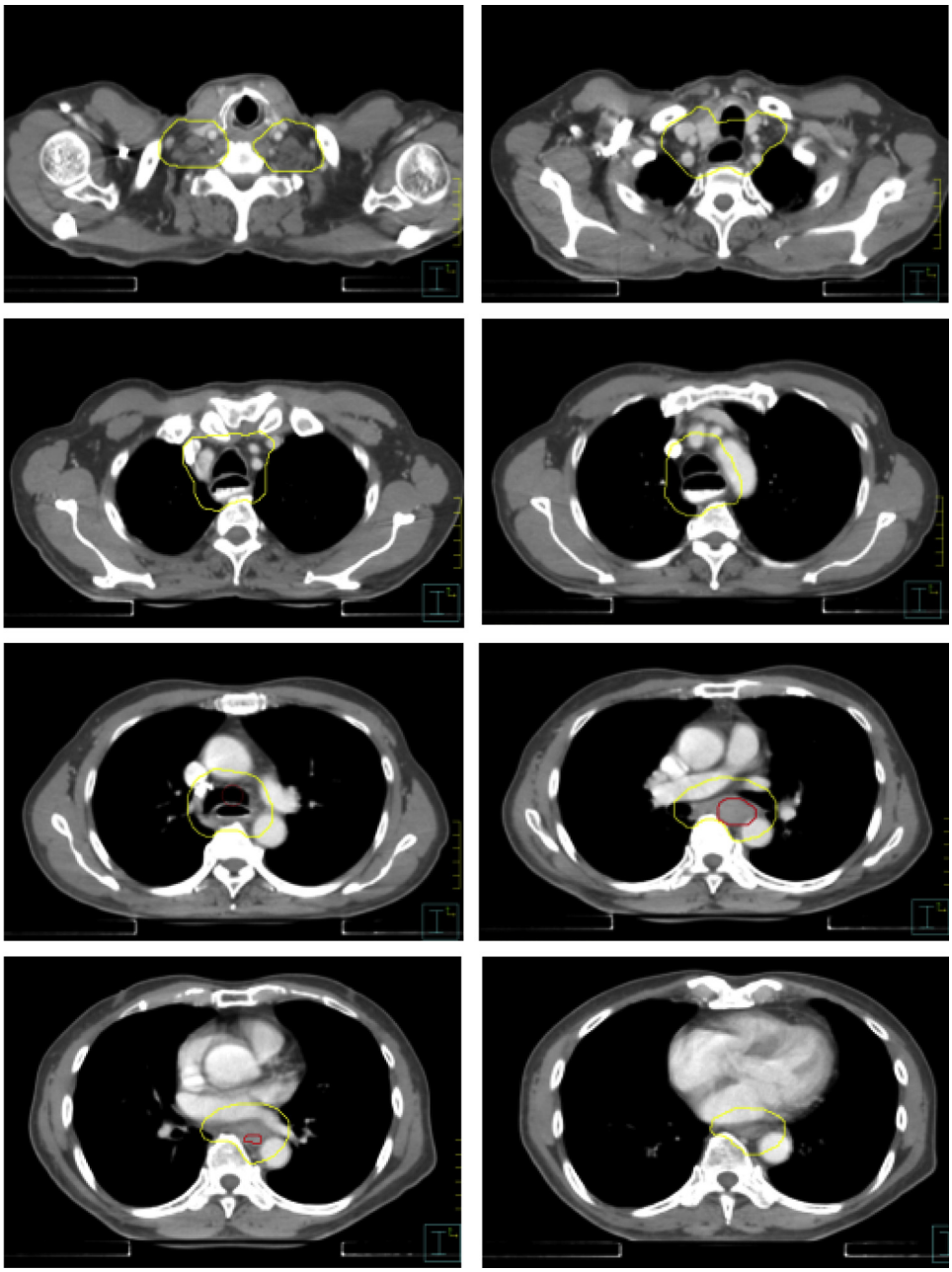

Fig. 5. Consensus contours for T3N1 proximal esophageal cancer.

regarding patterns of disease extension or recurrence relative to radiation treatment fields. Translating extant data on pathologic node involvement and patterns of failure directly into radiation therapy CTV guidelines is not straightforward, given the significant heterogeneity that exists in histology, anatomic site, T stage, and other factors that appear to modify the risk and location of lymph node involvement.

However, existing literature provides some support for our consensus guidelines. With respect to CTV margins on primary tumor, pathologic analysis of microscopic extension in resected tumor specimens indicates that proximal and distal mucosal margins of 3 cm may be sufficient for the majority of cases to encompass submucosal spread of disease (20). Clinicopathologic correlation of RT volumes with residual tumor location after surgery has also indicated that generous CTV margins are necessary to encompass the actual tumor within the RT field, because preoperative GTV delineation is frequently inaccurate (19). A retrospective study of local relapse patterns after definitive chemoradiation also indicated that CTV margins on the order of 3 cm appeared adequate (21). To allow for variations in clinical judgment and potential uncertainty when PET avidity is used to define GTV, we thought that a CTV range of 3 to 4 cm was appropriate to insure adequate coverage of the primary tumor and any subclinical spread. Note that

after adding a PTV margin of 0.5 to 1 cm, and accounting for penumbra, this expansion is consistent with the traditional practice of expanding the GTV 5 cm to block edge.

With respect to nodal target volumes, retrospective and limited prospective data have suggested no clear benefit to elective nodal irradiation (22-24). However, these datasets are based on squamous cell carcinomas in Asian populations, which may not be fully applicable to the distal adenocarcinomas that are the typical subject of current multicenter trials. A recent analysis of nodal involvement in a large series of patients with resected squamous cell carcinoma also supports the concept of elective mediastinal and supraclavicular node coverage in locally advanced proximal tumors (25). Regarding celiac nodal coverage, a contemporary series of mostly adenocarcinomas treated with definitive chemoradiation indicated a failure rate significant enough to justify elective coverage, particularly given the modest rates of associated toxicity with celiac irradiation (26). A large series of resected GEJ adenocarcinomas also indicated a rate of celiac nodal involvement of approximately 20%, which is at or above the threshold that many practitioners use to justify elective coverage (27).

Pathologic data also indicate that the most commonly involved nodes in GEJ cancers include the lesser curvature and paracardial regions, which are encompassed in our guidelines describing coverage of the gastrohepatic space (27, 28). These studies also indicate, as expected, that there is a significant rate of involvement of the paraesophageal nodes. For GEJ tumors in particular, there is also a lower but still substantial risk of pathologic involvement of additional abdominal nodal sites such as the greater curvature and splenic hilum nodes (27). Because the inclusion of these sites will significantly expand the CTV volume and increase dose to the stomach and left kidney, the panel did not recommend routinely treating these regions to a dose of 5040 cGy but thought that this could be considered on a case-by-case basis if patients are treated preoperatively to 4500 cGy or lower. We note that the evidence for benefit from routine elective nodal irradiation of any kind remains inconclusive, and if further study demonstrates that it can be safely omitted in distal esophageal and GEJ cancers, the therapeutic ratio of radiation therapy should improve.

Until more data are available—ideally, prospective data on patterns of failure in esophageal and GEJ adenocarcinoma—expert consensus guidelines will remain the most useful aids to promote optimal radiation therapy technique in clinical trials and general practice. The European Organization for Research and Treatment of Cancer has published radiation therapy guidelines for GEJ cancers that are broadly concurrent with our guidelines, but no contouring atlas is provided, and esophageal cancers proximal to the GEJ are not addressed (29). To our knowledge, no other peer-reviewed, consensus guidelines for cross-sectional delineation of esophageal cancers exist. Besides CALGB 80803, the other major ongoing North American trial of esophageal cancer chemoradiation is RTOG 1010, which provides similarly basic guidelines that are insufficiently detailed to ensure consistent CTV definition.

Because of the anatomic heterogeneity of esophageal cancer, in which the primary tumor and involved lymph nodes can present in multiple disparate regions in the body, it is impossible to provide a reference contour or a few contours that will cover every possible presentation of esophageal or GEJ cancer. Therefore, these atlas contours and guidelines should not be a substitute for clinical judgment based on individualized analysis of each patient.

In conclusion, a reference contouring atlas and contouring guidelines have been generated for thoracic esophageal and GEJ (Siewert I/II) cancers. This atlas will serve as a reference within the treatment planning process for patients being treated on prospective trials of radiation therapy in esophageal cancer, and it can also be used for patients being treated with IMRT or other highly conformal techniques in routine clinical practice.

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