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Basic Original Report

Consensus Guidelines for Delineation of Clinical Target Volumes for Intensity Modulated Radiation Therapy for Intact Cervical Cancer: An Update

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Purpose: Accurate target delineation is essential when using intensity modulated radiation therapy for intact cervical cancer. In 2011, the Radiation Therapy Oncology Group published a consensus guideline using magnetic resonance imaging (MRI). The current project expands on the previous atlas by including computed tomography (CT)-based contours, contours with MRI and positron emission tomography (PET) registrations, the addition of common and complex scenarios, and incorporating information on simulation and treatment planning techniques.

Methods and Materials: Twenty-eight experts in gynecologic radiation oncology contoured 3 cases, first on a noncontrast CT simulation scan and then with registered diagnostic scans. The cases included (1) International Federation of Gynecology and Obstetrics (FIGO) IIIC1 with a bulky tumor and vaginal metastasis, (2) FIGO IIB with calcified uterine fibromas, and (3) FIGO IIIC2 with large lymph nodes. The contours on all 6 data sets (3 CT simulations without diagnostic images and 3 with registered images) were analyzed for consistency of delineation using an expectation-maximization algorithm for simultaneous truth and performance level estimation with kappa statistics as a measure of agreement. The contours were reviewed, discussed, and edited in a group meeting prior to finalizing.

Results: Contours showed considerable agreement among experts in each of the cases, with kappa statistics from 0.67 to 0.72. For each case, diagnostic PET ± MRI was associated with an increase in volume. The largest increase was the clinical target volume (CTV) primary for case 2, with a 20% increase in volume and a 54% increase in simultaneous truth and performance level estimation volume, which may be due to variance in registration priorities. For the third case, 92.9% increased their CTVs based on the addition of the diagnostic PET scan. The main areas of variance were in determining the superior extent of CTV coverage, coverage of the mesorectum, and simulation and planning protocols.

Conclusions: This study shows the value and the challenges of using coregistered diagnostic imaging, with an average increase in volumes when incorporating MRI and PET.

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Introduction

Over the past 10 to 15 years, the treatment for locally advanced cervical cancer has dramatically evolved from 4-field box plans with 2-dimensional point-based brachytherapy to the use of intensity modulated radiation therapy (IMRT) with integrated boosts and image guided adaptive brachytherapy. Much of the advancement has come from the integration of diagnostic imaging, an improved understanding of patterns of failure, more conformal and dose-escalated external beam radiation therapy, the use of daily image guidance, and advances in brachytherapy techniques.[1,2]

The prior consensus guideline laid the groundwork for magnetic resonance imaging (MRI)-based clinical target volume (CTV) contouring to allow for the safe delivery of IMRT. Since that time, IMRT has become routine for women with cervical cancer to minimize acute and late toxicity.[3,4] Additionally, IMRT allows for the delivery of a simultaneous integrated boost to the nodal disease, which reduces overall treatment time and allows for increased conformality of dose compared with sequential nodal boosts. Data from EMBRACE-I and retroEMBRACE (image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced cErvical cancer) showed that women with positive pelvic nodes have a high risk of failure outside of the treatment fields, mainly in the para-aortic (PA) region.[5] Using IMRT to the PA nodal chain has not shown increased rates of toxicity as were seen in earlier trials using 3-dimensional (3D) conformal techniques. Therefore, this is increasingly used for women with both the International Federation of Gynecology and Obstetrics (FIGO) IIIC1 and IIIC2 nodal disease.

The aim of this project was to add to the existing cervical cancer contouring atlas, specifically using computed tomography (CT) data sets with fusions to positron emission tomography (PET) and MRI[6,7]. The cases were chosen to include both complex and common situations to determine practice variation and establish practice guidelines for these situations.

Methods and Materials

Within the larger structure of the NRG Oncology, the Radiation Therapy Oncology Group formed a working group called the Gynecologic Radiation Therapy Group. During the winter meeting in January 2021, a proposal was approved for an updated intact cervix contouring atlas. All members were invited to participate in this effort.

Physicians were encouraged to submit potential deidentified cases for contouring to include challenging

Table 1 Case descriptions, data sets, requested contours, and clinical questions

Case	Description	Data sets	Contours
1	A 50-year-old female with FIGO IIIC1 squamous cell carcinoma of the cervix with bulky tumor with mesorectal space invasion and a vaginal drop metastasis in the lower third of the vagina on the right lateral wall. There is a large right internal iliac lymph node, a smaller left pelvic sidewall node as well as multiple other shotty nodes.	CT sim PET T2MRI	CTV primary CTV nodes
2	A 54-year-old female with FIGO IIIC1 squamous cell carcinoma with parametrial disease and calcified uterine fibromas.	CT sim, PET T2MRI	CTV primary CTV nodes
3	A 59-year-old female with FIGO IIIC2 squamous cell cervical carcinoma with a bulky tumor and large necrotic lymph nodes up to the duodenum.	CT sim PET	CTV nodes

Abbreviations: CT = computed tomography; CTV = clinical target volume; FIGO = International Federation of Gynecology and Obstetrics; PET = positron emission tomography; sim = simulation; T2MRI = T2-weighted magnetic resonance imaging.

disease processes and/or anatomic variations, including posterior invasion into the mesorectal space, vaginal involvement, bulky nodal disease in the PA chain, bulky primary disease with parametrial and/or sidewall disease, large uterine fibroids, very thin patient, etc. Three cases with CT simulation and associated diagnostic images were chosen based on this criterion.

For the initial round, all participants were sent brief case descriptions and 3 sets of deidentified CT simulation Digital Imaging and Communications in Medicine files, which could be uploaded to their institutions' contouring software. For each case, physicians had some questions to answer about their contouring and/or planning techniques (Table 1).

Case 1 was named "bulky tumor with vaginal extension," with the circulated summary describing a "50-year-old thin female with FIGO IIIC1 squamous cell carcinoma of the cervix with bulky tumor with mesorectal space invasion and a vaginal drop metastasis in the lower 1/3 of the vagina on the right lateral wall. There is a large right internal iliac lymph node, a smaller left pelvic sidewall node as well as multiple other shotty nodes."

Case 2 was our "more standard locally advanced cervix case" with a description of a "54-year-old female with FIGO IIIC1 squamous cell carcinoma with parametrial disease and calcified uterine fibromas with a single lymph node in the left external iliac chain".

Case 3 had "Bulky pelvic and PA nodes" with an additional summary of a "59-year-old female with FIGO IIIC2 squamous cell cervical carcinoma with a bulky tumor and large necrotic lymph nodes up to the duodenum."

Physicians were given about 1 month to contour the CT simulation images and then were sent the corresponding diagnostic scans to import and register. Each physician was asked to register the diagnostic images using his/her own registration priorities to mirror how he/she would in practice. Each physician was able to edit his/her CTVs based on the added diagnostic information. Additional questions were sent asking each participant's registration priorities (bones, uterine cervix, nodes, other), which modality he/she finds most helpful for contouring nodes, the primary and normal structures, and whether each physician always orders both PET and pelvic MRI. Clinical questions are listed in Table 2 and imaging questions in Table 3.

Again, physicians were given about 1 month for the second set of contours, and then all 6 data sets were analyzed for consistency of delineation using an expectation-maximization algorithm for simultaneous truth and performance level estimation (STAPLE)[9] with kappa statistics as a measure of agreement between physicians.[10] STAPLE estimates were computed using the Computerized Environment for Radiation Research, an open-source MATLAB-based software tool (MathWorks). A conformity index, defined as the ratio of the mean volume and the volume of the union of all physician contours, was calculated for each CTV. Sensitivity and specificity values were also generated.

The STAPLE contours were sent out to the entire group by email for individual review in advance of a group review by video conference. Based on individual and group feedback, the contours were edited prior to finalizing.

Results

Twenty-eight radiation oncologists who focus on gynecologic radiation oncology and participate in the NRG Gynecologic Radiation Therapy working group contoured all 6 data sets, and 23 responded to the survey questions. The participants are from various regions in the US, from academic centers, and have different levels of expertise ranging from junior to senior physicians.

In general, the contours on the CT simulation scans without registered diagnostic images had the largest variance as measured by the conformity index (Table 4).

Case 1 had significant areas of variance in the superior extent of coverage, the posterior extent, and the coverage

Table 2 Clinical questions and participant answers

Clinical questions	Participant answers (N = 23)
Case 1	
Do you cover inguinal nodes prophylactically?	Yes n = 20, 87%
Do you cover the mesorectum/posteriorly to the lower sacrum?	Yes n = 20, 87%
Case 2	
Do you boost parametria/sidewall with an external beam or include it in brachytherapy volumes?	Brachy n = 14, 60.9% EBRT n = 3, 13% Both/varies n = 6, 26.1%
Do you include the entire uterus when there are fibroids?	Yes n = 19, 82.6%
Do you create an ITV with a full and empty bladder?	Yes n = 21, 91.3%
Case 3	
Do you contour the duodenum, small bowel, and large bowel separately?	Yes n = 13, 56.5% Only duodenum n = 7, 30.4% No n = 3, 13%
Do you use SIB for nodes?	Yes n = 22, 95.7%
What references do you use for bowel contouring?	1. EMBRACE-II protocol 2. Upper abdominal normal organ contouring guidelines and atlas: RTOG 3. NRG gynecologic protocols 4. E-contour 5. Dosimetric predictors of duodenal toxicity with PAN IMRT for cervix 6. Pelvic normal tissue contouring guidelines for radiation therapy: RTOG
What dose constraints do you use?	Duodenum V55 < 15 cm^3 Small bowel V40 < 100 cm^3, V40 ≤ 30 Gy, bowel bag V45 < 195 cm^3, V60 < 2 cm^3 sigmoid DMax 105% (47.3 Gy) EMBRACE-II Banerjee et al.[8]

Abbreviations: IMRT = intensity modulated radiation therapy; ITV = integrated target volume; RTOG = Radiation Therapy Oncology Group; SIB = simultaneous integrated boost; PAN = p.

Table 3 Imaging questions and participant answers

Imaging questions	Participant answers (N = 19)		
What is your registration priority?	Bones n = 14	Cervix n = 7	Register PET to bones for nodal contours and MRI to cervix for primary contours n = 6*
Best imaging modality for contouring nodes?	PET n = 16	PET and MRI n = 3	
Best imaging modality for contouring the primary?	MRI N = 19, 100%		
Best imaging modality for contouring OARs?	MRI n = 13	CT sim n = 6	

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; OAR = organ at risk; PET = positron emission tomography; sim = simulation.
*These numbers are included in the other groups as well.

Table 4 Results from contouring 3 cases on computed tomography simulation and then with registered diagnostic scans

	Case 1				Case 2				Case 3	
Structure Delineated using	CTV_P1 CT	CTV_P2 CT, PET, and T2MRI	CTV_N1 CT	CTV_N2 CT, PET, and T2MRI	CTV_P1 CT	CTV_P2 CT, PET, and T2MRI	CTV_N1 CT	CTV_N2 CT, PET, and T2MRI	CTV_N1 CT	CTV_N2 CT and PET
Sensitivity, %	74	73	69	63	74	59	70	64	72	73
Specificity, %	97	98	99	99	98	99	99	98	99	99
Vol. mean/min/max (SD) (cm^3)	317.7/164.4/631.1 (106.5)	328.7/166.2/565.3 (106.5)	493.3/281.4/965.1 (143.4)	505.5/300.5/969.2 (140.3)	197.5/92.0/359.1 (69.5)	236.3/94.3/479.7 (113.9)	328.3/204.0/476.2 (67.4)	331.2/204.0/462.4 (72.6)	667.8/194.0/986.5 (160.8)	731.3/316.0/1313.1 (182.9)
STAPLE/ intersection/ union vol. (cm^3)	356.8/119.4/772.4	375.4/120.3/798.1	599.1/100.8/1357.8	694.1/109.2/1390.1	222.8/74.8/511.4	342.8/78.4/657.9	413.0/53.3/846.6	451.4/41.8/982.6	826.6/128.4/1524.9	854.6/144.7/1878.3
Kappa	0.68	0.69	0.67	0.67	0.68	0.63	0.68	0.68	0.72	0.71
Conformity index	0.41	0.41	0.36	0.36	0.39	0.36	0.39	0.34	0.44	0.39

Abbreviations: CTV_P = clinical target volume primary; CYV_N = clinical target volume nodes; CT = computed tomography; PET = positron emission tomography; STAPLE = simultaneous truth and performance level estimation; T2MRI = T2-weighted magnetic resonance imaging.

of the inguinal lymph nodes (Fig. 1). Of 23 respondents, most (n = 20, 87%) said they cover the inguinal nodes when there is lower vaginal involvement, and most (n = 20, 87%) would cover the entire mesorectum when there is concern for invasion. Additionally, we recommend covering the mesorectum if there is any concern for mesorectal nodal involvement. There was significant variance on when to cover the PA nodal chain, with 10 (45.5%) covering when there are ≥3 pelvic nodes or a common iliac node per the EMBRACE 2 protocol, 6 (26.1%) only covering when there is a common iliac node-positive, 4 (17.4%) covering the next echelon of nodes, 2 if any pelvic node is positive, and 1 only if PA nodes are involved.

After the individual and group review of the contours, the following STAPLE CTVs changes were implemented: (1) the volumes were adjusted posteriorly and laterally to the inguinofemoral vessels, (2) extended superiorly to the level of the renal vessels, (3) expanded posteriorly to include the mesorectal space all the way to the levator muscles inferiorly, and (4) enlarged to ensure a margin on vaginal disease (Fig. 2). All CTVs were edited away from muscle and bone, but bowels were permitted in the CTV.

Case 2 demonstrated the value of having diagnostic imaging in the treatment position and at the same time as the simulation. There were large variations in the positioning of the cervix and uterus between the CT and both the MRI and PET due to no specific bladder or rectal filling protocol on the 3 image sets, which led to an expanded CTV primary volume.

Following individual and group reviews of the contours, the STAPLE CTVs were deleted from the ischiorectal fossa and the presacral grooves while narrowed around the uterine body (Fig. 3). Several of the participants (n = 19, 82.6%) recommended covering the entire uterus in the case of large uterine fibroids unless they were definitively considered unrelated to the disease.

Case 3 had the highest level of agreement among the 3 cases. On final review, the CTVs were edited out of muscle and bone but extended into the bowel in several places to allow for full coverage of the nodal regions. Based on the final contours, the recommendation was to contour the elective nodes to the level where the diaphragmatic crus join at about T12 (Fig. 4).

Generally, we recommend 5 to 7 mm CTV expansion on the vessels with respect to anatomic boundaries for elective lymph node coverage based on institutional preference. When using an integrated boost technique, that margin can be reduced to 5 mm.

For simulation, most (n = 15, 65.2%) participants used intravenous (IV) contrast for CT simulation but not oral contrast (n = 17, 73.4%). All 6 participants who use oral contrast routinely use both IV and oral contrast. Simulation aids included fiducial markers in the tumor (n = 7), a BB on the introitus (n = 4), a BB on the anus (n = 4), intravaginal marker or contrast (n = 3), and rectal

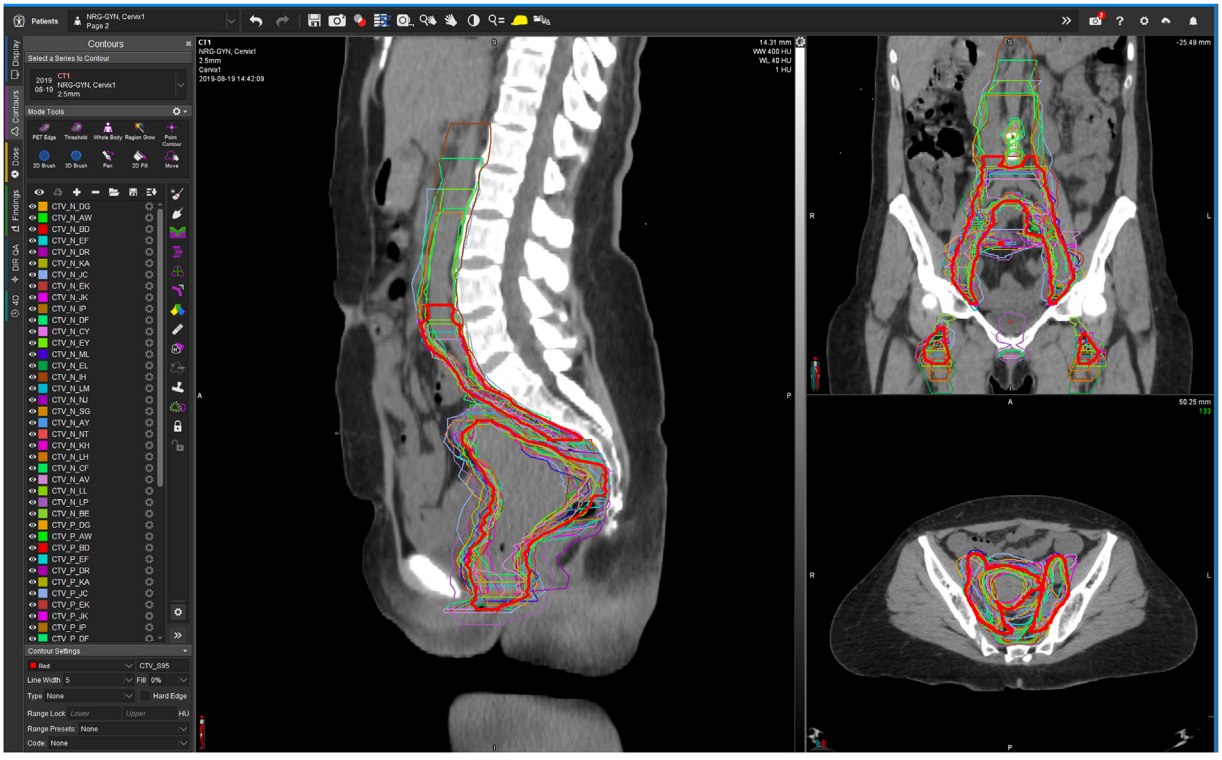

Figure 1 Consensus clinical target volume (CTV) contour (red) and individual contours from 28 physicians for case 1 showing the variance in coverage superiorly, posteriorly, and inferiorly (vaginal and inguinal extent) in the (A) sagittal, (B) coronal, and (C) axial planes.

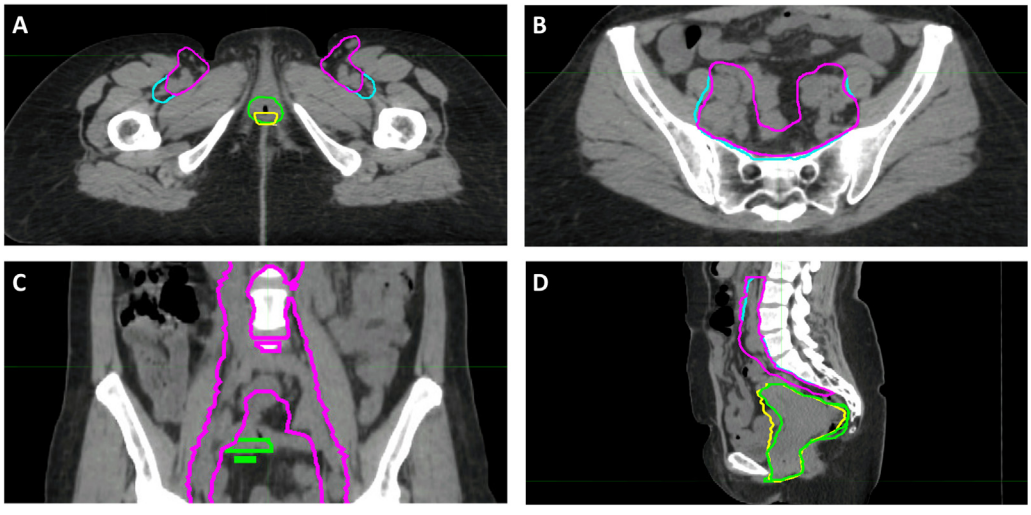

Figure 2 Changes to the simultaneous truth and performance level estimation (STAPLE) CTVs for case 1 after individual and group review (STAPLE CTV node contours are in magenta, STAPLE CTV primary contours are in yellow, and the edited CTV nodal contours are in cyan with edited CTV primary contours in green). (A) Axial computed tomography (CT) showing the STAPLE CTV was edited in the region of the inguinal nodes so as not to be posterior/lateral to the inguinofemoral vessels. (B) Axial CT showing the CTV edited to have a consistent margin on vessels with some extension into the bowel if needed but to exclude bone and muscle. (C) Coronal CT with CTV nodal extended superiorly to cover the level of the renal vessels. (D) Sagittal CT showing the edited CTV primary extended to include the mesorectal space to the levators with mesorectal invasion and inferiorly to ensure margin on vaginal disease and to cover the urethra.

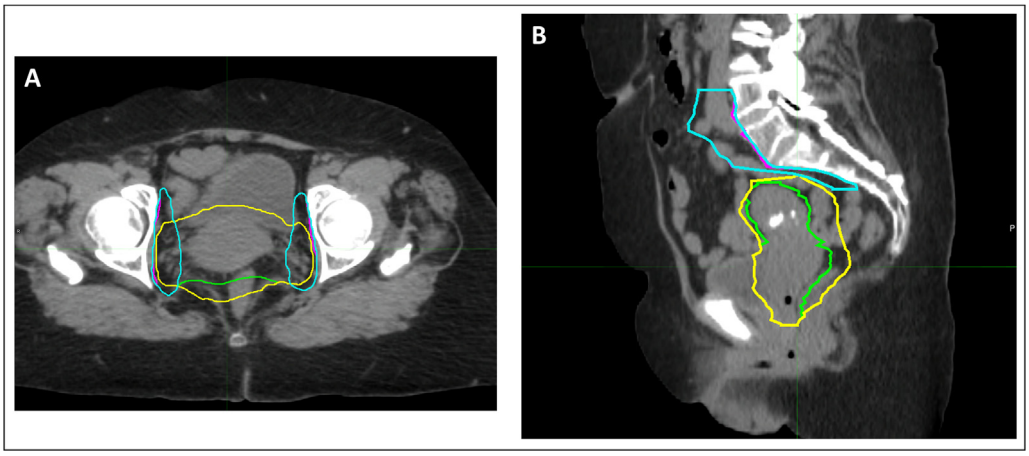

Figure 3 Edited simultaneous truth and performance level estimation (STAPLE) CTVs for case 2 (STAPLE CTV node contours are in magenta, STAPLE CTV primary contours are in yellow, and the edited CTV nodal contours are in cyan with edited CTV primary contours in green). (A) Axial computed tomography showing the CTV primary edited out of the ischiorectal fossa. (B) Sagittal computed tomography with the CTV primary tightened around the uterocervix.

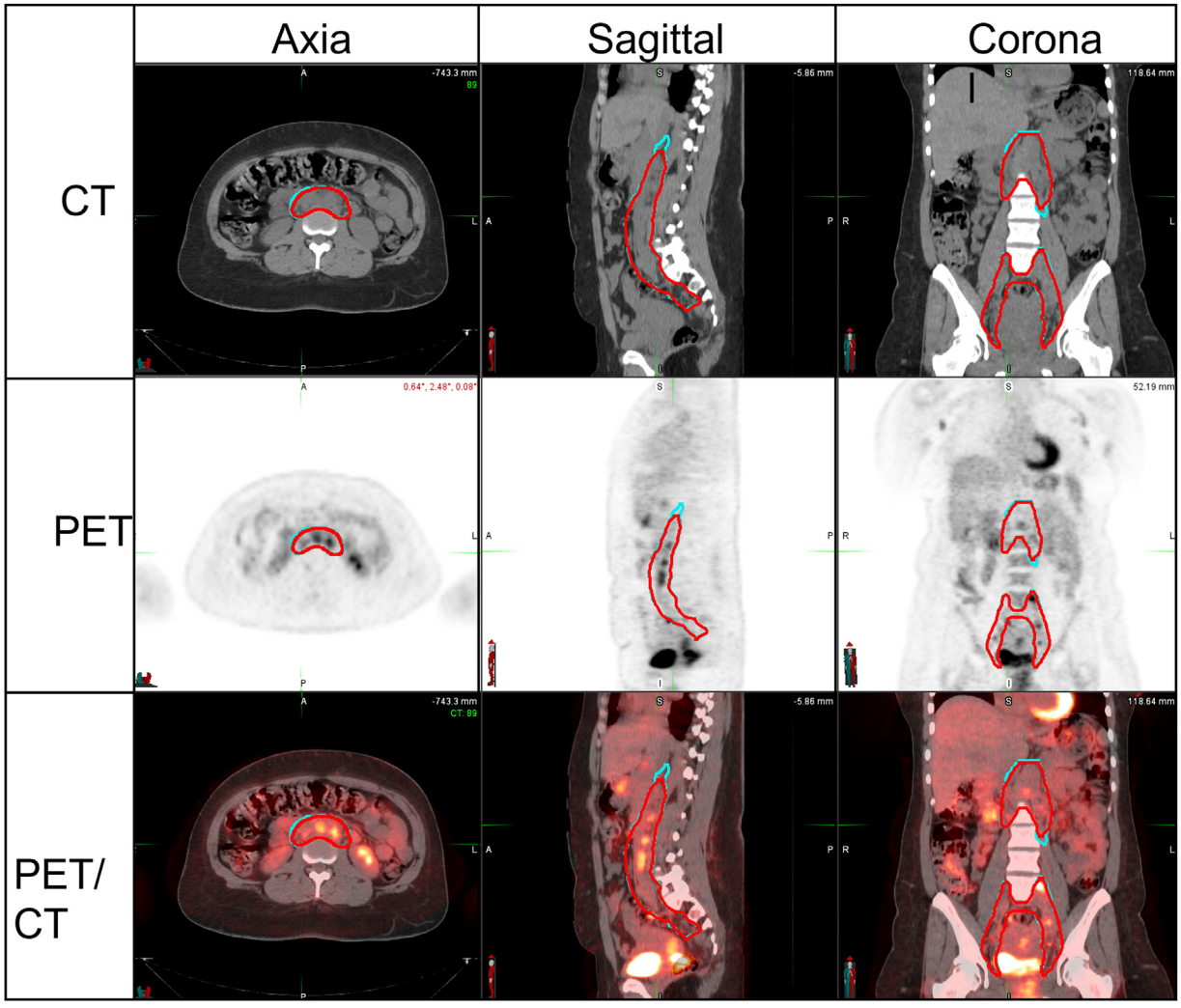

Figure 4 Case 3 showing high agreement between CTV nodal simultaneous truth and performance level estimation contours and edited versions. Contours were edited out of muscle and bone but extended into the bowel in several places to allow for full coverage of positive nodes.

contrast (n = 2). While 4 (17.4%) participants used multiple of these simulation aids, 7 (30.4%) used none. For extended field treatment, supine positioning is preferred. For pelvic treatment only, prone or supine is reasonable based on the patient and institutional preference.

Most participants did the simulation with full and empty bladder scans to create an integrated target volume (ITV) (n = 21, 91.3%), while 2 added larger margins to account for bladder and rectal changes during treatment.

The variability of the contours is reported quantitatively for all 3 cases in Table 4. Kappa statistics with values between +1 (perfect agreement) and −1 (complete disagreement) were computed for each CTV. Kappa values for all CTVs ranged from 0.63 to 0.72, indicating substantial agreement among physicians. The STAPLE estimate volume for our cases is larger than the mean volume as it is not an average of the expert contours but rather a probabilistic estimate of the (unknown) "true" volume computed from the expert contours, weighted by an estimate of the sensitivity and specificity of each.

Discussion

The evolution of imaging capabilities over the last 20 years has enabled a transition from 2-dimensional to 3D with IMRT volumetric modulated arc therapy planning. The EMBRACE studies, including EMBRACE I and II, have helped guide this transition by incorporating IMRT into the registry of 3DCT or MRI-based brachytherapy.[5] This has allowed improvements in disease-specific outcomes and survival, as well as decreased toxicity. Much of the advancement has come from the integration of diagnostic imaging, an improved understanding of patterns of failure, more conformal and dose-escalated external beam radiation therapy, the use of daily image guidance, and advances in brachytherapy techniques.[11] While the incidence of cervical cancer is anticipated to decrease with access to effective human papilloma virus (HPV) vaccination and screening, many still have limited access to care and may present with the need for curative radiation, including brachytherapy.[12]

The use of more focal techniques in radiation planning and dosimetry increases the need for an accurate and reproducible setup. Approaches include simulation and diagnostic imaging in the treatment position, as well as imaging fusion to accurately address target volumes and account for movement. The widespread adoption of IMRT, supported by the Radiation Therapy Oncology Group 1203 in postoperative settings and used commonly in intact uterus patients, allows for concavity and protection of normal tissue.[13,14] Additionally, simultaneous integrated boost allows for shortening of the course and achievement of completion of treatment in under 7 to 8 weeks, an important quality and outcome measure. At CT simulation, use of full and empty bladder scans to create an ITV, including the vaginal canal, cervix, and uterus, is important. Larger tumors that may be tethered laterally or impeding anteflexion can change setup drastically as tumors respond, and adaptive planning may help with this response and realignment.

During treatment, daily cone beam CT to assess hollow organ filling and the inclusion of the uterus and cervix in the treatment field minimizes the risk of geographic miss. Most practitioners would increase the margin along the uterus beyond the CTV/ITV by at least 2 cm to account for uterine motion and also verify on daily cone beam CT. Of note, a larger margin is necessary for the uterus due to the filling of the uterine bladder and rectum, which might displace the uterus by several centimeters. Using an ITV can help minimize uncertainty and decrease the margins needed for the planning treatment volume (PTV) expansion.

For PTV, nodal margins ranging between 5 and 7 mm are used by most practitioners; however, in obese patients, larger PTV margins might be considered.[15] Contours and PTV expansion should reflect the position of nodes, and a simple expansion of the blood vessels without evaluation is not recommended.

In determining appropriate nodal coverage, pelvic nodal burden and nodal location both affect the risk of PA nodal involvement and the need for coverage. Reasons to include the PA chain superiorly to the renal vessels include 3 or more pelvic lymph nodes and/or common iliac nodal involvement.[5] If PA nodes are involved (ie, above the common iliac bifurcation), then coverage to the renal vessels is mandatory, and superior PA nodes are considered for coverage in most cases. In cases with rectal or mesorectal involvement (including involvement of mesorectal lymph nodes), most experts would cover the entire mesorectum in the CTV and accept a higher volumetric dose to the rectum. Additionally, adding inguinal coverage for lower vaginal involvement is highlighted and reviewed in detail. These specific scenarios are uncommon but provide an opportunity to improve outcomes.

Study limitations include the inability to select all clinical scenarios to review and contour. We selected both common and difficult cases for primary tumor and nodal anatomy and covered other scenarios in accompanying questions that most participants responded to. Additionally, PTV expansion varied among the groups and practices. Finally, organ-at-risk contouring has previously been well covered and is not a focus of this study, but it may impact the ability to meet planning goals.

In conclusion, this analysis showed a high degree of concordance in contouring when integrating multimodal imaging from CT, MRI, and PET. The resultant contours are intended as a guide for select, but not all, challenging cases.

Disclosures

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