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### ► To cite this version:

Olivier de Hertogh, Guillaume Le Bihan, Thomas Zilli, Samuel Palumbo, Marjory Jolicoeur, et al.. Consensus Delineation Guidelines for Pelvic Lymph Node Radiation Therapy of Prostate Cancer : On Behalf of the Francophone Group of Urological Radiation Therapy (GFRU). International Journal of Radiation Oncology, Biology, Physics, 2024, 118 (1), pp.29-40. 10.1016/j.ijrobp.2023.07.020 . hal-04813729

**HAL Id: hal-04813729**

<https://hal.science/hal-04813729v1>

Submitted on 2 Dec 2024

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## CLINICAL INVESTIGATION

# Consensus Delineation Guidelines for Pelvic Lymph Node Radiation Therapy of Prostate Cancer: On Behalf of the Francophone Group of Urological Radiation Therapy (GFRU)



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Received Mar 8, 2023; Accepted for publication Jul 14, 2023

**Purpose:** Clinical target volume (CTV) delineation for pelvic lymph nodes in prostate cancer is currently based on 3 consensus guidelines with some inherent discrepancies. To improve the reproducibility in nodal delineation, the Francophone Group of Urological Radiotherapy (Groupe Francophone de Radiothérapie Urologique [GFRU]) worked toward proposing an easily applicable, reproducible, and practice-validated contouring guideline for pelvic nodal CTV.

**Methods and Materials:** The nodal CTV data sets of a high-risk node-negative prostate cancer clinical case contoured by 86 radiation oncologists participating in a GFRU contouring workshop were analyzed. CTV volumes were defined before and after a structured presentation of literature data on lymphatic drainage pathways and patterns of nodal involvement and relapse, illustrated using a reference contour (CRef) defined by 3 GFRU experts. The consistency between the participants' contours and CRef was assessed quantitatively by means of the Simultaneous Truth and Performance Level Estimation (STAPLE) method, the Dice coefficient, and the Hausdorff distance and qualitatively using a count map. These results combined with the literature review were thoroughly discussed among GFRU experts to reach a consensus.

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Disclosures: O.D.H. reports the following: OpenEyes (royalties, as copy-right holder); Aquilab (consulting fees); Accuray Inc, Janssen-Cilag, Astellas Pharma, and Becton-Dickinson (honoraria for lectures); Becton-Dickinson and Recordati (support for travel); Merck KGaA (board of experts/reviewers, TrilynX trial). T.Z. reports the following: Varian (grant); Swiss National Science Foundation (grant); Janssen, Debiopharm, and Astellas (consulting fees); Janssen and Debiopharm (support for travel).

T.D. reports the following: Sanofi and Novartis (honoraria for lectures); AbbVie, Tercera, and Knight Therapeutics (participation on a monitoring/advisory board). All other authors have no disclosures to report.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

**Acknowledgments**—The authors thank Aquilab (Loos, France) for the technical support and acknowledge the help of Clarisse Bartau in processing the statistical data. In addition, the authors thank Pippa McKelvie for medical writing assistance.

**Results:** From the 86 workshop participants, the volume of the STAPLE CTV was 591 cc compared with 502 cc for CRef. The Dice coefficient of the STAPLE CTV compared with the experts' CRef was 0.736 ( $\pm 0.084$ ) before and 0.823 ( $\pm 0.070$ ) after the workshop; the standard deviation decreased from 11.5% to 8.5% over the workshop. The Hausdorff distance of the STAPLE CTV compared with the CRef was 34.5 mm ( $\pm 12.4$ ) before the workshop and 21.8 mm ( $\pm 9.3$ ) after the workshop. Four areas of significant interobserver variability were identified, and a consensus was reached.

**Conclusions:** Using a robust methodology, our cooperative group proposed an easily applicable, reproducible, and practice-validated guideline for the delineation of the pelvic CTV in prostate cancer, useful for implementation in daily practice and clinical trials. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## Introduction

External beam radiation therapy is one of the standard treatments of prostate cancer. Prophylactic pelvic lymph node radiation therapy (PLNRT) is commonly proposed in patients with localized or locally advanced tumors harboring a risk of nodal dissemination<sup>1</sup> or in the postoperative setting at biochemical relapse.<sup>2</sup> However, pelvic lymph node delineation is challenging and suffers from a large variability among radiation oncologists,<sup>3</sup> with a potential effect on the oncological outcomes and treatment-related toxicities.

Historically, 3 cooperative groups defined recommendations for the delineation of the nodal clinical target volume (CTV).<sup>4-6</sup> Since these publications, it became obvious that updated contouring guidelines were required for several reasons. First, recent studies on the implementation of next-generation imaging like prostate-specific membrane antigen positron emission tomography/computed tomography (PET/CT) for staging and restaging of prostate cancer have changed our understanding of lymph node drainage pathways,<sup>7</sup> affecting how lymph node relapses are treated.<sup>8</sup> This is the reason why the NRG Oncology genitourinary core committee updated the consensus atlas for pelvic nodal contouring from the original Radiation Therapy Oncology Group (RTOG) atlas.<sup>9</sup> Second, these recommendations rely on experts' opinions and local treatment standards. For instance, the updated NRG guidelines are based on a consensus discussion by 18 expert radiation oncologists, with further help of expert urologists. Their work has not been confronted to the ability of common radiation oncologists nor validated in daily practice. Third, these recommendations show significant discrepancies, which might create confusion, lead to under- or overtreatment of some areas with a risk either of geographic miss or of increased toxicity, and further impair their implementation in clinical routine. A consensus is needed.

Using the unique data set of a dedicated contouring workshop realized before the NRG publication, the Francophone Group of Urological Radiotherapy (Groupe Francophone de Radiothérapie Urologique [GFRU]) tried to redefine a contouring consensus that would both be based on contemporary radio-anatomic data and be easily and reproducibly used for daily clinical treatment of patients with prostate cancer by average radiation oncologists.

## Methods and Materials

A MEDLINE-based literature review of available data regarding the lymph node drainage pathways of prostate cancer at the time of initial diagnosis and in case of postoperative biochemical relapse was performed by 3 radiation oncologists from the GFRU committee (ODH, PS, SP – *anonymized for review*). Keywords included “prostate cancer,” “radiotherapy,” “lymphadenectomy,” “lymphography,” “sentinel node(s),” “magnetic resonance imaging,” “computed tomography,” “PET,” “lymph node dissection,” “lymph node drainage,” and “nodal relapse.” The research algorithm used by the GETUG-AFU group<sup>6</sup> was updated for publications between 2015 and 2021. Original articles, consensus publications, reference articles, and review papers about lymph node drainage, imaging, and pelvic CTV contouring in prostate cancer were selected. Papers published in any language other than English, editorials, case reports, and letters to the editor were excluded from this literature selection and review. Additional references were identified from other sources. Based on this literature review, a reference contour (CRef) volume was generated for PLNRT using the images from a 68-year-old patient with localized T2b N0 M0, International Society of Urological Pathology grade group 3 prostate adenocarcinoma, with an initial prostate-specific antigen level of 24 ng/mL.

This CRef was compared with participants' individual contours performed at the time of 3 consecutive GFRU workshops by radiation oncologists with an interest in prostate cancer. During these workshops, the same clinical case was presented. On the anonymized DICOM (Digital Imaging and Communications in Medicine) data set of the patient, the participants were requested to delineate a prophylactic nodal CTV for this case of localized high-risk prostate cancer without delineating neither the prostate or seminal vesicles nor the organs at risk (OARs). They performed a first contour according to their own knowledge and local practice guidelines before the workshop; then, at the time of the workshop, the literature review results and CRef were presented to participants, and they were requested to delineate a second contour. Each participant's DICOM data of the CT scan subsets, and individual contours from both before the workshop (BWC, before-workshop contour) and after the workshop (AWC, after-workshop contour) were then transferred for comparison

with CRef using the exchange and evaluation platform from Aquilab (Loos, France).

For quantitative analysis, the Simultaneous Truth and Performance Level Estimation (STAPLE) method was used to generate a probabilistic contour representing the global aggregated result of all participants, the STAPLE CTV.<sup>10</sup> Contour analysis was performed using the Dice coefficient and the Hausdorff distance.<sup>11,12</sup> These metrics with standard deviation were calculated to compare the STAPLE CTV to the CRef and each individual participant's contour to the STAPLE CTV. For qualitative analysis, the CTV of each participant was used to create a count map with the same spatial resolution as the scanographic imaging modality used. In such a map, each voxel color is determined by the superposition of observers who included the corresponding image voxel in their CTV. It provided a visual representation of consensual areas delineated by most if not all radiation oncologists (warmer colors, from orange to bright red) and controversial areas where significant interobserver variability happened (colder colors, from blue to green and yellow). These areas were identified using the BWC and allowed experts to provide oriented teaching during the workshop to help participants overcome specific difficulties.

Results of this quantitative and qualitative analysis were presented to all GFRU experts in February 2021 via videoconferencing. All areas of discrepancies between CRef and the participant's contours were identified and discussed. The aim was to establish a consensus on the anatomic limits of the pelvic lymph node stations to be included in a recommended CTV for PLNRT.

## Results

### Quantitative and qualitative analysis

Eighty-six radiation oncologists from Belgium, Luxemburg, France, Switzerland, Morocco, Algeria, Tunisia, and Québec, aged 27 to 68 years, participated in the 3 consecutive contouring workshops organized by the GFRU.

For all 86 participants, the mean volume of the BWC was 364 cc ( $\pm 86$  cc) whereas the volume of AWC was 436 cc ( $\pm 60$  cc), the standard deviation decreasing from 23.5% to 13.6% over the workshop. The STAPLE CTV was 591 cc compared with 502 cc for CRef.

The Dice coefficient of the STAPLE CTV compared with the experts' CRef was 0.736 ( $\pm 0.084$ ) before the workshop and 0.823 ( $\pm 0.070$ ) after the workshop, the standard deviation decreasing from 11.5% to 8.5% over the workshop. The mean Dice coefficient of the individual participants' CTV compared with the STAPLE CTV was 0.716 ( $\pm 0.099$ ) before the workshop and 0.813 ( $\pm 0.073$ ) after the workshop, the standard deviation decreasing from 13.8% to 8.9% over the workshop.

The Hausdorff distance of the STAPLE CTV compared with the experts' CRef was 34.5 mm ( $\pm 12.4$ ) before the workshop and 21.8 mm ( $\pm 9.3$ ) after the workshop. The mean

Hausdorff distance of the individual participants' CTV compared with the STAPLE CTV was 40.3 mm ( $\pm 17.7$ ) before the workshop and 22.9 mm ( $\pm 9.4$ ) after the workshop.

Qualitative analysis of the counting zones provided a visual representation of controversial areas. The 4 main areas of discrepancy were (1) the upper limit of the CTV, namely the level up to which the common iliac region had to be delineated; (2) the transition from the inguinal to the external iliac region; (3) the width of the tissue strip linking the external and internal iliac regions and encompassing the obturator region; and (4) the definition of the presacral area (Fig. 1).

### Consensus

After the presentation and discussion of this quantitative and qualitative analysis, and in light of data from the literature, a consensus for the delineation of the pelvic CTV for PLNRT was reached (Fig. 2). The boundaries of each individual nodal area to be included in this CTV are summarized in Table 1.

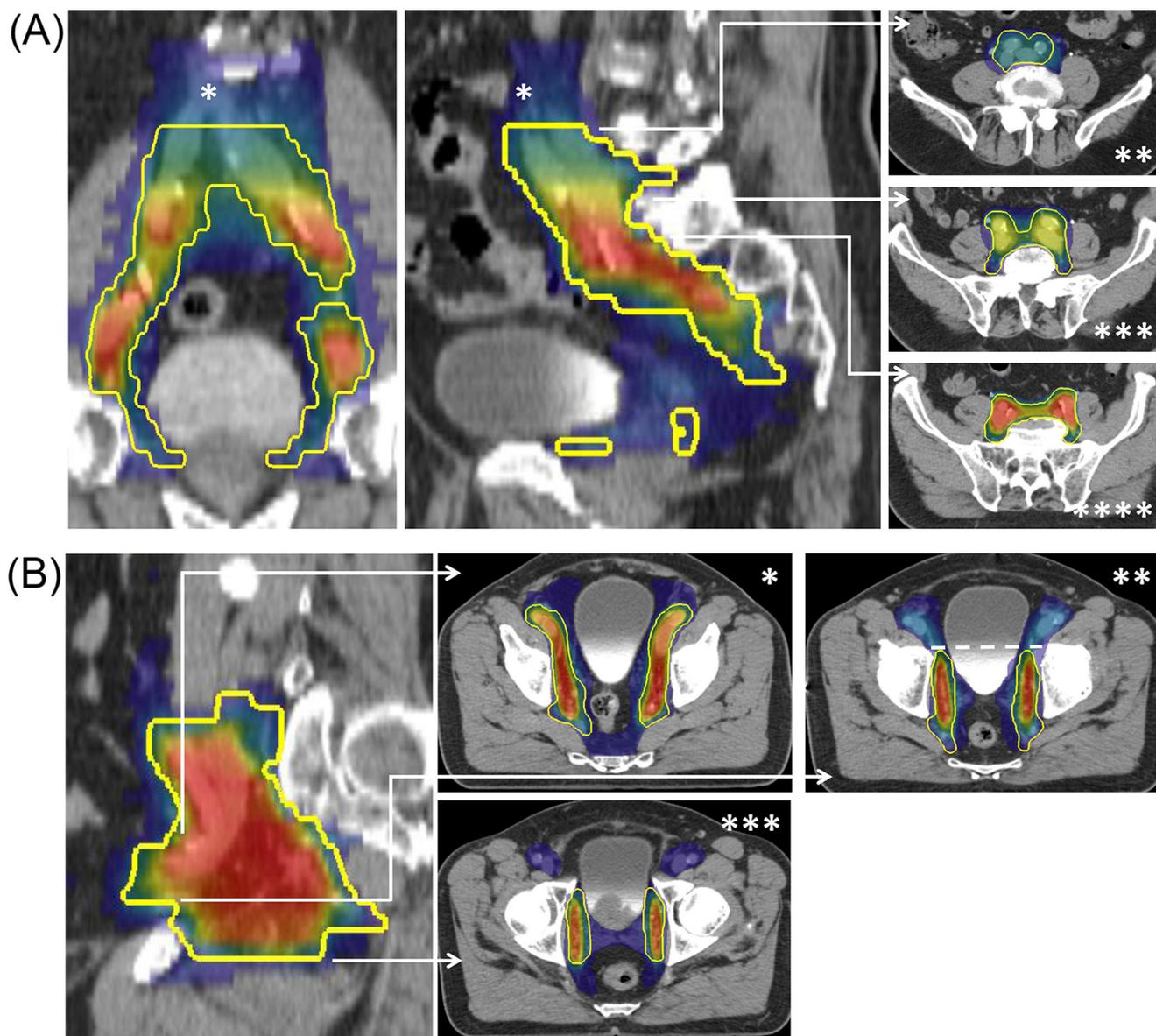
As a general principle, all experts considered that the nodal stations to be included in the pelvic CTV were the same in both the definitive and postoperative settings. The CTV should therefore be based on a vascular approach, accurately reflecting the lymph node drainage pathways<sup>13-16</sup> and the individual anatomic variations among patients, and not on an old-fashioned approach based on bony landmarks. Nevertheless, on some occasions, the proximity of a vascular landmark to a bony landmark was enlightened to help radiation oncologists locate the vascular landmark and transition from the old (bony) to the new (vascular) approach.

The delineation of the pelvic CTV includes both the vein and the artery with an additional margin of 7 mm around the blood vessels, according to magnetic resonance imaging (MRI) data obtained from the use of lymphotropic nanoparticles.<sup>14</sup> CTV margins are cropped for fixed and impassable anatomic barriers such as muscles and bones which are always excluded for the perivascular expansion margin (Fig. 2A). The interface between CTV margins and OARs was addressed during the workshops and remained a point of discussion. For instance, in the case of the bowel, some radiation oncologists would limit the CTV margin to the bowel bag (such as the GFRU experts) while others would allow the margin to extend within this mobile structure or would use a planning OAR volume. A certain degree of freedom should remain at the discretion of the radiation oncologist, depending on local practices and on the anatomy and comorbidities of the individual patient.

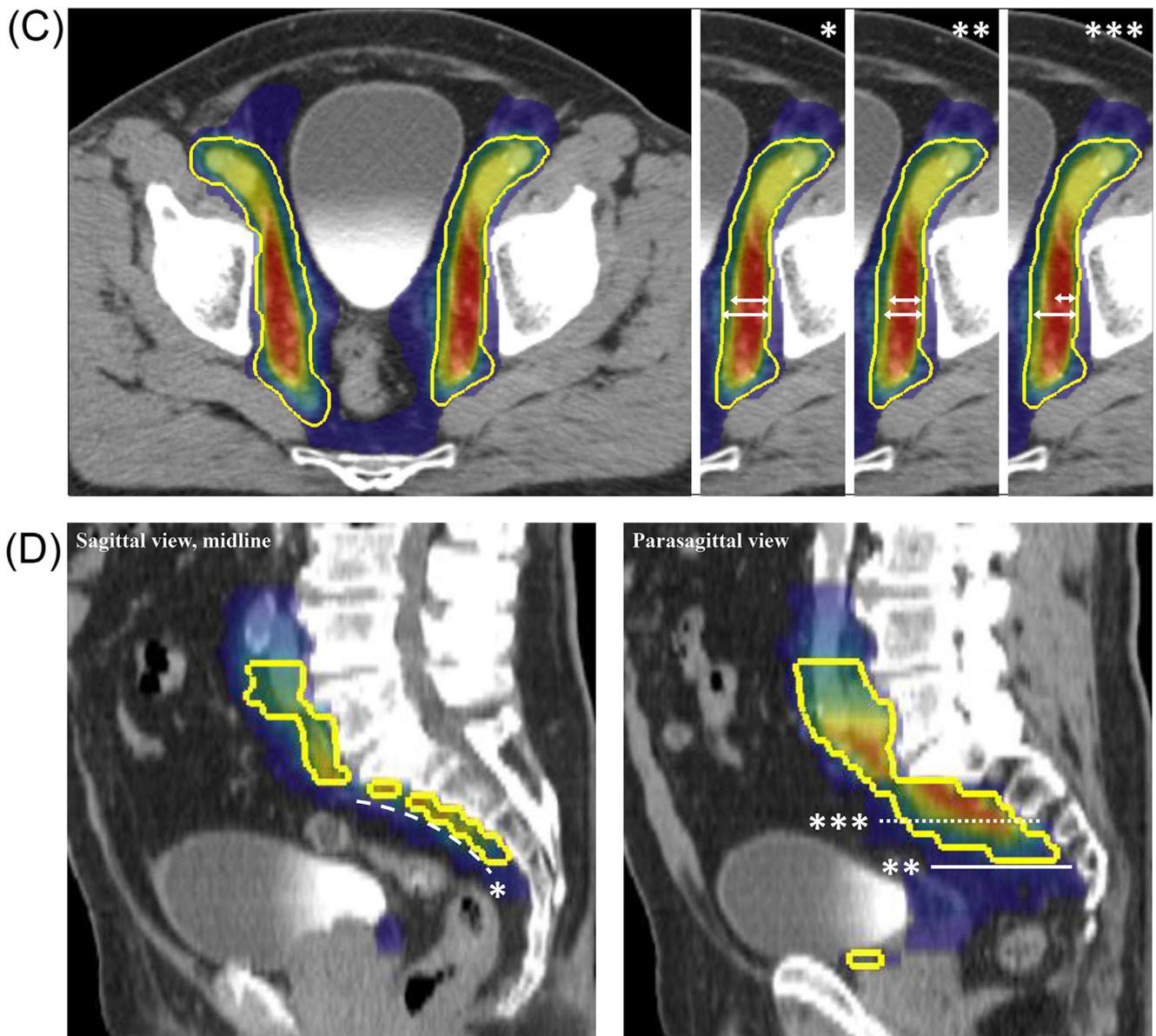
The cranial edge of the pelvic CTV is defined as the aortic bifurcation into the common iliac arteries (Fig. 2B, 2C). This means that the common iliac area would be delineated as a whole, including both its distal and proximal parts. The para-aortic area extending cranially to this bifurcation is not considered as part of the pelvic CTV. The posterior edge of the common iliac area is defined as the iliac psoas muscle

and the anterior edge of the lumbar and sacral vertebral pieces, without extending the contour into the sacral foramen (Fig. 2D). The medial edge of the area is defined by the same structures and by the presacral area caudally. The anterior and lateral edges of the area are limited to a 7-mm

expansion around the common iliac vessels. Nevertheless, this margin should be expanded posteriorly and laterally to include the fossa lumbo-sacralis of Cuneo and Marcille, as it contains the iliolumbar vessels who are anatomically part of the common iliac drainage pathway (Fig. 2E). Caudally, the



**Fig. 1.** Count maps showing controversial regions identified. (A) Upper limit of the CTV. Excessive extension of the contour above the aorto-iliac bifurcation into the paraortic region – 25% of participants (\*). Required extension of the contour up to the aorto-iliac bifurcation – 30% of participants (\*\*). Insufficient extension of the contour up to the sacral promontory – 60% of participants (\*\*\*) or the body of S1 – 85% of participants (\*\*\*\*). (B) Transition between the inguinofemoral and the external iliac regions. External iliac region starting when the vessels adopt a horizontal path above the upper edge of the iliopubic branch (\*). Limit of the external iliac region: coronal plane (dashed line) drawn between the anterior edges of the iliac bones (\*\*). Excessive extension of the contour into the inguinofemoral region – 40% of participants (\*\*\*). (C) Width of the tissue strip linking the external and internal iliac regions and encompassing the obturator region. Width according to GFRU guidelines: 18 (upper arrow) to 22 mm (lower arrow) (\*). Width according to NRG gynaecology guidelines: 15 (upper arrow) to 18 mm (lower arrow) (\*\*). Width according to NRG prostate guidelines: 10 (upper arrow) to 20 mm (lower arrow) (\*\*\*). (D) Presacral region. Anterior limit of the presacral region: 12 mm strip (dashed line \*) anterior to the bone. Caudal limit of the presacral region: lower edge of S3 (continuous line \*\*) at the S3-S4 interspace. Caudal limit most commonly delineated by the participants : lower edge of S2 (dotted line \*\*\*) at the S2-S3 interspace.



**Fig. 1.** Continued.

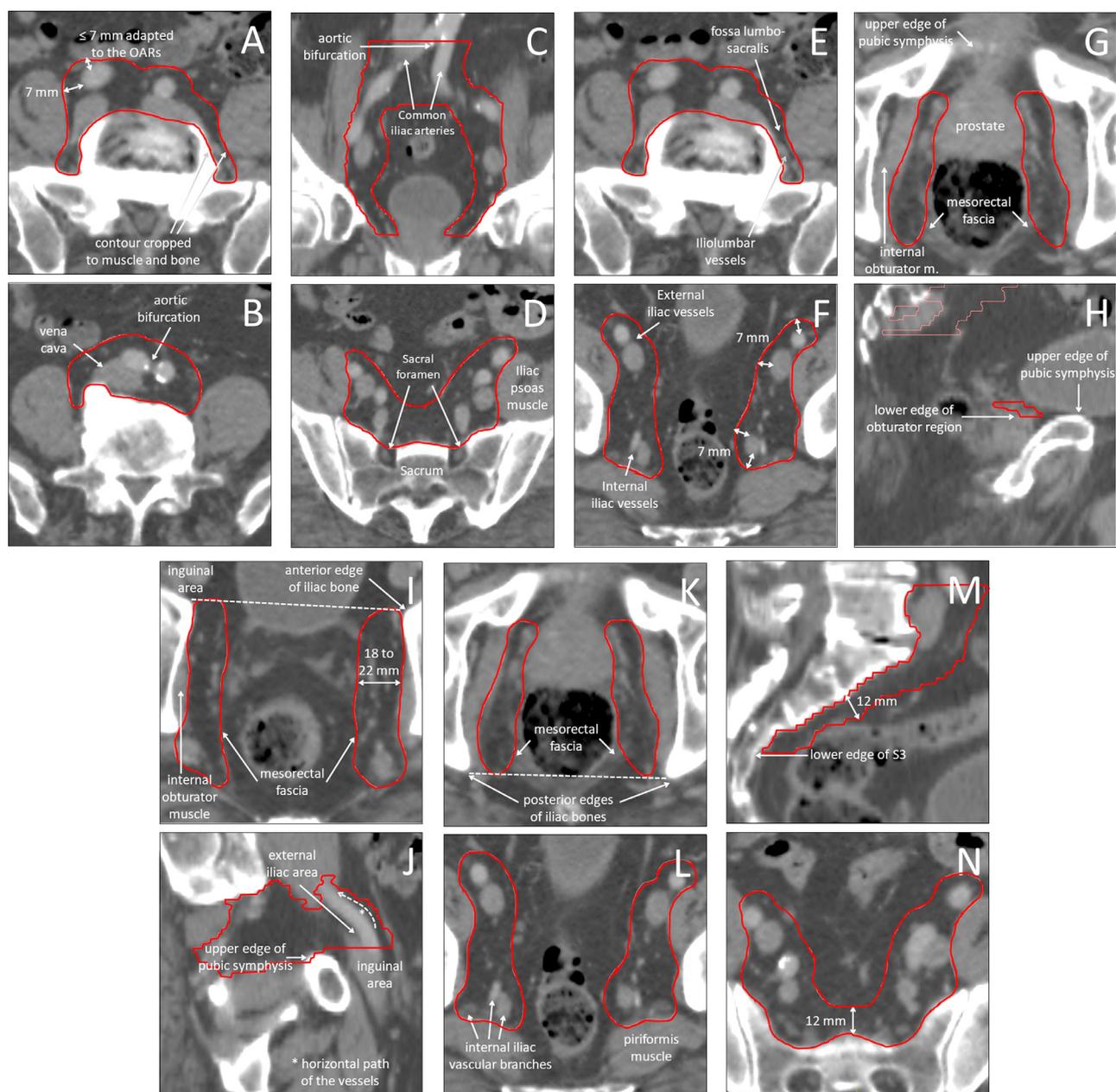
common iliac area ends with the birth of the internal and external iliac areas.

The internal iliac, external iliac, and obturator areas are included in the pelvic CTV. A margin of 7 mm (adjusted for the muscles and bony anatomy) is applied around the internal and external iliac vessels to define the corresponding nodal areas (Fig. 2F).

The caudal edge of the obturator region is defined by a horizontal plane tangential to the upper edge of the pubic symphysis (Fig. 2G, 2H). The obturator area is delineated as an 18 to 22-mm strip medial to the internal edge of the internal obturator muscle, the ilio-pubic branch and the iliopsoas muscle, adjusted to exclude the prostate, seminal vesicles, and mesorectum (Fig. 2G, 2I). The anterior edge of the obturator area is a coronal plane tangent to the anterior edges of the iliac bones (Fig. 2I, dashed line), thus not extending the contour to

the inguinal area before joining with the external iliac area when the vessels adopt a horizontal path above the upper edge of the ilio-pubic branch to enter the pelvis (Fig. 2J, dashed arrow). The posterior edge of the obturator area is a coronal plane tangent to the posterior edges of the iliac bones (Fig. 2K, dashed line), adjusted to the mesorectal fascia and piriformis muscle, before extending posteriorly when joining with the internal iliac area where the middle rectal, internal pudendal, and inferior gluteal vessels collide (Fig. 2K, 2L).

The presacral area is defined as a 12-mm prevertebral strip, adjusted for the bowel and peritoneal bag. It extends from a transversal plane tangent to the lower edge of S3 caudally, to the proximal common iliac region cranially (Fig. 2M, 2N). Its posterior edge is the anterior aspect of the sacrum, not reaching into the sacral foramina, and its lateral edge consists of the internal and common iliac areas.



**Fig. 2.** Consensus atlas for the delineation of the pelvic clinical target volume (CTV) for pelvic lymph node radiation therapy. (A) CTV margin applied around the blood vessels. (B, C) Cranial edge of the CTV. (D, E) Posterior edge of the common iliac area. (F) Internal iliac and external iliac areas. (G, H) Caudal edge of the obturator region. (I, J) Medial and anterior edges of the obturator region. (K, L) Posterior edge of the obturator region. (M, N) Presacral area. *Abbreviation:* OAR = organ at risk.

The perirectal, mesorectal, and paraaortic lymph node areas are not routinely included in the pelvis CTV for PLNRT.

## Discussion

Beyond the existence of anatomic guidelines explaining how to perform PLNRT, the rationale for performing PLNRT in prostate cancer remains controversial. The first trials investigating the role of whole-pelvis radiation therapy (WPRT)

over prostate-only radiation therapy reported mixed results,<sup>17,18</sup> probably due to an inconsistent definition of the pelvic target volumes.<sup>19</sup> On the other hand, the positive results of the POP-RT trial, which demonstrated an outcome benefit by adding WPRT in high-risk and locally advanced patients with a high risk of pelvic lymph nodes invasion, could be explained by the inclusion in the target volume of the whole common iliac region, together with the delivery of a 50 Gy prophylactic dose using image guidance and intensity modulated techniques.<sup>20</sup> Similarly, in the post-operative setting, the NRG Oncology/RTOG 0534 SPPORT

**Table 1 Francophone Group of Urological Radiotherapy consensus for the delineation of the pelvic clinical target volume for pelvic lymph node radiation therapy: Boundaries of the individual nodal areas**

Nodal areas	Boundaries					
	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Obturator area	Convergence of the internal and external iliac veins	Horizontal plane tangent to the upper edge of the pubic symphysis	Caudally, coronal plane tangent to the anterior edge of the iliac bones. Cranially, external iliac area.	Caudally, coronal plane tangent to the posterior edge of the iliac bones, further limited by the piriformis muscle and mesorectal fascia. Cranially, internal iliac area.	Medial edge of the obturator internus muscle	18- to 22-mm strip medial to the internal edge of the obturator internus muscle, adjusted for pelvic organs
External iliac area	Common iliac area	Transition from the inguinal area, when the vessels adopt a horizontal path above the upper edge of the iliopubic ramus	Blood vessels plus a 7-mm margin, adjusted for pelvic organs	Obturator area	Sartorius muscle, rectus femoris muscle, iliac bone, and obturator internus muscle	Blood vessels plus a 7-mm margin, adjusted for pelvic organs
Internal iliac area	Common iliac area	Convergence of the middle rectal, internal pudendal, and inferior gluteal vessels	Obturator area	Blood vessels plus a 7-mm margin, adjusted for the piriformis muscle	Medial edge of the iliac bone and piriformis muscle	Caudally, blood vessels plus a 7-mm margin, adjusted for pelvic organs. Cranially, presacral area.
Presacral area	Sacral promontory and convergence of the common iliac veins	Horizontal plane tangent to the inferior edge of S3	12-mm strip anterior to the sacrum, adjusted for pelvic organs	Anterior edge of the sacrum, not reaching into the sacral foramen	Piriform muscle and internal/common iliac areas	N/A
Common iliac area	Lower edge of the aortoiliac bifurcation, approximately at the level of the L4-L5 junction	Internal/external iliac areas	Blood vessels plus a 7-mm margin adjusted for pelvic organs	Iliac psoas muscle and anterior edge of the lumbar and sacral vertebral pieces, reaching into the fossa lumbo-sacralis of Cuneo and Marcille	Blood vessels plus a 7-mm margin adjusted for iliac psoas muscle	Caudally, presacral area. Cranially, lateral edge of the lumbar and sacral vertebral pieces.

*Abbreviation:* N/A = not applicable.

trial<sup>2,21</sup> showed a disease progression benefit at 5 years by adding WPRT to prostate bed irradiation in combination with short-term androgen deprivation therapy, while no

differences were observed in terms of metastasis-free, cancer-specific, and overall survivals. Although pending trials will help to define the real clinical role of WPRT for prostate

cancer (NCT01952223, NCT01368588, ISRCTN80146950), the use of a homogenous and reproducible delineation of pelvic lymph nodes among centers is of significance.

At the time of the GFRU contouring workshops, the updated NRG contouring guidelines were not published yet.<sup>9</sup> It is therefore very interesting to compare our results to these NRG guidelines (Table 2). NRG Oncology based its consensus guidelines on the previous RTOG pelvic guidelines, on an updated literature review, and on a quantitative and qualitative comparison of 18 international experts' contours. In analogy, we also used an updated literature review to create the CRef, but we compared it to the "real-world" pelvic contours of 86 radiation oncologists working worldwide. The flowcharts of both consensus process for pelvic contouring guidelines are shown in Fig. 3. Moreover, unlike the NRG guidelines, we decided not to differentiate the definitive and the postoperative setting, in the absence of literature data suggesting a modification of the pelvic lymphatic drainage pathways after radical prostatectomy.

From a quantitative standpoint, the mean NRG Oncology experts' CTV was 342 and 302 cc in the definitive setting and postoperative setting, respectively. In our study, the volume of CRef and the mean volumes of BWC and AWC were 502 cc, 364 cc, and 436 cc, respectively. Differences in absolute volume between the GFRU and NRG contours are difficult to interpret, as they could simply arise from the individual patient anatomic variations, even if differences in the contouring guidelines themselves might also play a part. For instance, the NRG guidelines recommend to contour approximately 5 to 7 mm around each iliac vessel, whereas our guidelines make it mandatory to respect a 7-mm margin according to MRI data obtained from the use of lymphotropic nanoparticles.<sup>13</sup> The NRG guidelines also advocate delineating an obturator region as thin as 10 mm, whereas our guidelines make it mandatory to delineate a tissue strip of a minimum of 18 mm medial to the internal obturator muscle. Both the NRG and GFRU volumes are larger than the historical RTOG guidelines volume (mean volume, 287 cc)<sup>5</sup> and PIVOTAL guidelines (mean volume, 310 cc),<sup>4</sup> which appears logical as an extended delineation of the common iliac regions up to the level of the aortic bifurcation is recommended nowadays by both guidelines.

Hall et al documented a mean Dice coefficient of 0.66 ( $\pm 0.18$ ) and 0.63 ( $\pm 0.13$ ) in the definitive and postoperative setting, respectively.<sup>9</sup> In our study, when comparing the STAPLE CTV to the experts' CRef, concordance appeared to be better from the start and was further improved after the workshop. When comparing the mean Dice coefficient of the individual participants' CTV to the STAPLE CTV, a similar improvement in concordance was observed over the course of the workshop. Hall et al documented a mean Hausdorff distance of 3.3 mm ( $\pm 2.4$ ) and 2.4 mm ( $\pm 1.3$ ) in the definitive and postoperative setting, respectively.<sup>9</sup> As for the Dice coefficient, the Hausdorff distance significantly decreased over the course of the workshop when respectively comparing the STAPLE CTV to CRef and the individual participants' CTV to the STAPLE. The larger Hausdorff

distance observed in the GFRU study may be related to background and educational differences between the radiation oncologists who submitted their contours for the NRG Oncology study and the GFRU study, respectively. The NRG group consists of a relatively small number (18) of highly selected experts in the field of prostate cancer expected to have a priori in-depth knowledge of the existing contouring guidelines and pitfalls, whereas the GFRU consists of a much larger number (86) of nonselected radiation oncologists with a self-declared need for a training in prostate cancer delineation. Furthermore, the GFRU group comes from different countries, health care systems, and academic or nonacademic hospitals, thus representing the broad spectrum of our profession and adequately illustrating the applicability of the GFRU guidelines and the potential benefit of the workshops.

From a qualitative standpoint, Hall et al<sup>9</sup> identified 4 areas of interobserver variability where experts struggled to reach an agreement: (1) the upper edge of the common iliac nodes; (2) the transition between the external iliac and inguinal nodes; (3) the inclusion of the periprostatic nodes; and (4) the inclusion of the perirectal nodes. Interestingly, during the GFRU validation workshops, the first 3 points also were deemed a matter of debate, the latter not being an issue. A fourth point of debate addressed during the workshops was the inferior limit of the presacral area. Each of the areas of discrepancy found in the GFRU workshops and illustrated in Fig. 1 is discussed next.

As far as the upper limit of the pelvic CTV is concerned, authors such as Spratt et al, Michaud et al, and Schiller et al<sup>15,22,23</sup> demonstrated the rationale for including the common iliac region, the limit being the inferior edge of the aortic bifurcation into the common iliac arteries (or, for the NRG only, the vena cava bifurcation if it is more cranial than the aorta's). In our study, 25% of participants initially extended their contour cranially above the bifurcation, within the paraaortic region. However, in node-positive nonmetastatic patients evaluated before the era of next-generation imaging modalities, the RTOG 7506 trial showed no benefit of elective periaortic irradiation in patients with detectable disease confined to the pelvis.<sup>24</sup> Therefore, we do not recommend this extension of the cranial limit of the pelvic CTV.

The inguinal area is a rare site of lymphatic spread for prostate cancer, with positive nodes on molecular imaging found in less than 5% of patients.<sup>25</sup> Considering this small figure, our guidelines do not recommend the inclusion of the inguinal areas in the CTV, similarly to the NRG guidelines. Nevertheless, GFRU and NRG use slightly different anatomic boundaries to define the transition between the inguinal and external iliac regions. In our guideline, we prioritize the vascular anatomy, the external iliac region starting when the vessels adopt a horizontal path above the upper edge of the iliopubic branch, crossing a coronal plane drawn between the anterior edges of the iliac bones. The NRG guidelines define the transition between the inguinal and external iliac regions as a plan drawn anteriorly from

**Table 2 Comparison between GFRU and NRG contouring guidelines**

Site	NRG guidelines	GFRU guidelines	Reason for differences between guidelines
Superior extent of LN-CTV	Bifurcation of the aorta into the common iliac arteries or the proximal inferior vena cava to the common iliac veins, whichever occurs superiorly.	Lower aspect of the aortic bifurcation into the common iliac arteries.	
Inferior extent of LN-CTV	End the obturator fossa contours when the seminal vesicles join the top of the prostate gland or the disappearance of the fat plane between the obturator internus muscle and the prostate gland, whichever is more superior.	Superior aspect of pubic symphysis.	We find it difficult to determine the exact level of the junction between the seminal vesicles and the prostatic base on the dosimetric CT and advocate for an easier way to determine the caudal limit of the obturator region. Furthermore, no LN occurrence has been documented by imaging and surgical studies caudally to this limit.
Vascular expansion margin applied	5-7 mm AP/laterally. Where clinically indicated, CTV margins can be more generous, particularly anterior to vessels (10 mm).	7 mm AP/laterally.	Our guidelines make it mandatory to respect a 7-mm margin according to MRI data obtained from the use of lymphotropic nanoparticles. <sup>14</sup>
Structures to be edited out of LN-CTV	Bowel, bladder, bone, muscle.	Bowel, bladder, bone, muscle.	
Presacral nodal volume	Includes the prevertebral, presacral, and posterior mesorectal nodes to the bottom of S3.	S1-S3, 12-mm prevertebral strip.	The study by Dinniwell et al <sup>13</sup> using ferumoxtran-10-based MRI showed that no drainage could be found 12 mm anteriorly to the sacrum.
Level at which the external iliac volume stops	The external iliac contours should typically end when the vessels are completely lateral to the most medial aspect of the acetabulum (near the mid-femoral head and fovea). At that point, the contours should be tapered off.	The anterior edge of the obturator area is a coronal plane tangent to the anterior edges of the iliac bones (thus not extending the contour to the inguinal area) before joining with the external iliac area when the vessels adopt a horizontal path above the upper edge of the iliopubic branch to enter the pelvis.	We consider the NRG guideline definition to include an unnecessary volume of extrapelvic vessels and tissue that is not consistent with the anatomical definition of the external iliac region or with the surgical limits for LN dissection.
Obturator nodes	The obturator nodes can be between 1 and 2 cm in width and should extend to the posterior edge of the obturator internus muscle, the anterior limit being located 1 cm anteriorly	The obturator area should be delineated as an 18- to 22-mm strip medial to the internal edge of the internal obturator muscle, the iliopubic branch, and the iliopsoas muscle. The anterior edge of the	According to the publications by Taylor et al <sup>16</sup> and Dinniwell et al, <sup>13</sup> the obturator lymphatic drainage can be found no further than an 18- to 22-mm-thick tissue strip. Our anterior limit appears to be

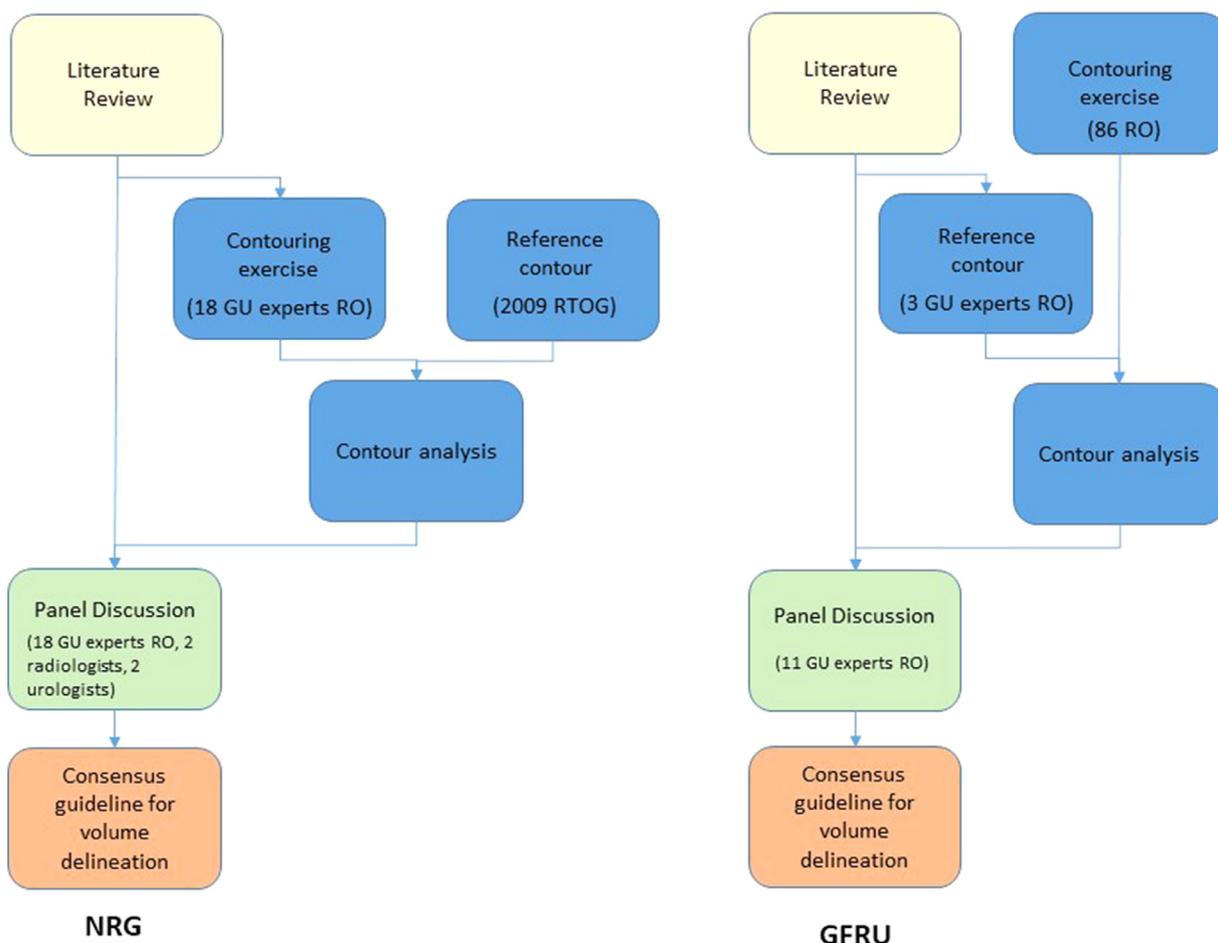
(Continued)

**Table 2** (Continued)

Site	NRG guidelines	GFRU guidelines	Reason for differences between guidelines
	from the anterior edge of the obturator muscle.	obturator area is a coronal plane tangent to the anterior edges of the iliac bones. The posterior edge of the obturator area consists of the mesorectal fascia and piriformis muscle.	anatomically more coherent with the boundaries of the external iliac region when transitioning from the inguinal area, and our posterior limit appears to be coherent with various studies demonstrating the low risk for pararectal drainage. <sup>23</sup>
<i>Abbreviations:</i> AP = antero-posteriorly; CT = computed tomography; CTV = clinical target volume; GFRU = Francophone Group of Urological Radiotherapy; LN = lymph node; MRI = magnetic resonance imaging.			

the medial edge of the acetabulum, the inguinal area being located on the outer side of this plan and the external iliac region on the internal (medial) side of this plan. Alternatively, NRG uses the entrance of the vessels in the inguinal canal and their passage under the inguinal ligament as the limit between the 2 areas. We consider the first of these

criteria to include an unnecessary volume of extrapelvic vessels and tissue which is not consistent neither with the anatomic definition of the external iliac region nor with the surgical limits for lymph node dissection, and the second to be trickier to use in daily routine with the risk of increase in interobserver variability.



**Fig. 3.** Flowchart of consensus process for NRG and Francophone Group of Urological Radiotherapy pelvic contouring guidelines. *Abbreviations:* GU = genitourinary; RO = radiation oncologists; RTOG = Radiation Therapy Oncology Group.

One additional issue that was not addressed by Hall et al<sup>9</sup> but was an important matter of debate and of interobserver variability during our contouring workshops was the thickness of the soft tissue strip to delineate medially to the internal edge of the obturator muscle. According to the respective publications by Taylor et al<sup>16</sup> and Dinniwell et al,<sup>13</sup> the obturator lymphatic drainage can be found no further than an 18- to 22-mm-thick tissue strip, linking the external to the internal iliac region and located internally to the medial edge of the obturator muscle. This definition proves to be very useful in clinical routine, as there are a lot of small vascular structures located medially further away from the obturator muscle whose inclusion (or not) by the participants to the GFRU workshops was the source of heavy interobserver variability. Such inclusion is both unnecessary from an anatomic point of view, and potentially harmful as it would increase dose to the neighboring OARs such as the rectum and bladder. A specific distance, either 18 or 22 mm, proves to be a much more robust definition, even if it diverges from the less precise 10 to 20 mm advocated by the NRG.<sup>9</sup> Interestingly, in a similar effort to Small et al<sup>26</sup> for the postoperative treatment of cervical and endometrial tumors, the proposed width for the obturator region is 15 to 18 mm medially to the obturator muscle, which is quite closer to the GFRU proposal.

The definition of the presacral area, even though it was absent from Hall et al's points of discussion, proved in our experience to be an important matter of debate, consistently questioned by participants during the GFRU workshops. Most radiation oncologists drew their contour no further caudally than the S2-S3 interspace, whereas mapping studies clearly show the possibility of a more caudal lymph node drainage indicating the need for expanding the contour to the S3-S4 interspace. GFRU and NRG guidelines are consistent in that matter. Moreover, we observed significant variation among the participants to our workshops regarding the thickness of the tissue strip delineated anteriorly to the sacrum. The study by Dinniwell et al using ferumoxtran-10-based MRI showed that no drainage could be found further anteriorly than 12 mm,<sup>13</sup> this being the margin that the GFRU proposes to use for delineating the presacral region. Even though the thickness of the presacral area is not defined in the work by Hall et al for prostate cancer, Small et al reported a quite similar 10 to 15 mm for gynecology.<sup>26</sup>

Last but not least, the GFRU and NRG propose different anatomic boundaries to define the obturator region. In the NRG guidelines, the anterior limit of the obturator region is located 1 cm anteriorly from the anterior edge of the obturator muscle, whereas the GFRU uses a coronal plane tangent to the anterior edge of the iliac bone, which appears to be anatomically more coherent with the boundaries of the external iliac region when transitioning from the inguinal area. Similarly, the NRG uses the posterior edge of the obturator muscle as a surrogate for the posterior limit of the obturator region, whereas the GFRU advocates for using the

anterior aspect of the mesorectal fascia and piriformis muscle. These anatomic boundaries appears to be coherent with various studies demonstrating the low risk for pararectal drainage.<sup>22</sup> Finally, the GFRU guidelines also diverge from the NRG regarding the caudal limit of the obturator region and its transition to the periprostatic region. The NRG uses the junction between the seminal vesicles and the prostatic base as a surrogate for this limit. We find this definition to be difficult to use in clinical routine, as the exact level of this "junction" might be difficult to assess on the planning CT. Even though the caudal limit of the obturator region might be anatomically defined by the entry of the obturator artery within the obturator foramen above and medially to the obturator muscle (ie, at the cranial edge of the obturator foramen), we advocate using a horizontal plane tangential to the upper edge of the pubic symphysis from a clinical standpoint, as imaging and surgical data show the absence of lymph node occurrence below this limit.<sup>27</sup>

Our study has several limitations. It is based on an experts' consensus; it does not exhaustively address all clinical situations in which PLNRT might be necessary, according, for instance, to the location of positive lymph nodes identified by MRI or next-generation imaging, and it does not address the issue of OAR constraints and sparing. Nevertheless, our study has 2 major strong points. First, it applied a validated methodology for the elaboration of a delineation consensus in radiation therapy as reported by Lin et al integrating 4 major steps: use of an experts' consensus based on a clinical case; realization of an exhaustive review of the literature; use of a quantitative analysis of contours; and illustration of a dedicated atlas.<sup>28</sup> Second, it was validated as a clinically applicable solution by a large population of real-life radiation oncologists treating patients with prostate cancer in various countries and hospitals, instead of being based on exclusively selected academic experts' opinions only.

## Conclusion

The method used by the GFRU, an objective index-based comparison of a large subset of contours, an identification of the areas of significant interobserver variability, and a further discussion of these inconsistencies, allowed our cooperative group to propose an easily applicable, reproducible, and practice-validated guideline for the delineation of the pelvic CTV in prostate cancer, useful for implementation in daily practice and clinical trials.

## References

1. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-974.

2. Pollack A, Karrison TG, Balogh AG, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): An international, multicentre, randomised phase 3 trial. *Lancet* 2022;399:1886-1901.
3. Lawton CA, Michalski J, El-Naqa I, et al. Variation in the definition of clinical target volumes for pelvic nodal conformal radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;74:377-382.
4. Harris VA, Staffurth J, Naismith O, et al. Consensus guidelines and contouring atlas for pelvic node delineation in prostate and pelvic node intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2015;92:874-883.
5. Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;74:383-387.
6. Sargos P, Guerif S, Latorzeff I, et al. Definition of lymph node areas for radiotherapy of prostate cancer: A critical literature review by the French Genito-Urinary Group and the French Association of Urology (GETUG-AFU). *Cancer Treat Rev* 2015;41:814-820.
7. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): A prospective, randomised, multicentre study. *Lancet* 2020;395:1208-1216.
8. Achard V, Bottero M, Rouzaud M, et al. Radiotherapy treatment volumes for oligorecurrent nodal prostate cancer: A systematic review. *Acta Oncol* 2020;59:1224-1234.
9. Hall WA, Paulson E, Davis BJ, et al. NRG Oncology updated international consensus atlas on pelvic lymph node volumes for intact and postoperative prostate cancer. *Int J Radiat Oncol Biol Phys* 2021;109:174-185.
10. Warfield SK, Zou KH, Wells WM. Simultaneous truth and performance level estimation (STAPLE): An algorithm for the validation of image segmentation. *IEEE Trans Med Imaging* 2004;23:903-921.
11. Hung W-L, Yang M-S. Similarity measures of intuitionistic fuzzy sets based on Hausdorff distance. *Pattern Recognit Lett* 2004;25:1603-1611.
12. Zou KH, Warfield SK, Bharatha A, et al. Statistical validation of image segmentation quality based on a spatial overlap index. *Acad Radiol* 2004;11:178-189.
13. Dinniwell R, Chan P, Czarnota G, et al. Pelvic lymph node topography for radiotherapy treatment planning from ferumoxtran-10 contrast-enhanced magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2009;74:844-851.
14. Shih HA, Harisinghani M, Zietman AL, Wolfgang JA, Saksena M, Weissleder R. Mapping of nodal disease in locally advanced prostate cancer: Rethinking the clinical target volume for pelvic nodal irradiation based on vascular rather than bony anatomy. *Int J Radiat Oncol Biol Phys* 2005;63:1262-1269.
15. Spratt DE, Vargas HA, Zumsteg ZS, et al. Patterns of lymph node failure after dose-escalated radiotherapy: Implications for extended pelvic lymph node coverage. *Eur Urol* 2017;71:37-43.
16. Taylor A, Rockall AG, Reznick RH, Powell ME. Mapping pelvic lymph nodes: Guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1604-1612.
17. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. *Int J Radiat Oncol Biol Phys* 2016;96:759-769.
18. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): Long-term results of a randomised, phase 3 trial. *Lancet Oncol* 2018;19:1504-1515.
19. De Meerleer G, Berghen C, Briganti A, et al. Elective nodal radiotherapy in prostate cancer. *Lancet Oncol* 2021;22:e348-e357.
20. Murthy V, Maitre P, Kannan S, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): Outcomes from phase III randomized controlled trial. *J Clin Oncol* 2021;39:1234-1242.
21. Pollack A, Karrison T, Balogh AG, et al. MP72-01 improvements in freedom from progression with short-term androgen deprivation therapy and pelvic lymph node treatment added to prostate bed salvage radiotherapy: The NRG Oncology/RTOG 0534 SPPORT trial. *J Urol* 2019;201(suppl 4):e1054-e1055.
22. Michaud AV, Samain B, Ferrer L, et al. Haute couture or ready-to-wear? Tailored pelvic radiotherapy for prostate cancer based on individualized sentinel lymph node detection. *Cancers* 2020;12:944.
23. Schiller K, Sauter K, Dewes S, et al. Patterns of failure after radical prostatectomy in prostate cancer - Implications for radiation therapy planning after (68)Ga-PSMA-PET imaging. *Eur J Nucl Med Mol Imaging* 2017;44:1656-1662.
24. Pilepich MV, Krall JM, Johnson RJ, et al. Extended field (periaortic) irradiation in carcinoma of the prostate—Analysis of RTOG 75-06. *Int J Radiat Oncol Biol Phys* 1986;12:345-351.
25. De Bruycker A, De Bleser E, Decaestecker K, et al. Nodal oligorecurrent prostate cancer: Anatomic pattern of possible treatment failure in relation to elective surgical and radiotherapy treatment templates. *Eur Urol* 2019;75:826-833.
26. Small Jr W, Bosch WR, Harkenrider MM, et al. NRG Oncology/RTOG consensus guidelines for delineation of clinical target volume for intensity modulated pelvic radiation therapy in postoperative treatment of endometrial and cervical cancer: An update. *Int J Radiat Oncol Biol Phys* 2021;109:413-424.
27. Gil-Vernet JM. Prostate cancer: Anatomical and surgical considerations. *Br J Urol* 1996;78:161-168.
28. Lin D, Lapen K, Sherer MV, et al. A systematic review of contouring guidelines in radiation oncology: Analysis of frequency, methodology, and delivery of consensus recommendations. *Int J Radiat Oncol Biol Phys* 2020;107:827-835.