



## Letter to the Editor

**In reply to Keenan et al. Anatomic principles as the basis of target volume definition**


In the current issue of *Radiotherapy and Oncology*, Keenan et al. [1] have published the latest of several analyses in which PET data have been used to evaluate regional metastatic patterns and define clinical target volumes for patients with gynecologic malignancies. In this latest study, the authors have focused on cervical cancers and their patterns of metastasis to para-aortic lymph nodes (PANs). There is a need for careful studies of datasets of this sort and the authors' efforts have certainly helped to validate previous anatomic studies of the PANs, including our own, published in 2013 [2] and further developed in 2017 [3]. However, we have several concerns about the methods used and the recommendations made by Keenan et al.

In their analysis, Keenan et al. based their measurements and recommendations on the distance from the center of each abnormal node to the most proximal border of the aorta or vena cava. In most cases, measurements were based on planning CTs taken after injection of IV contrast. Based on their analysis, the authors made recommendations for para-aortic target volume definition. These recommendations involved 9 steps, including complex expansions of varying distances from contours of the vena cava and aorta; the resulting contours were then modified to exclude adjacent structures.

The complexity of this method significantly limits its utility. In reality, few clinicians are likely to be able to recall the details without having the paper immediately at hand because the guidelines are based solely on empirically-derived landmarks and measurements rather than on an understanding of the anatomic principles that govern the relationship between the regional nodal bed and adjacent structures.

We believe that the use of such indirect methods is fraught with danger. Lymphatic vessels and nodes do not develop in concentric circles around major vessels. In fact, they do not follow arterial structures at all. The lymphatics, which arise during the mid-first trimester of fetal development, are endothelial structures that follow embryonal veins, flowing with them from the periphery towards the heart. In the case of the PANs, the lymphatics develop along the courses of two composite cardinal venous structures that flank the aorta between it and the right and left psoas muscles. The right-sided structure persists into adulthood as the vena cava; the left sided "vena cava" disappears (except in rare fetal anomalies) in the late first trimester, leaving behind a bed of lymphatics and lymph nodes in the space between the aorta and the left psoas muscle. It is for this reason that the para-aortic nodal basin is essentially symmetrical to the right and left of the aorta in the beds of the vena cava and absent left cardinal vein.

In our experience, right-sided nodes are always in direct contact with the vena cava, usually in the lateral retrocaval or aorto-caval spaces. On the left, the nodes can be some distance from the aorta, lying anywhere between the aorta and the psoas muscle. For this reason, we recommend a contour that includes the vena cava, aorta, aorto-caval space, and the entire space to the left of the aorta laterally to the left psoas muscle [3,4]. We have only once seen a node directly anterior to the aorta and this was in direct contact with the aorta at the level of the renal veins. For this reason, the anterior boundary of our CTV is at the anterior aspect of the aorta.

We have several other comments about the recommendations made by Keenan et al.:

- (1) The authors' method defines a PAN CTV. However, although we assume it was implied, the authors make no mention of a PTV margin for day-to-day variation. Any discussion of target volumes should be accompanied by a recommendation for an expansion that allows for set up errors. Very long extended fields typically require a relatively large PTV margin of 6–7 mm to allow for tilt errors and other uncertainties.
- (2) The authors based their contours on CTs taken with IV contrast. We do not recommend this, particularly in the PANs, because the osmotic load associated with contrast causes a marked expansion of the vena cava; this typically displaces the duodenum anteriorly by 5–10 mm. Treatments based on contrast CTs do not reflect the daily treatment situation and may result in unexpected duodenal toxicity. Our recommendations for duodenal dose constraints have all been based on non-contrast CTs; [5] they cannot be applied to treatments based on contrast CTs, although planning CTs can certainly be digitally fused with contrast studies or MRI to assist in contouring.
- (3) As the authors point out, the center of a grossly positive node does not correctly estimate its original location. In our experience, paracaval nodes are always in contact with the vena cava and regress towards the vessel. For this reason, we do not add an expansion anterior to the vena cava unless there is gross disease.

In summary, although we applaud efforts to refine the accuracy of target volume definition and find studies of the anatomic distributions of regional node metastases to be very useful, we believe it is time for radiation oncologists to get away from surrogate reference points and targets based on artificial expansions of major vessels. It is time for us to acknowledge the anatomic principles that govern the distribution of lymphatics so that we can more accurately define the target volumes that determine the effectiveness of our treatments.

## References

- [1] Keenan LG, Rock K, Azmi A, et al. An atlas to aid delineation of para-aortic lymph node region in cervical cancer: design and validation of contouring guidelines. *Radiotherapy Oncol* 2018.
- [2] Takiar V, Fontanilla HP, Eifel PJ, et al. Anatomic distribution of fluorodeoxyglucose-avid para-aortic lymph nodes in patients with cervical cancer. *Int J Radiat Oncol Biol Phys* 2013;85:1045–50.
- [3] Eifel PJ, Klopp AH. Applied anatomy and target volume definition Gynecologic radiation oncology. A practical guide. Philadelphia: Wolters Kluwer; 2017. p. 53–77.
- [4] Fontanilla HP, Klopp AH, Lindberg ME, et al. Anatomic distribution of [(18)F] fluorodeoxyglucose-avid lymph nodes in patients with cervical cancer. *Pract Radiat Oncol* 2013;3:45–53.
- [5] Verma J, Sulman EP, Jhingran A, et al. Dosimetric predictors of duodenal toxicity after intensity modulated radiation therapy for treatment of the para-aortic nodes in gynecologic cancer. *Int J Radiat Oncol Biol Phys* 2014;88:357–62.

Patricia J. Eifel

Ann H. Klopp

Received 7 May 2018

Accepted 16 June 2018

Available online 29 September 2018