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Letter to the Editor

## Delineation guideline for the para-aortic lymph node region in cervical cancer – Clarification letter

*To the Editor*

We would like to take this opportunity to respond to two letters in relation to our recently published paper [1]. The letters were authored by Dr Eifel and Dr Klopp [2], and Dr Lee et al. [3].

We would firstly like to thank Dr Eifel, Dr Klopp and Dr Lee et al for their comments and welcome any discussion on this topic. The queries which were raised are addressed below.

1. *'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.'*

The step-by-step guide allows for reproducibility in contouring. It may require referencing while contouring, as do many contouring guidelines. It is common practice to exclude adjacent uninvolved structures from a CTV but this has been included in the guide for completeness.

2. *'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, generally fatal 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. '*

We appreciate the authors point about the embryology of the lymphatic bed in the para-aortic region. It is a valid point that the lymph node bed does not have any direct embryological link with the aorta. However, the aorta is a significant landmark for the para-aortic lymph node region, as is the bifurcation of the aorta. While we acknowledge that the lymph node bed has not developed from the aorta itself, we have shown that a margin from the aorta can be used to create a suitable CTV for the para-aortic lymph node bed, and that the bifurcation of the aorta can be used as the inferior extent of that CTV. A validated step-by-step guide with specific expansion margins may be useful in increasing reproducibility of contouring and therefore comparability of radiotherapy outcomes. We do however state that clinical judgement should always prevail and that this study has a small sample size so results should be interpreted accordingly.

3. *'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 suggested anterior expansions of 8 mm from the IVC and 10 mm from the aorta.

Takiar et al. [4] do not give an anterior expansion margin for their CTV. They do provide images showing that their suggested anterior margin is tight to the aorta and possibly not covering the entire IVC on some of their axial slices. However, they do not detail the percentage coverage that would be expected with this CTV.

Similarly to our study, Kabolizadeh et al. [5] suggested using an anterior expansion of at least 7.5 mm from the major vessels to cover 95% of lymph nodes based on the location of PET positive nodes in their study.

In our study, based on the distribution of PET positive nodes, we found that there were lymph nodes immediately anterior to the vessels, particularly in the aortocaval and left para-aortic region which required the aforementioned margins. While there were few nodes that required this anterior margin, this was a relatively small sample size and we cannot recommend tighter margins based on our study. Larger studies are encouraged to review these margins. We acknowledge the need to keep the anterior margin as tight as reasonably possible to reduce dose to the bowels and have suggested cropping the CTV at natural boundaries such as the bowel.

4. *'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*

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*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.'*

The design and validation of a PTV margin is a separate consideration and a PTV margin could not be recommended from a study of the location of nodal disease such as this study.

5. *'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 noncontrast CTs; they cannot be applied to treatments based on contrast CTs.'*

The patients in the design cohort all had non-contrast CT scans and it is based on those scans that the CTV was created. This CTV was validated on a cohort of patients who had CT planning scans with iv contrast. We would agree that non-contrast CT scans are sufficient for contouring the major vessels in the PAN region and appreciate the authors point regarding potential displacement of the duodenum.

6. *'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.'*

See comment above regarding anterior margin. We have stated in our paper that one limitation of the study is that we assume that the lymph node origin is the lymph node centre, which may not always be the case as Dr Eifel and Dr Klopp correctly suggest.

7. *'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.'*

We agree that the accurate delineation of nodal CTVs for diverse primary cancer sites and stages of disease is based on anatomic principles. Accurate understanding of the pattern of involvement of nodal disease as described in our study is a component of this knowledge base. Our two approaches of delineating a CTV differ, i.e. drawing an anatomical area vs expansions on the vessels, but probably these two things will arrive at the same conclusion if we are both relying on accurate description of patterns of nodal spread for the cancer site under consideration.

8. *'The 15-mm left lateral margin, rather than the iliopsoas muscle, was used as a lateral anatomical landmark. However, I have concerns for this margin because of the risk of false negativity of micro-metastatic PANs on PET-CT. Ramirez et al. found that in patients with positive pelvic lymph nodes and negative PANs on PET-CT, the rate of histopathologically positive PANs was 22%'*

We have stated in our manuscript that a limitation of this study is that it is based on PET/CT positive lymph nodes and not on pathologically confirmed metastatic disease. We appreciate that there is a false negative rate with PET/CT.

Using our expansion margin of 1.5 cm lateral to the aorta, 97% of lymph node centres were covered. If we had used a 1 cm lateral aortic expansion, only 90% of lymph node centres would be covered. This shows the importance of using an adequate lateral margin on the aorta, as Lee et al have highlighted. However, we feel the 1.5 cm margin gives reasonable coverage in the elective setting.

Expanding this margin further posteriorly to the iliopsoas would not increase coverage in our study. The majority of the nodes are in the left lateral para aortic region. Takiar et al. [4] found that the majority of lymph nodes were anterior to the anterior aspect of the vertebral body. Paly et al. [6] also found very few lymph nodes posterior to the anterior aspect of the vertebral body – all be it in seminoma. Therefore, the benefit of expanding the CTV margin further posteriorly to the iliopsoas is unclear.

We hope this clarification is useful.

## References

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