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# Letter to the editor, Reply to: Cecile Colpaert et al.: Ultrastaging of sentinel lymph nodes in gynecological cancer: Repeating the story of breast cancer?

We would like thank Dr. Colpaert and colleagues (a group of pathologist from several centres in Belgium) for their interest in our review article "Sentinel Lymph Node (SLN) Concept in Cervical Cancer: Current Limitations and Unanswered Questions" (Cibula and McCluggage, 2019). They make an interesting point regarding the evolution of pathological examination of SLNs in breast cancer and suggest to utilise a similar protocol for examination of SLNs in cervical cancer as to what is currently undertaken in breast cancer. This represents a less intensive examination of SLNs in cervical cancer than the protocol we propose with the obvious advantages of being less labour intensive and time consuming and therefore more likely to be widely adopted by the pathology community.

The authors recall that in the early days of SLN assessment in breast cancer a detailed ultrastaging protocol was suggested in European guidelines similar to the protocol we propose in our review article (Perry et al., 2008). However, following the outcome data of two large randomized clinical trials (Giuliano et al., 2011; Weaver et al., 2011) which showed that the occult metastases detected by the detailed ultrastaging protocol had no significant effect on tumour recurrence or patient survival, this procedure was generally abandoned and replaced by a more "relaxed" protocol. The protocols vary from region to region but the Belgian Working Group for Breast Pathology recommends slicing nodes at 2 mm intervals and examining sections (H/E and cytokeratin if no tumour is identified on the H/E) at 500 μm intervals. This would theoretically detect all macrometastases and most micrometastases. Dr. Colpaert and colleagues recommend (through the Belgian Working Group for Gynecological Pathology) that a similar ultrastaging protocol be applied to SLNs in cervical cancer and also cancer of the vulva and endometrium.

However, as acknowledged by Colpaert et al., different cancers in different organs vary in biological behaviour making it impossible to extrapolate from one site to another. They also make the point that in vulval cancer (which as we stated in our review is probably the closest to cervical cancer in terms of the presence of anatomically well-defined regional nodes and the crucial importance of nodal involvement for patient prognosis), sections of SLNs were cut at 500 μm intervals in the GROINS-V-I study.

Although we accept the oncological safety of a more "relaxed" SLN ultrastaging protocol in breast cancer, this information, as admitted by the authors, is currently not available for cervical cancer. While it is impossible to develop an ultrastaging protocol detailed enough to detect all isolated tumour cells (ITCs), the protocol we suggest (cutting through each 2 mm tumour block at 200 μm intervals) should theoretically detect all macrometastases and almost all micrometastases (> 0.2 mm and up to 2 mm). In contrast, cutting the sections at 500 μm intervals will likely miss some micrometastases (those up to 0.5 mm or even larger of irregular shape).

Cervical cancer has an excellent prognosis in early stages but it is a deadly disease if it recurs. We have recently learnt from a randomized controlled study that even the surgical approach can significantly impact local control of the disease (Ramirez et al., 2018). Oncological outcome depends on the quality of the complex management, including preoperative imaging, treatment planning, tailored surgery, adjuvant treatment and also pathological assessment. Lymph node involvement remains the most important prognostic factor. Several studies showed that not only macrometastases but also micrometastases are associated with a worse prognosis (Cibula et al., 2012; Colturato et al., 2016). In our current daily practice, we are liberal in instituting adjuvant radiotherapy based on a combination of tumour-related risk factors, such as lymphovascular space invasion or depth of stromal invasion, although the evidence for such an approach comes from only one old trial (Sedlis et al., 1999). At the same time, we are hesitant to strive to identify the additional 10% of patients with only micrometastases in their lymph nodes; these patients are very likely at a much higher risk of treatment failure. Based on available data, any type of metastasis in lymph nodes should be used as the most important factor to guide the management, either indicating primary chemoradiotherapy or adjuvant radiotherapy. Until the clinical significance of micrometastases in cervical cancer is established, we feel it is prudent to implement a more detailed ultrastaging process such as the one we suggest rather than the one suggested by Colpaert et al. While we accept that it is possible that a more "relaxed" cervical SLN ultrastaging process similar to that proposed may prove to be oncologically safe and thus employed in the future, we do not currently have the necessary evidence to suggest this.

## Conflict of interest

The authors have no conflicts to declare.

## Author contribution

Both authors contributed equally.

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