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Ultrastaging of sentinel lymph nodes in gynecological cancer: Repeating the story of breast cancer? Letter to the editor, Reply to Cibula D, McCluggage WG. Sentinel lymph node (SLN) concept in cervical cancer: Current limitations and unanswered questions. Gynecol Oncol 2019;152:202–7

With interest we have read this review article describing the current knowledge and unanswered questions concerning the sentinel lymph node (SLN) biopsy concept in cervical cancer (Cibula and McCluggage, 2019).

The authors emphasize that SLN biopsy without additional pelvic lymph node (LN) dissection is an unreliable method of LN staging if pathological ultrastaging of the SLN is not performed. The minimal evaluation method should include processing of all SLNs in their entirety and, if metastases are not identified on initial sections, examination of multiple levels and cytokeratin immunohistochemical staining in order to detect as many macro- and micrometastases as possible. The method proposed by the authors is slicing each SLN at 2 mm intervals, embedding all tissue slices in paraffin blocks and cutting paraffin sections at 200 micron intervals through the whole block with at least 2 sections per level; one section from each level is stained with H&E and one section with a cytokeratin antibody if no tumor is seen on the H&E stained slides. Additional unstained sections available at each level are useful in case there is a problem with the H&E or cytokeratin stain.

Although this method is labor-intensive and time-consuming for pathologists and laboratory staff, the authors hope that national and international pathology societies will recommend standardized ultrastaging protocols. However, till now it is still a matter of debate which ultrastaging protocol should be the recommended standard.

The proposed methodology reminds us of the European guidelines for SLN examination in breast cancer formulated in 2006 (Perry et al., 2008). These guidelines recommended step-sections stained with H&E at 150–200 μm intervals through the paraffin block in order to identify all micrometastases over 0.2 mm. We have used this methodology for SLN examination in patients with breast cancer for several years untill the outcome data of two large randomized clinical trials were published in 2011 (Giuliano et al., 2011; Weaver et al., 2011) showing that the occult metastases found by step-sectioning of the SLN paraffin block had no significant effect on recurrence or survival. A subgroup analysis by Weaver et al. indicated that smaller metastases had less effect on outcome than larger metastases (Weaver et al., 2009).

Based on the evidence of these trials, the Belgian Working Group for Breast Pathology then recommended a minimal SLN evaluation protocol submitting tissue sections of the SLN that are not thicker than 2 mm and assuring that at least one microscopic section is examined every 2 mm through the node (Colpaert and Lambein, 2012). Additionally, the evaluation of three H&E stained sections of the block, one from the surface and two step-sections at 500μm intervals, was also recommended to detect all macrometastases -even if the gross sectioning and paraffin embedding were suboptimal- and most of the larger micrometastases.

As mentioned by Cibula and McCluggage (Cibula and McCluggage, 2019), cancers arising in different organs differ in biological behavior making it impossible to extrapolate from one organ site to another.

However, as the authors state, vulvar cancer is probably close to cervical cancer in terms of lymphatic spread, the presence of anatomically well-defined regional lymph nodes and the crucial importance of lymph node involvement for patient prognosis. SLN biopsy is now considered the standard of care in vulvar cancer since the publication of the GROINSS-V-I study results (Van der Zee et al., 2008; Oonk et al., 2010). In these studies, ultrastaging of the SLN was performed if no tumor was found on routine histopathology: additional pairs of sections were cut at 500μm interval or 3 pairs of sections/mm tissue. One section of each pair was stained with H&E; if negative, cytokeratin immunohistochemistry was performed on the other section. This SLN evaluation method proved its diagnostic accuracy for more than a decade now and is still used today by the Groningen pathologists (home town of the GROINSS-V studies; Harry Hollema, personal communication) despite the fact that the finding of small micrometastases (smaller than 1 mm) and even isolated tumor cells is considered important to select the patients that should have additional groin treatment (Oonk et al., 2010).

SLN biopsy has recently also appeared in international guidelines regarding endometrial cancer, like the NCCN guideline. There is no general recommendation for the ultrastaging of these SLN. A meta-analysis of 55 studies with 4915 patients with endometrial cancer showed similar sensitivity of the SLN biopsy in studies with and without ultrastaging (Bodurtha Smith et al., 2017). The prognostic significance of isolated tumor cells and micrometastases in endometrial cancer is still unknown.

In cervical cancer, limited data are available about the importance of micrometastases and isolated tumor cells for the prognosis and management of patients (Cibula et al., 2012). More data on this prognostic significance should be obtained from ongoing prospective trials (SENTIX trial and SENTICOL III trial, results expected in 2020 and 2025, respectively). Hopefully, these trials will also examine the importance of the size of the micrometastasis. If only the larger ones are prognostically important e.g. larger than 500 μm, pathologists can adapt their ultrastaging protocols to this knowledge.

Awaiting further evidence from these trials, the Belgian Working Group for Gynecological Pathology agreed upon a method for SLN evaluation in patients with cancer of vulva, cervix or endometrium:

- Indications for intra-operative examination are to be discussed with the local surgeon. The therapeutic consequences of intra-operative SLN results are highest in patients with cervical cancer. Both frozen section and imprint cytology are optional depending on the experience of the pathologist.
- SLN should be sliced in 2 mm sections and totally embedded.

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- A minimum of 3 levels of each paraffin block is examined with a maximal interval of 500 μm between the levels. Each level is examined by H&E. If negative, pan-cytokeratin immunohistochemistry is performed on at least one level.

The proposed method will detect all macrometastases and also the larger micrometastases. It has the advantage of being less labor-intensive and time-consuming than the method proposed by Cibula and might therefore gain wider acceptance. It can be adapted if more convincing evidence is emerging about the prognostic importance of low volume SLN disease. Evidently, for patients included in the prospective SENTIX and SENTICOL III trials, the specific trial protocols will be respected.

Conflict of interest statement

The authors have no conflict of interest.

Author's contribution

All authors reviewed the literature, discussed the topic and agreed with the proposed consensus. CC and GJ wrote the text.

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