Pathologic Protocols for Sentinel Lymph Nodes Ultrastaging in Cervical Cancer

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**Context.**—Ultrastaging of sentinel lymph nodes (SLNs) is a crucial aspect in the approach to SLN processing. No consensual protocol for pathologic ultrastaging has been approved by international societies to date.

**Objective.**—To provide a review of the ultrastaging protocol and all its aspects related to the processing of SLNs in patients with cervical cancer.

**Data Sources.**—In total, 127 publications reporting data from 9085 cases were identified in the literature. In 24% of studies, the information about SLN processing is entirely missing. No ultrastaging protocol was used in 7% of publications. When described, the differences in all aspects of SLN processing among the studies and institutions are substantial. This includes grossing of the SLN, which is not completely sliced and processed in almost 20% of studies. The reported protocols varied in all aspects of SLN processing, including the thickness of slices (range, 1–5 mm), the number of levels (range, 0–cut out until no tissue left), distance between the levels (range, 40–1000 μm), and number of sections per level (range, 1–5).

**Conclusions.**—We found substantial differences in protocols used for SLN pathologic ultrastaging, which can impact sensitivity for detection of micrometastases and even small macrometastases. Since the involvement of pelvic lymph nodes is the most important negative prognostic factor, such profound discrepancies influence the referral of patients to adjuvant radiotherapy and could potentially cause treatment failure. It is urgent that international societies agree on a consensual protocol before SLN biopsy without pelvic lymphadenectomy is introduced into routine clinical practice.

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an ultrastaging protocol. It has been shown that SLN ultrastaging can detect an additional 10% to 15% of patients with micrometastases (MICs).5,7 Some retrospective studies have shown that the presence of MICs is associated with a comparable negative impact on survival as the presence of macrometastasis (MAC).8,9 Nonetheless, the published data are not uniform. Recently, a group of French authors10 reviewed SLNs from 139 patients enrolled in their prospective trial and did not find a higher recurrence rate in cases with MICs. However, most recurrences (11 of 13) occurred in LN-negative patients, and even the presence of MAC was not found to be a negative prognostic factor.10 Also, SLNs are found elsewhere than in the external iliac region and obturator fossa in about 10% of cases.5 In these cases, SLN detection can help to detect and remove the key LN that could be otherwise overlooked. Importantly, it has been shown that in some patients with MICs in SLNs, MAC can be detected in other pelvic LNs.8 In a large retrospective study that included 645 patients, despite the 18 cases (2.8%) with false-negative SLNs, an additional 23 cases (3.6%) with MICs or isolated tumor cells (ITCs) in SLNs, but with MAC in non-SLNs, were found.8 These cases would have been undetected if SLN ultrastaging had not been performed, which is particularly important for the safety of patients in the “SLN biopsy only” concept. All these patients would have probably had a relapse and may have possibly died because their positive LNs would remain in situ and they would not have received any adjuvant treatment. Therefore, SLN ultrastaging must be part of the management if routine pelvic lymphadenectomy is replaced by SLN biopsy only. However, there are still some unsolved issues, including SLN detection rate, which may be influenced by methodology (number and type of tracers) and type of surgical approach, diagnostic accuracy, and sensitivity and specificity of the procedure.11 All these factors influence the routine use of SLN biopsy in practice. Sensitivity and specificity of the procedure are closely related to optimal bilateral detection of SLNs and also to the pathologic examination of the SLN, although the pathology protocol for SLN examination has not yet been standardized. It has been proved that SLN ultrastaging improves the negative predictive value, up to from 91% to 100%.5,12,13 At least some aspects of the ultrastaging protocol are used in most institutions, but there is no generally accepted approach to this procedure, which differs substantially. The goal of our study is to review all available literature data regarding SLNs in patients with cervical cancer, primarily concerning pathologic examination of SLNs (ultrastaging protocols), including the approach to gross processing of the LNs (especially slicing and thickness of slices), number and distance between levels (series), number of sections (slides) per level, and use of immunohistochemistry (IHC). Other issues are reviewed as well, including the significance of ultrastaging for the sensitivity of SLN examination; percentage of MACs, MICs, and ITCs; false negativity of SLN with metastasis in non-SLNs; number of SLNs per patient; approach to the processing of non-SLNs; and detection ratio of SLNs, including unilateral versus bilateral detection.

**METHODS**

A comprehensive review of all available literature published on the subject of SLNs in cervical cancer was performed. The data were obtained through a database search using the MeSH (Medical Subject Headings) terms sentinel, node, cervical, and cervix in combination with sentinel node cervical and sentinel node cervix, which resulted in 1883 and 158 outputs, respectively, found until January 10, 2019. Data were mined from the PubMed/MEDLINE database. Once a thorough search was performed, the authors reviewed all the articles to determine their relevance. Primarily, all articles not relevant to SLNs in uterine cervix were excluded (such as articles concerning head and neck tumors). Thereafter we excluded review articles; meta-analyses; studies focusing only on the methodology of SLN detection without reporting the results; methodology studies reporting the results of cervical SLNs together with the SLN result at other locations, such as the vulva and endometrium, which were impossible to separate; and duplicate data, if recognizable.

Finally, we selected 127 studies, which are the basis of this review.6,7,14–138 In total, 9085 patients were involved in these studies. In every study, we searched for the following parameters: number of patients; number of patients with SLN detection (unilateral/bilateral); number of SLNs per patient (total, mean, median, range—if available); gross processing of the SLNs and ultrastaging protocol (if yes, number of series and the width of the intervals); IHC (if yes, which antibody); number of patients with SLN metastasis (if reported, number of MACs, MICs, and ITCs; total number of SLN metastases in all patients); false negativity of SLN with metastasis in non-SLNs; and processing of non-SLNs.

**RESULTS**

**Results of SLN Detection**

Information about the total number of patients and unilateral and bilateral SLN detection was available in 88 of 127 studies. In these studies, 6723 patients were involved. At least 1 SLN was detected in 5918 patients (88%), whereas bilateral SLN detection was reported for 4330 patients (64.4%). However, the goal of our review is not to provide deeper insight into the problematics of SLN detection, which would require correlation with the methodology and the surgical approach used. This topic has already been reviewed in other articles.3,12,13,140

**Pathologic Processing of SLNs**

**Gross Processing of the Lymph Node.**—After dissecting the surrounding adipose tissue, SLN processing varies among institutions. This information was available in 49 of 127 studies (Figure 1). Sentinel lymph nodes were processed in whole as slices of the following thicknesses: 1 mm (1 of 49 studies), 2 mm (18 of 49 studies), 2 to 3 mm (4 of 49 studies), 3 mm (10 of 49 studies), 3 to 4 mm (2 of 49 studies), and 5 mm (5 of 49 studies). In the remaining studies, the SLNs were either dissected into 2 halves (5 of 49 studies), or only 1 slice was examined from the whole SLN, either longitudinal to the long axis (2 of 49 studies), or perpendicular to the long axis (2 of 49 studies). In 40 studies, the information about sectioning that concerned the relation of sections to the long axis was present. In 27 of 40 studies, the SLNs were dissected perpendicularly to the long axis, in 13 of 40 studies, longitudinally to the long axis.

**SLN Ultrastaging Protocols.**—In 96 of 127 studies, information about SLN processing was available. No ultrastaging protocol was used in 7 of 96 studies in which the authors reported processing and examination of SLNs in routine manners. In 21 of 96 studies, the authors stated that an ultrastaging protocol was used but no other details were provided. In 68 of 96 studies, at least some aspects of the ultrastaging protocol were described.

During the SLN ultrastaging, each block should be examined in a defined manner, including the number of levels (series), the distance between the levels (series), and the number of sections (slides) per level.
The information about the number of levels (series) was available in 51 studies (Figure 2). The number was 0 in 6 of 51 studies—in these studies, the ultrastaging was defined as 1 hematoxylin-eosin (H&E)–stained slide accompanied by the second section from the same level examined by IHC. In the other 45 studies, the ultrastaging encompasses an examination of at least 1 deeper level. In these studies, the number of levels was 1 (3 of 45 studies), 2 (7 of 45 studies), 3 (4 of 45 studies), 4 (16 of 45 studies), 5 (4 of 45 studies), 6 (2 of 45 studies), and 8 (1 of 45 studies). In the last two (6 and 8 series), the SLNs were sliced into 5 mm in 1 case, bisected in 1 case, while in the third study the sectioning was not described. Finally, in 8 of 45 studies, the number of series was unlimited and the whole SLNs were cut out until no tissue was left.

The distance between the levels was described in 57 studies (Figure 3). The distance was 40 μm in 9 of 57 studies, 50 μm in 5 of 57 studies, 100 μm in 2 of 57 studies, 150 μm in 14 of 57 studies, 200 μm in 13 of 57 studies, 250 μm in 8 of 57 studies, and 400 μm in 1 of 57 studies. In another 4 of 57 studies, the distance was defined as the following ranges: 10 to 40 μm, 40 to 80 μm, 200 to 300 μm, and 500 to 1000 μm. In the latter study with the largest distance, the slicing of SLNs was as follows: SLNs up to 5 mm were bisected, while larger SLNs were processed each in 3 blocks. In 1 of 57 studies encompassing 8 centers, 7 centers used the interval in the range 150 to 250 μm; and 1 center, the interval of 500 μm.

Generally, at least 2 sections (slides) in each series should be taken, one for H&E and the second for IHC staining. However, because the tissue—which is cut out between the series—is permanently lost, a suggestion is to prepare more than 2 sections for each level for the purpose of additional studies or for H&E staining in cases in which technical issues prevent assessment of the first H&E-stained slide in that level.

The number of sections (slides) per level was mentioned in 29 studies (Figure 4). From these, the number was 1 (2 of 29 studies), 2 (7 of 29 studies), 3 (9 of 29 studies), 4 (10 of 29 studies), and 5 (1 of 29 studies).

Concerning IHC use in ultrastaging protocols, in 40 of 127 studies the information is not mentioned. In 7 of 87 studies, no IHC was used. In the remaining 80 of 87 studies, some IHC was used. The spectrum of antibodies includes cytokeratin AE1/AE3 (45 of 80 studies), cytokeratin MNF116 (4 of 80 studies), cytokeratin KL-1 (2 of 80 studies), and 1 study each with cytokeratin 19 and epithelial membrane antigen (EMA). In 5 of 80 studies, a mix of more than 1 primary antibody was used, variously combining antibodies against cytokeratin 7, cytokeratin 8, cytokeratin 18, cytokeratin MNF 116, cytokeratin AE1/AE3, and cytokeratin CAM 5.2. In 20 of 80 studies, the type of the antibody used was not specified.
Results of SLN Examination

Information about the number of detected SLNs paired with the number of positive SLNs was available in 107 of 127 studies. In these studies, a total of 7030 SLNs were detected, of which 1590 were positive (22.6%). The average number of SLNs was noted in 87 of 128 studies and amounted to 2.7 SLNs per patient.

Information about the whole number of positive SLNs divided into MACs, MICs, and ITCs was recorded in 17 of 127 studies. In these studies, 217 patients had positive SLNs (from 987 patients involved in these studies with detected SLNs), which included 132 patients with MACs (61%), 59 with MICs (27%), and 26 with ITCs (12%).

Sentinel lymph node ultrastaging is performed in patients if the first H&E section is negative. However, only 11 studies separately described the number of patients with SLN metastasis detected only by ultrastaging. In summary, 933 patients were involved in these studies and 171 had positive SLNs (18.4%). In 36 of 171 patients (21%), LN involvement was detected only after ultrastaging.

False-Negative Ratio of SLNs

Information about false negativity was available in 82 of 127 studies. In summary, 5734 patients were involved in these studies and 137 had falsely negative SLNs (2.4%). We also analyzed the data concerning false negativity related to the positivity of non-SLNs for patients with unilateral SLN detection and contralateral positivity of non-SLNs. This information was available in 28 of 127 studies. To summarize the results, in these studies 32 of 81 of the falsely negative SLNs (39.5%) were located on the unmapped side. Lastly, we focused on the number of positive non-SLN LNs in the parametrial location in patients with false-negative SLNs. This information was available in 29 of 127 studies. To sum up, 20 of 73 patients with falsely negative SLNs (27.4%) had metastasis in the parametrial LNs.

Processing Non-SLNs

Approach to the examination of non-SLNs was described in 33 of 127 studies. In 1 study, all non-SLNs were processed according to the protocol of SLNs owing to the purpose of the study, rather than as a routine approach, and this study was excluded from further analysis. From the remaining studies, only 1 section per LN was examined in 14 of 32 studies; LNs were bisected (2 of 32 studies) or were sliced into more blocks according to LN size, but without further specification concerning the thickness of the slices (1 of 32 studies). In the remaining 15 of 32 studies, the LNs were processed in whole in slices of the following thicknesses: 2 mm (4 of 32 studies), 2 to 3 mm (1 of 32 studies), 3 mm (8 of 32 studies), 3 to 4 mm (1 of 32 studies), and 5 mm (1 of 32 studies).

Figure 3. Distance between the levels in step-sectioning protocols used in sentinel lymph node examination. Data from 57 of 127 studies when available.

Figure 4. Number of sections (slides) per level. Data from 29 of 127 studies when available.
Sentinel lymph node examination is a crucial step for the SLN concept in patients with cervical cancer. It has been shown that SLN metastases are present in up to 27% of patients with early-stage cervical cancer. The metastases are generally classified by size into MACs (>2 mm), MICs (>0.2 mm up to 2 mm), and ITCs (up to 0.2 mm). However, this approach is based on the classification of the size of the LN metastases in patients with breast cancer and currently there is no evidence that this approach is valid for cervical cancer as well. Also, the classification of ITCs as pN0(i+c) is debatable and more data are needed to advocate this approach.

In the studies reviewed in our article, a total of 7030 SLNs were detected, of which 1590 were positive (22.6%). However, the size (type) of metastasis was not mentioned in most studies and positivity included not only MACs and MICs but also ITCs, which should be classified as pT0(i+c). Nevertheless, from the 17 studies where data were available (the total number of patients with positive SLNs was 217 from 987 patients involved in these studies with detected SLNs), the distribution of MACs, MICs, and ITCs was as follows: 132 patients with MACs (61%), 59 with MICs (27%), and 26 with ITCs (12%). It should be noted that data are pooled to patients (the data concerning LNs were missing in almost all studies) and for patients with more metastases from which at least 1 fulfilled the criteria for MACs, the latter were classified as MACs, regardless of the size of other metastases. The result of other studies including all pelvic LNs are different, but cumulative data are missing.9

For the concept of replacing pelvic lymphadenectomy by SLN biopsy only, the false negativity of SLN staging is the key aspect for the safety of patients. In general, false negativity of SLN is defined as a negative SLN with positive non-SLN. In some studies false-negative SLNs are classified only in those cases in which the positive non-SLN is on the same side as the mapped and histologically negative SLN. This approach seems to be justifiable, as in patients with unilateral detection of SLN a contralateral pelvic lymphadenectomy is performed. Other studies, however, classify as false-negative SLNs even those cases involving patients with unilateral SLN detection and contralateral non-SLN positivity. The data about false negativity were available in 127 studies, and the false-negative ratio was 2.4% (137 of 5734 patients). However, if we stratify these data with respect to unilateral SLN detection and contralateral positivity of non-SLNs, 39.5% (32 of 81 patients from 28 of 127 studies) of false negativity was related to this setting.

Another limitation is caused by the different pathologic assessment of SLNs and non-SLNs. Very few studies with small cohorts evaluated non-SLNs with an ultrastaging protocol, so the false-negative rate mostly compares the result of SLN ultrastaging with non-SLN standard assessment.5,19,20,25,91 Finally, 27.4% (20 of 73 patients from 29 of 127 studies) of patients with false-negative results had SLNs located in the parametrical LN. This should not be considered as a false-negative result, since parametria are anatomically located between the cervix and regions of pelvic lymphadenectomy. Moreover, parametria are removed during radical hysterectomy (radical parametrecomy), and not as a part of pelvic lymphadenectomy.

It has been proved that an ultrastaging protocol increases the sensitivity of the detection of LN involvement.6,7,12,142 However, the procedure has not yet been standardized and, despite being recommended by international societies, guidelines concerning ultrastaging procedure are not available.4 Owing to multiple protocols used across institutions and studies, it is difficult to suggest the best and generally most acceptable protocol. This has implications, especially for the expense and also for the labor intensiveness of the ultrastaging, which is very time-consuming both for laboratory staff and pathologists. However, standardization is desirable for the following main reasons: (1) improvement of sensitivity of SLN status for pelvic LN status; (2) detection of an additional group of patients with MICs only, who should be considered LN positive and should receive adjuvant treatment; and (3) the possibility to compare results from studies and between institutions.

Our results showed that in most studies at least some aspects of the ultrastaging protocol were used. Only 7 of 97 studies (7.2%) reported they did not use any ultrastaging. In another 6 of 97 studies (6.2%), only 1 additional slide stained with IHC was used without deeper sectioning, which cannot be regarded as true ultrastaging. Altogether, 84 of 97 studies (86.6%) used SLN ultrastaging; however, in 27 of 97 no further description was given. Our review showed that there are plenty of approaches to ultrastaging protocols, which varied substantially amongst the studies and institutions. Nevertheless, there were some general rules that could be found in most protocols. When we selected the most common features concerning slicing (gross processing) of the SLNs, the number of levels (series) and the number of sections (slides) per level, the distance between the levels (thickness of cut-out tissue), and the IHC used, the “average,” that is, most common, protocol is as follows.

The SLN should be processed in whole and sliced in 2-mm intervals perpendicularly to the long axis. If the initial H&E finding is negative, then the ultrastaging protocol is as follows: 4 levels at 150-μm intervals, 4 slides from each level (1 H&E, 1 IHC, 2 left unstained), and IHC with antibody cytokeratin AE1/3 (Figure 5, A). The second most common interval for each level was 200 μm, which was used in 13 of 57 studies (22.8%), compared to the most common interval of 150 μm, which was used in 14 of 57 studies (24.6%). With regard to the number of levels (series), it is important to mention that although the most common number of levels was 4, in 8 of 40 studies, the number of levels was unlimited and the whole SLN was processed until no tissue was left.

With respect to IHC used, 7 of 87 (8%) used no IHC, while the remaining 80 of 87 studies (92%) used IHC, which was unspecified with respect to the type of antibody in 20 of 80 studies. From the remaining studies, the most common antibody was cytokeratin AE1/3, which was used in 45 of 60 studies (75%).

The number of levels (series) and the distance (thickness of tissue cut out) between them is important in regard to the sensitivity of the ultrastaging protocol. The clinical significance of MICs and ITCs in SLNs for patients with cervical cancer has not been proved with certainty yet. However, some studies suggested that the presence of MICs was a strong prognostic factor and, therefore, the purpose of ultrastaging should be the detection of almost all MICs and as many ITCs as possible.6,8,143 However, the complete processing of all SLNs at a few micrometer intervals would result in hundreds of slides per node and this is not possible in routine practice. So, it is necessary to find a reasonable compromise between sensitivity, expense, and labor intensity. A recent review144 suggested a protocol that was
designed to pick up almost all MICs. This protocol consists of slicing an SLN at 2-mm intervals and cutting it into 4 sections (slides) at 200-μm levels (1 H&E, 1 IHC pan-cytokeratin antibody, 2 unstained sections, which can be used for assessing whether the tumor focus becomes larger) (Figure 5, B). This protocol results in approximately 20 pairs of H&E- and IHC-stained slides per SLN (assuming that 1 SLN would be processed in more sections, altogether in 2 paraffin blocks). The suggested protocol is more intensive than the “average” protocol described above, but, owing to the importance of MIC and ITC detection, it seems to be a reasonable solution.

The SLN procedure is commonly accompanied by pelvic lymphadenectomy. The pelvic LNs should be carefully examined as well, but the approach to their processing varies across studies.

From the remaining studies, only 1 section per lymph node was examined in 14 of 32 studies; LNs were bisected (2

Figure 5. Comparison between the “average” sentinel lymph node protocol based on these review data (A) and protocol suggested as optimal concerning its sensitivity for micrometastases detection (B). Abbreviations: FFPE, formalin-fixed, paraffin-embedded; HE, hematoxylin-eosin stain; IHC, immunohistochemistry.
of 32 studies) or were sliced into more blocks according to LN size, but without further specification concerning the thickness of the slices (1 of 32 studies). In the remaining 15 of 32 studies, the LNs were processed in whole in slices of the following thicknesses: 2 mm (4 of 32 studies), 2 to 3 mm (1 of 32 studies), 3 mm (8 of 32 studies), 3 to 4 mm (1 of 32 studies), and 5 mm (1 of 32 studies).

Altogether, in only 15 of 32 studies (46.9%) were the LNs processed in whole in 2- to 5-mm slices. In 16 of 32 studies (50%), only 1 or 2 slices from each nonsentinel LN were examined. In 1 of 32 studies, the number of slices was LN-size dependent, but without clear specifications. This result is rather surprising, since the goal of each LN examination in patients with cancer should be the detection of metastases (ie, tumor foci >2 mm). On this basis, the processing of each LN in 2-mm intervals is reasonable. However, this approach was used in only 4 of 32 studies (12.5%).

In summary, the knowledge of SLN processing methodology is crucial for comparison of the results among studies. From this viewpoint, it is surprising that in 24% of studies reporting SLN results, the information about SLN processing is entirely missing. When mentioned, in 7% of studies no ultrastaging protocol was used, and in 22% of studies the authors mentioned that an ultrastaging protocol was used but gave no other details about the procedure. In most studies, at least some aspects of ultrastaging protocol were used. However, the differences amongst studies and institutions regarding SLN processing are substantial. The differences concern all aspects, including grossing of the SLN, which is not completely sliced and processed in almost 20% of studies. This is a very unexpected finding because without complete processing of the LN (optimally in 2-mm slices) the metastasis may be missed and there is a risk of false negativity not only for MICs but also for MACs. Other aspects include the number of levels (range, 0–cut out until no tissue left); distance between the levels (range, 40–1000 μm); and number of sections per level (range, 1–5). Concerning the abovementioned discrepancies, the sensitivity in detection of MICs especially varies substantially among the studies. It makes any comparison across the studies inaccurate if not impossible.

In conclusion, we offer a comprehensive review of the methodology used for ultrastaging protocol in the literature. We believe that the presented data can be beneficial for all institutions preparing their own ultrastaging protocols. There should be a discussion of the optimal ultrastaging protocol in international societies, resulting in a guideline recommendation and standardization of the procedure such as is in breast cancer and melanoma.145,146 This is, however, closely related to assessing the clinical significance of MICs. This topic can be answered by currently ongoing prospective studies.10,147,148 We believe that an ultrastaging protocol aimed at the detection of as many MICs and ITCs as possible should be favored over a more limited approach, until more data regarding their clinical significance are obtained. However, regarding the significance of ITCs, it would be difficult to gain data that would allow us to assess their prognostic meaning even from prospective trials.

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