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Risk of micrometastases in non-sentinel pelvic lymph nodes in cervical cancer

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HIGHLIGHTS

- Sensitivity of SLN ultrastaging is high for the presence of both macrometastases and micrometastases in non-SLN pelvic lymph nodes.
- Intraoperative pathologic SLN evaluation has high false negative rate in tumors at high risk of LN involvement.
- SLN status does not represent the status of the parametrial LNs.

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ABSTRACT

Objective. A high sensitivity of sentinel lymph nodes (SLN) for pelvic lymph node (LN) staging has been repeatedly shown in patients with cervical cancer. However, since only SLN are evaluated by pathologic ultrastaging, the risk of small metastases, including small macrometastases (MAC) and micrometastases (MIC), in non-SLN is unknown. This can be a critical limitation for the oncological safety of abandoning a pelvic lymphadenectomy.

Methods. The patients selected for the study had cervical cancer and were at high risk for LN positivity (stage IB–IIA, biggest diameter ≥ 3 cm). The patients had no enlarged or suspicious LN on pre-operative imaging; SLNs were detected bilaterally and were negative on intra-operative pathologic evaluation. All SLNs and all other pelvic LNs were examined using an ultrastaging protocol and processed completely in intervals of 150 μm.

Results. In all, 17 patients were enrolled into the study. The mean number of removed pelvic LNs was 30. A total of 573 pelvic LNs were examined through ultrastaging protocol (5762 slides). Metastatic involvement was detected in SLNs of 8 patients (1× MAC; 4× MIC; 3× ITC) and in non-SLNs in 2 patients (2× MIC). In both cases with positive pelvic non-SLNs, there were found MIC in ipsilateral SLNs. No metastasis in pelvic non-SLNs was found by pathologic ultrastaging in any of the patients with negative SLN Side-specific sensitivity was 100% for MAC and MIC. There was one case of ITC detected in non-SLN, negative ipsilateral SLN, but MIC in SLN on the other pelvic side.

Conclusions. After processing all pelvic LNs by pathologic ultrastaging, there were found no false-negative cases of positive non-SLN (MAC or MIC) and negative SLN. SLN ultrastaging reached 100% sensitivity for the presence of both MAC and MIC in pelvic LNs.

1. Introduction

The reliability of sentinel lymph node (SLN) evaluation for pelvic lymph node (LN) staging has been assessed in many single institutional studies, in large retrospective cohorts, and also in prospective multicenter studies [1–4]. In the only prospective trial, which involved pathologic SLN ultrastaging, and in which the primary end point was post-operative morbidity, there was no false-negative case for patients with bilaterally detected SLN [3]. In the largest retrospective study to date, on 645 patients, the sensitivity in an identical subgroup of patients, with bilateral detection of SLN, reached 97% [2]. In all of these studies, pathologic ultrastaging was

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solely used to process SLNs. The risk of MIC in non-SLN has not been assessed in any of these studies.

Whereas pelvic LNs are, during standard pathologic evaluation, mostly processed in 2 to 3 mm slices, pathologic ultrastaging of SLNs includes additional levels in very small intervals, usually 150–250 μm. This protocol enables the detection of small metastases, which could otherwise be missed: both small macrometastases (MAC), and, especially, micrometastases (MIC). Micrometastases are not a rare finding in early-stage cervical cancer; they are found in 10–15% patients and their prevalence increases with tumor size and stage of disease, as well as the prevalence of MAC [3,5–7]. Even though the prognostic importance of low-volume disease (micrometastases (MIC) and isolated tumor cells (ITC)) has not been established yet, in a large retrospective study the presence of MIC but not ITC was associated with significantly decreased overall survival, and the survival was not different from those with MAC in LN [5].

Currently, the possibility of abandoning systematic pelvic lymphadenectomy and replacing it with SLN biopsy is broadly discussed. Even though prospective controlled trials are only being initiated, the first papers are appearing, and they report small cohorts relying solely on SLN biopsy [8,9].

The primary aim of this pilot study was to evaluate the risk of MIC in pelvic LN in patients with negative SLN. All removed LN, including non-SLN and all SLN from both sides, were processed by pathologic ultrastaging. The risk of LN involvement was increased by the selection of cases with larger tumors.

2. Methods

2.1. Selection of patients

Patients with a high risk of LN involvement but negative intraoperative pathologic SLN assessment were enrolled in the study. The following inclusion criteria were used: a) squamous cancer, adenocancer, or adenosquamous cancer of the uterine cervix confirmed by histology; b) bulky cervical tumor (≥3 cm of the largest diameter); c) no bulky or suspicious LNs on preoperative imaging; d) planned surgical treatment, including LN staging. Only those patients with bilateral SLN detection and negative intraoperative pathologic SLN evaluation were included.

2.2. Surgery

A combined technique with both radioactive tracer (99Tc, long protocol, application 12 h before surgery) and blue dye (application at the beginning of the surgery) was used for SLN detection either by laparoscopy or by laparotomy. The application technique was modified in cases with large tumors, as previously published (application into the residual stroma by a spinal needle, continuous control of vaginal leak when injected into the necrotic tissue) [10]. All identified SLNs were submitted for intraoperative pathologic evaluation according to a standard protocol (see below). Lymph node staging continued with a systematic pelvic lymphadenectomy. Lymph nodes were removed from 7 standard regions in the pelvis (external iliac left and right, obturator left and right, common iliac left and right, presacral). Patients with MAC detected on intraoperative assessment were excluded from further analysis. All pelvic LNs, including SLNs and non-SLNs, were processed according to the pathological protocol for SLN ultrastaging (see below).

2.3. Pathologic processing

At the time of surgery, the SLNs were cut along their longest axis and both halves of each node were examined with frozen sectioning techniques. SLNs with a diameter of <3 mm were processed as a whole and examined in the frozen section. All patients with MAC were excluded from further analysis.

After that, SLNs as well as all other non-SLNs were fixed in 10% formalin. After fixation, all LNs were sliced at 2 mm intervals and embedded in paraffin. All LNs were further examined by the ultrastaging protocol in its entirety. This protocol consisted of 2 consecutive sections (4 μm thick) obtained in regular 150 μm intervals, which were cut from each paraffin block until there was no lymph node tissue left. The first section was stained with H&E and the second section was examined immunohistochemically with antibody against cytokeratins (AE1/AE3, 1:50 dilution; Dako, Glostrup, Denmark) (Fig. 1).

The presence of MAC, MIC, and ITC was recorded and classified according to the TNM system. Macrometastasis was defined as a metastasis >2 mm in diameter, MIC as a metastasis between 0.2 and 2 mm, and ITC as individual tumor cells or small clusters of cells <0.2 mm in diameter.

2.4. Statistics

Standard summary statistics were applied in the analyses; the median supported by the 5th–95th percentile range or by the min–max range for continuous variables and absolute and relative frequencies for categorical variables. The diagnostic power of examinations was assessed on the basis of Receiver Operating Characteristics curves. The ROC analysis was performed using a ROC calculator for the AUC computation and testing (SPSS Inc., 2012) and MedCalc 11.1.0.0 (MedCalc Software 1993–2009) was used for the computation of sensitivity and specificity. The significance of the ROC analysis was based on the calculated area under the curve (AUC), with a corresponding 95% confidence interval. The computation was based on binormal assumption.

The predictive power of the assessed examination was described by sensitivity, specificity, negative and positive predictive value, overall accuracy, and ROC-derived area under curve; all measures of predictive power were supplied by 95% confidence intervals and statistical significance.

Analyses were performed using SPSS 21 (IBM Corporation, 2012).

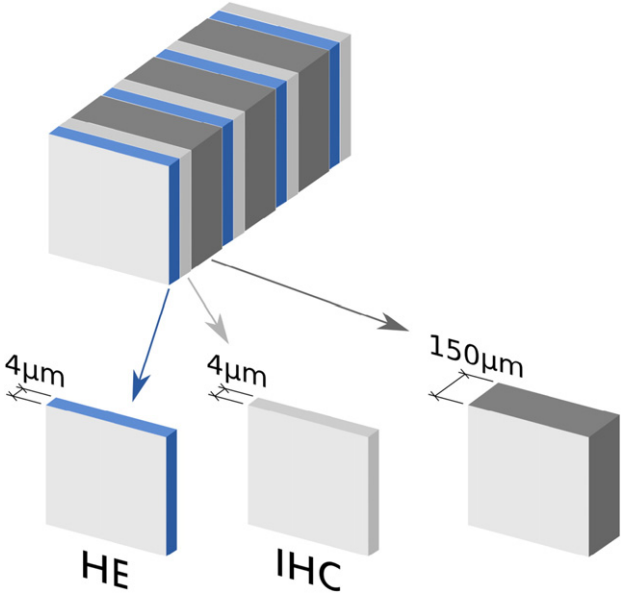

Fig. 1. Protocol for pathologic processing of SLNs and all pelvic lymph nodes. The ultrastaging protocol consisted of processing of each lymph node in the whole. Two consecutive sections (4 μm-thick) were obtained in regular 150 μm intervals. The first section was stained with H&E and the second section was examined immunohistochemically with antibody against cytokeratins (AE1/AE3).