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SLN biopsy in cervical cancer patients with tumors larger than 2 cm and 4 cm

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HIGHLIGHTS

- SLN biopsy is feasible and reliable in LN staging in tumors over 2 cm in size.
- Technique of tracer application should be modified for larger tumors.
- SLN pathologic ultrastaging allows detection of micrometastases in 8% of patients.
- Equal detection rate can be achieved in stage pT1 tumors > 2 cm as in smaller ones.
- SLN false negative rate for pelvic LN staging is very low, irrespective of tumor size.

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ABSTRACT

Objectives. The aim of this study was to assess the detection rate, false-negative rate and sensitivity of SLN in LN staging in tumors over 2 cm on a large cohort of patients.

Methods. Data from patients with stages pT1a – pT2 cervical cancer who underwent surgical treatment, including SLN biopsy followed by systematic pelvic lymphadenectomy, were retrospectively analyzed. A combined technique with blue dye and radiocolloid was modified in larger tumors to inject the tracer into the residual cervical stroma.

Results. The study included 350 patients with stages pT1a - pT2. Macrometastases, micrometastases, and isolated tumor cells were found in 10%, 8%, and 4% of cases. Bilateral detection rate was similar in subgroups with tumors < 2 cm, 2–3.9 cm, and ≥4 cm (79%, 83%, 76%) (P = 0.460). There were only two cases with false-negative SLN ultrastaging for pelvic LN status among those with bilateral SLN detection. The false negative rate was very low in all three subgroups of different tumor sizes (0.9%, 0.9%, and 0.0%; P = 0.999). Sensitivity reached 96% in the whole group and was high in all three groups (93%, 93%, 100%; P = 0.510).

Conclusions. If the tracer application technique is adjusted in larger tumors, SLN biopsy can be equally reliable in pelvic LN staging in tumors smaller and larger than 2 cm. The bilateral detection rate and false negative rate did not differ in subgroups of patients with tumors < 2 cm, 2–3.9 cm, and ≥4 cm.

1. Introduction

The concept of sentinel lymph node (SLN) biopsy is increasingly used in pelvic lymph node (LN) staging of cervical cancer and it is considered reliable especially in patients with tumors smaller than 2 cm [1]. A lower detection rate and sensitivity were reported for patients with larger tumors in some studies [2,3]. It was hypothesized that lymphatic channels in larger tumors might be occluded by metastases. Another limitation for SLN use in larger tumors was the technique of tracer application. Whereas the tracer is applied superficially around the tumor to the exocervix in smaller tumors, in larger tumors with exophytic growth often no healthy tissue is apparent vaginally. There is, however, a growing incidence of LN involvement with the increasing size of the tumor, thus the value of LN staging increases with the size of the tumor. The SLN concept not only improves the accuracy of staging due to pathologic ultrastaging but also enables intraoperative assessment and triaging of patients into radical surgery or primary chemoradiotherapy.

We have been using SLN detection in our department since 2005 for all patients referred for surgical treatment, irrespective of tumor size or stage of the disease. In 2009, we reported the technique of tracer application and SLN detection in 44 patients with tumors bigger than 3 cm

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[4]. Our more than ten years of experience has enabled us to retrospectively analyze the detection rate (DR) and false-negative rate (FNR) in tumors > 2 cm and even >4 cm, and compare the outcome with that for small tumors, in which the concept of SLN has been traditionally used. To our knowledge, this study is the first report on reliability of SLN biopsy in pelvic LN staging in large cervical cancer tumors.

2. Methods

2.1. Selection of patients

Patients with cervical cancer who had been treated between 2006 and the end of 2015 were enrolled in this study. Patients with one of the three most frequent histological cancer types (squamous, adenocarcinoma, adenosquamous cancer) who were referred for primary surgical treatment with curative intent, including SLN biopsy followed by systematic pelvic lymphadenectomy, were enrolled. Excluded patients were those who had undergone neoadjuvant chemotherapy, those referred for staging surgery before primary chemoradiotherapy, those with rare histological types, and those in whom pelvic lymphadenectomy was not performed.

The study was approved by the Local Ethical Committee of the First Faculty of Medicine and General University Hospital in Prague (No1587/17 S-IV).

2.2. SLN detection technique

For the detection of SLN, a combined technique with both radioactive tracer (99Tc, long protocol, application 12 h before surgery, 4 × 20 MBq) and blue dye (application at the beginning of the surgery) was used in all patients. In small tumors, both tracers were applied superficially into the cervical stroma. The syringe was kept in place a few seconds after application to avoid retrograde leakage of the tracer.

The technique was modified for large tumors and was described in our 2009 publication [4]. The tumor localization in cervical stroma was thoroughly described pre-operatively by transvaginal and/or transrectal ultrasound. A spinal needle was used for the application; the blue dye volume was increased by dilution (2:1; until 2009 the proportion was 4:1). Maximum effort was made to apply the tracer into the residual stroma around the tumor (Fig. 1). Application into the cervical stroma was controlled in two ways. Any leakage through the cervical canal indicating application into a necrotic part of the tumor was carefully monitored vaginally. The other important factor was resistance against the tracer application, which is higher when applied into stroma but drops lower when inserted into tumor or parametria.

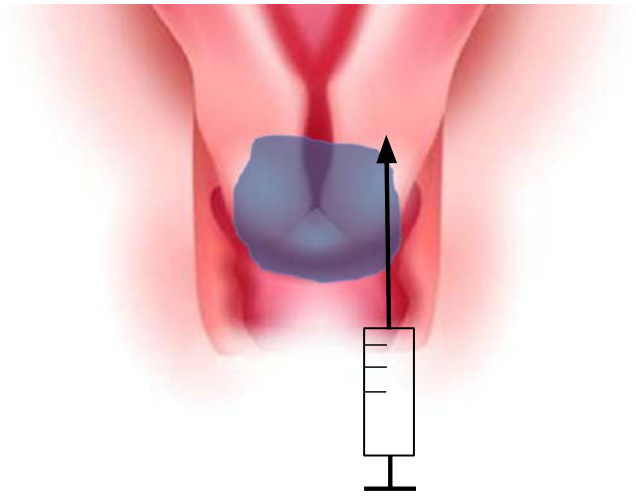

Fig. 1. Technique of tracer application in larger tumors.

Every 'hot' and/or blue lymph node detected was considered to be a SLN and was removed separately from each pelvic side.

2.3. Pelvic lymphadenectomy

After an attempt to detect any SLN, lymph node staging continued with a systematic pelvic lymphadenectomy. Lymph nodes were removed from seven standard regions in the pelvis (external iliac left and right, obturator left and right, common iliac left and right, presacral). Anatomical landmarks of regions were described previously [4].

2.4. Pathologic SLN and pelvic non-SLN processing

SLN, as well as all other pelvic LN, were fixed in 10% buffered formalin. After fixation, all LN were sliced at 2 mm intervals and embedded in paraffin. All SLN were further examined by the ultrastaging protocol. This protocol consisted of two consecutive sections (4 μm thick) obtained in regular 150 μm intervals, which were cut from each paraffin block at least in four levels or until there was no lymph node tissue left. The first section from each level was stained with H&E and, if negative, the second section was examined immunohistochemically with antibody against cytokeratins (AE1/AE3, 1:50 dilution; Dako, Glostrup, Denmark).

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.

2.5. Evaluated parameters

Data about the type of uterine procedure, radicality of parametrectomy, and oncological outcome are not included in this article, since they are not relevant to the objective of this study. The SLN detection rate was analyzed for the whole cohort. Overall DR expresses the proportion of patients in whom SLN was detected on at least one side of the pelvis. Bilateral DR expresses the proportion of cases in which SLN was detected on both sides.

All patients in whom no SLN was detected (7%), were excluded from the assessment of FNR. FNR was defined as a proportion of patients with negative SLN but positive non-SLN among all patients.

The oncological outcome was verified by comparing the database with the National Oncologic Registry and National Database of Death.

3. Data analyses

Standard measures of summary statistics were used to describe primary data: relative and absolute frequencies, arithmetic mean supplied with the standard deviation of mean (SD), median supplied with the 5th–95th percentile range. Non-parametric Mann-Whitney *U* test or Kruskal–Wallis test was applied for mutual comparison of the groups on the basis of continuous variables, while Fisher's exact test was applied to compare experimental variants in categorical variables. Diagnostic measures of the SLN detection rate were evaluated using estimates of the false-negative rate. The rate measures were compared between various categories of patients on the basis of Fisher's exact test.

4. Results

4.1. Group characteristics

In total, 350 patients were enrolled into the study with stages pT1a (6%), pT1b1 (67%), pT1b2 (13%), and pT2 (14%). Groups characteristics are shown in Table 1. The group was divided according to the largest pathologic tumor diameter into three subgroups (<2 cm, 2–3.9 cm,

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