**Sentinel node biopsy is reliable in early-stage cervical cancer but not in locally advanced disease**

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**Background:** Sentinel lymph node (SN) biopsy based on dual labeling with blue dye and radiocolloid can reliably determine lymph node status in early-stage cervical cancer, but few data are available on its accuracy in more advanced disease. We examined the influence of tumor stage on the accuracy of SN biopsy in patients with cervical cancer.

**Methods:** Between July 2001 and June 2004, 33 patients (mean age 52 years) with early-stage or locally advanced cervical cancer underwent laparoscopic SN biopsy based on dual labeling with patent blue and radiocolloid. Patients with early-stage cervical cancer (stages IA and IB1, 23 patients) underwent complete laparoscopic pelvic lymphadenectomy after the SN procedure. Patients with locally advanced cervical cancer (stage IB2, IIA or IIB, 10 patients) underwent laparoscopic pelvic and para-aortic lymphadenectomy after SN biopsy and prior neoadjuvant concomitant chemoradiotherapy. The SN identification rates and false-negative rates of patients with early-stage and locally advanced disease were compared.

**Results:** The mean numbers of SNs identified per patient with early-stage and locally advanced cervical cancer were 2.3 (range 0–4) and 1.9 (range 0–4), respectively. SNs were identified in 86.9% (20/23) of patients with early-stage disease and in 80% (8/10) of patients with locally advanced disease. When analyzed according to the side of dissection, the identification rate was lower, especially in the patients with locally advanced disease (55% compared with 67.4%). The false-negative rate per patient was zero in early-stage disease and 20% (1/5) in locally advanced disease (no significant difference). When the side of dissection was taken into account, the false-negative rate improved to 42.9% (3/7) in patients with locally advanced disease and remained at zero in early-stage disease ($P=0.038$). Isolated blue dye was taken up in 53.3% of SNs in patients with locally advanced disease, compared with only 6.4% in patients with early-stage disease.

**Conclusions:** This study suggests that the SN biopsy technique with dual labeling is less accurate in locally advanced cervical cancer than in early-stage cervical cancer.

**Key words:** cervical cancer, combined detection, laparoscopy, locally advanced disease, sentinel node biopsy

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**Introduction**

Cervical cancer is the third most frequent female malignancy worldwide, despite a gradual fall in its frequency in North America and Europe [1]. Patients continue to be diagnosed with locally advanced disease, despite better screening in some countries [1].

Lymph node status is a major prognostic factor and a decision criterion for adjuvant therapy in this setting. Pelvic lymph node metastases are detected in 0%–4.8% and 0%–17% of patients with stage IA and IB cervical cancer, respectively, compared with 12%–27% and 25%–39% of patients with stage IIA and IIB disease, respectively [2–5]. Lymphadenectomy may not be necessary in the former patients.

With the aim of avoiding unnecessary systematic lymphadenectomy and to minimize associated complications, the sentinel node (SN) concept has been accepted in many malignancies, including melanoma [6] and, more recently, breast cancer [7]. The SN method is well established in vulvar cancer [8–10]. Although the feasibility and accuracy of SN biopsy have been demonstrated in women undergoing primary surgery for early-stage cervical cancer [11–26], few data are available on its use in locally advanced disease.

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Neoadjuvant chemoradiotherapy is recommended for locally advanced disease in an attempt to improve locoregional tumor control and patient survival [27–30]. However, accurate staging of the pelvic and para-aortic lymph nodes remains problematic. Surgical staging may offer prognostic information only, and SN biopsy would avoid the associated morbidity [31]. No data are available on the feasibility of the SN biopsy in patients with locally advanced cervical cancer.

The aim of this study was to determine the influence of tumor stage on the accuracy of SN biopsy in patients with cervical cancer.

Patients and methods

Patients

Thirty-three consecutive patients referred to our institution with cervical cancer were enrolled in the study from July 2001 to June 2004. The inclusion criteria were age between 18 and 80 years, biopsy-confirmed cervical cancer and no suspicious nodes on MRI. Patients who had undergone neoadjuvant chemoradiotherapy were excluded. All patients underwent preoperative blood sampling, chest X-ray examination and MRI. Disease stage was classified as recommended by the International Federation of Gynecology and Obstetrics (FIGO) [32]. Patients with early-stage disease (stages IA and IB1) and those with locally advanced disease who had not received preoperative neoadjuvant chemoradiotherapy (stages IB2 and II) were eligible for the study.

Patients with stage IA or IB1 disease (n = 23) underwent laparoscopic SN biopsy, systematic bilateral pelvic lymphadenectomy, laparoscopic radical hysterectomy (Piver type III) and either the Schauta–Amreich operation or trachelectomy, depending on tumor size and the patient’s desire to preserve her childbearing potential. In accordance with our institutional guidelines, para-aortic lymphadenectomy was performed when the patient had metastatic pelvic SN lymph nodes (detected by intraoperative imprint cytology) or an involved para-aortic SN.

Patients with stage IB2, IIA or IIB disease (n = 10), who qualified for neoadjuvant concomitant chemoradiotherapy, underwent laparoscopic SN biopsy and pelvic and para-aortic lymphadenectomy before neoadjuvant therapy (external irradiation and brachytherapy with concomitant chemotherapy). In the absence of lymph node involvement, neoadjuvant therapy was followed by radical hysterectomy (Piver type II). Chemoradiotherapy alone was administered when lymph node involvement was discovered at final histology.

All patients gave their written consent after receiving all relevant information, including the potential adverse effects of patent blue, radiocolloid, general anesthesia and the laparoscopic procedure, and the possible need to convert to open surgery.

SN biopsy

Four injections of 0.2 ml (20 MBq each) of unfiltered technetium sulfur colloid (Nanocis, CIS Bi International, Saclay, France) were made with a 25-gauge spinal needle in each quadrant of the cervix the day before surgery. Scintigraphic images were obtained using a triple-head gamma camera (Irix, Marconi Corporation, Cleveland, OH, USA) 2 h after the injections and then every 30 min until the SN was visualized. A 5-min static anterior projection was acquired with a low-energy high-resolution collimator. Under general anesthesia, the patient was placed in a low lithotomy position. A speculum was placed in the vagina and patent blue (Bleu PatenîV, Guerbet Laboratory, Issy les Moulineaux, France) was injected pericervically with a 25-gauge spinal needle at the 3 o’clock and 9 o’clock positions (1 ml per injection).

In the laparoscopic procedure, after pneumoperitoneal insufflation using a Veress needle, a 10-mm laparoscope was inserted through an umbilical incision and connected to a video monitor. Three stab incisions were made in the suprapubic area: one of 12 mm in the midline (Versaport, Auto Suture Company, Elancourt, France) and one of 5.5 mm in each iliac fossa. Six instruments were used: unipolar and bipolar electrocautery forceps, scissors, grasping forceps, and a lavage system.

After patent blue injection the pelvic and lower para-aortic regions were carefully inspected for lymph ducts and specific dye uptake by lymph nodes. ‘Hot’ pelvic and para-aortic nodes were located with an endoscopic gamma probe (Eurorad, Strasbourg, France) inserted through the 12-mm suprapubic trocar. Hot nodes were sought before opening the peritoneum. The gamma probe was angled laterally to avoid detection of residual radioactivity emitted from the injection site.

After locating the SN, the peritoneum was opened above the external iliac vessels to the round ligament. Each blue and/or hot node was removed separately in an endoscopic bag (Auto Suture Company, Elancourt, France). The position of each SN relative to the major pelvic vessels and the count rate were recorded.

Laparoscopic bilateral pelvic lymphadenectomy with or without para-aortic lymphadenectomy was performed systematically after the SN procedure. All nodal tissue was removed and extracted in an endoscopic bag.

The absence of residual pelvic or para-aortic radioactivity was verified. Patients with early-stage disease underwent laparoscopic radical hysterectomy (Piver type III) or the Schauta–Amreich operation or trachelectomy as previously described [33–35]. All patients with locally advanced disease underwent laparoscopic pelvic and para-aortic lymphadenectomy alone. All the patients were operated on by the same surgeons (E.D. and E.B.).

Histopathology

SNs and other nodes were inspected by a pathologist. Grossly metastatic nodes were sectioned. SNs which appeared to be normal were cut perpendicularly to the long axis. All SNs were submitted to intraoperative imprint cytology. Air-dried cytologic smears were prepared by scraping the cut surfaces and staining with a rapid May–Grünsfeld–Giemsa method. Each half-SN was sectioned at 3-mm intervals. Each 3-mm section was analyzed at four additional levels of 150 μm and four parallel sections; one was used for hematoxylin and eosin (H&E) staining, and H&E-negative sections were examined by immunohistochemistry (IHC) with an anti-cytokeratin antibody cocktail (Cytokeratin AE1-AE3, Dako Corporation, Glostrup, Denmark). Other nodes were totally submitted and blocked individually following 3-mm distances and H&E staining.

The size of nodal metastases was estimated with an eyepiece micrometer. Micrometastasis was defined as a single focus of metastatic tumor cells was also recorded. SNs were considered to be positive if they contained macrometastases, micrometastases or isolated tumor cells.

Analysis of SNs

SNs were recorded as blue and/or hot (in vivo count exceeding three times the background). The false-negative rate was calculated as the ratio of the number of procedures with a negative SN and one or more positive non-sentinel nodes to the number of procedures with any positive pelvic lymph node.

Statistical analysis

Parametric and non-parametric continuous variables were compared with Student’s t-test and categorical variables with the χ²-test, Fisher’s exact
test, or the Mann–Whitney U-test as appropriate. \( P \) values <0.05 were considered to be statistically significant.

### Results

Thirty-three patients were enrolled in the study. All underwent laparoscopic SN biopsy with dual detection. Their mean age was 51.9 years (range 30–77 years). Demographic data and histologic findings are shown in Table 1 according to the tumor stage (early compared with locally advanced disease). No differences in mean age, gestity, the proportion of nulliparous patients, body mass index (BMI), menopausal status, previous cervical conization or histologic type were observed.

Of the 23 patients with early-stage cervical cancer, 19 had stage IB1 disease and four had stage IA2 disease. Following laparoscopic SN biopsy and laparoscopic pelvic lymphadenectomy, 18 (78.3%) of these patients underwent laparoscopic radical hysterectomy, three (13%) had the Schauta–Amreich operation and two (8.7%) underwent trachelectomy.

Of the 10 patients with locally advanced disease, one had stage IB2 disease, three had stage IIA disease and six had stage IIB disease. These 10 patients underwent laparoscopic SN biopsy, laparoscopic pelvic lymphadenectomy and laparoscopic para-aortic lymphadenectomy only.

An average of 10.7 pelvic lymph nodes (range 4–18) were retrieved from patients with early-stage disease. A mean of 12.6 (range 8–17) pelvic lymph nodes and 14.1 (range 6–25) para-aortic lymph nodes were retrieved from the patients with locally advanced disease.

The mean number of SNs identified per patient with early-stage and locally advanced disease was 2.3 (range 0–4) and 1.9 (range 0–4), respectively (Table 2). The total numbers of SNs removed from patients with early-stage and locally advanced disease were 47 and 15, respectively. In patients with locally advanced disease, most SNs were solely blue (53.3% compared with 6.4% in early-stage disease) (Table 2), suggesting that the radioisotope diffused less efficiently than the blue dye in patients with locally advanced disease.

SNs were identified in 86.9% (20/23) of patients with early-stage disease and 80% (8/10) of patients with locally advanced disease (Table 2). When analyzed according to the side of dissection, the SN identification rate was lower, especially in the locally advanced disease group (55% compared with 67.4%). This variation between groups was not statistically significant. Bilateral SN identification was less frequent in patients with locally advanced disease (37.5%) than in patients with early-stage disease (60%), although the difference was not statistically significant.

The rate of false-negative SN biopsies, i.e. the situation where an SN was identified and considered negative but where a non-sentinel node was involved, was zero in the early-stage cervical cancer group and 20% (1/5) in the locally advanced disease group (not statistically significant). When analyzed according to the side of dissection, the false-negative rate increased to 42.9% (3/7) in patients with locally advanced disease and remained at zero in patients with early-stage disease \( (P=0.038) \).

The locations of the SNs in the two groups are shown in Table 3. The most common site was the external iliac region (no difference between the groups). No parametrial or para-aortic SNs were found. The patient with a common-iliac SN had two other SNs, both in the ipsilateral external iliac region.

### Table 1. Demographic data and histologic findings according to tumor stage

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Early-stage disease (stage IA/IB1)</th>
<th>Locally advanced disease (stage IB2/II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Mean age (range) (years)</td>
<td>51.7 (30–77)</td>
<td>53.5 (41–75)</td>
</tr>
<tr>
<td>Mean BMI (range) (kg/m²)</td>
<td>24.6 (17.9–34.7)</td>
<td>23.9 (19.0–31.3)</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>14 (60.8)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Mean gestity (range)</td>
<td>2.3 (0–9)</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>4 (17.4)</td>
<td>0</td>
</tr>
<tr>
<td>Preoperative cervical conization (%)</td>
<td>9 (39.1)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous (%)</td>
<td>15 (65.2)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Adenocarcinoma (%)</td>
<td>8 (34.8)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Type of associated surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic radical hysterectomy and LPND</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Schauta–Amreich operation</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal radical hysterectomy and LPND</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Laparoscopic para-aortic lymphadenectomy and LPND only</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

LPND, laparoscopic pelvic lymph node dissection.
There were no anaphylactic reactions to patent blue, no complications due to the laparoscopic SN procedure and no conversions to laparotomy.

Thirteen positive SNs were found in nine patients (27.3%). Eight positive SNs were found in four patients (17.4%) with early-stage disease. Four of these eight positive SNs were identified by H&E staining (two macrometastases and two micrometastases) and four by IHC (two micrometastases and two isolated tumor cells). The SNs were the only positive lymph nodes in these four patients. Four SNs from five (50%) of the 10 patients with locally advanced disease were positive, including four macrometastases (H&E) and one micrometastasis (IHC). Positive non-sentinel nodes were found in three patients with a metastatic SN. In the first patient (stage IIA), SN biopsy revealed one SN containing a macrometastasis. Pelvic and para-aortic lymphadenectomy revealed only one other positive node, a micrometastasis in a para-aortic node. The second patient (stage IIA) had one right external iliac SN containing a macrometastasis (6 mm). Pelvic and para-aortic lymphadenectomy revealed a micrometastasis in a right pelvic node and a macrometastasis in a left pelvic node. The third patient (stage IIB) had one right external iliac SN containing a micrometastasis. Pelvic and para-aortic lymphadenectomy revealed a micrometastasis in a left pelvic node.

In a patient with stage IIB disease, SN biopsy identified only one left-sided uninvolved SN, while pelvic and para-aortic lymphadenectomy revealed macrometastases in two contralateral pelvic non-sentinel nodes. A second patient with stage IIB disease had an uninvolved left external iliac SN, while pelvic and para-aortic lymphadenectomy revealed micrometastases in one right and one left pelvic lymph node. Therefore SN biopsy was false negative in both these patients.

Discussion

This is the first report of laparoscopic SN biopsy in patients with locally advanced cervical cancer. We found that SN biopsy with dual patent blue–radiocolloid labeling was less accurate in locally advanced than in early-stage disease.

At least one SN was identified in 87% of patients with early-stage cervical cancer and in 80% of patients with locally advanced disease, comparing well with the results of previous studies based on dual labeling [13, 14, 18–20, 22, 25, 26, 36, 37].

The cervix, being a midline structure, should have bilateral drainage, but bilateral pelvic node involvement is found in only about 50% of patients with cervical cancer [38, 39] It is not possible to predict the preferential side of lymphatic drainage in this setting. Thus, ideally, at least one SN should be studied on each side of the pelvis, and the SN identification
rate should be reported not only per patient but also per side. If the SN procedure is performed without systematic lymphadenectomy, patients with unilaterally identified SNs should undergo complete contralateral lymphadenectomy. In our study, the SN identification rate per pelvic side was 67% in patients with early-stage cervical cancer and 55% in those with locally advanced disease. The bilateral SN identification rate was only 38% in patients with locally advanced disease compared with 60% in those with early-stage disease. With the exception of one series, the reported bilateral SN identification rate ranges from 33% to 95%. The low SN identification rate per pelvic side observed here significantly reduces the value of the SN procedure for patients with locally advanced disease.

The most important performance index of the SN procedure is the false-negative rate, i.e. the ratio of number of procedures in which all SNs are negative but one or more pelvic non-SNs are positive to the number of procedures in which any pelvic lymph node is positive. A false-negative finding risks understaging the patient, resulting in an incorrect decision regarding the need for adjuvant therapy. We recently reported a study of 18 patients with cervical cancer who underwent a laparoscopic SN procedure using combined detection [40]. If the SN was free from metastasis by both H&E and IHC staining, all non-SNs were also examined by the combined staining method. In 13 patients, no metastatic SN involvement was detected by H&E and IHC staining. In these 13 patients, non-SNs were examined by serial sectioning and IHC, and none was found to be metastatic. This confirms that the SN procedure appears to give a reliable prediction of the metastatic status of the regional lymphatic basin in patients with cervical cancer. In our study the false-negative rate was zero in patients with early-stage disease and 20% (1/5) in patients with locally advanced disease. When analyzed according to the side of dissection, the false-negative rate increased to 42.9% (3/7) in patients with locally advanced disease but remained zero in patients with early-stage disease ($P=0.038$). This high false-negative rate in patients with locally advanced disease conflicts with the results of previous studies based on dual detection. Previously published studies of SN biopsy mention a total of 467 patients with cervical cancer. Only four false-negative results were reported, giving a rate of approximately 4%. Levenback et al. [13] reported one false-negative result in a patient with a positive medial parametrial non-SN that had been resected along with the primary tumor and was not identified by blue dye or gamma detection, probably because of the proximity of the cervical injection sites. Buist et al. [25] also observed one false-negative result in a patient with a positive non-SN in the resected parametrium close to the cervix. Malur et al. [16] observed one false-negative result in a series of 50 patients; this patient underwent an SN procedure with blue dye alone, and the SNs were evaluated using the standard H&E method and not with serial sectioning and IHC. Rhim et al. [36] also reported one false-negative case.

In our patients with locally advanced disease, only 47% of identified SNs were ‘hot’ compared with 94% in patients with early-stage disease, suggesting that the radioisotope diffuses less efficiently than blue dye in the former patients. One possible explanation is that large cervical tumors clog lymphatic channels, allowing only the smaller particles of blue dye to diffuse.

In conclusion, this study suggests that the dual-label SN biopsy is less accurate in patients with locally advanced cervical cancer than in patients with early-stage cervical cancer. Larger studies will be needed to confirm our preliminary results. Therefore laparoscopic pelvic and para-aortic lymphadenectomy might be preferable to laparoscopic SN biopsy in women with locally advanced cervical cancer. Until the results of further randomized studies are available, SN biopsy should not be performed exclusively, and full pelvic and/or para-aortic lymphadenectomy associated with SN biopsy should remain the standard of surgical practice in cervical cancer.

References


