The Sentinel Node in Cervical Cancer Patients: Role of Tumor Size and Invasion of Lymphatic Vascular Space

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Abstract. Background: The sentinel lymph node (SLN) technique aims at predicting the absence of regional nodal metastasis and seems promising in the management of cervical cancer patients. Patients and Methods: Forty patients undergoing surgery for early cervical cancer were submitted to the SLN procedure, using Blue Patente alone in 3, radiocolloid injection alone in 4 and both methods in 33 (82.5%). All patients underwent radical hysterectomy and pelvic lymphadenectomy. Results: The detection rate was as follows: overall 85%, blue dye alone 66%, radiocolloid alone 75%, dual method 87%. Detection was successful in 34 patients, with one false-negative result. No micrometastases were demonstrated during ultrastaging of the sentinels. The detection rate was higher in tumors <2 cm (94.1%) than in larger tumors (78.2%, p>0.09). Significant negative correlation between lymphatic vascular space invasion (LVSI) and detection rate was found (p<0.001). Conclusion: SLN detection is feasible in early cervical cancer but presence of LVSI and a tumor size >2 cm negatively affect the detection rate and may increase the incidence of false negatives.

Lymph node metastasis is a central phenomenon in the natural history of patients with cervical carcinoma. It represents one of the most important prognostic factors and a valuable piece of information needed for adjuvant therapy decision-making. The sentinel lymph node technique aims at the accurate prediction of lymph node metastases, more exactly at the accurate prediction of the lack of them, when the sentinel node itself is disease-free. This concept was introduced as early as 1977 by Cabanas (1), meaning that the sentinel node is the first node of a lymphatic basin, receiving drainage from the tumor. It therefore represents the initial site of metastatic tumor implantation and its pathologic evaluation should thus predict the status of the remaining lymph nodes (2, 3). This technique has since been used in patients with melanoma (4), breast cancer (5), in trials for vulvar cancer (6) and more recently in studies of cervical cancer (7-13). The sentinel node concept aims at providing oncologically acceptable surgical treatment while simultaneously avoiding systematic lymphadenectomy (11-13).

We decided to investigate the feasibility, safety, accuracy and false–negative rate of this method in patients with early-stage cervical carcinoma and examine the role of tumor size and LVSI presence on the reliability of the method.

Patients and Methods

Between January 2006 and May 2008, SLN mapping was performed in 40 patients for whom a radical surgery for cervical cancer was planned. All patients signed an informed consent. Eligibility criteria for enrollment were the histological documentation of the disease and clinical stage up to IIA. Patients who had received neo-adjuvant treatment, radiotherapy/chemotherapy or both, were excluded from the study.

In most circumstances, 33 out of 40 patients (82.5%), the dual approach was utilized i.e. the combination of radioactive colloid with the injection of blue dye. In all cases where radioactive colloid was employed, 37 out of 40 patients (92.5%), preoperative lymphoscintigraphy under a gamma camera was performed.

Injection of radiocolloid and preoperative lymphoscintigraphy. Injection of radiocolloid followed the same protocol (timing, dosages and injection sites) in all patients. It was performed the afternoon before surgery, approximately 18 hours before the beginning of the operation. The total amount of radiocolloid injected was 3 mCi of $^{99m}$Tc divided equally into four separate injections of 0.2 ml applied at the four quadrants of the cervix, always at the periphery of any visible tumor or inflammation. Each full injection...
contained 0.75 mCi of Technetium – 99 colloid albumins (Nanocoll, Amersham) measured again on the spot just before the application. Injection of radiocolloid was carried out according to the instructions given in the literature for better detection rates (14). Using a short length (10 mm) 27-gauge hypodermic needle, the total amount of radiocolloid was delivered slowly to a depth of 2-5 mm into the stroma of the cervix. A hand-held surgical vessel clamp was occasionally used to stabilize the needle in place.

One hour after the injection, a static scintigram under a gamma camera was taken to document radioactive colloid uptake and to determine the anatomic location of the sentinel node(s). The skin was marked at the site(s) of sentinel node detection.

Injection of blue dye. Injection of the blue dye (Blue Patente, Guerbet AG, Zürich, Switzerland) was carried out immediately before surgery, after induction of anesthesia and intubation. The 2 ml ampoule of Blue Patente was diluted in 4 ml of normal saline, which was then divided into 4 separate injections of 1.5 ml each. These were delivered separately in the four quadrants of the cervix always at the periphery of the tumor, in the same manner as was described for the radiocolloid injections.

Intraoperative lymphatic mapping & surgical technique. At surgery, a type II or III radical hysterectomy with systematic pelvic lymphadenectomy was performed. Intraoperative identification of sentinel nodes was made using a hand-held collimated gamma probe (GPS Navigator) with a threshold setting for 99mTc (125-155 keV) designed for transperitoneal localization. Measurement of the radioactive background and of hot spots was performed immediately after opening the abdomen. Any region that produced approximately 10-fold higher counts than the background was considered to host a sentinel node, according to the literature (15-17). Resected hot sentinel nodes were re-measured ex vivo for residual radiation, and for comparison with the non-sentinel nodes. Simultaneously, the diffusion of the blue dye was inspected. Any node that was stained blue was labeled as sentinel. The median time of the procedure was 25 minutes (15-30 minutes range). Gradual discoloration of the sentinel nodes was observed as the operation proceeded.

Pathological evaluation. The lymph nodes were sent for histological examination in groups as obturator, internal iliac, external iliac and common iliac. Sentinel lymph nodes were sent separately, marking their location and the mode by which they were identified (blue, hot, or both). Standard histological evaluation was carried out for non-sentinel nodes, while an enhanced pathological analysis was reserved for sentinel nodes.

These were first sectioned at 3 mm intervals and then each separate block was cut at 400 μm intervals (15-20 sections per node). All sections were stained by H&E and examined separately. At least five of them were also examined by immunohistochemistry using cytokeratin staining.

Tumor size was measured after formalin fixation. LVSI was defined as absent if none or only one focus of invasion was recognized around the tumor and as present if multiple foci were recognized around the tumor, or if there was massive LVSI with a spray-like growth.

Results

A total of 40 patients were included in the study. Disease characteristics and SLN detection are presented in Table I. The overall number of sentinel nodes found was 48 out of 34 successful detections (48/34=1.4 sentinel nodes per patient). The total number of nodes removed was 761 (on average, 19 nodes per patient). Seventeen of the patients had tumors up to 2 cm in diameter (42.5% ) and 23 had larger (>2-4 cm) tumors (57.5% ). LVSI was present in 7 out of 40 cases (17.5% ). In 8 of the patients, pelvic lymph node metastasis was found (20% ). The overall SLN detection rate was 85% (34/40).

The detection method used was dual in 33/40 cases (82.5% ), while lymphoscintigraphy alone was used in 4/40 (10% ) of patients and blue dye alone in 3/40 (7.5% ). The detection rate per method was 87%, 75% and 66%
respectively (Table II). In the presence of LVSI, the SLN detection rate was significantly lower (42.85%) than in the absence of LVSI (93.3%) (Table III). No serious side effects were observed from use of either the blue dye or the radiocolloid. Two of the patients on whom blue dye was used demonstrated transient low pulse oximetry readings during the operation.

Increased tumor size also influenced negatively the SLN detection rate and the possibility of false-negative results. In this series, the median tumor size was 2.2 cm. Seventeen (42.5%) patients had tumors up to 2 cm and a detection rate of 94.1% (16/17) without any false-negative cases. In tumors larger than 2 cm, the detection rate was 78.2% (18 successful detections out of 23 patients) with one false-negative case. The overall false-negative rate per node positive patients (and successful detection) was 20% (1 false-negative case out of a total of 5 node positive patients on whom detection was successful) (Table IV). In total, of eight patients with lymph node metastases, we failed to detect a sentinel node in three.

In Table V, the detection rate in relation to both tumor size and LVSI is presented. In patients with small tumors and no LVSI, the SLN identification rate was 93.75% , while in those with greater tumors and LVSI, it was 33%. The overall diagnostic indices of the SLN technique were as follows: sensitivity 75% , specificity 96.7% , negative predictive value 96.7% , positive predictive value 75% and accuracy 94.1% (calculated from Table VI).

**Discussion**

The applicability of the SLN technique in cervical cancer has been investigated by several groups reporting detection rates of 60% to 100% (10, 16, 18-20). The variation of the existing data may be attributed to differences regarding the operative procedure (open, laparoscopic, or vaginal approach), the detection method (scintigraphy, blue dye...
alone, or in combination) and the characteristics of the patients (e.g.: stage of the disease and neoadjuvant therapies). In this study, detection of SLN was feasible in 87% of patients undergoing open radical hysterectomy for early stage (IA2-IIA) cervical cancer as primary treatment when the dual method was used. Both lymphoscintigraphy and blue dye technique alone were less successful in detecting SLN (75% and 66% respectively) in this series, a finding well demonstrated in previous studies (10, 16, 19, 20).

Using the SLN technique, false-negative rates are of major concern. In this study, false-negatives were defined as these cases with detected but free of metastasis SLN node(s), in patients with positive non-sentinel nodes. In 8 of our patients with nodal metastasis, SLN detection was successful in 5, but 1 of these 5 was free of metastatic involvement. This false-negative SLN rate per node positive patients (1/5) is not considerably different from the data previously reported by Levenback et al. (1 in 8) (15) and Buist et al. (1 in 10) (16), using the same definition, given the small sample size. In other studies, the false-negative rate has been calculated as the percentage of false-negative cases over the total number of successful SLN detections (1/34 - 2.9% in our series). Marnitz et al. (22) using this definition reported a false negative rate of 4% . In yet other studies, with no false-negative results at all, a 0% rate was reported (18, 24-27).

The possibility of micrometastatic involvement of the SLN missed at frozen section diagnosis has also been of concern. Buist et al. found a 7% increase in false negative rate of SLN examination in final ultrastaging compared with conventional frozen section (16). In our study, all 4 positive SLN were diagnosed with the standard pathological examination and no micrometastases were found in the ultrastaging applied in the remaining 44 SLNs. Likewise, Plante et al. (12) in their large study identified only one and Levenback et al. (15) no SLN with micrometastasis in ultrastaging. It has been observed that micrometastatic disease is more frequent in tumors with LVSI (28,29). However, our data show that identification of SLN is less often successful in the presence of LVSI (failure of detection in 4 out of 7 tumors with LVSI). Moreover, micrometastatic disease may be present in non-sentinel nodes as was shown by multilevel sectioning and immunohisto-chemistry applied to all non-sentinel nodes in the study by Marchiol et al. (28).

The importance of the primary tumor dimensions and the influence it may have on the sentinel node detection rate is well emphasized in the literature. O’Boyle et al. reported that tumor size may negatively affect the sentinel node detection rate (7). In a 2007 study by Darai et al. (30), it was also found that detection rate was higher (90%) in patients with early-stage disease than in patients with more advanced stages (66.6%), including 15 cases (27.8%) with stage IIB tumors. Similarly, Di Stefano et al. (21) reported an overall detection rate of 90%, with 33% failures for tumors >4 cm. Barranger et al. in their 2005 study concluded that sentinel node biopsy is reliable in early-stage cervical cancer but not in locally advanced disease, signifying a negative effect of tumor size on the sentinel node detection and false-negative rates (31). In a more recent study from Canada (18), reporting detection rate of 98%, only 5 out of 39 patients had tumors larger than 2 cm. Our results are in accordance with these data. Detection rate in patients with tumors ≤2 cm was 94%, while in those with larger tumors it was 78.2%. This difference, although indicative, did not reach statistical significance (p>0.09).

It is well known that LVSI is associated with increased risk of nodal metastasis and poorer prognosis in patients with cervical cancer. It has also been reported that LVSI increases the prevalence of sentinel node micrometastatic disease (28-29). To our knowledge, this is the first study which directly correlates the SLN detection rate with the presence of LVSI. In only 3 out of 7 patients with pronounced LVSI was detection of the sentinel lymph node possible (42.9%) compared with a detection rate of 93.3% achieved in 33 patients without LVSI (p=0.001). We also noticed that the simultaneous presence of both LVSI and tumor size >2 cm further increases the failure rate (from 57.2% to 66.7%). In the group of patients with larger tumors (n=23), all cases (n=8) with positive lymph nodes were included (prevalence 34.7%). The detection rate in this group was 78.2% and the false-negative-rate per positive node patients was 20% (1/5). These findings suggest that SLN technique may fail more frequently when the possibility of nodal metastasis increases. Notably, 50% of patients in whom the SLN technique failed in this study had pelvic lymph node metastasis.

In conclusion, these data show that sentinel node detection in cervical cancer patients is feasible and safe to perform, with a high detection rate (94%) in early disease with optimal characteristics, when the dual method is used. However, the rate of failures is high (57.2%) in the presence of pronounced LVSI and the risk of false-negative findings is considerable in tumors larger than 2 cm in diameter. Since patients with tumors of these features are often candidates for surgical treatment, more studies are needed to determine the clinical value and limitations of the SLN technique in cervical cancer.

References


