

Sentinel node detection with the blue dye technique in early cervical cancer

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Summary

Objective: The aim of this study was to investigate the feasibility of sentinel node detection with the blue dye technique in early cervical cancer.

Methods: In a retrospective study conducted between January 2000 and February 2005, 47 women with early cervical cancer (6 patients FIGO Stage I A, 38 patients FIGO Stage I B, 2 patients FIGO Stage II A, 1 patient FIGO Stage II B) who underwent class II-III radical hysterectomy with pelvic lymphadenectomy were identified. Prior to surgery 1 ml of blue dye (lymphazurin 1%) was injected into the four quadrants of the cervix.

Results: The detection rate for sentinel nodes was 83% (39/47 patients). The median number of sentinel lymph nodes per patient was two. Nine patients had positive sentinel nodes. In one patient the sentinel lymph node procedure revealed to be false-negative. Positive predictive value and specificity were both 100%. The sensitivity and negative predictive value were 90% and 97%, respectively.

Conclusions: Sentinel node detection has become a main field of interest in gynecological oncology. Our detection rate and sensitivity rate using the blue dye technique in cervical cancer are comparable to those in previously published data. However, recent data on a combined radioactively labeled albumin and blue dye technique show even more promising results. The clinical validity of the combined techniques must be evaluated prospectively in larger studies.

Key words: Sentinel lymph node; Cervical cancer; Blue dye technique.

Introduction

Cervical cancer is one of the leading malignancies in women worldwide.

Early stages can be cured with surgery and/or radiotherapy. Radical hysterectomy with pelvic lymphadenectomy is the commonly performed surgical procedure.

However, the majority of these patients do not benefit from radical systematic lymph node dissection. Only in 10%-17% pelvic lymph node metastases are expected [1].

The five-year survival rate for patients with positive lymph nodes is approximately 40%-63%.

Lymphedema, vascular and neural injury, adhesion formation and seroceles can follow radical surgery and increase morbidity.

Less radical surgery is therefore warranted. Sentinel lymph node dissection is an interesting improvement in radical surgery.

The term sentinel lymph node was first used by Gould *et al.* [2] in 1960 in the parotid. The concept of sentinel lymph node mapping was used by Cabanas in 1977 in patients with penile cancer [3].

Morton *et al.* applied the same concept to cutaneous melanoma [4], Giuliano *et al.* and Veronesi *et al.* to breast cancer [5, 6] and Levenback and Burke *et al.* [7] for vulvar cancer.

In breast cancer the sentinel node technique is integrated in routine clinical staging [6, 9].

Efforts are also under way to use intraoperative lymphatic mapping and sentinel node identification for patients with early cervical cancer.

The sentinel lymph node is defined as the first draining lymph node of an anatomical region. It should reflect the overall status of the entire regional drainage area.

If the sentinel lymph node is histologically negative, the other non-sentinel lymph nodes can also be assumed to be negative for metastases.

The aim of this study was to investigate the feasibility of intraoperative lymph node mapping with the blue dye technique in patients with early cervical cancer undergoing radical hysterectomy with systematic lymphonodectomy.

Patients and Methods

From January 2000 to February 2005, 47 patients with early cervical cancer (6 patients FIGO Stage I A, 38 patients FIGO Stage I B, 2 patients FIGO Stage II A, 1 patient FIGO Stage II B) underwent class II-III radical hysterectomy with pelvic lymphadenectomy. In 20 patients paraaortic lymphadenectomy was also performed. Five patients received neoadjuvant chemotherapy.

In 45 patients the Wertheim Meigs operation with pelvic lymphadenectomy was performed, 19 of whom also underwent paraaortic lymphadenectomy. Two patients underwent a Schauta operation with pelvic lymphadenectomy and one patient the same procedure with paraaortic lymphadenectomy.

Tumor characteristics and demographic data are summarized in Table 1.

Table 1. — Characteristics and demographic data.

Stage	No. of patients (%)
I A	6 (13)
I B	38 (81)
II A	2 (4)
II B	1 (2)
<i>Surgery</i>	
W + pelv L	25 (53)
W + pelv L + paraa L	19 (41)
S + pelv L	2 (4)
S + pelv + paraa L	1 (2)
<i>Neoadjuvant chemotherapy</i>	5 (11)
<i>Grading</i>	
G1	10 (21)
G2	22 (47)
G3	13 (28)
not evaluated	2 (4)
<i>Histology</i>	
Squamous	32 (68)
Adenocarcinoma	12 (26)
Adenosquamous	3 (6)

W: Wertheim Meigs operation; pelv L: pelvic lymphonodectomy; paraa L: paraaortal lymphonodectomy; S: Schauta operation.

On the day of surgery, after induction of general anesthesia, 1 ml of 1% lymphazurin was injected ten minutes preoperatively into each quadrant of the cervix at the 0, 3, 6 and 9 o'clock positions.

Sentinel lymph nodes (lymph nodes with blue dye uptake) as well as non-sentinel lymph nodes (lymph nodes without blue dye uptake) were removed.

In 35 of 39 patients sentinel lymph nodes were intraoperatively analyzed with fresh frozen tissue.

All sentinel lymph nodes were analyzed by hematoxylin and eosin staining of serial sections.

In 30 patients an additional immunohistochemical analysis of cytokeratin antibodies (AE1/AE3) for the detection of micrometastases followed according to the protocol of the "Austrian Society of Pathology for Breast Cancer SLN"(www.pathology.at).

Micrometastases were defined as a single focus of metastatic cells per node measuring no more than 2 mm.

Sentinel nodes were considered positive when they contained macrometastases, micrometastases or isolated tumor cells.

The false-negative rate was defined as the number of cases with negative sentinel lymph nodes but one or more positive non-sentinel lymph nodes.

Results

The median age of the study population was 47 years (range, 20 to 71 years).

At least one sentinel node was found in 39 (83%) of the 47 patients.

A total of 1117 lymph nodes were removed from these 39 patients and 111 sentinel nodes were identified.

The median number of lymph nodes removed (including sentinel nodes) was 28 per patient (range, 9 to 50).

The median number of sentinel lymph nodes per patient was two (range, 1 to 9).

Positive sentinel lymph nodes were detected in nine (23%) of 39 patients.

In five patients hematoxylin and eosin staining of sentinel lymph nodes revealed metastases, whereas in four patients micrometastases were detected only by immunohistochemistry (Table 2).

Table 2. — Characteristics with positive lymph nodes (total).

Stage	tl	ts	pl	ps	Histology
<i>Histology pos. SN:</i>					
I B1	14	1	2	1	Squamous
I B	30	3	2	1	Squamous
I B1	24	1	4	1	Adenocarcinoma
I B	20	1	1	1	Adenocarcinoma
I B1	19	1	2	1	Adenocarcinoma
<i>Immunohistochemistry pos. SN:</i>					
I B1	25	2	2i+	2i+	Squamous
I B1	22	1	1i+	1i+	Adenosquamous
I B1	31	4	1i+	1i+	Squamous
II B	17	4	1i+	1i+	Squamous
<i>False-negative SN:</i>					
I B	37	4	2	0	Squamous

pos. SN: positive sentinel lymph node; i+: micrometastases; t l: total removed lymph nodes; t s: total removed sentinel lymph nodes; p l: positive lymph nodes; p s: positive sentinel lymph nodes.

In 35 patients sentinel lymph nodes were analyzed intraoperatively with fresh frozen tissue and in 34 cases the results agreed with those obtained with paraffin-embedded hematoxylin and eosin stained sections. In four of these 34 patients immunohistochemistry detected micrometastases although paraffin-embedded hematoxylin and eosin stained sections showed no metastatic involvement.

Patients with positive sentinel lymph nodes were classed in eight cases as FIGO Stage I B and in one case as FIGO Stage IIB.

False-negative sentinel lymph nodes were found in one patient (3%) classed as FIGO Stage I B. Of the 37 lymph nodes retrieved from her, four were negative sentinel lymph nodes and two were positive non-sentinel lymph nodes (Table 2).

In eight patients (17%) no sentinel node was detected, and two of them were treated with neoadjuvant chemotherapy. In one of these two patients with neoadjuvant chemotherapy all nodes were negative, while the second patient showed lymph node metastases.

Lymph node metastases were found in three of the eight patients with no sentinel node detection.

The sensitivity of the sentinel node procedure was 90% and the negative predictive value was 97%. Positive predictive value and specificity were both 100%.

Discussion

Lymphatic mapping is a promising strategy for the intraoperative assessment of nodal status as shown for different tumor entities like breast cancer and melanoma [4-6, 9, 11]. In published data the sentinel lymph node detection rate in breast cancer with combined techniques is more than 89% and the false-negative rate less than 6%.

In patients with early cervical cancer several lymphatic mapping studies using the blue dye technique and/or radioactively labeled albumin (lymphoscintigraphy) have been performed [12-21], and detection rates ranged from 40% to 100% [12-15, 17-21], Table 3.

Especially trials using combined techniques such as those conducted by Levenback *et al.* [21] and Martinez-Palones *et al.* [20] showed promising results with a 100% detection rate (Table 3).

Table 3. — Detection rate in the literature.

Authors	Technique	Patients (n)	SN (n)	Detection Rate
Verheijen <i>et al.</i> [13]	B	10	4	40%
Malur <i>et al.</i> [17]	B	9	5	55.5%
O'Boyle <i>et al.</i> [12]	B	20	12	60%
Current study	B	47	39	83%
Medl <i>et al.</i> [18]	B	3	3	100%
Dargent <i>et al.</i> [8]	B	35	35	100%
Malur <i>et al.</i> [17]	B/R	50	39	78%
Verheijen <i>et al.</i> [13]	B/R	10	8	80%
Barranger <i>et al.</i> [14]	B/R	13	12	92%
Levenback <i>et al.</i> [21]	B/R	39	39	100%
Martinez-Palones <i>et al.</i> [20]	B/R	25	25	100%

B: blue dye; B/R: blue dye and radioisotope; patients (n): patients total; SN (n): patients with sentinel lymph nodes.

Preliminary results from a prospective multicenter study, the "AGO Uterus III Study", showed that in 307 patients (105 patients underwent the blue dye technique, 58 patients lymphoscintigraphy and 144 patients underwent both techniques) the combination of radioisotope and blue dye technique can increase the detection rate to up to 99% as compared to 84% for the blue dye technique alone [23].

The present study explored the feasibility of lymphatic mapping with the blue dye technique and intraoperative histopathological examination using fresh frozen tissue in patients with early cervical cancer undergoing radical hysterectomy and lymphonodectomy.

The sentinel node detection rate was 83% (39 of 47 patients), which is a very promising value and comparable to that found by Verheijen *et al.* [12] and Malur *et al.* [17], who used combined techniques (radioactively labeled albumin and blue dye) (Table 3).

However, from the literature we conducted that the sentinel lymph node detection rate can be significantly improved by teaming it with lymphoscintigraphy.

In analogy to the treatment of breast cancer, patients with neoadjuvant chemotherapy should be excluded from sentinel node detection techniques [22].

In 38 (97%) of the 39 patients who underwent histological analysis of all removed lymph nodes histological findings agreed with the results predicted by sentinel lymph node analysis.

Moreover 34 (97%) of the 35 patients who underwent sentinel lymph node detection showed agreement between intraoperative fresh frozen tissue analysis and subsequent paraffin-embedded hematoxylin and eosin stained sections.

Only one patient (3%) showed a false-negative result. Also, other trials reported low rates of false-negative results ranging from 0% to 17% [12-21].

In this special case correct classification would have indicated a systematic lymphonodectomy, and a five-year survival rate of 73% could have been expected [24].

The false-negative result of this patient has to be weighed against the remaining 29 patients who would undergo radical systematic lymphonodectomy, without benefit.

Most centers, as ours, use standard hematoxylin and eosin staining and immunohistochemistry with cytokeratin antibodies according to national or international guidelines for breast cancer.

In the present study 10% (4 of 39 patients) of sentinel lymph nodes showed micrometastases only with immunohistochemistry and cytokeratin antibodies although paraffin-embedded hematoxylin and eosin stained sections showed no metastatic involvement. These cases were recorded as lymph node positive.

Barranger *et al.* also found micrometastases when using immunohistochemistry in cases that hematoxylin and eosin staining had shown to be negative. In two out of 13 patients four sentinel lymph nodes with micrometastases and isolated tumor cells were detected.

However, other authors did not identify additional micrometastases when using immunohistochemistry with cytokeratin antibodies [13, 19, 21].

The clinical significance of these micrometastases remains unclear, and there are no recommendations for adjuvant treatment.

Conclusion

Sentinel node detection in early cervical cancer permits the surgical intervention time to be shortened.

Patients with neoadjuvant chemotherapy should be excluded from the sentinel node detection technique, because sensitivity may be reduced due to chemotherapy.

Patients with no detectable sentinel nodes should undergo hysterectomy and radical systematic lymphonodectomy.

Although the sentinel node detection rate in early cervical cancer, namely 83% when using blue dye only, is satisfactory, it can be improved with lymphoscintigraphy.

In 97% of the histological analysis all removed sentinel and non-sentinel lymph nodes showed the same results and in only 3% was a false-negative result detected.

These results are so promising that it is justifiable to reduce the rate of radical systematic lymphonodectomy.

In order to enhance the validity of our findings we decided to prolong the study.

Standardized pathological protocols for the evaluation of micrometastases in sentinel nodes are needed.

The validity of the routine use of sentinel node detection in early cervical cancer and intraoperative fresh frozen tissue analysis needs to be further investigated in large multicenter studies.

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