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Bilateral ultrastaging of sentinel lymph node in cervical cancer: Lowering the false-negative rate and improving the detection of micrometastasis ☆

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HIGHLIGHTS

► Bilateral SN detection substantially decreases the false-negative rate of SN ultrastaging and increases detection of metastases, especially micrometastasis.
► SN ultrastaging improves metastatic lymph node detection, especially low-volume disease, including micrometastasis and isolated tumor cells.
► In patients with bilateral SN detection, sensitivity of SN ultrastaging is not reduced in more advanced stages of the disease.

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ABSTRACT

Objective. To evaluate the sensitivity of sentinel node (SN) ultrastaging and to define parameters that may reduce the overall false-negative rate in women with early-stage cervical cancer.

Methods. We analyzed data from a large retrospective multicenter cohort group with FIGO stages IA–IIB cervical cancer in whom at least one SN was identified and systematic pelvic lymphadenectomy was uniformly performed. All who were SN negative by initial evaluation were subjected to ultrastaging.

Results. In all, 645 patients were evaluable. SN were detected bilaterally in 72% of cases and unilaterally in 28%. Patients with optimal bilateral SN detection were significantly more likely to have any metastasis detected (33.3% vs. 19.2%; $P<0.001$) as well as micrometastasis detected in their SN (39.6% vs. 11.4%). SN ultrastaging resulted in a low overall false-negative rate of 2.8% (whole group) and an even lower false-negative rate of 1.3% for patients with optimal bilateral mapping. Patients with false-negative SN after ultrastaging had a higher prevalence of LVSI and more frequent unilateral SN detection. Sensitivity of SN ultrastaging was 91% (95% CI: 86%–95%) for the whole group and 97% (95% CI: 91%–99%) in the subgroup with bilateral SN detection.

Conclusion. These data confirm previous observations that optimal bilateral SN detection substantially decreases the false negative rate of SN ultrastaging and increases detection of micrometastasis. In patients with bilateral SN detection, the sensitivity of SN ultrastaging is not reduced in more advanced stages of the disease. SN mapping and ultrastaging should become standard practice in the surgical management of early-stage cervical cancer.

Introduction

Metastatic involvement of pelvic lymph nodes is the most important prognostic factor in early-stage cervical cancer. The use of sentinel lymph node (SN) biopsy is being explored extensively in this population. SN evaluation has been reported to improve the accuracy of lymph node staging [1–3], assist in triaging patients toward surgery or radiotherapy [4], and facilitate the selection of candidates for

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fertility-sparing treatment [5]. Furthermore, detection of nodal metastasis is potentially improved by pathologic ultrastaging, which includes multiple serial sectioning and immunohistochemical assessment of the SN. SN ultrastaging allows for the detection of low-volume metastasis of less than 2 mm, including both micrometastasis (MM) and isolated tumor cells (ITC). We have recently shown that micrometastasis but not isolated tumor cells are associated with an equivalent risk for overall survival as the presence of macrometastasis [2].

The major concern about performing SN alone (that is, without simultaneous systematic pelvic lymphadenectomy) is that the SN biopsy will yield false-negative staging results. In other words, there may be a metastasis present in a regional non-sentinel lymph node that is not detected with SN ultrastaging. Low false-negative rates of SN staging in cervical cancer patients have been reported from single institutional experiences, especially in tumors smaller than 2 cm [6–9]. In contrast, a German multicenter validation study observed an unsatisfactory sensitivity of SN biopsy (77.7%); however, ultrastaging of SN had not been performed in this group's study, so important data on micrometastasis were missing for the analysis [10]. More recently, a French group reported on a prospective study in which SN staging reached a sensitivity of 92% in the whole cohort of 135 patients with small tumors of stages IA to IB1 and no false-negative case was found in a subset of patients with a bilaterally detected SN [11].

The aims of this study were to evaluate the false-negative rate of SN ultrastaging in patients with operable stages IA–IIB cervical cancer, and to identify parameters that may have a negative impact on SN sensitivity. To our knowledge, this is the largest study on the SN concept in early-stage cervical cancer published so far.

Patients and methods

We analyzed data from a multicenter retrospective cohort study that included 645 patients in whom SN biopsy followed by systematic pelvic lymphadenectomy was performed, and from whom SN ultrastaging data were available.

The following inclusion criteria were applied for enrollment into the study: FIGO stages IA–IIB cervical cancer, primary surgical treatment, SN detection on at least one pelvic side followed by systematic pelvic lymphadenectomy in standard anatomical regions, ultrastaging protocol for SN pathologic processing (serial sectioning and IHC), and histological types of either squamous cell cancer, adenocarcinoma, or adenosquamous. In all, 645 patients were included from 8 centers (Ostrava (195), Prague (119), Amsterdam/Utrecht (115), New York (90), Toulouse (57), Krakow (48), Paris (21)) with long-term experience with SN biopsy in cervical cancer patients. Median follow-up for the whole group reached 40 months.

Techniques of SN biopsy and SN pathologic processing were described in a previous publication [2]. In brief, SN were detected using blue dye alone or in combination with a radioisotopic tracer. SN biopsy was followed in all patients by systematic pelvic lymphadenectomy, combined with simple hysterectomy, simple trachelectomy, radical trachelectomy, or radical hysterectomy. Non-sentinel nodes were processed by single section of each node examined by routine. All SN that were negative for metastasis on the initial routine section stained by H&E were further examined according to the pathologic ultrastaging protocol. The entire node was cut at regular intervals that measured $\leq$250 μm in 98% of cases. Three consecutive sections (5 μm thick) were obtained at each interval. The first slide was stained with H&E; if negative, the second slide was used for immunohistochemical staining for cytokeratin.

Low-volume disease included both micrometastasis (MM) and isolated tumor cells (ITC), as defined for breast cancer by the American Joint Committee on Cancer (AJCC) [12]. Macrometastases were defined as tumor deposits $>$2 mm, and micrometastases were defined as deposits between 0.2 and 2 mm. Isolated tumor cells were defined as deposits no larger than 0.2 mm, including the presence of single non-cohesive cytokeratin-positive tumor cells.

The status of non-sentinel nodes (nSN) reflected results from pathologic processing of all removed pelvic nodes except for the SN, while sentinel node status referred to the results obtained from routine and ultrastaging of all detected SLN. Final lymph node status combined the results from all pelvic nodes together (SLN + nSLN).

Protocols for sentinel node biopsy and evaluation of data in a retrospective study were approved by ethical committees of the individual institutions.

Data analyses

All analyses were performed using SPSS software [13]. A value $\alpha = 0.05$ was used as the limit of statistical significance in all performed analyses. Standard robust summary statistics were used to describe primary data: relative and absolute frequency, median, and 5th–95th percentile range. ML-Chi^2 test and Fisher exact test were applied to assess mutual associations between binary or categorical variables in contingency tables. The Kruskal–Wallis test and the Mann–Whitney *U* test were applied to compare different groups of patients in age and number of removed pelvic nSN as continuous variables. Diagnostic power of examined methods was assessed using standard measures of sensitivity and specificity, supported by 95% confidence intervals [14].

Results

Basic characteristics of the total study population are summarized in Table 1. Final lymph node status based on a combination of SN ultrastaging and nSN evaluation showed ITC in 4% of cases, micrometastasis in 7%, macrometastasis in 21%, and negative nodes in 68%.

SN were accurately detected on both sides (bilateral optimal mapping) in 72% of cases ($n = 463$), while unilateral detection was noted in 28% ($n = 182$) (Table 2). The majority of unilaterally detected SN were found on the right side (83.5%). Positive SN were equally distributed between the left and right sides in both groups with unilaterally or bilaterally detected SN (Table 2).

Metastases to SN were found significantly more often ($P<0.001$) in patients with bilaterally detected SN (33.3%) than in patients with only unilateral SN detection (19.2%) (Table 2). In a subgroup with bilateral SN detection and any SN positivity ($n = 154$), the majority of SN were positive only unilaterally (74.7%) ($P<0.001$).

The nature and burden of nodal metastases were significantly different between the groups with unilaterally and bilaterally detected SN. Micrometastases were found significantly more frequently ($P = 0.003$) in patients with bilateral SN detection than in those with unilateral detection (39.6% vs. 11.4%; based on SN positive cases, $n = 189$) (Table 2). The opposite trend was observed for macrometastases (44.8% vs. 74.3% in bilateral vs. unilateral SN detection; again based on SLN positive cases, $n = 189$). No significant difference was found for ITC (14.3% vs. 15.6% in unilateral vs. bilateral SN detection).

Results of SN ultrastaging and non-sentinel lymph node (nSN) examination, together with the final lymph node status combining both parts of staging, are shown in Table 3. In 118 patients (18%), nodal metastasis were detected only in the SN, while all other removed pelvic nSN were negative. Both SN ultrastaging and evaluation of all pelvic nSN were negative in 68% of patients ($n = 438$).

The result of SN ultrastaging was up-staged (in terms of types of metastasis) in only 4% of patients. In these patients, ITC or micrometastasis was found in the SN but macrometastasis was noted in other pelvic nSN. Most importantly, the false-negative rate of SN ultrastaging was only 2.8% (i.e., patients in whom SN ultrastaging was negative while macrometastases were still detected in other pelvic nSN).

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Table 1
Basic description of patients ($n=645$).

Parameter	Statistics[a]
Patients	
Follow-up (months)[b]	40 (0.6; 116)
Age (years)	46 (23; 93)
Age > 50 years	$n=236$ (36.6%)
Age > 65 years	$n=66$ (10.2%)
Histology	
Adeno	$n=164$ (25.4%)
Squamo	$n=460$ (71.3%)
Adenosquamo	$n=19$ (3.0%)
Stage	
Stage I	$n=590$ (91.5%)
IA1	$n=25$ (3.9%)
IA2	$n=30$ (4.6%)
IB1	$n=477$ (74.0%)
IB2	$n=58$ (9.0%)
Stage II	$n=55$ (8.5%)
IIA	$n=36$ (5.6%)
IIB	$n=19$ (2.9%)
LVSI	$n=169$ (26.2%)
Parametrial involvement	$n=46$ (7.1%)
Vaginal involvement	$n=46$ (7.1%)
Final lymph node status	
(SN ultrastaging and pelvic nSN)	
Macrometastases	$n=136$ (21.1%)
Micrometastases	$n=46$ (7.1%)
ITC	$n=25$ (3.9%)
Negative	$n=438$ (67.9%)

[a] Continuous parameters are described using median and min/max range; categorical parameters are described by number of cases (n) and percentages of given categories.
[b] The data survey included all cases retrospectively reported from participating centers with overall follow-up up to 120 months.

Table 2
Laterality of SN detection and positivity.

Laterality of positive findings
(the whole sample, $n=645=100\%$)

SN detection	Positivity	Statistical test (ML χ^2)
Unilateral ($n=182$)	$n=35$ (19.2%)	$P<0.001$
(unilateral—right side: $n=152$; 23.6%)		
Bilateral ($n=463$)	$n=154$ (33.3%)	
Unilateral positivity	$n=115$ (24.8%)	$P<0.001$
Bilateral positivity	$n=39$ (8.4%)	

Side of SN detection and positivity
(the whole sample, $n=645=100\%$)

SN detection	Positivity	
Unilateral ($n=182$)		
Positive: right side	$n=29$ (19.1%)	$P=0.959$
Positive: left side	$n=6$ (20%)	
Bilateral ($n=463$)		
Positive: right side	$n=58$ (12.5%)	$P=0.524$
Positive: left side	$n=57$ (12.3%)	
Positive: bilateral	$n=39$ (8.4%)	

Type of SN metastasis according to laterality of SN detection
(cases with positive ultrastaging, $n=189=100\%$)

SN detection	Type of metastasis		
Unilateral	ITC	$n=5$ (14.3%)	$P=0.003$
($n=35$)	Micrometa	$n=4$ (11.4%)	
	Macrometa	$n=26$ (74.3%)	
Bilateral	ITC	$n=24$ (15.6%)	
($n=154$)	Micrometa	$n=61$ (39.6%)	
	Macrometa	$n=69$ (44.8%)	

Table 4 shows a comparison of selected parameters between 3 groups stratified according to the agreement between SN and nSN status: Group I—with both SN and nSN negative; Group II—with SN positive and nSN either positive or negative; and Group III—with SN falsely negative (SN negative but nSN positive). The patients with false-negative SN ultrastaging significantly differed from both other groups in 2 parameters: higher prevalence of lymphovascular space invasion (LVSI) (56% vs. 26%), and more frequent unilateral detection of SN (67% vs. 27%). No difference was found between the groups in age, stage of the disease, histological type of tumor, or total number of removed pelvic lymph nodes.

The sensitivity of SN ultrastaging reached 91% (95% CI, 86%–95%) in the whole group, 97% (95% CI, 92%–98%) in the subgroup with optimal bilateral SN detection ($n=463$), and 97% (95% CI, 91.0%–99.0%) in the subgroup with bilaterally detected SN and negative LVSI ($n=348$).

Discussion

In this large multicenter study we observed a high sensitivity (97%) and low false-negative rate (1.3%) of SN staging when SN were detected bilaterally. Bilateral SN detection and pathologic ultrastaging increased the detection of micrometastasis. Furthermore, pathologic ultrastaging of SN allowed for the identification of lymph node metastasis in 11% of patients with only low-volume disease in SN that would be missed by standard pathologic processing.

The main limitation of our study is its retrospective nature, which however did not impact the primary outcome of the evaluation of the false-negative rate of SN ultrastaging. It was not possible to analyze the detection rate of SN in our study because we enrolled only patients with successfully detected SN at least on one side. Another limitation was the lack of uniformity in technique of SN detection between institutions, which did not allow for evaluation of the impact of detection technique on bilateral SN detection rate. It is however reassuring that bilateral detection in our study (72%) corresponded well to the results from the prospective French study (76.5%) with a well standardized combined technique used in almost all enrolled cases.

Sensitivity of SN ultrastaging varied in single-institution studies between 80% and 100% [3,4,7–9,15]. False-negative cases were found in many studies in more advanced tumors [6,7,16], while accuracy of SN detection in stage IB1 or in tumors smaller than 2 cm reached 100% [6–9]. Besides stage of disease and tumor volume, an additional factor influencing the sensitivity of SN staging was the technique of SN detection. In the largest to date experience from a single institution, on 183 patients, a single false-negative case was identified in a subgroup using blue dye only, but no false-negative case was found in a subset of patients with the application of the combined technique [8]. In 2008 the first validation multicenter study yielded disappointing results [10]. In a cohort of 507 patients from 18 centers, sensitivity was only 77.4%; however, sensitivity improved in a subset of patients with bilateral SN detection (87.2%), and in patients with small tumors up to 2 cm in size (90.9%). Low sensitivity was most likely caused by a combination of factors, including early experience with SN detection, and absence of comprehensive SN ultrastaging. Nodes were cut into 3–4 mm sections and immunohistochemistry was not included in the protocol. Thus, data on the presence of low-volume disease in SN were not available for the final analysis of sensitivity.

Recently, LeCuru et al. reported on a prospective French study in which a protocol of SN detection and pathologic processing was incorporated into their multicenter practices [11]. The study enrolled 135 patients with small tumors of stages IA–IB1. An overall sensitivity of 92% in the whole cohort was improved to 100% if SN were detected bilaterally. The importance of bilateral SN detection ("optimal mapping") and side-specific pelvic lymphadenectomy for those cases with

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Table 3
Lymph node status—combined results of SN ultrastaging and pelvic nSN examination.

SN ultrastaging[1]	Pelvic nSN status	Final lymph node status	n (%)
Negative	Negative	Negative	n = 438 (67.9 %)
Negative	Positive	Macrometastases False negativity of ultrastaging	n = 18 (2.8 %)
Low volume disease	Positive	Macro-metastases	n = 23 (3.6 %)
ITC (n = 4)		Up-staged ultrastaging	
Micro-metastases (n = 19)			
Positive			
ITC (n = 25)	Negative	ITC	n = 118 (18.3 %)
Micro-metastases (n = 46)		Micro-metastases	
Macro-metastases (n = 47)		Macro-metastases	
Macro-metastases	Positive	Macro-metastases	n = 48 (7.4 %)
Summary of SN ultrastaging[1]			
True negative findings		n = 438 (67.9 %)	
False negative findings		n = 18 (2.8 %)	
Positive findings		n = 189 (29.3 %)	
nSN negative		n = 118 (18.3 %)	
nSN positive		n = 71 (11.0 %)	
Sensitivity (95% confidence interval)		0.91 (0.86-0.95)	
Specificity		1.00	

[a] Only outcomes of ultrastaging, without correction based on nSN examination.
[b] Calculation which takes macro-metastases in microstaging accompanied by negative nSN as false negative outcome of nSN examination.

unilateral mapping was shown previously in locally advanced tumors [4] as well as in stage I patients undergoing radical surgery [3].

In the current study, the false-negative rate of SN ultrastaging was low: below 3% of cases. Moreover, in 2/3 of these false-negative cases ($n = 12$), SN were detected only unilaterally. If considering only the subset of patients with "optimal" bilaterally detected SN ($n = 463$), the false-negative rate would drop to 1.3% and the sensitivity of ultrastaging would increase to 97%.

Besides the impact of bilateral SN detection, we did not find any difference in distribution of clinical stages between the group with false-negative SN and other patients (true negative or true positive SN). The sensitivity of SN staging in small tumors of stage IB1 was lower (89%) (95% CI, 82%–93%) than in the whole cohort (91%). The false-negative rate was not influenced by other factors such as age, histological type of tumor, or number of removed pelvic lymph nodes. For clinical practice these results show that if surgical staging is adequately achieved on both pelvic sides (optimal bilateral mapping), its sensitivity is not impaired in more advanced tumors, older patients, or in adenocarcinomas. The only single parameter that was significantly more frequent in a subgroup with false-negative results was the presence of LVSI. The reason for significantly higher prevalence of LVSI in a subgroup with false negative SN can only be hypothesized—one

Table 4
Comparison of three groups according to SN and nSN status ($n = 645$).

Parameter —evaluated categories	Patients classified according to ultrastaging and pelvic nSN status[a]			*P* value[b]	
	I ($n = 438$)	II ($n = 182$)	III ($n = 18$)		
	% of row categories within column groups			III vs. I	III vs. II
Patients—*age*					
Years[c]	46 (30; 73)	49 (33; 72)	50 (31; 78)	0.169	0.208
Age > 65 years	$n = 39$ (8.9%)	$n = 24$ (12.7%)	$n = 3$ (16.7%)	0.308	0.644
Histology—Adeno	N = 140 (31.9%)	N = 41 (21.7%)	N = 2 (11.1%)	0.041	0.259
Clinical staging					
IA	$n = 46$ (10.5%)	$n = 9$ (4.8%)	$n = 0$	0.245	0.141
IB1	$n = 337$ (76.9%)	$n = 124$ (65.6%)	$n = 16$ (88.9%)		
IB2	$n = 34$ (7.8%)	$n = 23$ (12.2%)	$n = 1$ (5.6%)		
IIAB	$n = 21$ (4.8%)	$n = 33$ (17.5%)	$n = 1$ (5.6%)		
Clinical staging—*aggregated*					
IA and IB1	$n = 383$ (87.4%)	$n = 133$ (70.4%)	$n = 16$ (88.9%)	0.853	0.069
IB2 and 2AB	$n = 55$ (12.6%)	$n = 56$ (29.6%)	$n = 2$ (11.1%)		
LVSI	$n = 98$ (22.4%)	$n = 61$ (32.2%)	$n = 10$ (55.6%)	**0.003**	**0.046**
No. pelvic nSN removed					
Number[c]	27 (9; 51)	28 (11; 51)	26 (14; 67)	0.271	0.465
SN detection					
Unilateral	$n = 135$ (30.8%)	$n = 35$ (18.5%)	$n = 12$ (66.7%)	**0.002**	<**0.001**
Unilateral—right side	114 (26.0%)	29 (15.3%)	9 (50.0%)	0.025	0.001
Unilateral—left side	21 (4.8%)	6 (3.2%)	3 (16.7%)	0.026	0.010

[a] Categories of agreement/disagreement between SN ultrastaging and pelvic nSN examination: I—SN and nSN negative; II—SN positive and nSN positive or negative; III—SN negative and nSN positive (false negative SN ultrastaging).
[b] Significance level of tests of differences among categories of patients I–III: ML-χ^2 test in case of categorical/ binary variables; Mann–Whitney *U*-test for age and no. of nSN removed as quantitative variables.
[c] Continuous variables expressed as median and 5th–95th percentile range (in parentheses).

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theoretical explanation is a tendency to more irregular metastatic spread in the presence of LVSI. At the same time, we should be aware that even in this large group, number of cases with SN false negativity is too low to make any firm conclusion. Moreover, if SN was detected bilaterally, absence of LVSI did not improve sensitivity of SN ultrastaging any further.

The bilateral SN detection significantly increased the probability of detecting lymph node metastasis ($P<0.001$). The importance of bilateral SN evaluation was also supported by the fact that in patients in whom SN were detected on both sides and who had any positivity, the majority of SN were positive only unilaterally (75%). Furthermore, significantly decreased positivity in unilaterally detected SN was reflected in the lower detection rate of micrometastasis (11.4% vs. 39.6% in unilateral vs. bilateral SN detection).

The most significant contribution of SN ultrastaging in current clinical management is improvement of metastatic lymph node detection, especially low-volume disease, including micrometastasis and isolated tumor cells [1–3]. In breast cancer many reports showed poorer prognosis in patients with micrometastasis in SN [17,18]. Recently we reported on a retrospective multicenter study which showed a similar trend in patients with early-stage cervical cancer [2]. In this study, an identical negative impact on survival was observed in patients with micrometastasis (HR = 6.85; 95% CI, 2.59–18.05) and macrometastasis (HR = 6.86; 95% CI, 2.09–22.61). Prevalence of low-volume disease in SN from patients with early-stage cervical cancer is being reported between 4% and 15% [19]. While the prevalence of macrometastasis and micrometastasis is increasing with the stage of disease, it remains stable in isolated tumor cells [2]. In the present study, the SN concept was crucial for the detection of lymph node involvement in the 11% of patients in whom the only positivity was the presence of micrometastasis or isolated tumor cells detected in SN on ultrastaging. These cases would be missed if ultrastaging was not performed and if all nodes were processed by standard pathologic evaluation alone.

Results of our study also support high reliability of the SN concept if bilateral detection is achieved. At the same time, it should be emphasized that none of available data, including a prospective French study [11], may sufficiently address the question, what is the risk of abandoning full lymphadenectomy in cases with negative SN. This can be answered only by a prospective study with an adequate size and length of the follow-up. Even a small increase in recurrence rate would be hardly acceptable in this group of usually young patients with an excellent prognosis after an adequate surgical treatment [20,21].

To our knowledge this is the largest multicenter retrospective study on the SN concept in cervical cancer. Our data confirmed previous observations that bilateral "optimal" SN detection substantially decreases the false-negative rate of SN ultrastaging and increases the detection rate of micrometastases. If a SN is detected on both sides, sensitivity of SN ultrastaging is high, reaching 97%. In a subset of patients with bilateral SN detection, sensitivity is not influenced by age, histological type, number of removed lymph nodes, or, most importantly, more advanced tumor stage. This, in combination with our previous publication, which showed significantly decreased survival associated with micrometastasis in SN [2], support the need for implementation of SN identification and ultrastaging in the management of surgically treated cervical cancer patients.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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References

[1] Euscher ED, Malpica A, Atkinson EN, Levenback CF, Frumovitz M, Deavers MT. Ultrastaging improves detection of metastases in sentinel lymph nodes of uterine cervix squamous cell carcinoma. Am J Surg Pathol 2008;32:1336-43.
[2] Cibula D, Abu-Rustum NR, Dusek L, Zikan M, Zaal A, Sevcik L, et al. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. Gynecol Oncol 2012;124:496-501.
[3] Cormier B, Diaz JP, Shih K, Sampson RM, Sonoda Y, Park KJ, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. Gynecol Oncol 2011;122:275-80.
[4] Cibula D, Kuzel D, Slama J, Fischerova D, Dundr P, Freitag P, et al. Sentinel node (SLN) biopsy in the management of locally advanced cervical cancer. Gynecol Oncol 2009;115:46-50.
[5] Du XL, Sheng XG, Jiang T, Li Q, Yu H, Pan C, et al. Sentinel lymph node biopsy as guidance for radical trachelectomy in young patients with early stage cervical cancer. BMC Cancer 2011;11:157.
[6] Barranger E, Coutant C, Cortez A, Uzan S, Darai E. Sentinel node biopsy is reliable in early-stage cervical cancer but not in locally advanced disease. Ann Oncol 2005;16:1237-42.
[7] Wydra D, Sawicki S, Wojtylak S, Bandurski T, Emerich J. Sentinel node identification in cervical cancer patients undergoing transperitoneal radical hysterectomy: a study of 100 cases. Int J Gynecol Cancer 2006;16:649-54.
[8] Rob L, Charvata M, Robova H, Strnad P, Pluta M, Halaska M, et al. Sentinel lymph node identification (SLNI) in the management of conservative surgery in early cervical cancer: is it acceptable? Gynecol Oncol 2005;99:S147-8.
[9] Angioli R, Palaia I, Cipriani C, Muzii L, Calcagno M, Gullotta G, et al. Role of sentinel lymph node biopsy procedure in cervical cancer: a critical point of view. Gynecol Oncol 2005;96:504-9.
[10] Altgassen C, Hertel H, Brandstadt A, Kohler C, Durst M, Schneider A. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. J Clin Oncol 2008;26:2943-51.
[11] Lecuru F, Mathevet P, Querleu D, Leblanc E, Morice P, Darai E, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. J Clin Oncol 2011;29:1686-91.
[12] Schwartz GF, Giuliano AE, Veronesi U. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19–22, 2001, Philadelphia, Pennsylvania. Cancer 2002;94:2542-51.
[13] SPSS. SPSS for Windows. In. 12.0.1.2003 ed. Chicago; 2003.
[14] Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857-72.
[15] Plante M, Renaud MC, Tetu B, Harel F, Roy M. Laparoscopic sentinel node mapping in early-stage cervical cancer. Gynecol Oncol 2003;91:494-503.
[16] Coutant C, Morel O, Delpech Y, Uzan S, Darai E, Barranger E. Laparoscopic sentinel node biopsy in cervical cancer using a combined detection: 5-years experience. Ann Surg Oncol 2007;14:2392-9.
[17] Patani N, Mokbel K. The clinical significance of sentinel lymph node micrometastasis in breast cancer. Breast Cancer Res Treat 2009;114:393-402.
[18] van Diest PJ, de Boer M, van Deurzen CH, Tjan-Heijnen VC. Micrometastases and isolated tumor cells in breast cancer are indeed associated with poorer outcome. J Clin Oncol 2010;28:e140; author reply e141–2.
[19] Darai E, Rouzier R, Ballester M, Barranger E, Coutant C. Sentinel lymph node biopsy in gynaecological cancers: the importance of micrometastases in cervical cancer. Surg Oncol 2008;17:227-35.
[20] Cibula D, Pinkavova I, Dusek L, Slama J, Zikan M, Fischerova D, et al. Local control after tailored surgical treatment of early cervical cancer. Int J Gynecol Cancer 2011 May;21(4):690-8.
[21] Höckel M, Horn LC, Manthey N, Braumann UD, Wolf U, Teichmann G, et al. Resection of the embryologically defined uterovaginal (Müllerian) compartment and pelvic control in patients with cervical cancer: a prospective analysis. Lancet Oncol 2009 Jul;10(7):683-92.

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