Title

Pelvic lymphadenectomy improves survival in cervical cancer patients with low volume disease in the sentinel node; a retrospective multicentre cohort study

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Structured abstract

Objective: In this study we aim to describe the value of pelvic lymph node dissection (LND) following a sentinel lymph node (SN) biopsy in early stage cervical cancer for different outcomes of the SN procedure. The SN biopsy is currently routinely followed by pelvic LND. Before pelvic LND can be abandoned in favour of performing SN biopsy alone, it needs to be clarified whether the assessment of nodal status by pelvic LND, as well as its extent, is solely diagnostic, or whether it also has an effect on survival. Design: Retrospective multicentre cohort study. Setting: Eight gynaecological oncology departments. Population: 645 women with FIGO stage IA to IIB cervical cancer of squamous, adeno or adenosquamous histological type without clinical or radiological signs of lymphadenopathy who underwent SN sampling followed by pelvic LND. Methods: Radioisotope tracers and blue dye were used to localise the SN, and pathologic ultrastaging of the SN was performed. Main Outcome Measures: Overall and disease free survival. Results: Among patients with low volume disease in the SN the overall survival was significantly better (p=0.046) if more than 16 non sentinel lymph nodes (nSNs) were removed during pelvic LND than patients in whom less than 16 nSNs were removed. No such significant difference in survival was detected in patients with negative or macrometastatic SN. Conclusions: Patients with negative or macrometastatic SN did not profit from additional LND. Conversely; our data suggest that the survival of patients with low volume disease is improved when more than 16 nSNs are removed.

Keywords: uterine cervical cancer; lymph node metastasis; micrometastasis; isolated tumour cells; low volume disease; sentinel lymph node; lymph node dissection; survival

Introduction

Cervical cancer is the second most common type of cancer in women worldwide, with an estimated age standardised incidence rate of 15.2 per 100.000 (530.232 patients) and a mortality rate of 7.8 per 100.000 (275.008 patients)[1]. In the European Union, it is the seventh most common type of cancer in women with an age standardised incidence rate of 9.0 per 100.000 (31.038 patients) and a mortality rate of 3.0 per 100.000 (13.430 patients) [1]. Cervical cancer is clinically staged according to definitions set by the International Federation of Gynaecology and Obstetrics (FIGO)[2;3]. As opposed to the staging of other gynaecological tumours, lymph node metastases are not included in the staging of cervical cancer. However, it is important to asses the lymph node status in this disease, as it is an independent prognostic factor for cervical cancer survival [4] and it determines the choice of initial therapy, as well as the need for adjuvant treatment [5].

Cervical cancer is known to spread to the pelvic lymphatic system via the first draining lymph node, the sentinel lymph node (SN)[6;7]. If this SN is tumour free, the other draining lymph nodes (non (n)SNs) are assumed not to contain tumour. Currently, the gold standard for assessing the nodal status in cervical cancer is systematic pelvic lymph node dissection (LND)[8]. Such an extensive lymphadenectomy leads to lymphocyst formation in about 20% and to lymphedema in approximately ten percent of patients with FIGO IB to IIA disease[9;10]. In order to minimise these complications the SN biopsy is currently being evaluated for adoption as the standard of care in early stage cervical cancer[11;12]. This procedure entails detection and excision of the SN after submucosal injection of a radioisotope tracer and/or blue dye around the primary tumour[13]. Optimal histopathological evaluation of the SN is achieved by serial sectioning and immunohistochemistry (IHC)[14;15]. Compared to pelvic LND, SN biopsy increases the detection rate of metastases up to 2.8 fold[16]. As a consequence,

SN biopsy increases the detection rate of low volume disease (LVD; micrometastasis (0.2-2 mm) or isolated tumour cells (<0.2 mm)) [17].

If a SN biopsy is currently routinely followed by pelvic LND. Before pelvic LND can be abandoned in favour of performing SN biopsy alone, the sensitivity of the latter to detect metastases needs to be similar (or higher) than that of pelvic LND. Furthermore, it needs to be clarified whether the assessment of nodal status by pelvic LND, as well as its extent, is solely diagnostic, or whether it also has an effect on survival[18-20]. Importantly, the addition of SN ultrastaging provides information (micrometastases) that hitherto was not available and used to determine further management. In particular, adjuvant therapy is commonly decided on the presence of macrometastases. If there is an effect on survival of LVD, it needs to be assessed whether outcome of disease is influenced by the extent of nodal dissection.

Therefore, in this study we aimed to clarify whether the extent of pelvic LND affects survival in patients with a negative SN, in patients with LVD and in patients with macrometastasis in the SN.

Methods

Patients

Our study population consisted of 645 patients from 8 centres (Ostrava and Prague, Czech Republic; Amsterdam and Utrecht, The Netherlands; New York, USA; Paris and Toulouse, France, and Krakow, Poland). In this study population of 645 patients we previously described the clinical significance of micrometastasis in the lymph nodes[21]. Patients with FIGO stage IA to IIB cervical cancer of squamous, adeno or adenosquamous histological type

without clinical or radiological signs of lymphadenopathy were included. In cases no SN ultrastaging was performed and/or survival endpoints were inadequately documented, patients were excluded from the study. The database included all patients retrospectively reported from participating centres with an overall follow-up of up to 116 months. Data obtained from individual centres were carefully controlled for the completeness in key items.

Therapeutic procedures and pathologic evaluation

Radioisotope tracers and blue dye were injected pre-operatively and intra-operatively respectively around the primary tumour in order to be able to detect the SN at laparoscopy or laparotomy by visual inspection and gamma probe detection. Fresh frozen analysis of the excised SN with subsequent paraffin embedding and pathologic ultrastaging was performed (for details see[22]). Lymph node involvement was defined as isolated tumour cells or clusters smaller than 0.2mm in greatest diameter (ITC), micrometastasis (smaller than 2mm in greatest diameter) or macrometastasis (equal or larger than 2mm)[17].

After the SN biopsy, pelvic LND and simple hysterectomy (N=3), radical hysterectomy (N=532), simple trachelectomy (N=22) or radical trachelectomy (N=88) was performed. The surgical specimens of the latter procedures were evaluated according to standard histopathological practice. Adjuvant therapy (radiotherapy, chemotherapy or both) was administered according to national or institutional guidelines to 213/645 (33.0%) of the patients. Considering the final lymph node status, adjuvant therapy was administered to 116/136 (85.3%) of patients with macrometastasis, 38/46 (82.6%) with micrometastasis, 13/25 (52%) with ITC and 46/438 (10.5%) with negative pelvic nodes.

Statistical analyses

Standard summary statistics were used to describe primary data, i.e. frequency tables and median supplied with 5^{th}-95^{th} percentile range. Maximum Likelihood (ML) and chi square (χ^2) testing was performed to compare categorical variables and Kruskal-Wallis followed by Mann-Whitney U testing was applied for mutual comparisons of variants in continuous variables. Kaplan-Meier survival probability estimates with log rank testing were used to describe and compare variants in time-to-event endpoints, i.e. overall survival and relapse-free survival. Time to event was calculated from time of surgery. We were not able to correct for start and duration of adjuvant therapy, because these data were not available. Univariate and multivariate proportional hazard Cox regression models were applied to quantify the association of potential risk factors and survival. Firstly, estimates of hazard ratio (with 95% confidence intervals) were tested using Wald χ^2 test. Subsequently, parameters with potential risk power ($p < 0.10$ in univariate Cox regression) were subjected to stepwise selection algorithm in multivariate Cox regression. For all statistical tests a two-tailed p-value of < 0.05 was considered significant. Statistical power to detect differences within groups was limited, mainly in the stratified analysis.

Results

Characteristics of patients and tumours

Patient and tumour characteristics were stratified according to the result of the SN ultrastaging (Table 1). With increasing FIGO stage, there was a significant increase in the size of SN metastases (ML- χ^2 $p < 0.001$). Similarly, vaginal and parametrial involvement and metastasis in the nSNs were associated with the size of metastases in SN ($p <0.001$). No

significant association was found with age, histological subtype or the presence of lymphovascular space invasion (LVSI).

Factors associated with lymph node involvement and survival

To define the diagnostic properties of the extent of pelvic LND, firstly we explored the association between the number of nSLN removed and the number of pelvic nSLN with macrometastasis (Online figure 1). The number of positive nSNs was a significant predictor for the development of recurrence and the risk of death (Table 2), both as a continuous variable and when analysed in categories. The hazard ratio for recurrence and death was 8.80 (95%CI 3.10-24.96) and 8.89 (95%CI 2.02-39.37), respectively, if more than 5 positive nodes were detected.

Clinical impact of the number of removed pelvic lymph nodes

In order to relate the number of removed nodes to outcome, Kaplan Meier analysis was performed with overall (OS) and recurrence free survival (RFS) as endpoints.

No statistically significant difference in RFS or OS in relation to the number of nSNs removed was observed among patients with FIGO stage IA to IB1 disease (Figure 1A and B). However, in patients with FIGO stage IB2 to II both RFS (p=0.032) and OS (p=0.014) was significantly better in patients in whom 16 or more nodes were removed (Figure 1C and D) than in patients in whom less than 16 nSNs were removed.

The above findings were tested using univariate and multivariate Cox proportional hazard regression analysis in order to exclude a possible confounding effect of other parameters (Table 3). Both models confirmed that removing a minimum of 16 nSLNs significantly

reduced the risk of recurrence as well as the risk of death in patients with FIGO stage 1B2 to II disease. Adjuvant treatment was used as a covariate in multivariate models, but no significant multivariate–adjusted effect on the time-to-event end-points was found.

To determine whether the better survival among patients with more than 16 removed nSNs was dependent on status of the SN we stratified patients for SN status (Figure 2). Three categories were defined: SN negative (N=456), LVD (including ITC and micrometastasis, N=94) and macrometastasis (N=95). We showed that only among patients with LVD in the SN the OS was significantly better (p=0.046) if more than 16 nSNs were removed than in patients in whom less than 16 nSNs were removed. No statistically significant differences were observed if less or more than 16 lymph nodes were removed among patients with negative SN or macrometastasis in the SN. Number of patients with LVD were too small to assess whether this is also true for lower (FIGO IA2 and IB1) and higher (FIGO IB2 - II) stages. Unfortunately, because of lack in power, we were not able to stratify the LVD results into ITC or micrometastases.

Of the 94 patients with LVD in the SN, 71 (75.5%) had no metastasis detected in any of the nSNs. The Kaplan Meier analysis was repeated for this sub population of women (with LVD in the SN but with negative nSNs, Figure 3) and showed a trend towards better overall survival in women with more than 16 nSNs removed (p=0.055) than in patients in whom less than 16 nSNs were removed.

Discussion

In this multicentre cohort study we studied 645 patients whom had undergone a SN biopsy with pathologic ultrastaging and subsequent pelvic LND. This is the largest multicentre retrospective study of its kind to date, which provided sufficient numbers to analyse the effect of LND after SN biopsy in the subset of patients with LVD.

We showed that known risk factors (FIGO stage, vaginal and parametrial involvement) were not only related to the occurrence of lymph node metastasis but also to the size of metastases. In other words, when vaginal or parametrial involvement was detected, or if a tumour was diagnosed at a higher FIGO stage, the size of metastasis in lymph nodes tended to be larger. Furthermore, in this study we confirmed the finding that the number of positive nSNs is associated with survival and recurrence [4;23;24].

Besides having a diagnostic value, we can conclude that systematic pelvic lymphadenectomy performed in addition to SN was associated with better survival only for patients with LVD in the SN. Removing more than 16 nSNs led to a better survival in patients with low volume disease in the SN than in patients in whom less than 16 nSNs were removed.

To asses whether this effect was due to increased detection of lymph node metastases or whether this was a true therapeutic effect we performed survival analysis in patients with LVD in the SN and negative nSNs. We detected a trend towards better overall survival in the latter group ($p=0.055$). This possible therapeutic effect could be explained by removing additional low volume disease in nSNs, which is not detected by routine pathologic assessment. Unfortunately we were unable to stratify for both FIGO stage and SN status due to the limited number of events.

Previous studies have shown a therapeutic impact of lymph node dissection in patients with cervical cancer that underwent LND without SN biopsy[25-27]. Excising at least 15 lymph nodes was associated with better survival (p=0.01) than in patients in whom less than 15 lymph nodes were removed.[28]. Whether this better survival is achieved in patients with negative as well as positive lymph nodes has been investigated by two research groups that found contradicting results. One group found that in 63 lymph node positive FIGO stage I-IIa cervical cancer patients complete LND better disease free survival (DFS, HR 3.2, p=0.011)[18]. In a subsequent analysis they showed that in 136 lymph node positive patients, a longer DFS (p=0.014) was detected if complete LND was performed, whereas in 331 lymph node negative patients there was no effect on survival[19]. Conversely, in 873 lymph node positive FIGO stage IA2-IIA cervical cancer patients from the SEER database it was demonstrated that there was no effect of completing LND, whereas in case of negative lymph node nodes (N=4648) there was a better survival if more than 20 nodes were removed than in patients in whom less than 20 nSNs were removed.[20].

Our finding, that completion of LND only showed better survival in case of LVD in the SN appears to contradict the outcome of the recent SEER study. However, SN biopsy, as used in our analysis, provides a more sensitive procedure to detect metastases. The SEER study could only analyse patients with macrometastases and left patients with LVD undetected. The beneficial effect of full LND in node negative patients might therefore be due to treatment of LVD, included in the SEER node negative patients. In contrast with two previous studies [18;19] and in line with the SEER data, we could not find evidence that performing LND showed better survival in patients with macrometastatic lymph nodes than in patients in whom less

than 16 nSNs were removed. This difference may be explained by the fact that we excluded patients with evidently involved nodes, either by radiological or visual enlargement, whereas the two studies that found a beneficial effect of LND also included clearly if not bulky enlarged nodes.

Whether our results warrant clinical implementation of full LND in a subgroup remains to be further validated, preferably in a randomised controlled trial. In such prospective study, it should be assessed whether patients in whom a SN procedure is performed and who are found to have low volume disease do indeed benefit from additional lymphadenectomy and/or radiotherapy, as this retrospective cohort analysis suggests.

Conclusion

This study suggests that in patients with LVD in the SN, survival is improved in patients in whom more than 16 additional lymph nodes are removed. Conversely, in the more common cases of negative or macrometastatic SN, prognosis is not influenced by additional LND or by removing a higher number of nSNs.

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Disclosure of Interests

The authors have no conflicts of interest to declare.

Contribution to Authorship

All 16 authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. Furthermore, all authors participated in drafting or revision of the manuscript. Finally, all authors gave final approval of the manuscript to be published.

Details of Ethics Approval

This study conformed to Good Clinical Practice. Since the research does not imply that people will receive a particular treatment, nor imposes on the behaviour of persons, the Medical Research Involving Human Subjects Act (WMO) does not apply.

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Figure Legends

Figure 1. Kaplan-Meier survival probability estimates with log rank testing were used to describe and compare relapse free survival (RFS) and overall survival (OS) in months stratified according to the number of removed non sentinel nodes (nSNs). RFS in patients with FIGO stage IA and IBI (A), OS in FIGO IA and IBI (B), RFS in FIGO IB2 and IIAB (C) and OS in FIGO IB2 and IIAB cervical cancer (D). Number of patients at risk can be seen from the tables below the graphs.

Figure 2. Kaplan-Meier survival probability estimates with log rank testing were used to describe and compare relapse free survival (RFS) and overall survival (OS) in months stratified according to the number of removed non sentinel nodes (nSNs). RFS in patients with negative SN (A), OS in patients with negative SN (B), RFS in patients with LVD in the SN (C), OS in patients with LVD in the SN (D), RFS in patients with macrometastatic SN (E) and OS in patients with macrometastatic SN (F). Number of patients at risk can be seen from the tables below the graphs.

Figure 3. Kaplan-Meier survival probability estimates with log rank testing were used to describe and compare relapse free survival (RFS) and overall survival (OS) in months stratified according to the number of removed non sentinel nodes (nSNs). RFS in patients with LVD in the SN but with negative nSNs (A) and OS with LVD in the SN but with negative nSNs (B). Number of patients at risk can be seen from the tables below the graphs.

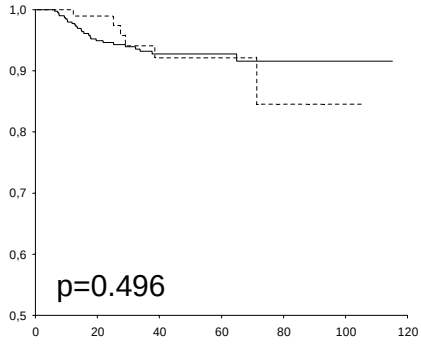
Online Only

Online Figure 1. Scatter plot of the number of removed pelvic nSNs in relation to the number of positive lymph nodes in the total study population (A), and in the patients with negative nodes (B), low volume disease (C) or with macrometastases (D) at pathologic ultrastaging.

Word count: 2508

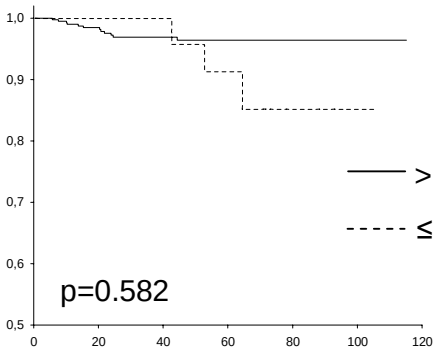
Figure 1

A RFS FIGO IA and IBI



Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	417	361	283	209	144	82	38	21	4	0
nSNs ≤ 16	115	87	63	46	22	14	8	6	1	0

B OS FIGO IA and IBI



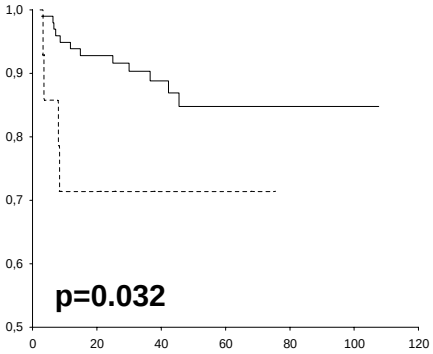
Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	417	369	293	219	152	89	43	24	5	0
nSNs ≤ 16	115	88	64	50	24	15	8	6	1	0

> 16 nSNs removed

≤ 16 nSNs removed

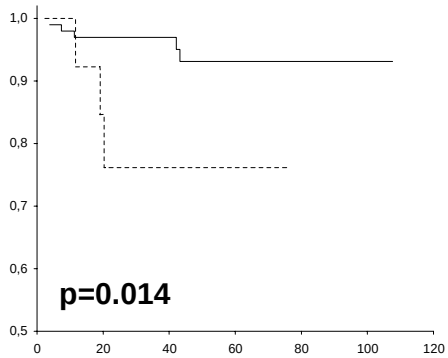
→ Proportion of surviving / proportion recurrence free

C RFS FIGO IB2 and IIAB



Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	98	89	74	57	37	25	20	16	8	0
nSNs ≤ 16	15	9	7	4	3	3	1	0	0	0

D OS FIGO IB2 and IIAB

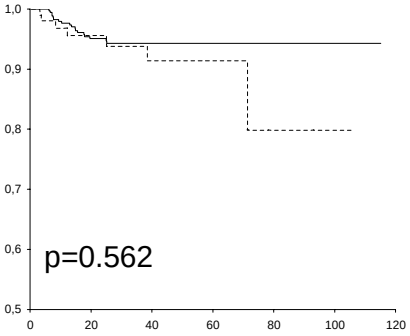


Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	98	92	79	61	41	29	24	20	10	0
nSNs ≤ 16	15	12	7	4	3	3	1	0	0	0

→ Time (months)

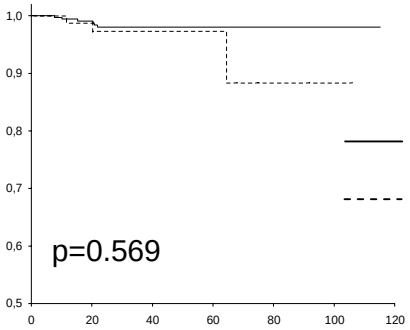
Figure 2

A RFS SN Negative N=456



Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	354	311	238	168	107	51	21	12	3	0
nSNs ≤ 16	102	72	51	36	17	10	4	3	1	0

B OS SN Negative N=456



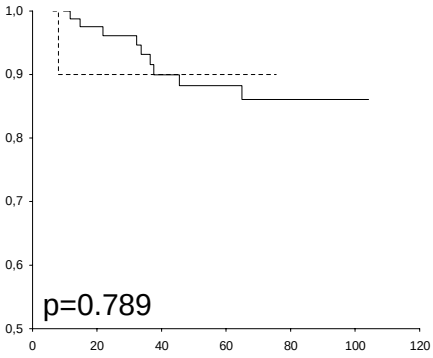
Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	354	318	249	174	111	54	24	14	4	0
nSNs ≤ 16	102	75	52	38	18	11	4	3	1	0

> 16 nSNs removed

≤ 16 nSNs removed

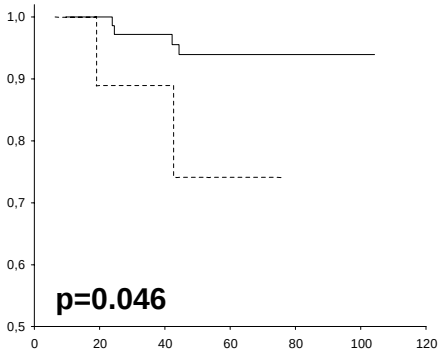
→ Proportion of surviving / proportion recurrence free

C RFS LVD in SN N=94



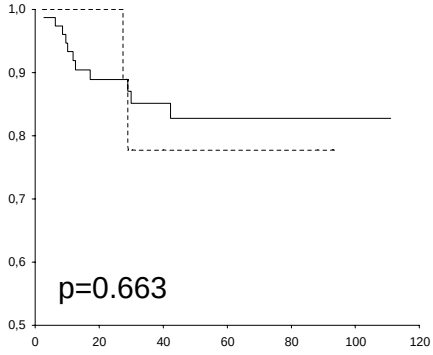
Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	83	74	66	56	50	43	36	25	10	0
nSNs ≤ 16	11	8	7	7	4	3	2	0	0	0

D OS LVD in SN N=94



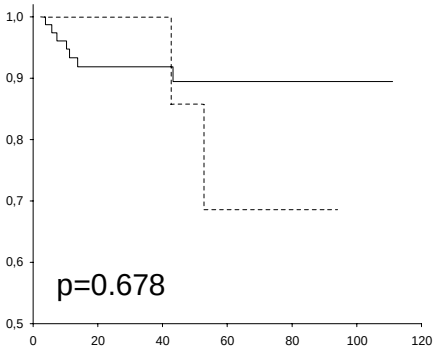
Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	83	76	67	60	54	47	40	29	12	0
nSNs ≤ 16	11	9	7	7	4	3	2	0	0	0

E RFS Macrometastasis in SN N=95



Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	78	60	50	38	22	14	6	6	3	0
nSNs ≤ 16	17	15	10	6	4	4	4	4	0	0

F OS Macrometastasis in SN N=95



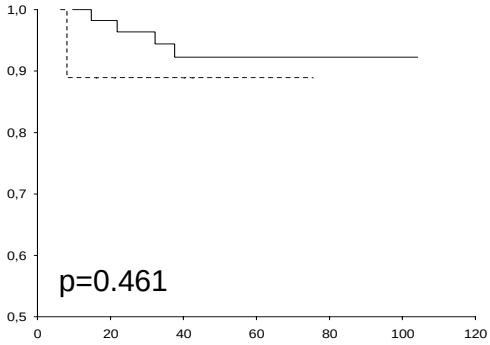
Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	78	62	53	42	26	18	8	8	3	0
nSNs ≤ 16	17	15	10	8	5	4	4	4	0	0

→ Time (months)

Figure 3

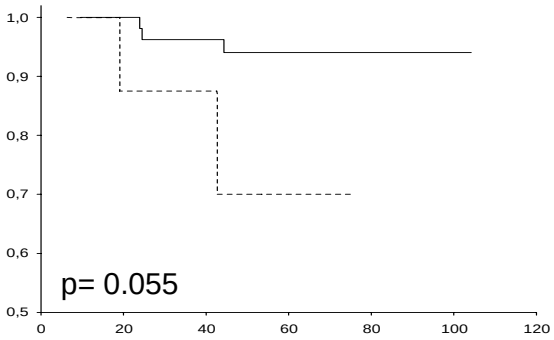
→ Proportion of surviving / proportion of recurrence

A RFS LVD in SN but nSN negative N=71



Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	61	53	50	43	39	35	29	20	9	0
nSNs ≤ 16	10	7	6	6	3	2	1	0	0	0

B OS LVD in SN but nSN negative N=71



Time (months)	0	12	24	36	48	60	72	84	96	108
nSNs > 16	61	54	50	45	40	36	29	20	9	0
nSNs ≤ 16	10	8	6	6	3	2	1	0	0	0

→ Time (months)

——— > 16 nSNs removed

- - - - - ≤ 16 nSNs removed

Online Figure 1

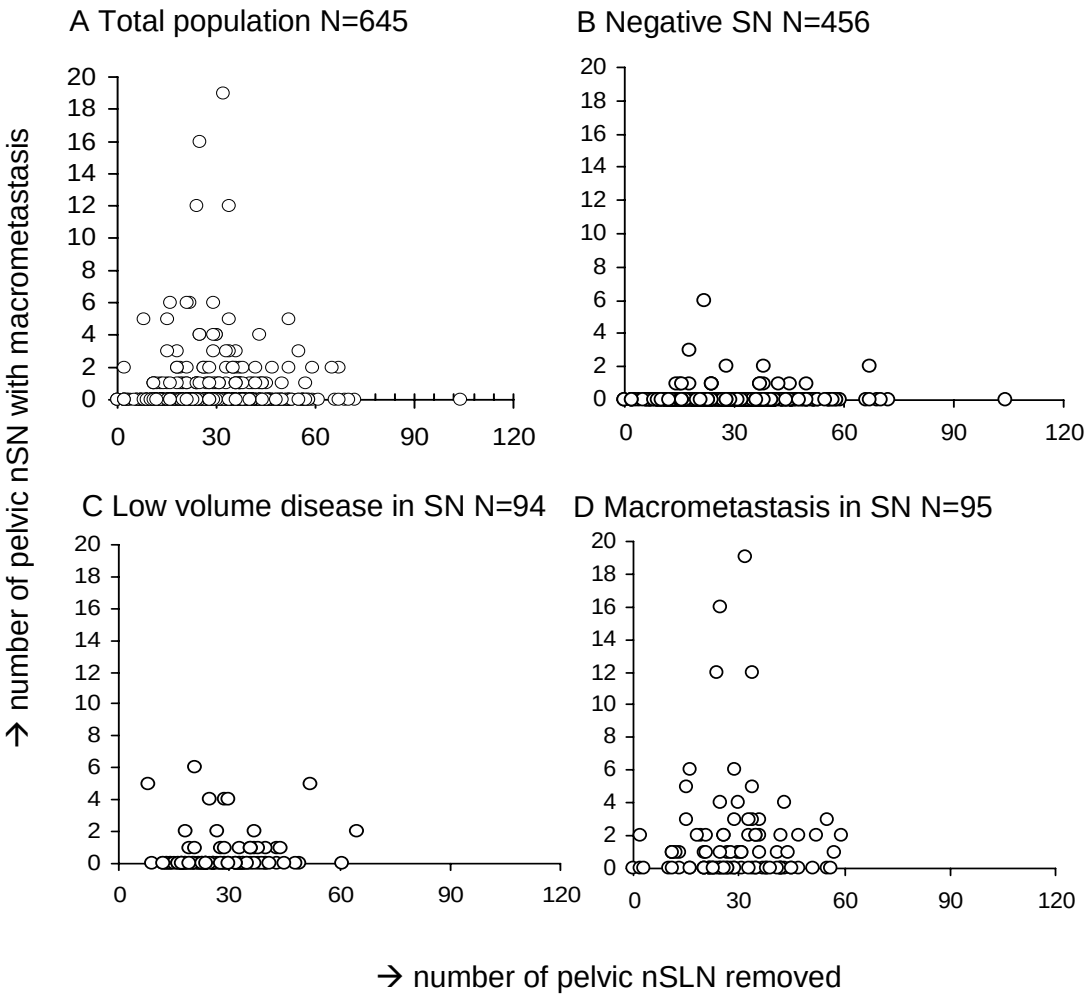


Table 1. Baseline characteristics of the patients included in this study stratified according to the final diagnosis based only on the SN ultrastaging. Isolated tumor cells (ITC), micrometastases (Micro), macrometastases (Macro), Lymphovascular space involvement (LVSI), squamous (SCC), adeno (ACC) or adenosquamous (ASCC) carcinoma.

Factor n (%)	**SN ultrastaging result** [1]				
	Negative	ITC	Micro	Macro	**p value** [1]
Age					
median [range]	45 [30 - 70]	47 [32 - 64]	50 [33 - 70]	40 [33 - 74]	0.009
≤ 50 yrs	301 (73.6)	17 (4.2)	34 (8.3)	57 (13.9)	
> 50 yrs	155 (65.7)	12 (5.1)	31 (13.1)	38 (16.1)	0.143
Histology					
ACC	129 (78.7)	10 (6.1)	7 (4.3)	18 (10.9)	
SCC	312 (67.8)	18 (3.9)	55 (12.0)	75 (16.3)	
ASCC	13 (68.4)	1 (5.3)	3 (15.8)	2 (10.5)	0.174
FIGO stage					
IA	46 (83.6)*	2 (3.6)	3 (5.5)	4 (7.3)	
IB1	353 (74.0)	18 (3.8)	41 (8.6)	65 (13.6)	
IB2	35 (60.3)	3 (5.2)	10 (17.2)*	10 (17.2)	
IIAB	22 (40.0)*	6 (10.9)*	11 (20.0)*	16 (29.1)*	< 0.001
LVSI					
No	348 (73.1)	21 (4.4)	46 (9.7)	61 (12.8)	
Yes	108 (63.9)	8 (4.7)	19 (11.2)	34 (20.1)	0.107
Parametrial involvement					
No	440 (73.5)	28 (4.7)	55 (9.2)	76 (12.7)	
Yes	16 (34.8)*	1 (2.2)	10 (21.7)*	19 (41.3)*	< 0.001
Vaginal involvement					
No	439 (73.3)	23 (3.8)	57 (9.5)	80 (13.4)	
Yes	17 (36.9)*	6 (13.0)*	8 (17.4)*	15 (32.6)*	< 0.001
Pelvic nSN examination					
Negative	438 (78.8)	25 (4.5)	46 (8.3)	47 (8.5)	
Positive	18 (20.2)*	4 (4.5)	19 (21.4)*	48 (53.9)*	< 0.001
Events					
Recurrences	25 (52.1)	1 (2.1)	9 (18.7)	13 (27.1)	
Deaths	9 (37.5)	0 (0)	6 (25)	9 (37.5)	-
Total study population (N = 645)	N = 456 (70.7 %)	N = 29 (4.5 %)	N = 65 (10.1 %)	N = 95 (14.7 %)	

[1] Overall level of statistical significance of association between given factor and results of pathologic ultrastaging (p value of ML- χ^2 test)

* significantly lower/higher value in comparison with the other values within this subgroup (ML- χ^2 test; $p < 0.05$)

Table 2. Number of positive (Pos) nSNs in relation to relapse-free survival (RFS) and overall survival (OS) in the total study population (N=645). HR and p values are calculated for the total number of positive nSNs and consequently per stratum of more than zero to more than five positive lymph nodes, compared to negative (Neg) nSNs.

	RFS		**OS**	
pos nSNs	HR (95% CI) [1]	p value	HR (95% CI) [1]	p value
	1.18 (1.11; 1.26)	< 0.001	1.13 (1.02; 1.26)	0.018
categories				
> 0	3.47 (1.92; 6.26)	< 0.001	5.10 (2.28; 11.39)	< 0.001
> 1	4.81 (2.47; 9.36)	< 0.001	5.94 (1.93; 18.32)	< 0.001
> 2	5.59 (2.56; 12.21)	< 0.001	6.21 (2.47; 15.59)	< 0.001
> 3	6.38 (2.80; 14.54)	< 0.001	7.78 (2.52; 24.02)	< 0.001
> 4	6.72 (2.61; 17.32)	< 0.001	8.11 (2.29; 28.63)	< 0.001
> 5	8.80 (3.10; 24.96)	< 0.001	8.98 (2.02; 39.37)	0.008

[1] HR: hazard ratio (univariate Cox proportional hazard regression); CI: confidence interval

Table 3. Univariate and multivariate-adjusted hazard ratio of the threshold of 16 or more removed nSNs as potential predictor of survival in Cox proportional hazard models.

	RFS		**OS**	
	HR (95% CI) [1]	p value	HR (95% CI) [1]	p value
Total population (n=645)				
Stage IA & IB1 (N = 532)				
Univariate HR	1.03 (0.42; 2.50)	0.490	0.67 (0.22; 2.09)	0.580
Multivariate Adjusted HR[2]	0.94 (0.38; 2.94)	0.885	0.66 (0.21; 2.08)	0.473
Stage IB2 & IIAB (N = 113)				
Univariate HR	0.32 (0.10; 0.99)	0.032	0.19 (0.04; 0.79)	0.013
Multivariate Adjusted HR[2]	0.30 (0.11; 0.99)	0.047	0.17 (0.04; 0.79)	0.023
Cases with any positivity in SN or nSNs (N =207)				
Univariate HR	0.63 (0.24; 1.68)	0.358	0.32 (0.12; 0.84)	0.021
Multivariate Adjusted HR[2]	0.58 (0.22; 1.56)	0.281	0.31 (0.11; 0.85)	0.022
Cases with LVD in SN (n=94)				
Univariate HR	0.95 (0.12; 7.50)	0.789	0.19 (0.04; 0.99)	0.047
Multivariate Adjusted HR[2]	0.85 (0.11; 6.92)	0.879	0.17 (0.03; 0.96)	0.044

[1] HR: hazard ratio (univariate Cox proportional hazard regression); CI: confidence interval

[2] Only factors which reached a p value < 0.1 in univariate Cox regression were selected for multivariate analysis from the following list: age, stage, histological subtype, LVSI, vaginal involvement, parametrial involvement, (neo) adjuvant therapy, number positive nSNs (strata 0, 1, 2, 3, 4, ≥ 5).