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SLN mapping in early-stage cervical cancer as a minimal-invasive triaging tool for multimodal treatment

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ABSTRACT

Background: To evaluate sensitivity, false negative rate and negative predictive value of the combination of sentinel lymph node (SLN) mapping and frozen section (FS) in triaging cervical cancer patients to a definitive chemo-radiotherapy.
Methods: A retrospective analysis of patients with histologically proven cervical cancer undergoing laparoscopic SLN mapping and frozen section of the SLNs followed by a completion radical hysterectomy, pelvic and/or paraarotic lymphadenectomy. Sensitivity, false negative rate and negative predictive value of the SLN mapping, of the frozen section and of the combination of the two in identifying micro- and macrometastases were calculated.
Results: One-hundred and four patients with cervical cancer underwent surgery. Of these, 87 (83.7%) had bilateral detection rates at the SLN mapping and underwent FS evaluation and were selected for statistical analysis. Twenty-five patients had lymph nodal metastases at H&E staining. Of these, 24 displayed metastatic disease to the SLNs and one to a NSLN accounting for a FN rate of 4.0%. Metastases were identified in 21 patients at the FS analysis. Four patients had metastases in the SLNs that were missed at the FS analysis. The FN rate of the FS is 12.5% if we excluded isolated tumour cells in the analysis. The FN rate of the combined methodology (SLN mapping and FS of the SLN) is 16%. Twenty-one out of 25 patients (84.0%) could correctly be triaged to a definitive chemo-radiotherapy.
Conclusions: The combination of SLN mapping and FS of the SLNs is efficient in triaging patients to a definitive chemo-radiotherapy.

Introduction

In cervical cancer, lymph node metastasis is the most important prognostic factor that influences treatment [1]. Concomitant chemo-radiotherapy is indicated when nodal involvement is demonstrated [2]. Combination of radical surgery and adjuvant radiotherapy is not associated with a better oncologic outcome and should be avoided, whenever possible [3]. The new ESGO-ESTRO-ESP guidelines for the management of cervical cancer, recommend to avoid a combined treatment with radical surgery and adjuvant radiotherapy [4]. Patients in whom the indication for an adjuvant radiotherapy is known prior to surgery should be directly referred for primary chemo-radiotherapy. In these cases, the volume of the external beam radiotherapy covers the gross disease, its surrounding tissue and the nodal volume considered to be at risk [5]. For patients with negative lymph nodes the volume includes the lymph nodes located along the internal and external iliac arteries, in the obturator fossa and in the presacral area. In case of suspected or documented pelvic lymph node metastases, the volume is extended to cover the area of the common iliac vessels and if the lymph node involvement extends to the common iliac area or in the paraaortic region an extended field of radiation to these area or cephalad thereof is indicated [5].

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In patients with pelvic lymph node involvement, the estimated risk of metastatic disease to the para-aortic lymph nodes is 20% and according to the ESMO-ESTRO-ESP guidelines a paraaortic lymphadenectomy at least up to the inferior mesenteric artery may be considered [4,6,7]. A conventional radiation field to the pelvis might undertreat a significant number of patients whereas an extension of the radiation field to the para-aortic area might lead to unnecessary toxicity.

The intraoperative identification of pathologically proven pelvic lymph node metastases may be helpful in determining the ultimate treatment plan and is encouraged by the European guidelines [4]. A potentially unnecessary radical hysterectomy could be avoided in favor of a para-aortic lymphadenectomy for staging purposes. The extension of the irradiation field could then be tailored based on pathological information of the lymph nodes gathered during the surgical procedure thus reducing the risk of under- and overtreatment.

According to NCCN guidelines, sentinel lymph node (SLN) mapping is an acceptable alternative to a systematic pelvic lymphadenectomy in selected cases of FIGO stage I cervical cancer [5]. The best detection rates and results are in tumors <2 cm. According to ESGMO-ESTRO-ESP guidelines, a SLN mapping should be offered in early stage cervical cancer patients in addition to a full pelvic lymphadenectomy [4]. In selected cases with small tumor or in the context of clinical trials a SLN can be considered as an alternative to a systematic pelvic lymphadenectomy. With indocyanine green (ICG) as tracer, excellent results in terms of detection rates, false negative rates and negative predictive value (NPV) have been recorded [8–12].

SLN mapping with frozen section of the SLN may help determine the best treatment strategy for the patient. In cases with metastatic pelvic lymph nodes, a radical surgery could be avoided in favor of para-aortic lymphadenectomy and a tailored chemo-radiotherapy. The ability to determine metastatic disease to the sentinel lymph nodes at frozen section varies widely among the published series [13–21].

The aim of our study was to evaluate the sensitivity, false negative rate and NPV of SLN mapping and frozen section to identify the subgroup of patients who will not receive any benefit from radical surgery plus chemo-radiotherapy.

Materials and methods

A retrospective analysis of patients with cervical cancer undergoing SLN mapping and frozen section of the SLNs from April 2008 to December 2017 at the Department of Obstetrics and Gynecology, University Hospital of Bern and University of Bern was performed. Demographic, clinical and pathologic data were retrieved from an electronic database. The current electronic database in use at the University Hospital of Bern and University of Bern has been introduced in 2010 and have progressively been implemented through the years. Surgical reports and clinical charts were used to retrieve data from patients treated prior to the introduction of the electronic database and to integrate missing data. The study was IRB approved.

Patients with histologically confirmed cervical carcinoma, International Federation of Gynecology and Obstetrics (FIGO) stage IA1 with positive lymph vascular space invasion (LVSI) – IIB who underwent SLN mapping followed by laparoscopic lymph node biopsy and frozen section analysis were included in the study. The study population was divided into two cohorts: cohort A with stage IA with LVSI – IB1 cervical cancer patients and cohort B with stage IB2-IIB cervical cancer patients (Fig. 1). In cohort A, if metastatic disease to the SLN was identified at frozen section, the radical procedure was aborted in favor of concurrent chemoradiotherapy. In these cases, a laparoscopic para-aortic lymphadenectomy was performed in order to determine the extension of the radiation field. The upper landmark of the paraaortic lymphadenectomy was the inferior mesenteric artery or, in selected cases, the left renal vein. In case of negative results for SLN metastases at frozen section, a radical hysterectomy and a full pelvic lymphadenectomy was performed. In cohort B, the SLN mapping procedure was performed to determine whether to perform a para-aortic lymphadenectomy to determine the extent of the radiation fields. In these cases, a radical hysterectomy was neither planned nor performed. Non SLNs (NSLNs) that appeared macroscopically suspicious were removed and sent for frozen section as well. At final histopathological analysis a complete ultrastaging was performed in all cases (three slides HE 200 μm, pancytokeratin immunohistochemistry (IHC) in case of absence of metastatic disease at conventional staining). All the surgeries were performed by physicians trained in gynecologic oncology and in minimally invasive surgery and the pathological analysis of all the specimens were performed by dedicated gynecologic pathologists.

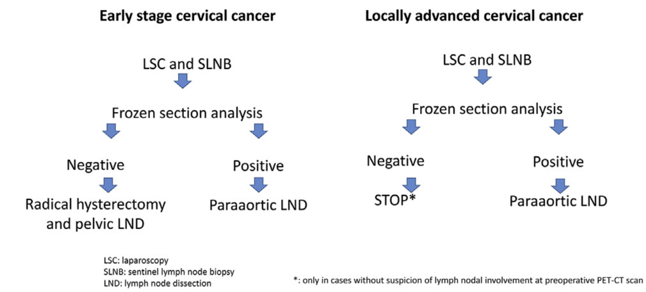

Fig. 1. Flow-chart depicting treatment strategy based on initial diagnosis and intraoperative evaluation of the sentinel lymph node.

Pretreatment evaluation included medical history collection, physical examination, Positron Emission Tomography - CT scan and examination under anesthesia and a Magnetic Resonance Imaging of the pelvis to rule out parametrial invasion when indicated and based on phyisician's judgement.

Throughout the study period, two different techniques for SLN mapping were used [8]. From April 2008 until January 2011 SLN mapping was performed with a preoperative 99m-Tc injection and lymphoscintigram with fusion computer tomogram (SPECT) in combination with or without intraoperative patent blue dye injection. From January 2011 until December 2017 SLN mapping was performed with intraoperative ICG injection. Details on the SLN mapping techniques have been described previously [8]. Data on part of this cohort of patients have been published with a different aim.

Demographic and clinical-pathologic characteristics were evaluated using the basic descriptive statistics. For the purpose of the analysis, only patients with bilateral detection of SLNs who underwent a frozen section analysis of the SLNs were included.

A true positive SLN was defined as a positive SLN identified with histopathological techniques, independent of regional lymph node status. Further analysis follows the pathological workup in step-sectioning at first instance. Herein, only metastatic lymph nodes in which the metastases were diagnosed at H&E staining were considered as positive. Next, lymph nodes with metastatic disease diagnosed at IHC were integrated, but with their limited value for accurate intra-operative assessment as this kind of metastases would not have been detected by any means on frozen section analysis. A false negative SLN was defined as a negative SLN in combination with metastatic NSLNs.

Since the accuracy of this triage model depends on the false negative rate of both the SLN mapping and of the frozen section analysis of the SLNs a three-step analysis was performed. First, the sensitivity, the false negative rate and the NPV of the SLN mapping were calculated. Then, the sensitivity, the false negative rate and the NPV of the frozen section analysis were calculated. Finally, the sensitivity, the false negative rate and the NPV for the triage method based on SLN mapping and frozen section analysis of the SLNs were calculated.

Results

During the study period, 104 patients with cervical cancer underwent SLN mapping. Of these, 90 (86.5%) patients had bilateral mapping, 13 (12.5%) had unilateral mapping and 1 (1%) had no mapping. Of the patients with bilateral SLN detection, 87 patients had the SLNs analyzed intraoperatively at frozen section and constitute the cohort of this study. In the other three cases, the SLNs were not analyzed at frozen section. Sixty-five patients (74.7%) had SLN mapping with ICG only, 18 patients had a combination of Tc-99 and blue dye, 2 patients had ICG and Tc-99 and 2 patients had only Tc-99.

The median age of the patients was 45 years (range 26–77 years). Median body mass index (BMI) was 23.7 (range 13.2–35.4). Two-thirds (66.7%) of the patients had a BMI lower than 25 kg/m2. The majority of the patients had a FIGO Stage IB1 cervical cancer (54.0%), followed by IB2 (14.9%). Histology was squamous cell carcinoma in 70% of the cases and adenocarcinoma in 24.1%. Other histological types included clear cell carcinoma, small cell neuroendocrine and adenosquamous carcinoma. Grading was well, moderately and poorly differentiated in 3.4%, 52.4% and 39.1% of the cases respectively. Lymph vascular space invasion was present in 46% of the patient and 60.9% of the patients had tumors bigger than 2 cm. Characteristics of the patients are presented in Table 1.

A total of 3712 lymph nodes were removed, of which 424 were SLNs. The median number of SLNs removed per patient was 3 (range 2–15). Forty-one SLNs were positive for metastasis and 24 patients had SLNs with metastatic disease at final pathological diagnosis. The metastatic SLNs were mainly located in the obturator fossa (56.1%) and along the external iliac vessels (29.3%). Of the 41 positive SLNs, metastases were macro-metastases in 85.4% of the cases, micro-metastases in 12.2% of the cases and isolated tumor cells in 2.4% of the cases. Details on the SLN characteristics are presented in Table 2.

Nineteen (21.8%) patients had lymph nodal macro-metastasis, four (4.6%) patients had micro-metastasis and one (1.1%) patient had isolated tumor cells. One (1.1%) patient had metastasis to a NSLN with bilaterally negative SLNs, accounting for a FN rate of the SLN mapping of 4%. The sensitivity and NPV of the SLN mapping are 96.0% and 98.4% respectively. Four patients had metastases to the SLNs, which were missed on frozen section. These were two macro-metastasis, one micro-metastasis and one isolated tumor cells in one patient each. By excluding the patient with isolated tumor cells in the SLN, the false negative rate, the sensitivity and the NPV of the frozen section are 12.5%, 87.5% and 95.5% respectively. The FN rate, the sensitivity and the NPV value for the whole process (SLN mapping and frozen section of the SLNs) are 16%, 84% and 93.9% respectively. Data are summarized in Tables 3 and 4. It means that by applying both techniques, we were able to identify 84% of patients who were triaged to optimal treatment for cervical cancer.

Three out of 20 patients (15%) with SLN metastases discovered with intraoperative frozen section had para-aortic lymph node metastases. All of these were macro-metastases.

Among the 13 patients with unilateral SLN mapping, majority of them had squamous cell carcinoma (9/13) with two adenocarcinoma and one adenosquamous tumour. All but one of the patients (12/13) had tumour size of more than 2 cm. All patients had stage IB1 disease and above. The median age in this group was 47.5 years with a range of 41–71 years. Median BMI was 23.5 kg/m2 with a range of 20.8–41.5 kg/m2.

Table 1
Characteristics of the patients.

	N = 87 (%)
Median Age in years (range)	45 (26–77)
Median BMI in kg/m^2 (range)	23.7 (13.2–35.4)
FIGO stage	
IA1	9 (10.4)
IA2	4 (4.6)
IB1	47 (54.0)
IB2	13 (14.9)
IIA1	6 (6.9)
IIA2	2 (2.3)
IIB	6 (6.9)
Histology	
squamous cell carcinoma	60 (69)
adenocarcinoma	21 (24.1)
adenosquamous carcinoma	2 (2.3)
clear cell carcinoma	1 (1.2)
others	3 (3.4)
Tumor size	
≤2 cm	34 (39.1)
>2 cm	53 (60.9)
LVSI	
negative	47 (54.0)
positive	40 (46.0)

Table 2
Sentinel Lymph node characteristics.

Total number of SLN removed	424
Total number of positive SLN	41
	N (range)
Median number of SLN removed	3 (2–15)
Median number of positive SLN	1 (1–5)
Localization	N (%)
Obturator fossa	22 (53.7)
Iliac	3 (7.3)
Common iliac	1 (2.4)
External iliac	8 (19.5)
Internal iliac	1 (2.4)
Para-aortal	2 (4.9)
Pelvic	4 (9.8)

Table 3
FN rate, sensitivity and NPV of treatment strategy.

	FN rate	Sensitivity	NPV
SLN mapping	4%	96.0%	98.4%
Frozen section	12.5%	87.5%	95.5%
Combined strategy	16%	84.0%	93.9%

SLN: sentinel lymph node, FN: false negative, NPV: negative predictive value.

Table 4
Characteristics of SLN metastasis.

Type of metastasis	Number of SLN	Number of patients
Macro-metastasis	35	19
Micro-metastasis	5	4
ITC	1	1
Total	41	24

Discussion

Current guidelines and common practices in many gynecological oncology centers involve full pelvic lymphadenectomy as a standard procedure to assess lymph node status in patients with early-stage cervical cancer. Recently, SLN mapping has been proposed as an acceptable alternative to a full pelvic lymphadenectomy in selected cervical cancer patients [5]. On the contrary, European guidelines recommend the use of SLN mapping as an alternative to a full lymphadenectomy only within clinical trials [4]. Our center has been incorporating SLN mapping into the management of these patients since 2008. We do not use SLN mapping as opposed to a full lymphadenectomy, but we use it to triage patients to radical surgery or definitive chemo-radiotherapy based on absence or evidence of metastatic nodal disease at frozen section analysis.

Our results for SLN mapping correlate well with various recent studies on the efficacy and reliability of SLN mapping. Tax et al. in a meta-analysis of 44 studies comprising 3931 patients found an overall sensitivity of the SLN biopsy and ultrastaging to be 94% [22]. Similarly, a retrospective review of 188 patients with early-stage cervical cancer showed a sensitivity of 96.4% and negative predictive value of 99.3% [23]. We had only one FN case with the patient having a metastatic NSLN in the right pelvis. This patient had a Stage IIB disease with a tumor larger than 2 cm and also bilateral SLN mapping. Studies have shown that more advanced stages and tumor size more than 2 cm were associated with lower detection rates and poorer sensitivity for SLN mapping and biopsy [22–24].

In our series, overall and bilateral detection rates were very high: 99% and 86.5% respectively. The fact that the majority of the patients underwent an ICG SLN mapping is probably the reason explaining these excellent results. ICG SLN mapping technique has consistently shown to improved detection rates as compared to radiocolloid/blue dye mapping [25,26].

Our results for intraoperative frozen section examination of the SLNs are good compared to some studies with poor sensitivity for frozen section [13,14]. Bats et al. [13] found that the sensitivity for frozen section of SLN was only 19.1%. Even for the diagnosis of macro-metastasis, the sensitivity was only 55.6% [13]. Martinez et al. showed that the sensitivity of frozen section was 100% for tumor deposits of more than 2 mm in diameter [15]. Sensitivity and NPV for all types of lymph node metastasis was 64.3% and 98% respectively [15]. The range of sensitivities moves from a low-medium rate [13,14,16,17] to almost 100% [15,18–21]. These accentuated differences are consequence of the accuracy of detection of micro-metastasis and isolated tumor cells. A plausible reason for our good frozen section results is that our study population includes a larger proportion of patients with macro-metastases as patients with larger tumors were included. The intrinsic characteristics of our study (its retrospective nature and the inclusion criteria adopted which include bilateralism of the mapping) may also be responsible of these differences.

Of the lymph nodes, in which metastatic disease was not identified at frozen section two were macro-metastases, 1 micro-metastasis and 1 isolated tumor cells in one patient each. Three of the patients had stage IB1 disease and 1 with stage IB2. All of these patients had tumor size of more than 2 cm. We speculate that the detection rates would probably be lower in a cohort with a different macro-to micrometastases ratio. This has to be kept in mind when adopting this strategy in clinical practice. Small volume metastatic disease may remain undetected at frozen section when time constrains do not allow the performance of an ultrastaging. However, micrometastatic lymph nodal disease worsens patients' outcome and failing to identify it at frozen section will ultimately lead to a combined treatment of radical surgery and adjuvant chemoradiotherapy [27]. Still, we believe that this is the best method we have to triage patients to the proper treatment modality.

Pathological assessment started with proper macroscopic evaluation. Sentinel lymph nodes sent for frozen sections were bi-valved or sliced into sections of 2 mm. Careful attention to suspicious areas was paid as well as to the control of size and shape after frozen section delivery to the pathologist. Frozen sections were taken on one layer of each block. Definite H&E histology was based on sections at 200 μm steps to allow for micro-metastasis detection. Pan-cytokeratin immunohistochemistry was performed on negative SLNs only. Pan-cytokeratin IHC only revealed one additional patient with isolated tumor cells in our study. However, this procedure of ultra-staging increases the certainty about micrometastasis as well. The enormous shifts in treatment options based on the SLN justify these additional measurements, which can now be considered as standard according to the ESGO-ESTRO-ESP guidelines and current literature [4,28].

Correct intraoperative triage to a radical surgery versus a definitive chemo-radiotherapy was possible in over 80% of the patients in whom SLNs were detected bilaterally. Advantages of such an approach include an optimization of the treatment strategy that reduces therapy-induced morbidity and costs without jeopardizing oncologic outcome. In patients with metastatic lymph nodes, radical surgery and adjuvant chemo-radiotherapy can be avoided. In view of the recently published results of the LACC trial that show a negative effect of a minimally invasive approach as compared to a laparotomy in cervical cancer patients undergoing radical hysterectomy an approached based on a minimally invasive SLN mapping with intraoperative pathological evaluation may avoid the performance of an unnecessary radical surgery and of a laparotomy [26]. Additionally, an intraoperative identification of patients with pelvic lymph node metastases allows for a surgical staging via para-aortic lymphadenectomy in order to determine the extent of the irradiation fields [5,6,28,29,30]. In our series, 15% of the patients with metastatic pelvic SLNs who also underwent a para-aortic lymphadenectomy displayed metastatic diseases in the para-aortic area as well.

A prospective randomized trial, the LiLAC trial, planned to investigate whether the extension of the radiation fields is associated with a survival improvement in patients with metastatic para-aortic disease identified after a laparoscopic surgical staging [7]. However, this phase III trial, which was planned to start in December 2016, never started recruiting patients.

According to NCCN guidelines, a PET-CT scan is indicated in locally advanced cervical cancer patients to rule out distant spread of disease [5]. However, both sensitivity and specificity of PET-CT scan is relatively low as compared to a pathologic assessment of the lymph nodes [6].

Limitations of the study include its retrospective nature, the relative long period over which patients were included and the relative heterogeneity of patient cohort studied. Surgeons' experience have changed and progressed over this period and the SLN mapping has significantly developed in cervical cancer in the past 10 years. All these factors may have had an impact of our results. Strengths of the study include the relatively large size of the analyzed cohort and the consistency of the technique and strategy adopted.

In conclusion, a treatment strategy based on SLN mapping and frozen section analysis of the SLNs in cervical cancer patients seems to be reliable in triaging patients to optimal treatment.

Conflict of interest

All authors have participated in the work and take public responsibility for it.

None of the authors has a conflict of interest.

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