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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

The combination of preoperative PET/CT and sentinel lymph node biopsy in the surgical management of early-stage cervical cancer

Andrea Papadia[1] · Maria Luisa Gasparri[1] · Sophie Genoud[1] · Klaeser Bernd[2] · Michael D. Mueller[1]

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Abstract
Introduction The aim of the study was to evaluate the use of PET/CT and/or SLN mapping alone or in combination in cervical cancer patients.
Materials and methods Data on stage IA1-IIA cervical cancer patients undergoing PET/CT and SLN mapping were retrospectively collected. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PET/CT and SLN mapping, alone or in combination, in identifying cervical cancer patients with lymph node metastases were calculated.
Results Sixty patients met the inclusion criteria. PET/CT showed a sensitivity of 68%, a specificity of 84%, a PPV of 61% and a NPV of 88% in detecting lymph nodal metastases. SLN mapping showed a sensitivity of 93%, a specificity of 100%, a PPV of 100% and a NPV of 97%. The combination of PET/CT and SLN mapping showed a sensitivity of 100%, a specificity of 86%, a PPV of 72% and a NPV of 100%. For patients with tumors of >2 cm in diameter, the PET/CT showed a sensitivity of 68%, a specificity of 72%, a PPV of 61% and a NPV of 86%. SLN mapping showed a sensitivity of 93%, a specificity of 100%, a PPV of 100% and a NPV of 95%. The combination of PET/CT and SLN mapping showed a sensitivity of 100%, a specificity of 76%, a PPV of 72% and a NPV of 100%.
Conclusion PET/CT represents a "safety net" that helps the surgeon in identifying metastatic lymph nodes, especially in patients with larger tumors.

Keywords Cervical cancer · Sentinel lymph node biopsy · Positron emission tomography · Indocyanine green · Laparoscopy

Introduction

Early-stage cervical cancer is mainly managed surgically with a radical hysterectomy and pelvic lymphadenectomy. Although the extrauterine spread of the disease to the lymph nodes does not change stage, it represents the most important prognostic risk factor, is associated with shorter survival and indicates adjuvant treatment (Delgado et al. 1990; Peters et al. 2000; Sedlis et al. 1999; Rotman et al. 2006). Lymph nodal status represents a crucial piece of information for the oncologic management of cervical cancer patients. For this reason, a pelvic lymphadenectomy is always associated with a radical hysterectomy since Meigs first proposed it in the 1950s (Meigs 1956). Unfortunately, the pelvic lymphadenectomy is associated with a significant morbidity that mainly includes, but is not limited to the formation of lymphocysts and lower extremity lymphedema (Matsuura et al. 2006). Furthermore, the majority of the patients with operable cervical cancer will have negative lymph nodes. In an attempt to reduce this surgical morbidity, various institutions have tried to apply the sentinel lymph node (SLN) mapping in this setting.

For a SLN mapping to be reliable, it needs to be characterized by a low number of false-negative results. In other words, a pathologically negative SLN should truly represent a negative pathological status of the ipsilateral pelvic

✉ Andrea Papadia
andrea.papadia@insel.ch

[1] Department of Obstetrics and Gynecology, University Hospital of Bern and University of Bern, Effingerstrasse 102, 3010 Bern, Switzerland

[2] Department of Nuclear Medicine, Bern University Hospital and University of Bern, Bern, Switzerland

lymph nodes. So far, the majority of the studies have concentrated on patients with small cervical cancer lesions. In these instances, the SLN mapping has demonstrated to be reliable and it is now recognized as an alternative to a full lymphadenectomy in selected cases according to the NCCN guidelines (NCCN 2016). In the last few years, the adoption of indocyanine green (ICG) along with minimally invasive near-infrared (NIR) technology has significantly improved the performance of the SLN mapping in uterine malignancies (Imboden et al. 2015; Buda et al. 2016; Ruscito et al. 2016; Papadia et al. 2016a, b, c, 2017; Di Martino et al. 2017). However, for patients with cervical lesions with a diameter greater than 2 cm the results of the SLN mapping are more heterogeneous and, therefore, less reliable.

Positron emission tomography combined with CT (PET/CT) is considered the most useful non-invasive method to identify patients with lymph nodal metastases (Yen et al. 2006; Choi et al. 2010). However, because of limited spatial resolution and associated partial volume effects, small metastatic lesions in lymph nodes may remain undetected (Nogami et al. 2015).

In case of advanced disease or evidence of nodal spread of a resectable cervical cancer other treatment options can be considered such as chemo-radiotherapy or neoadjuvant chemotherapy followed by radical surgery. In this view, a precise identification of lymph node-positive and lymph node-negative patients is desirable to optimizing oncologic management and reducing treatment-related morbidity at the same time.

A treatment strategy based on a combination of PET/CT and SLN mapping has been described for high-risk endometrial cancer patients but not for cervical cancer patients (Signorelli et al. 2015; Bese et al. 2016). The aim of our study was to evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the preoperative PET/CT and SLN mapping, alone or in combination, in identifying cervical cancer patients with lymph node metastases.

Materials and methods

A retrospective analysis of all the patients with clinical stage IA1–IIA cervical cancer undergoing PET/CT and SLN mapping at our Institution between December 2008 and November 2016 was conducted. Demographic, clinical and pathologic data were retrieved from an electronic database. Missing data were integrated using surgical reports and clinical charts. Since January 2011, the data for all patients receiving ICG SLN mapping were prospectively collected. The study was approved by the local ethics committee, and all patients signed informed consent.

Inclusion criteria included: histological diagnosis of cervical cancer, International Federation of Gynecology and Obstetrics (FIGO) stage IA1 with positive lymph vascular space invasion (LVSI)—IIA, preoperative PET/CT and laparoscopic SLN mapping. If clinical stage was unclear, a magnetic resonance imaging of the pelvis was performed to rule out parametrial invasion.

PET/CT was performed as part of the clinical routine staging procedures. All patients had a carbohydrate-free diet at least 6 h before the exam. Image acquisition was done with an integrated PET/CT system (Siemens Biograph 16 or Siemens mCT 128). Attenuation-corrected PET images of the trunk (neck to the pelvis, matrix size 168 × 168 or 200 × 200, 5 mm Gauss filtering, voxel size 4 mm) were obtained 90 min after injection of 4–7 MBq F18-FDG and co-registered with a low-dose CT (100–120 kV, 50–80 mAs, reconstructed slice thickness 2 mm). Beginning from 06/2010, additional high-resolution PET images of the pelvis and lower abdomen were acquired (matrix size of 512 × 512, 2 mm Gauss filtering, voxel size of 1.6 mm), complemented by a contrast-enhanced CT of the abdomen and pelvis (100–120 kV, 150 mAs, reconstructed slice thickness 2 mm). Clinical review and reporting of PET/CT was done by two board-certified nuclear medicine physicians. In this retrospective analysis, PET/CT results were obtained by review of original reports and classified as suspicious or non-suspicious for SLN metastases based on the original interpretation of the nuclear medicine physicians.

Throughout the study period, different tracers were used for the laparoscopic SLN mapping as previously described (Imboden et al. 2015). In every case, the tracers were injected intracervically. Briefly, from April 2008 until January 2011, a combination of Tc-99 m-Nanocoll and blue dye were used for SLN mapping. In these cases, a total amount of 120 MBq of Tc-99 m-Nanocoll (4 injections, 30 MBq per quadrant of the cervix) was injected 1 day prior to surgery, and planar SPECT/CT using an integrated system (Philips Precedence 6) was performed 1 h after injection to preoperatively locate the SLNs. In addition, patent blue was injected in the operating room after induction of anesthesia and prior to incision (total volume 5 ml). SLNs were identified with the use of a laparoscopic gamma probe (Navigator; Autosuture, Norwalk, CT, USA) and under direct visualization. From January 2011 until December 2016, SLN mapping was performed with intraoperative injection of 8 ml of a solution of ICG at a concentration of 5 mg/ml (Pulsion®). A SPIES Full HD D-Light P ICG technology (Karl Storz, GmbH & CO, Mittelstrasse, Tuttlingen, Germany) was used to detect the fluorescent signal.

SLNs and clinically suspicious non-SLNs (NSLN) were removed and analyzed at frozen section. If the lymph nodes were found to be disease free, a laparoscopic radical

hysterectomy and a pelvic lymphadenectomy were performed. On the contrary, if metastatic disease was diagnosed, the planned surgical procedure was aborted in favor of a concomitant chemo-radiotherapy.

Histopathological findings were analyzed by experienced pathologists. SLNs were processed in a standardized manner by ultrastaging (three slides HE 200 µm). Data on a subset of the patients in this cohort were previously published in retrospective cohort studies evaluating other aims (Imboden et al. 2015; Buda et al. 2016; Ruscito et al. 2016; Papadia et al. 2016a, b; Di Martino et al. 2017).

Clinical–pathologic characteristics were evaluated using the basic descriptive statistics. The sensitivity, specificity, PPV, NPV of PET/CT, SLN biopsy and the combination of PET/CT and SLN biopsy in identifying metastatic lymph nodes were calculated. A true positive was defined as a positive PET/CT and/or SLN in the presence of metastatic disease to the pelvic lymph nodes. A true negative was defined as a negative PET/CT and/or SLN in the absence of metastatic disease to the pelvic lymph nodes. A false positive was defined as a positive PET/CT in the absence of metastatic disease to the pelvic lymph nodes. The false-positive rate of the SLN biopsy was set at zero. A false negative was defined as a negative PET/CT or SLN in the presence of metastatic disease to the pelvic lymph nodes. Ninety-five percent confidence intervals (CIs) were calculated according to the standard normal distribution. These analyses were performed for the entire population and for the subgroup of patients with a tumor diameter of greater than 2 cm. Statistical analysis was performed with Graph Pad Prism 5.

Table 1 Patients' characteristics

	$N = 60$ (%)
Median age (range)	47 (27–72) years
Median BMI (range)	24 (18.4–35.2) kg/m^2
FIGO stage	
IA1	1 (1.7%)
IA2	2 (3.3%)
IB1	36 (60%)
IB2	11 (18.3%)
IIA	10 (16.7%)
Median tumor diameter (range)	30 (6–77) mm
Tumor diameter (cm)	
≤2	19 (31.7%)
>2	41 (68.3%)
Histology	
Squamous cell carcinoma	45 (75%)
Adenosquamous cell carcinoma	11 (18.3%)
Adenocarcinoma	1 (1.7%)
Clear cell carcinoma	2 (3.3%)
Neuroendocrine carcinoma	1 (1.7%)
LVSI	
n.a.	7 (11.7%)
No	23 (38.3%)
Yes	28 (46.7%)
Grade	
n.a.	2 (3.3%)
Grade 1	1 (%)
Grade 2	31 (51.7%)
Grade 3	25 (41.7%)

BMI body mass index, *n.a.* not available

Results

During the study period, 60 patients with stage I–IIA cervical cancer met inclusion criteria. Patients' characteristics are summarized in Table 1. Briefly, median age of the patients was 47 years and median BMI was 24 kg/m^2. FIGO stage distribution was as follows: stage IA1: 1 patient (1.7%), stage IA2: 2 patients (3.3%), stage IB1: 36 patients (60%), stage IB2: 11 patients (18.3%) and stage IIA: 10 patients (16.7%). Median tumor diameter was 30 mm. Nineteen patients (31.7%) had a tumor diameter of 2 cm or less, whereas 41 patients (68.3%) had a tumor diameter of greater than 2 cm. Histology was squamous cell carcinoma, adenosquamous cell carcinoma or adenocarcinoma in 96% of the cases.

PET/CT was negative for lymph node metastases in 42 patients (70%) and positive in 18 patients (30%). PET/CT-positive lymph nodes were located in the pelvis in every case. One patient presented additionally with a PET/CT-positive para-aortic lymph node. PET/CT-positive lymph nodes were single in 6 cases and multiple in 12.

The laparoscopic SLN mapping was performed with a combination of Tc-99 m-Nanocoll and patent blue in 22 patients (36.7%) and with ICG in 38 patients (63.3%). Overall and bilateral detection rates for the entire cohort of patients were 91.7 and 83.4%, respectively.

Sixteen patients (26.7%) presented with metastatic disease to the pelvic lymph nodes. SLNs were positive in 14 patients. Of the two patients with metastatic disease to the NSLNs only, the SLN mapping failed in one case in which no SLN could be identified after combined Tc99 and patent blue injection. This patient had a squamous cell carcinoma with a maximum tumor diameter of 2.3 cm. A preoperative PET/CT showed multiple metastatic pelvic lymph nodes.

The second patient presented with bilateral negative SLNs and one metastatic NSLN. This patient had a stage IIA squamous cell carcinoma of the cervix with a maximum diameter of 4.7 cm and presented with positive

lymph nodes at preoperative PET/CT. During the surgery an enlarged clinically suspicious NSLN was identified and excised. A frozen section analysis of this NSLN revealed metastatic disease. Although this does not necessarily represent a false negative in the context of a SLN mapping algorithm as proposed by MSKCC in which every SLN as well as suspicious NSLN are removed and site-specific lymphadenectomies are performed in hemipelvises that do not trace; we considered this case as a false-negative case for the SLN mapping and a true-positive case for the PET/CT (Cormier et al. 2011). All the patients with lymph nodal metastases had a tumor diameter of greater than 2 cm. Pet/CT and SLN mapping results are summarized in Table 2.

For the entire cohort of patients PET/CT showed a sensitivity of 68%, a specificity of 84%, a PPV of 61% and a NPV of 88% in detecting metastatic lymph nodal disease. SLN mapping showed a sensitivity of 93%, a specificity of 100%, a PPV of 100% and a NPV of 97% in detecting metastatic lymph nodal disease. The combination of PET/CT and SLN mapping showed a sensitivity of 100%, a specificity of 86%, a PPV of 72% and a NPV of 100% in detecting metastatic lymph nodal disease. Results are summarized in Table 3.

Considering the patients with a tumor diameter of greater than 2 cm, PET/CT showed a sensitivity of 68%, a specificity of 72%, a PPV of 61% and a NPV of 86% in detecting metastatic lymph nodal disease. SLN mapping showed a sensitivity of 93%, a specificity of 100%, a PPV of 100% and a NPV of 95% in detecting metastatic lymph nodal disease. The combination of PET/CT and SLN mapping showed a sensitivity of 100%, a specificity of 76%, a PPV of 72% and a NPV of 100% in detecting metastatic lymph nodal disease. Results are summarized in Table 4.

Discussion

Our data show that the adoption of a preoperative PET/CT in early-stage cervical cancer patients undergoing surgery and SLN mapping may increase the ability to detect patients with metastatic lymph nodes. In particular, the NPV of the combination of SLN mapping and preoperative PET/CT was higher as compared to that of each method considered alone. This ensures oncologic safety reducing the risk of omitting to identify patients with metastatic lymph nodes who require chemo-radiotherapy. Similarly, the sensitivity and NPV were increased through the combination of both methodologies. This increase in performance was recorded both for patients with smaller and larger cervical lesions.

Table 2 Lymph nodal mapping

	$N = 60$ (%)
PET/CT	
Negative for LN metastases	42 (70%)
Positive for LN metastases	18 (30%)
Localization of PET/CT-positive LN	
Pelvic	18
Para-aortal	1
Number of PET/CT-positive LN	
1	6
≥2	12
SLN mapping	
Tracer	
ICG	38 (63.3%)
Tc99 + blue dye	22 (36.7%)
Detection rate	
None	5 (8.3%)
Unilateral[a]	5 (8.3%)
Bilateral	50 (83.4%)
Median number of SLNs (range)	
Location of SLNs	3 (0–15)
Pelvis	54 (%)
Para-aortal	5 (%)
Pathologic status of SLNs	
n.a.	5 (8.3%)
Negative	41 (68.3%)
Positive	14 (23.3%)
ITC	0
Micrometastasis	1 (1.7%)
Macrometastasis	13 (21.7%)
Location of metastatic SLNs	
Pelvis	14
Para-aortal	0
Median number of NSLNs (range)	36 (1–82)
Pathologic status of NSLNs	
n.a.	1 (1.7%)
Negative	54 (90%)
Positive	5 (8.3%)
Micrometastasis	0
Macrometastasis	5
Location of metastatic NSLNs	
Pelvis	3
Para-aortal	2

LN lymph nodes, *SLN* sentinel lymph nodes, *NSLN* non sentinel lymph nodes

[a] In one patient, the SLN was aborted secondary of evidence of metastatic LN on the first SLN identified. The contralateral hemipelvis was, therefore, not explored

Table 3 Performance of PET/CT and SLN mapping alone and in combination in identifying lymph node-positive stage I–IIA cervical cancer patients

	PET/CT	SLN mapping	PET/CT and SLN mapping
Sensitivity	68% (CI 95%;: 0.55–0.79)	93% (CI 95%; 0.82–0.98)	100% (CI 95%; 0.92–1)
Specificity	84% (CI 95%; 0.71–0.91)	100% (CI 95%; 0.91–0.1)	86% (CI 95%; 0.74–0.93)
PPV	61% (CI 95%; 0.47–0.73)	100% (CI 95%; 0.91–0.1)	72% (CI 95%; 0.59–0.83)
NPV	88% (CI 95%; 0.76–0.94)	97% (CI 95%; 0.88–0.99)	100% (CI 95;: 0.92–1)

CI confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

Table 4 Performance of PET/CT and SLN mapping alone and in combination in identifying lymph node metastases in patients with stage I–IIA cervical cancer and tumor diameter greater than 2 cm

	PET/CT	SLN mapping	PET/CT and SLN mapping
Sensitivity	68% (CI 95%; 0.52–0.81)	93% (CI 95%; 0.78–0.98)	100% (CI 95%; 0.92–1)
Specificity	72% (CI 95%; 0.55–0.84)	100% (CI 95%; 0.88–1)	76% (CI 95%; 0.50–0.87)
PPV	61% (CI 95%; 0.44–0.75)	100% (CI 95%; 0.88–1)	72% (CI 95%; 0.56–0.84)
NPV	86% (CI 95%; 0.72–0.89)	95% (CI 95%; 0.81–0.99)	100% (CI 95%; 0.89–1)

CI confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

So far, the majority of the research in SLN mapping and cervical cancer has focused on patients with smaller lesions and, currently, NCCN guidelines recognize SLN mapping a valid alternative to a full lymphadenectomy in selected cases with tumors <2 cm in diameter (NCCN clinical practice guidelines in oncology 2016). The largest prospective trial on SLN mapping in cervical cancer, the SENTICOL study, showed a detection rate of 97.8% and a NPV of 98.2% (Lécuru et al. 2011). Of note that, although all the early-stage cervical cancer patients were considered eligible to be enrolled, the mean tumor diameter recorded in the SENTICOL study was only 1.3 cm.

On the contrary, an AGO trial on SLN mapping in which patients with larger tumors were enrolled showed a lower detection rate and sensitivity (Altgassen et al. 2008). It is generally believed that both detection rate and sensitivity of the SLN mapping decrease in patients with tumors of greater than 2 cm (Lukas et al. 2013). In case of larger tumors, a hampered lymphatic flow resulting from lymph vascular space invasion and massive replacement of metastatic lymph nodes along with the higher prevalence of metastatic lymph nodes may compromise the results of a SLN mapping.

It has been suggested that a PET/CT should not been routinely performed in early-stage cervical cancer patients due to low sensitivity (Crivellaro et al. 2012). This is mainly related to the fact that small volume lesions to the lymph nodes may not be detected with clinically sufficient sensitivity. In a large retrospective study on the role of PET/CT in predicting lymph node metastases in early-stage cervical cancer, the sensitivity of the methodology went from 25 to 32% if patients with tumors of <2 or ≥2 cm were considered (Lukas et al. 2013). In our series, PET/CT performed better with a sensitivity of 68%. This difference may be explained technically by the use of high-resolution PET/CT acquisitions with minimized partial volume effect detecting small lymph node metastases as well as by a different proportion of patients presenting with larger lymph node metastases in our patient collective.

Although the combination of a preoperative PET/CT and SNL mapping gained the highest results in terms of sensitivity, specificity, NPV and PPV, it has to be pointed out that through the adoption of a SLN mapping algorithm as proposed by Cormier et al. in which every enlarged lymph node is removed and non-mapping hemipelvises are subjected to a full lymphadenectomy, all the patients presenting with lymph nodal metastases possibly would have been correctly identified even in the absence of the preoperative PET/CT (Cormier et al. 2011). Given the nature of the study, it is not possible to exclude that the positive PET/CT result may have influenced the surgeon to look with more persistence for enlarged lymph nodes thus allowing the identification of a clinically suspicious metastatic NSLN in a patient with bilateral negative SLNs.

Limitations of the study include its retrospective design, the relatively small number of cases involved and the heterogeneity of the tracers and protocols used for SLN mapping. The most important strength of this study is that it is the first one evaluating a clinical staging protocol combining preoperative PET/CT and SLN mapping in patients with early-stage cervical cancer. Additionally, the homogeneity of the cohort of patients, of the radiologic evaluation and of the surgical management delivered, is high. Additionally, for a significant proportion of the patients, the data on the SLN mapping have been collected prospectively.

In conclusion, the SLN mapping in cervical cancer seems to perform well both for patients with lesions < and ≥2 cm in diameter, especially when adopted along with a SLN mapping algorithm. In our cohort, the combination with a preoperative PET/CT as part of the staging procedure increased sensitivity and NPV of the SLN mapping.

We believe that the PET/CT may represent a "safety net" to avoid missing metastatic lymph nodes especially in cases with larger cervical lesions. Additionally, it may be helpful in those patients in whom the access to the operative field may be partly compromised such as in patients with elevated BMI, where the identification of an enlarged lymph node may be compromised by the habitus of the patients.

Compliance with ethical standards

Conflict of interest All of the authors declare no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. IRB approval was obtained.

Informed consent Informed consent was obtained from all individual participants included in the study.

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