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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

FIGO stage IIIC endometrial cancer identification among patients with complex atypical hyperplasia, grade 1 and 2 endometrioid endometrial cancer: laparoscopic indocyanine green sentinel lymph node mapping versus frozen section of the uterus, why get around the problem?

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Abstract
Purpose To compare two surgical strategies used to identify lymph node metastases in patients with preoperative diagnosis of complex atypical hyperplasia (CAH), grade 1 and 2 endometrial cancer (EC).
Methods Data on patients with preoperative diagnosis of CAH, grade 1 and 2 EC undergoing laparoscopic indocyanine green (ICG) sentinel lymph node (SLN) mapping followed by frozen section of the uterus were collected. When risk factors were identified at frozen section, patients were subjected to a systematic lymphadenectomy. False negative (FN) rates, negative predictive values (NPV), positive predictive values (PPV) and correlation with stage IIIC EC were calculated for the systematic lymphadenectomy based on frozen section of the uterus and for the SLN mapping.
Results Six (9.5%) out of 63 patients had lymph nodal metastases. Based on frozen section of the uterus, 22 (34.9%) and 15 (22.2%) patients underwent a pelvic and a pelvic and paraaortic lymphadenectomy, respectively. Five patients with stage IIIC disease were identified with a FN rate of 16.7% and a NPV and PPV of 97.6 and 27.3%, respectively. Overall and bilateral detection rates of ICG SLN mapping were 100 and 97.6%, respectively; no FN were recorded. The identification of patients with stage IIIC disease with ICG SLN mapping showed a NPV and PPV of 100%. Correlation between indication to lymphadenectomy and stage IIIC disease was poor ($\kappa = 0.244$) when based on frozen section of the uterus and excellent ($\kappa = 1$) when based on SLN mapping.
Conclusions ICG SLN mapping reduces the number of unnecessary systematic lymphadenectomies and the risk of underdiagnosing patients with metastatic lymph nodes.

Keywords Endometrial cancer · Sentinel lymph node mapping · Indocyanine green · Laparoscopy · Frozen section · Surgical staging

Introduction

Surgical staging in endometrial cancer (EC) is controversial. EC is a relatively indolent disease characterized by a low risk of extrauterine spread to the lymph nodes, and it is therefore believed that performing a pelvic (PLND) and paraaortic lymphadenectomy (PALND) in every patient is harmful rather than helpful. For approximately three decades, it has been a widespread clinical practice to select the patients who may benefit the most form a lymphadenectomy based on the identification of intrauterine risk factor at frozen section (Kumar et al. 2012; Papadia et al. 2009; Morotti et al. 2012; Laufer et al. 2013).

Depending on the definition of high risk factors, a different percentage of patients will be surgically staged. In order to reduce the risk of missing patients with metastatic lymph nodes, a high number of patients have to be surgically staged. This will inevitably lead to a high number of patients who undergo a full lymphadenectomy without having metastatic lymph nodal disease. This is particularly relevant in presumed low-risk EC patients who have a relatively low incidence of lymph nodal metastases. Mariani et al. reported no lymph node metastases or recurrences

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in patients with endometrioid EC, FIGO grade 1 or 2 and myometrial invasion limited to the inner half (Mariani et al. 2000). These data have subsequently been validated (Dowdy et al. 2012; Todo et al. 2013; Laufer et al. 2013). In these patients, a lymphadenectomy only adds morbidity (Mariani et al. 2000). However, based on these criteria, the majority of the patients with EC will undergo a full surgical staging. The price that has to be paid to reduce this number of unnecessary lymphadenectomies is a higher false negative rate (Sala et al. 2014).

Although the adoption of a minimally invasive approach has significantly improved the surgical outcome of these patients, a relevant number of patients will still present with long-term complications as the result of a systematic lymphadenectomy (Papadia et al. 2004; Walker et al. 2009). In the recent past, clinical practice seems to shift from this method to the integration of a sentinel lymph node (SLN) mapping in EC patients (Abu-Rustum 2013; Kitchener 2011; Ditto et al. 2015). It's application remains somewhat controversial since the National Comprehensive Cancer Network (NCCN) guidelines recognize it as an appropriate procedure in selected cases, whereas the ESGO-ESMO-ESTRO guidelines still consider it an experimental procedure (NCCN guidelines 2015; Colombo et al. 2016). The main advantage of the SLN mapping is that it provides pathologic lymph node information on virtually every patient. We and others have previously demonstrated that SLN mapping with indocyanine green (ICG) in conjunction with a near-infrared (NIR) fluorescence imaging system seems to stand out over a SLN mapping performed with conventional dyes and is characterized by low false negative rates when adopted in EC (Jewell et al. 2014; Imboden et al. 2015; Papadia et al. 2016a, b; Ruscito et al. 2016; Tanner et al. 2015; Buda et al. 2015, 2016a, b).

As compared to a risk stratification model based on intraoperative uterine frozen section analysis, SLN mapping may simultaneously reduce the number of patients undergoing an unnecessary full retroperitoneal lymphadenectomy and the risk of missing patients with metastatic lymph nodes.

Aim of the study is to compare the efficacy in identifying lymph node metastases in patients with resumed low-risk EC based on two surgical strategies: (1) systematic lymphadenectomy tailored on frozen section analysis of the uterus and (2) laparoscopic ICG SLN mapping.

Materials and methods

A retrospective analysis on all patients with grade 1 and grade 2 EC or complex atypical hyperplasia (CAH) on preoperative endometrial biopsy undergoing laparoscopic ICG SLN mapping followed by hysterectomy (TLH) with bilateral salpingo-oophorectomy (BSO) and pelvic (PLND) and/or paraaortic lymphadenectomy (PALND) based on uterine risk factors evaluated at intraoperative frozen section at our Institution between December 2012 and July 2016 was performed. The data on SLN mapping were prospectively collected in an electronic database. The study was approved by the ethical committee. Informed consent was signed by all the patients prior to surgery. Data on a subset of the patients in this cohort were previously published with a different aim (Papadia et al. 2016a, b).

Routine preoperative work-up included a transvaginal sonogram and a chest X-ray. At our Institution, patients with CAH, grade 1 and 2 EC on preoperative endometrial biopsy undergo a laparoscopic ICG SLN biopsy followed by TLH/BSO. After removal, a frozen section analysis of the uterus is performed to assess for uterine risk factors, and based on these and on clinical judgment, a completion of the surgical staging is performed. Patients with grade 3 EC or deeply invasive lesions undergo a pelvic and paraaortic lymphadenectomy (PPALND); patients with grade 1 EC confined to the inner half of the myometrium undergo a SLN biopsy only. In the other cases, a PLND is performed. Only those patients for whom both the ICG SLN mapping and the frozen section analysis of the uterus were performed represent the cohort of our study.

ICG SLN mapping was performed as previously described (Papadia et al. 2016a). Briefly, after having performed a diagnostic laparoscopy to assess for evidence of extrauterine disease, a cervical injection of approximately 8 ml ICG is performed in the four quadrants of the cervix, superficially and approximately 1 cm deep in the stroma. One vial of 25 mg ICG powder (Pulsion®) is diluted with 5 ml of sterile water. The NIR signal is identified and followed to the SLN which is excised. All the independently draining SLNs and clinically suspicious non SLNs (NSLNs) are removed. A frozen section evaluation of the SLN is not routinely performed.

Clinical–pathologic characteristics of the patients are evaluated using the basic descriptive statistics. For the evaluation of the method that triages patients to a systematic lymphadenectomy based on frozen section, as true positives (TP) were considered those patients in whom a lymphadenectomy was indicated based on frozen section and who presented metastatic disease to the lymph nodes. As false negatives (FN) were considered those patients in whom a lymphadenectomy was not indicated based on frozen section and who presented metastatic disease to the SLNs. As true negatives (TN) were defined those patients in whom, based on frozen section analysis of the uterus a lymphadenectomy was not performed, and who had negative SLNs. As false positives (FP) were considered those patients who

underwent a lymphadenectomy based on frozen section of the uterus and who did not have metastatic lymph nodes. Negative predictive value (NPV) and positive predictive value (PPV) for this method were calculated.

For the SLN mapping, overall and bilateral detection rates, NPV, PPV and FN rate of the SLN mapping were calculated. The false positive rate was defined as zero. The overall detection rate was calculated by dividing the number of procedures in which at least 1 SLN was identified by the total number of procedures performed. The bilateral detection rate was calculated by dividing the number of procedures in which at least 1 SLN was identified on each side of the pelvis by the total number of procedures performed. As TP SLN was defined a positive SLN identified at final pathological analysis (either at H&E staining or at immunohistochemistry), independent of regional lymph node status. As FN SLN mapping was defined a bilateral negative SLN in combination with a metastatic NSLN.

The κ statistics was used to measure the agreement between indication to lymphadenectomy based on frozen section analysis of the uterus and lymph nodal metastasis. Then, the κ statistics was used to measure the agreement between SLN metastasis and lymph nodal metastasis. The correlation coefficient κ measures the strength and direction of a linear relationship between two variables on a scatterplot. κ result should be interpreted as follows: values <0 as indicating no agreement, 0.01–0.20 as none to slight (very mild concordance), 0.21–0.40 as fair (mild concordance), 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1.00 as almost perfect agreement.

Statistical analyses were performed using the R software (version 3.1.0). All p values were two-sided. p values <0.05 were considered statistically significant. Data analysis were performed with GraphPad version 5 for Mac (GraphPad Software, San Diego CA).

Results

During the study period, 116 patients with EC or CAH underwent a laparoscopic ICG SLN mapping at our institution. Out of this cohort, 63 patients with CAH or grade 1 or 2 EC at preoperative diagnosis underwent both SLN mapping and frozen section analysis of the uterus to assess for uterine risk factors. In the other cases a frozen section of the uterus was not performed secondary to preoperative diagnosis of poorly differentiated EC, intraoperative diagnosis of extrauterine disease or poor performance status of the patient. Data on the SLN mapping on part of this cohort of patients have already been published elsewhere with a different aim (Papadia et al. 2016a, b).

Table 1 Patients' characteristics ($N = 63\%$)

Median age (range)	62 (38–83)
Median BMI (range)	28 (18.8–47)
Preoperative diagnosis	
Complex atypical hyperplasia	2 (3.2)
Endometrial cancer	61 (96.8)
Grading	
NA	2 (3.2)
G1	23 (36.5)
G2	38 (60.3)
Frozen section analysis	
No tumor	10 (15.9)
Complex atypical hyperplasia	1 (1.6)
Endometrial cancer	52 (82.5)
Grading	
NA	0 (3.2)
G1	21 (33.3)
G2	28 (44.4)
G3	2 (3.2)
FIGO stage at frozen section	
IA	38 (60.3)
IB	12 (19)
II	2 (3.2)
Permanent section analysis	
Complex atypical hyperplasia	1 (1.6)
Endometrial cancer	62 (98.4)
Grading	
NA	1 (1.6)
G1	28 (44.4)
G2	32 (50.8)
G3	2 (3.2)
FIGO stage IA	43 (68.3)
FIGO stage IB	11 (17.5)
FIGO stage II	2 (3.2)
FIGO stage IIIC1	3 (4.8)
FIGO stage IIIC2	3 (4.8)

NA: not applicable

Clinical–pathologic characteristics of the patients are presented in Table 1. Briefly, median age of the patients was 62 years, median BMI was 28 kg/m^2. Preoperative diagnosis showed CAH, grade 1 and 2 EC in 2, 23 and 38 patients, respectively. Six (9.5%) patients presented with metastatic lymph nodes. In five cases, these were macrometastasis and in one case micrometastasis. Metastatic lymph nodes were located in the pelvis in every case, additionally; three (4.8%) patients also had metastatic paraaortal lymph nodes. Lymph nodal data are presented in Table 2.

After frozen section, 23 (36.5%) and 14 (22.2%) patients underwent a PLND and a PPALND, respectively.

Table 2 Surgical data on the two proposed strategies

	N (%)
Pelvic lymph node dissection	22 (34.9)
Median number pelvic lymph nodes	21 (2–60)
Paraaortic lymph node dissection	14 (22.2)
Median number paraaortic lymph nodes	13 (1–56)
Median number SLNs	3 (1–11)
Overall detection rate	63 (100)
Bilateral detection rate	59 (93.7)
Patients with positive pelvic lymph nodes	6
Patients with positive paraaortic lymph nodes	3 (4.8)
Type of metastasis to the SLNs	
Micrometastasis	1
Macrometastasis	5

In 5 (80%) of the 6 patients with metastatic lymph nodes, a PLND or a PPALND was performed based on intrauterine risk factors identified at frozen section analysis of the uterus. In one case, frozen section of the uterus failed to identify a small clear cell carcinoma that had already metastasized to the lymph nodes. After the identification of metastatic disease to one SLN at permanent section, the patient underwent a completion PPALND that revealed 23 additional metastatic paraaortic lymph nodes. The false negative rate of the frozen section in identifying metastatic lymph nodes was 16.7% with a NPV and a PPV of 97.6 and 27.3%, respectively. Based on intrauterine risk factors identified at frozen section, 6 patients have to be staged to identify one with lymph node metastases. Additionally, if surgical staging had been performed based only on intrauterine risk factors 16.7% of the patients with lymph node metastasis would have been missed. Correlation between indication to lymph node dissection at frozen section and metastatic disease to the lymph nodes was mild ($\kappa = 0.244$).

For the SLN mapping, overall and bilateral detection rates were 100 and 93.7%, respectively. SLNs were positive in 6 patients. In this cohort of patients, the FN rate of the SLN mapping was 0%, with a NPV and a PPV of 100% in both cases. Correlation between metastatic SLNs and metastatic disease to the lymph nodes was excellent ($\kappa = 1$). The performance of the two surgical methods is presented in Table 3.

Discussion

Since its definition in 1988, surgical staging with a PPALND in EC has been controversial and a matter of debate (Creasman et al. 1987). Currently, various surgical approaches with different complexity and radicality can be adopted when managing an early stage EC: (1) TLH and BSO; (2) TLH and BSO with a SLN mapping; (3) TLH, BSO, frozen section of the uterus to triage for PLND and/or PPALND in selected, high risk cases; (4) TLH, BSO, PPALND in every case. Intuitively, the more radical the operation, the greater the pathological information that can help determine the need and tailor the type and amount of adjuvant treatment, the less radical the operation, the lesser the morbidity.

In our series of selected cases with a preoperative diagnosis of CAH, grade 1 and 2 EC, the incidence of lymph nodal metastases was 9.5%. This percentage may seem unexpectedly high. This may in part be explained by the fact that the vast majority of the preoperative endometrial biopsies were performed with a Pipelle device which may be less accurate than a biopsy performed during a hysteroscopy or via D&C. On the other hand, Creasman et al. in their seminal GOG surgical–pathologic trial reported a lymph nodal metastases rate ranging from 3 to 9% for patients with grade 1 and lesions (Creasman et al. 1987). Similarly, the occurrence of an EC with metastatic lymph nodal disease in patients with a preoperative diagnosis of CAH has been widely described before (Trimble et al. 2006; Morotti et al. 2014).

If we had treated our patients with a TLH/BSO, we would have understaged 10% of the patients. Omitting a lymphadenectomy does not only make the identification of stage IIIC disease patients impossible, but it also increases the risk of receiving potentially unnecessary adjuvant treatment. Although the need for an adjuvant treatment is at time determined based on uterine risk factors, it has been reported that the likelihood of recommending further therapy in women with all stages and grades was significantly less if a complete staging procedure including lymph nodal dissection had been performed (Simpkins et al. 2013; Naumann et al. 1999). On the other hand, if a full surgical staging had been performed on every patient, we would have performed potentially unnecessary lymphadenectomies in

Table 3 Performance of the two surgical strategies in identifying low-risk endometrial cancer patients with lymph nodal metastases

	FN rate (%)	PPV (%)	NPV (%)	Correlation κ
Triage to LND based on frozen section of the uterus	17.7 (1/6)	27.3	97.6	0.244
SLN mapping	0	100	100	1

LND lymph node dissection, *SLN* sentinel lymph node, *FN* false negative, *PPV* positive predictive value, *NPV* negative predictive value

90% of the patients, subjecting them to the surgical morbidity of this procedure.

In this series, the NPV of the model that triages to a lymphadenectomy patient with uterine risk factors at intraoperative frozen section analysis had a NPV of 97.6% and a false negative rate of 16.7%. These data suggest that a significant amount of patients with metastatic lymph nodal disease will be missed. Furthermore, it can be argued that the patient presenting with the micrometastasis might have been missed had the ultrastaging not been performed as this is typically performed only on the SLNs. Additionally, the PPV of 27.3% of this model is low leading to a significant number of lymphadenectomies that are performed in patients with negative lymph nodes.

Further open issues regarding the adoption of this model include the fact that the frozen section analysis is mainly used to determine if a lesion is malignant or benign but has intrinsic limitations in giving more detailed information on the architectural and cytological characteristics of the lesion. Time constraints, the fast freezing of the specimen that produces artifacts and the need to leave the tissue for the permanent section may lead to erroneous interpretation and inadequate sampling. These explain the variable results reported in literature on the accuracy of the intraoperative identification of uterine risk factors (1–5). In general, even in this setting, the lower the bar for the indication to a full surgical staging is set, the lower the risk of omitting a lymphadenectomy in a patient with lymph nodal metastases and the higher the number of lymphadenectomies performed. Still, in the patients who are intraoperatively identified to be at low risk, no information on the lymph node status will be gathered.

As opposed to this model, the adoption of the a SLN mapping, in these selected series, allowed to identify all the patients with metastatic lymph nodes with a false negative rate, NPV and PPV of 0, 100 and 100%, respectively. This model simultaneously reduces the risk of omitting a lymphadenectomy in patients with metastatic lymph nodal disease and the risk of performing an unnecessary lymphadenectomy suggesting that SLN mapping may perform better in identifying EC patients with metastatic lymph nodal disease than a model that triages patients to a full surgical staging based on uterine risk factor identification at frozen section.

These results are synthesized in the results of the correlation that was calculated between need for a full lymphadenectomy and the identification of lymph nodal metastasis which is mild with a κ of 0.244 for the model based on uterine risk factor evaluation at frozen section and excellent for the SLN mapping model.

Recently, Sinno et al. proposed an operative strategy that omits universal frozen section and restricts its use to cases with failed SLN mapping (Sinno et al. 2016). In their series of low-risk EC patients, the adoption of this strategy would have reduced the number of systematic lymphadenectomies from 36.8 to 9.8% of the patients.

SLN mapping in EC is rapidly been adopted worldwide as a form of surgical staging. However, several questions remain unanswered: (1) should the dye be injected cervically or intratumorally via hysteroscopy as described by some authors (Ditto et al. 2015), (2) should a lymphadenectomy be performed in patients with positive SLNs, (3) should a frozen section of the SLNs be performed to identify patients who might benefit from a full lymphadenectomy.

Although the lymphatic drainage of the uterus follows three different ways, the majority of the authors agree in recommending a cervical dye injection which seems to be easy and reliable (NCCN guidelines 2015; Rossi et al. 2013). There are no data to suggest that patients with metastatic lymph nodes benefit from a full lymphadenectomy. At our institution, we believe that the surgical removal of metastatic lymph nodes may improve outcome. However, patients with stage IIIC EC are typically recommended adjuvant therapy that includes radiotherapy and or chemotherapy and there is no evidence that the combination of surgery and adjuvant treatment does improve outcome. At some institutions if a patient is diagnosed with metastatic disease to the lymph nodes, she is recommended adjuvant treatment without a completion of the lymphadenectomy.

Depending on the oncologic strategy adopted, the identification of metastatic disease to the lymph nodes at final pathology may lead to a second surgery to complete PPALND. The adoption of the frozen section analysis of the SLN may help reduce the occurrence of this clinical setting. At our institution, we do not routinely perform a frozen section analysis of the SLNs in EC patients. It is argued that the performance of the frozen section analysis of the SLNs is characterized by high FN rates and may interfere with a proper ultrastaging at permanent section. Recently, a retrospective cohort study on cervical cancer patients showed that frozen section examination of the SLNs had a sensitivity and specificity of 86.7 and 100%, respectively (Gubbala et al. 2016). In this setting, offering a frozen section analysis of the SLNs in EC patients may help to reduce the number of patients who will have to undergo a two-step procedure.

The limitations of this study include its retrospective nature and the limited sample size. On the other hand, the prospective data collection on SLN mapping, the vast experience in laparoscopic ICG SLN mapping at our institution and the strict selection of patients who have been included in our cohort represent the strength of this study.

In conclusion, laparoscopic ICG SLN mapping performs very well in identifying EC patients with metastatic lymph nodes and in reducing the number of unnecessary

lymphadenectomies and is an efficient alternative to the selection of patients to be surgically staged based on intrauterine risk factor identification at frozen section.

Compliance with ethical standards

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

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.

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

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