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REVIEW – CLINICAL ONCOLOGY

Surgical staging in endometrial cancer

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Abstract
In several malignancies, it has been demonstrated that the lymph nodal status is the most important pathologic factor affecting prognosis and giving the indication to further adjuvant treatment. The surgical assessment of the lymph nodal status in endometrial cancer is debated since 30 years. Recently, the sentinel lymph node mapping is rapidly gaining clinical acceptance in endometrial cancer. The adoption of Indocyanine Green as a safe and user friendly tracer for sentinel lymph node mapping increased the speed to which this procedure is getting applied in clinical practice. As a consequence of this rapid growth, several fundamental questions have been raised and are still debatable. In this manuscript, we discuss the importance of a known pathological lymph nodal status, the technique of the sentinel lymph node mapping with the reported false negative rates and detection rates according to the different tracers adopted, and the clinical scenarios in which a sentinel lymph node mapping could be employed.

Keywords Endometrial cancer · Laparoscopy · Sentinel lymph node mapping · Indocyanine green · Fluorescence

Introduction

In the management of endometrial cancer patients, the staging lymphadenectomy has been controversial since 30 years (Fig. 1). In 1988, following the results of a seminal Gynecologic Oncology Group (GOG) study, the GOG#33 trial, FIGO transitioned from a clinical to a surgical staging (Creasman et al. 1987; FIGO Stages 1989). This surgical-pathological study conducted on 621 patients with Stage I carcinoma of the endometrium showed that an appreciable number of patients with clinical early stage cancer present with disease outside of the uterus.

Despite this change in FIGO staging, a low adherence to the staging procedure among physicians was recorded (Maggino et al. 1995, 1998). The relatively indolent biological behavior of endometrial cancer, the surgical complexity of a pelvic and para-aortic lymphadenectomy and the typical clinical characteristics (obese, affected by multiple comorbidities including diabetes and hypertension) of these patients can probably explain the low adherence to a full surgical staging with a pelvic and para-aortic lymphadenectomy. In an attempt to reduce the risk of lymphoceles and lymphatic complications occurring after a systematic lymphadenectomy, the prophylactic use of fibrin sealant patches has been investigated with promising results (Gasparri et al. 2017).

Different methods have been proposed to identify the patients that benefit the most from a full surgical staging. The most widespread method to triage patients to a full lymphadenectomy is based on intrauterine risk factor identification at frozen section analysis of the uterus. However, this methodology does not seem to be accurate and reproducible since different series have led to different results (Kumar et al. 2012; Sala et al. 2014; Papadia et al. 2009; Morotti et al. 2012; Laufer et al. 2013). This approach is limited in that a large number of patients with negative lymph nodes have to undergo a full lymphadenectomy to keep the false negative rate of the triage low. Furthermore, in patients not undergoing a full lymphadenectomy, no pathologic information on lymph node status is provided.

In 2008 and 2009, two large randomized prospective clinical trials were published (Panici et al. 2008; ASTEC et al.

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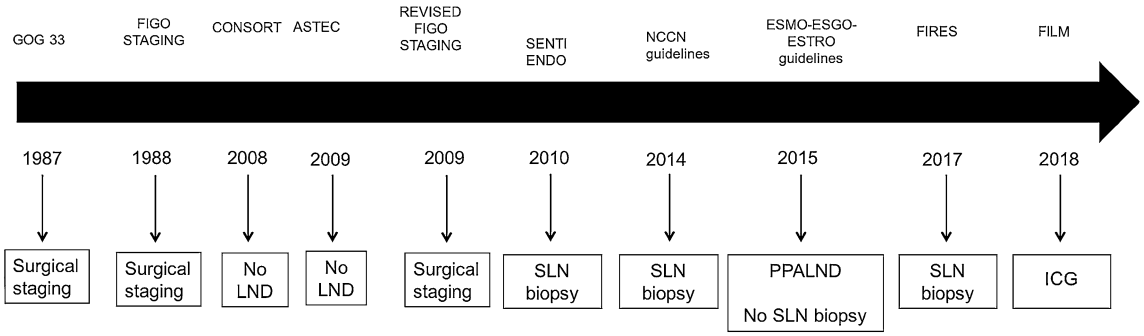

Fig. 1 Landmark studies and steps in the surgical staging of endometrial cancer. *LND* lymphadenectomy, *SNL* sentinel lymph node, *PPALND* pelvic and paraaortic lymphadenectomy, *ICG* indocyanine green

2009). These two large prospective trials proved that the surgical staging does not provide any survival benefit. However, the lymphadenectomy is still recommended in selected cases of endometrial cancer by several guidelines (NCCN Guidelines 2018; Colombo et al. 2016; Creasman 2009). Although a systematic lymphadenectomy does not have a direct effect on survival, it provides important pathologic information that define prognosis and can help determine the most appropriate adjuvant treatment. Although at times adjuvant therapy is already indicated based on uterine risk factors, the postoperative management of high-intermediate and high risk endometrial cancer patients changes, according to the ESMO–ESGO–ESTRO consensus conference, based on the availability of a pathologically proven negative lymph nodal status (Colombo et al. 2016, Simpkins et al. 2013). It has been proven that patients with pathologically negative lymph nodes are subjected less often to adjuvant radiotherapy as compared to patients in whom the lymph nodal status is unknown (Bogani et al. 2014; Sharma et al. 2011). Interestingly, in a large multicenter retrospective study on patients with high-intermediate and high risk endometrial cancer patients, the worst survival was recorded for those patients in whom the lymph nodal status was unknown. Both patients with negative and positive lymph nodal status had better overall survival than those in whom the lymph nodal status was unknown (Ouldamer et al. 2017).

In this setting, if proven reliable and safe, the sentinel lymph node mapping may represent a balanced option. In this manuscript, we will review and discuss the current literature on sentinel lymph node mapping in endometrial cancer.

Surgical technique

Sentinel lymph node mapping was first described in penile cancer by Cabanas (Cabanas 1977). Since then it has become standard of care in the surgical management of melanomas, breast and vulvar cancer where it has replaced a systematic lymphadenectomy for staging purposes (Morton et al. 2006; Veronesi et al. 2003; Van der Zee et al. 2008). Through the identification of the first lymph node draining the tumor, the sentinel lymph node mapping allows a concomitant improvement of the detection of metastatic disease and a reduction in surgical morbidity.

In endometrial cancer, the sentinel lymph node mapping is performed via intracervical injection of the tracer in the majority of the centers. The cervix is injected submucosally and deep in the stroma. Depending on the tracer used the timing of the injection is different. The major characteristics of the tracers most commonly employed for sentinel lymph node mapping are summarized in Table 1.

Table 1 Characteristics of the tracers most commonly adopted for SLN mapping in endometrial cancer

	Tc-99m	Blue dyes	ICG
Timing of injection	Prior to surgery. It requires lymphoscintigraphy/SPECT	In the operating room	In the operating room
Duration of the signal	It depends on the injected dose and on the time of decay. Usually it lasts approximately 24 h	Approximately 30 min	Persistent
Severe allergic reactions	1–6/100,000	2%	0.05%
Other toxicity	Radioactivity	Discoloration of skin Skin necrosis Transient interference with pulse oximetry readings	–

Tracers

Technetium-99 radiocolloid (Tc-99m) is the most commonly used medical radioisotope in diagnostic procedures (Segrè and Seaborg 1938; Richards et al. 1982). Its short half-life of 6 h is ideal for diagnostic procedures such as the sentinel lymph node mapping. After injection, the radioactive signal is identified through the audiometric signal emitted from a gamma probe. Prior to surgery, a lymphoscintigraphy or a SPECT is performed to detect the number and location of the sentinel lymph nodes. Tc-99m is usually injected the day prior to surgery in a radio-protected setting. This allows enough time to acquire the preoperative radiologic imaging. The relatively short decay time of this tracer can jeopardize the effectiveness of the planned sentinel lymph node mapping should the scheduled procedure be delayed.

Various blue dyes including methylene blue, isosulfan blue and patent blue have been used as tracers for sentinel lymph node mapping. Following interstitial administration, they travel rapidly through the lymphatic channels to the sentinel lymph nodes that become blue. This methodology is therefore simple and user friendly. However, the visual signal only lasts approximately 20 min and the amount of time available to detect the sentinel lymph nodes is limited. Furthermore, it exacerbates allergic reactions in up to 2% of the cases (Papadia et al. 2017a).

Indocyanine green (ICG) is a dye that shows diffuse fluorescence when excited by near-infrared light (NIR) (700–900 nm). ICG is FDA approved for intravenous administration since over 50 years and has been widely employed in ophthalmology for retinal fluorangiographies. In the past few years, it has been adopted as tracer for sentinel lymph node mapping. Its ease of use has been crucial in accelerating the development and clinical acceptance of the sentinel lymph node mapping in gynecological oncology. ICG is considered to be a safe tracer, it should, however, be avoided in patients with iodine allergies as it contains iodine. Allergic reactions to ICG have been described even in the absence of iodine allergy (Papadia et al. 2017b). ICG has been injected both intracervically and peritumorally under hysteroscopic guidance (Papadia et al. 2017c; Ditto et al. 2015).

Sentinel lymph node pathological analysis

The sentinel lymph nodes are processed according to an ultrastaging protocol. After an initial examination by routine Hematoxylin and Eosin (H&E) staining, an ultrastaging is performed on metastases free sentinel lymph nodes. This is performed by cutting two adjacent 5-µm sections at each of two levels, 50–200-µm apart, from each paraffin block lacking metastatic carcinoma. At each level, one slide is stained with H&E and with immunohistochemistry (IHC) using anticytokeratin antibodies. According to the definition of the American Joint Committee on Cancer, metastatic disease to the sentinel lymph nodes is then classified as follows (Greene et al. 2003):

- macrometastases if the identified tumor deposits are larger than 2.0 mm;
- micrometastases if the identified tumor deposits are larger than 0.2 mm and up to 2 mm;
- isolated tumor cells if the identified tumor deposits do not exceed 0.2 mm in size.

As a result of this more thorough pathological examination of the sentinel lymph nodes, the incidence of patients diagnosed with lymph nodal metastases has increased. Consequently, a larger amount of patients have been subjected to adjuvant therapy although the real biological significance of small volume nodal disease still has to be clarified.

Validation data

In medicine, the false negative rate is defined as the rate of occurrence of negative test results in subjects known to have the disease for which an individual is being tested. When applied to the sentinel lymph node mapping, the false negative rate represents the amount of patients with non-affected sentinel lymph nodes who do actually harbor metastatic disease to other lymph nodes. This is probably the most critical characteristic of a sentinel lymph node mapping. For the procedure to be safe, the false negative rate has to be low to avoid under staging patients.

In our retrospective series of fully staged endometrial cancer patients, we recorded a false negative rate of 8.3% for the ICG sentinel lymph node mapping (Papadia et al. 2016a). This result correlates well with those reported by other series (Barlin et al. 2012). To improve the false negative rate and to take into account that the uterus is a midline structure that requires bilateral lymph nodal sampling, a sentinel lymph node mapping algorithm (Memorial Sloan Kettering Cancer Center algorithm) has been proposed and should be adopted whenever performing a sentinel lymph node mapping instead of a full lymphadenectomy (NCCN Guidelines 2018; Barlin et al. 2012). This algorithm recommends to remove every lymph node that appears clinically suspicious in addition to the sentinel lymph nodes and to perform a side-specific pelvic lymphadenectomy when the detection of a sentinel lymph node fails on one side; a

para-aortic lymphadenectomy should be performed on physicians' discretion (Barlin et al. 2012).

Since their publication, their algorithm has been incorporated in the majority of the centers. In 2017, the largest prospective validation trial on sentinel lymph node mapping in endometrial cancer, the FIRES trial, was published (Rossi et al. 2017). Three hundred and forty patients with endometrial cancer underwent a robotic ICG sentinel lymph node mapping followed by a systematic pelvic lymphadenectomy in every case and by a para-aortic lymphadenectomy in 58% of the cases. In this trial, the sentinel lymph node mapping algorithm as described by Barlin was applied and a false negative rate of 3% was recorded confirming the data derived by the previously published retrospective analysis (Barlin et al. 2012; Rossi et al. 2017).

Detection rates

Another aspect that defines a successful sentinel lymph node mapping is a high detection rate. As previously mentioned, to have a complete and successful mapping, sentinel lymph nodes need to be detected on both sides of the pelvis. This will reduce the number of side-specific lymphadenectomies performed when the sentinel lymph node mapping algorithm is applied (Barlin et al. 2012).

Probably, the single most important variable affecting bilateral detection rate is the type of tracer used. The most commonly used traces for sentinel lymph node mapping in endometrial cancer patients include Tc-99m, blue dyes and ICG, alone or in combination. In our first series, in which all the patients underwent an ICG laparoscopic sentinel lymph node mapping, the overall and bilateral detection rates were 96% and 88%, respectively (Papadia et al. 2016a). We had previously reported a comparison of detection rates with different tracers in cervical cancer patients (Imboden et al. 2015). This model is very similar to that adopted in endometrial cancer since the tracer is injected intracervically in both cases. In our experience, the bilateral detection rate was higher after intracervical injection of ICG as compared to a combination of Tc-99 and blue dye. These results were later confirmed by several other series (Papadia et al. 2017d; Buda et al. 2016, 2018a; Di Martino et al. 2017; Holloway et al. 2012).

Among these, our multicenter experience is the largest, so far, confirming the higher bilateral detection rates seen when ICG is adopted as compared to a combination of blue dye and Tc-99m (84.1% versus 73.5%; $p = 0.007$) (Papadia et al. 2017d). Similar data have been recorded in the robotic setting, where mappings performed with ICG have consistently higher bilateral detection rates as compared to those performed with other tracers (Holloway et al. 2012, 2017; Sinno et al. 2014; Tanner et al. 2015; How et al. 2015; Eriksson et al. 2017). Overall, these results suggest that NIR-ICG sentinel lymph node mapping has higher bilateral detection rates as compared to those recorded with the combination of Tc-99m and blue dye and have higher overall and bilateral detection rates as compared to blue dye alone. Recently, a prospective randomized trial confirmed that ICG yields a significantly higher number of sentinel lymph nodes and a significantly higher bilateral detection rate in patients with endometrial and cervical cancer (Frumovitz et al. 2018). Table 2 summarizes the results on bilateral detection rates reported by the most relevant studies. Finally, three meta-analyses have confirmed these results (Ruscito et al. 2016; Bodurtha et al. 2017; Lin et al. 2017).

Sentinel lymph nodes, echelon nodes and the optimal number of retrieved sentinel lymph nodes

Although the sentinel lymph node is defined as the first lymph node draining the tumor, most of the times, multiple sentinel lymph nodes are identified. These can be sentinel lymph nodes draining independent lymphatic pathways or echelon lymph nodes situated downstream of a real sentinel lymph node. Differentiating between these two entities is

Table 2 Comparison of bilateral detection rates based on tracer used for SLN mapping in endometrial cancer

Authors	No. of patients			*p* value
		Tc-99m + blue dye	*ICG*	
Papadia et al. (2017d)	342	75.3%	84.1%	0.03
		Blue dye	*Blue dye + ICG*	
Holloway et al. (2012)	35	77%	97%	0.02
Holloway et al. (2017)	200	40%	83.9%	< 0.001
		Blue dye	*ICG*	
Sinno et al. (2014)	71	42.4%	78.9%	0.02
Eriksson et al. (2016)	471	54%	85%	< 0.001
Frumovitz et al. (2018)*	180	81%	32%	< 0.0001

*This study involved both endometrial and cervical cancer patients

not always easy. Although echelon lymph nodes are often removed during a sentinel lymph node mapping, the removal of additional lymph nodes other than the sentinel ones may, at least in part, reduce the benefit of the sentinel lymph node mapping. On the other hand, removing all the lymph nodes draining the tracer, regardless if they are sentinel or echelon lymph nodes, may reduce the false negative rate thus increasing the safety of the mapping.

Interestingly, in our experience, the false negative rate did not differ significantly based on sentinel lymph node count (Papadia et al. 2016b). The only two patients with false negative sentinel lymph nodes had isolated para-aortic lymph nodal metastases with negative pelvic sentinel and non-sentinel lymph nodes. These results are concordant with the risk of isolated para-aortic lymph nodal metastasis reported by Mariani et al. in fully staged high-risk endometrial cancer patients (Kumar et al. 2014). We determined that the only factor associated with the number of removed sentinel lymph nodes at multivariate analysis was the expertise of the surgeon (Papadia et al. 2016b). Surgeons who had performed more than 20 laparoscopic ICG sentinel lymph node mappings were those who retrieved a smaller number of sentinel lymph nodes without increasing the false negative rate of the procedure (Papadia et al. 2016b). With greater specific experience in ICG sentinel lymph node mapping, surgeons may be more confident in their ability to correctly detect and differentiate between sentinel and echelon lymph nodes. These data are in agreement with those of McMasters et al., which identified 20 cases as the cases needed to be performed in breast cancer surgery to be proficient in sentinel lymph node mapping (McMasters et al. 2001). ICG drains quickly through the lymphatic vessels to the sentinel lymph nodes. However, as compared to blue dyes, the signal of which disappears after 30 min, the fluorescent signal of ICG persists in the lymph nodes for a long time. These characteristics allow for a "pressure-free" interval of time during which the sentinel lymph nodes can be located and most likely is the reason why detection rates are higher when this tracer is adopted. On the other hand, however, the same characteristic may be responsible for the removal of a higher number of fluorescent lymph nodes (sentinel and echelon lymph nodes) that have stained during the surgery, especially in those cases in which a significant amount of time elapses between tracer injection and retroperitoneal exploration.

In breast cancer, Martin et al. suggest to remove every sentinel lymph node that has a count per minute of 10% of the hottest sentinel lymph node removed, when Tc-99m is adopted as tracer (Martin et al. 2000). Other authors suggested that excising more than four sentinel lymph nodes does not significantly improve the accuracy of the mapping when a combination of Tc-99m and blue dyes is used (Zakaria et al. 2007; Goyal et al. 2006; McCarter et al. 2001; Woznick et al. 2006; Vaidya et al. 2005; Chagpar et al. 2007). Wilke et al. demonstrated that the incidence of complications (such as seromas and wound infections) increases with the removal of five or more sentinel lymph nodes (Wilke et al. 2006).

Influence of the dose of ICG on sentinel lymph node mapping

Since ICG is not FDA approved for interstitial injection, the doses of tracer adopted for sentinel lymph node mapping have been empirically set. There is some evidence that low concentrations and large volumes of ICG seem to perform better (Xiong et al. 2014). Persson et al. have suggested that a larger volume of intracervically injected ICG does not increase the bilateral detection rate of the sentinel lymph node mapping but increases the bilateral detection rate of the two major lymphatic pathways (upper and lower paracervical lymphatic pathway) in each hemipelvis (Persson et al. 2017). We tried to establish if different volumes and concentrations of ICG had an influence on the bilateral detection rate and on the number of identified sentinel lymph nodes in a multicenter retrospective cohort study (Papadia et al. 2018a). At multivariate analysis, we were unable to identify variables affecting the bilateral detection rate. It has to be pointed out, however, that we did not differentiate the lymphatic pathways as Persson et al. did. On the contrary, in our analysis of 181 patients, dose and volume of injected ICG had an impact on the number of removed sentinel lymph nodes. Significantly more sentinel lymph nodes were removed after injecting a larger dose and volume of ICG. This is the first study analyzing the impact of the dose of ICG injected on sentinel lymph node mapping in uterine cancer.

Sentinel lymph node mapping in low-risk endometrial cancer

It could be argued that a pathological lymph nodal assessment is unnecessary in low-risk endometrial cancer patients. However, the definition of low-risk endometrial cancer occurs postoperatively after permanent pathological examination of the uterine specimen and patient considered to be at low risk preoperatively or intraoperatively at frozen section analysis of the uterus may end up having a high risk endometrial carcinoma with a risk of lymph nodal metastases that can reach 40% (Ouldamer et al. 2017). Lack of pathological information of lymph nodal status in these patients will result in a more generous indication to an adjuvant radiotherapy that may otherwise have been safely omitted and potentially to a survival disadvantage (Colombo et al. 2016; Bogani et al. 2014; Sharma et al. 2011).

In our series of patients with a preoperative diagnosis of complex atypical hyperplasia or grade 1 or 2 endometrial cancer, we show that a strategy based on sentinel lymph node mapping is more accurate in detecting patients with lymph nodal metastases as compared to a strategy based on triage to a systematic lymphadenectomy based on intraoperative frozen section analysis of the uterus (Papadia et al. 2017e). All the patients with lymph nodal metastases were correctly identified with the strategy based on sentinel lymph node mapping, whereas one out of six patients with nodal metastases was missed with the strategy that relies on a full lymphadenectomy when uterine risk factors are identified at frozen section. The latter strategy has a false negative rate of 16.7% at the cost of performing a systematic lymphadenectomy in approximately one-third of patients considered to be at low risk preoperatively (Fig. 2). The sentinel lymph node mapping had an excellent correlation with final FIGO stage IIIC, whereas the system adopting the frozen section as a triage to a systemic lymphadenectomy had only a mild correlation with final FIGO stage IIIC.

Accordingly, Sinno et al. recommend performing a sentinel lymph node mapping in patients who are preoperatively considered to be at low risk (Sinno et al. 2016). A frozen section of the uterus is performed only in those cases in which the sentinel lymph node mapping fails and a bilateral or side specific pelvic lymphadenectomy is performed only in case the frozen section analysis of the uterus defines the endometrial cancer as a high risk one (Barlin et al. 2012; Sinno et al. 2016).

In patients with these pathological characteristics, a large multicenter retrospective comparison among the patients treated at Mayo Clinic and at the Memorial Sloan Kettering Cancer Center was performed (Eriksson et al. 2016). Patients were subjected to a systematic lymphadenectomy at the first institution and to a sentinel lymph node mapping at the second, and an excellent and comparable 3-year survival was reported for both groups, suggesting that the sentinel lymph node mapping does not jeopardize survival in this setting.

Sentinel lymph node mapping in high-risk endometrial cancer

Recently, several series have assessed the validity of the sentinel lymph node mapping in high risk endometrial cancer patients such as grade 3 endometrioid endometrial carcinomas, uterine papillary serous carcinomas, clear cell carcinomas and carcinosarcomas. As opposed to patients with low-risk endometrial cancer, patients presenting with these characteristics (high-grade and high-risk histology) have a high incidence of lymph nodal metastases. Consequently, there is concern that the results recorded in the low-risk setting may not be easily translated in this setting, as the reported high negative predictive value reported may be the result of high proportion of true negatives in a population with a low prevalence of metastatic disease to the lymph nodes.

In our series of high-risk endometrial cancer patients, we recorded a prevalence of lymph node metastases of 23.8% (Papadia et al. 2018b). Additionally, in the majority of the cases, the lymph node metastases were not isolated but several lymph nodes were affected and in the majority of the cases the metastases were macrometastases. In our series, we recorded a single patient with a false negative mapping, accounting for a negative predictive value of 97.1% and a false negative rate of 10% (Papadia et al. 2018b). This specific case had an isolated para-aortic lymph node metastasis. Interestingly, during the surgery, the affected para-aortic lymph node appeared clinically suspicious and was sent for frozen section pathology that confirmed the presence of disease. It could be argued that given its intraoperative detection, the false negative rate would drop to 0% for the sentinel lymph node mapping algorithm (Barlin et al. 2012). Given these results, we strongly believe that a thorough exploration

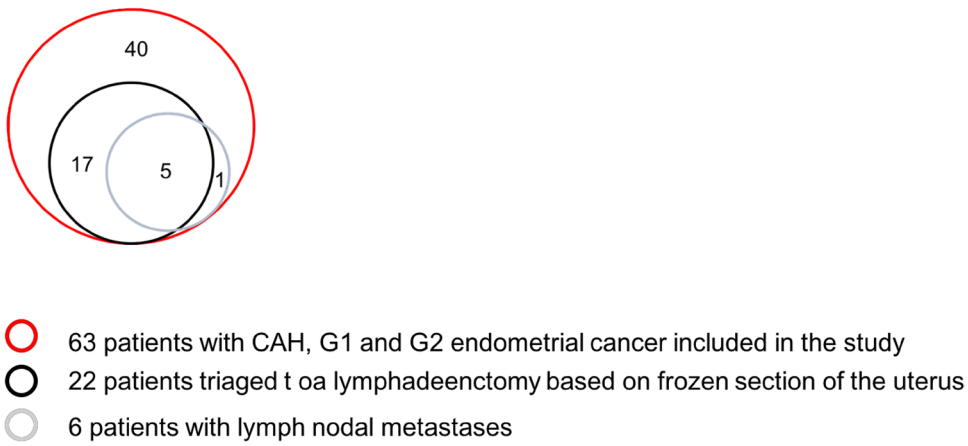

Fig. 2 Figural depicted performance of frozen section of the uterus versus sentinel node lymph node mapping in identifying low-risk endometrial cancer patients with lymph nodal metastases

of the pelvic and para-aortic area is mandatory in this subset of patients when a sentinel lymph node mapping is adopted as opposed to a systematic lymphadenectomy. This is crucial as, often, the para-aortic area is explored with less accuracy than the pelvic region.

With the exception of one retrospective multicenter French series that reports a false negative rate of 20% in this setting, all the other series and validation studies report reasonably low false negative rates and are roughly comparable to those reported in the low-risk setting (Holloway et al. 2017; Ehrisman et al. 2016; Naoura et al. 2015; Soliman et al. 2017; Ballester et al. 2011; Touhami et al. 2017). In the FIRES trial, in which 100 patients presented with high-risk histologies and in which the sentinel lymph node mapping algorithm was adopted, the reported false negative rate is 5% (Rossi et al. 2017).

Finally, considering the oncologic outcome in these patients, we did not record any differences in patients with high-intermediate risk endometrial cancer undergoing sentinel lymph node mapping algorithm or a sentinel lymph node mapping followed by a systematic lymphadenectomy at 5 years (79.2% versus 81.6%; $p = 0.831$) (Buda et al. 2018b). Of note, that stage and histotype were predictors of recurrence-free survival at multivariate analysis, whereas adjuvant therapy was not. These data suggest that the completion lymphadenectomy may be omitted even in this subset of patients without jeopardizing oncological outcome given that a sentinel lymph node mapping is adopted.

Conclusions

In 2014, the National Comprehensive Cancer Network (NCCN) guidelines first recognized the sentinel lymph node mapping as an acceptable alternative to a systematic lymphadenectomy in selected cases of endometrial cancer. Since then, the NCCN guidelines have extended the indication to a sentinel lymph node mapping algorithm even in high-risk endometrial cancer patients (NCCN Guidelines 2018). On the contrary the ESMO–ESGO–ESTRO guidelines, recommend the adoption of the sentinel lymph node mapping in endometrial cancer patients only within controlled trials. These consensus guidelines have been last updated in 2015 and we are confident that, given the additional scientific evidence produced since then, a new revision of these guidelines may lead to a different recommendation, more in line with those produced by the NCCN. As opposed to a dual "everything or nothing at all" system in which a lymphadenectomy is either omitted or performed in a radical manner, we believe that the sentinel lymph node mapping represents a solomonic solution that allows to obtain relevant pathologic information on the status of the lymph nodes without subjecting the patients to an extensive surgical procedure and its related morbidity.

Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest.

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