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ORIGINAL ARTICLE

The accuracy and clinical impact of intraoperative frozen section in determining the extent of surgical intervention in patients with early stage endometrial cancer

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ABSTRACT

The aim of this study was to compare intraoperative frozen section (FS) with the final pathology (FP), and determine its clinical impact in clinically apparent early stage endometrial cancer (EC) at the American University of Beirut Medical Center (AUBMC). Data for patients 18 years or older, with clinically apparent early stage, grade 1 or 2, endometrioid EC, who underwent hysterectomy ± lymph node dissection (LND) at AUBMC between January 1st 1996 and June 30th 2016 were retrospectively reviewed. 70 patients were included. The overall concordance between FS and FP was 92.3% for histological subtype, 77% for tumour grade, 82% for Myometrial invasion (MI) and 100% for tumour size. At a median follow up of 30 months, 8 recurrences (11.4%) were noted, with a 5-year PFS and OS of 76 and 84% respectively, with a trend towards lower recurrence and improved survival in patients who underwent FS or LND.

IMPACT STATEMENT

- **What is already known on this subject?** Hysterectomy and bilateral salpingo-oophorectomy is the standard surgery for stage I endometrial cancer (EC). Intraoperative frozen section (FS) facilitates the decision on performing lymph node dissection (LND). However, its accuracy and clinical impact have been questioned.
- **What do the results of this study add?** Our objective is to compare FS with the final pathology (FP), and determine its clinical impact in clinically apparent early stage EC at the American University of Beirut Medical Center (AUBMC). There is a lack of standardisation regarding FS use and reporting at AUBMC.
- **What are the implications of these findings for clinical practice and/or further research?** The strong correlation between FS and FP can serve as a tool to guide decision to perform LND in patients with apparent early stage disease, where use of sentinel LN biopsy technique is not available.

KEYWORDS
Endometrial cancer; lymph node dissection; frozen section; final pathology

Introduction

Endometrial cancer is the most common gynaecologic malignancy in developed countries and ranks second after cervical cancer in developing countries (Bray et al. 2018). The majority of women with endometrial cancer present at an early stage and almost 70% have disease confined to the uterus at the time of diagnosis (Creasman et al. 2006). Total extrafascial hysterectomy with bilateral salpingo-oophorectomy with pelvic and paraaortic lymph node dissection (LND) is considered the standard staging procedure for endometrial carcinoma (Boronow et al. 1984). Although this is still considered the standard of staging for endometrial carcinoma, it has now been largely replaced by sentinel lymph node mapping to enable tailored treatment (Abu-Rustum 2014; Holloway et al. 2017; Sozzi et al. 2020).

Pelvic and paraaortic lymph node (LN) involvement is closely related to tumour grade and depth of myometrial invasion (MI). In early stage disease (stage I), low grade tumours (grades 1 and 2) invading less than 50% of the myometrium are associated with less than 3 and 1% involvement of pelvic and paraaortic LN respectively. However, pelvic and paraaortic node metastases are reported in 11 and 6% respectively in tumours with more than 50% MI (Creasman et al. 1987).

Many studies have failed to demonstrate any benefit from LND in low grade stage I disease with no improvement in progression free survival (PFS) or overall survival (OS)

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(Benedetti Panici et al. 2008; Kitchener et al. 2009). In addition to being costly, lymphadenectomy is associated with serious complications such as bleeding, injury to adjacent structures, as well as lymphedema and lymphocyst formation (Abu Rustum et al. 2006; Querleu et al. 2006; Clements et al. 2013). Therefore, many gynaecologic oncologists refrain from performing lymphadenectomy for 'low risk' endometrial cancer patients.

Tumour size is also considered an independent predictor of LN involvement, and tumours $\leq$2 cm in size were associated with LN involvement in less than 4% of cases (Schink et al. 1987).

In 2000, Mariani et al. from Mayo Clinic conducted a retrospective study on early disease and were able to define a subset of endometrial cancers with favourable characteristics which included three low risk features: 1) tumour size $\leq$2 cm; 2) grade 1 or 2; and 3) depth of MI $\leq$50%. Patients who fulfilled these criteria, known later as the 'Mayo criteria', in addition to absence of intraoperative evidence of macroscopic disease could safely undergo hysterectomy alone.

Intraoperative frozen section (FS) provides information on such uterine factors facilitating the decision on performing LND. However, the accuracy of FS has been questioned. Several studies compared the FS to the final pathology (FP), and found its concordance with the paraffin section to be between 80 and 90% for the tumour grade, and above 90% for the MI (Quinlivan et al. 2001; Stephan et al. 2014; Acikalin et al. 2015). Lymphovascular space invasion (LVSI) is another factor that predicts LN involvement, especially in patients with early stage endometrial cancer (Guntupalli et al. 2014); however, LVSI is difficult to assess on intraoperative FS. In recent findings, low lymphovascular space invasion score was associated with low risk of LVSI and thus may avoid unnecessary lymphadenectomy when sentinel lymph node is not detected (Capozzi et al. 2020).

The objective of our study is to compare the intraoperative FS with the FP in clinically apparent early stage endometrial cancer patients, with regard to tumour grade, depth of MI, tumour size, and histologic type at the American University of Beirut Medical Center (AUBMC).

Materials and methods

Patients

Patients 18 years or older, with clinically apparent early stage (clinical stage I), grade 1 or 2, endometrioid endometrial adenocarcinoma or suspected apparent early stage endometrial cancer, who underwent surgery at the AUBMC, between January 1st 1996 and June 30th 2016, were included. Preoperative endometrial sampling results which were performed outside our institution are routinely reviewed at our pathology department prior to surgery.

Patients with a preoperative endometrial biopsy showing grade 3 endometrioid, serous or clear cell histology, carcinosarcoma or sarcoma, patients with evidence of extra-uterine disease or enlarged LNs on clinical examination or preoperative imaging, and those with intraoperative evidence of extra uterine disease were excluded. Patients who had undergone previous pelvic radiation were also excluded.

The primary surgical procedure consisted of total hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic LND through an open or via a minimally invasive (laparoscopic or robotic) approach. When the uterus is removed, some surgeons would elect to open the uterus and visually assess the size of any visible tumour as well as the apparent MI, before it is submitted to the pathology department for either FS or final assessment.

Objectives

At the AUBMC, the lack of a standardised reporting method on FS pathology results causes a significant burden on the gynaecologic oncologist. Utilisation of intraoperative FS and comparing it to the FP would enable the surgeon to take the proper intraoperative decision with respect to lymphadenectomy.

Our primary outcome was to compare the FS and FP results with respect to histologic type, tumour grade, size and MI.

Secondary outcomes were:

- To determine the basis of decision for intraoperative LND in patients with apparent early stage endometrial cancer.
- To determine the impact of FS on the intraoperative decision to perform LND.
- To determine the importance of FS in predicting recurrence and its impact on survival.
- To determine the impact of omitting LND on recurrence and survival, reoperation rate and need for adjuvant radiation.

Study design

After obtaining approval from the American University of Beirut's Institutional Review Board, we conducted an observational retrospective cohort study recruiting patients from January 1st 1996 and June 30th 2016. The medical records were reviewed manually between 1996–2009 and through the electronic health care system after 2009.

Statistical analysis

Patients' characteristics as well as operative and postoperative parameters were described on the whole sample and described and compared by FS and lymphadenectomy status. Categorical variables were described using frequency and percentage whereas continuous variables were described using mean and standard deviation. The chi square test and the independent t-test were used to compare categorical and continuous variables respectively between the subgroups. Outcomes of adjuvant treatment, recurrence and death were described and compared by FS status and by LN status. 5-years survival analyses were further performed using the Kaplan Meier methods where the log-rank test was used to

Table 1. Patients' characteristics.

Patient characteristics ($N = 70$)	
Average age of diagnosis, years (SD)	61.15 (10.2)
Menopausal at the time of diagnosis	60 (85.7%)
Average BMI, Kg (SD)	32.07 (5.35)
Symptom at presentation	
Post-menopausal bleeding	57 (81.4%)
Abnormal uterine bleeding	10 (14.3%)
Others	3 (4.3%)
Use of hormonal treatment	3 (4.3%)
Personal medical history	
Diabetes	6 (8.6%)
Coronary artery disease	2 (2.8%)
Hypertension	30 (42.8%)
Dyslipidemia	12 (17.4%)
Breast CA	1 (1.4%)
Family Hx (first degree relative with cancer)	
Endometrial CA	1 (1.4%)
Breast CA	3 (4.3%)
Ovarian CA	2 (2.8%)
Other	4 (5.7%)
Preoperative grade ($N = 60$)	
Grade 1	40 (66.7%)
Grade 2	20 (33.3%)

Table 2. Operative and post-operative findings.

Operative and postoperative parameters	
Type of operation, *N* (%)	
Open	60 (85.7%)
Conventional Laparoscopy	9 (13%)
Robotic	1 (1.4%)
Lymph node dissection, *N* (%)	
Pelvic	43 (61.4%)
Paraaortic	2 (2.8%)
Basis of intraop LN dissection, *N* (%)	
Physician preference	31 (72%)
Intra-op enlarged LN	6 (14%)
Frozen Section	3 (7%)
Pre-op imaging	3 (7%)
Patients with positive LN	0
Re-operations, *N* (%)	1 (1.4%)
Reason for reoperation	
Staging	1
Average operative time (minutes)	173.5
Average hospital stay (days)	4.4
Post op complications, *N* (%)	3 (4.3%)
Post-op stage, *N* (%)	
Stage I	64 (91.5%)
Higher	6 (8.5%)

compare survival outcomes by groups. The IBM® SPSS® software 2009, was used to conduct our statistical analysis.

Results

Between January 1996 and June 2016, a total of 245 patients were managed for endometrial cancer at our institution. 70 patients met the inclusion criteria. Intraoperative FS was performed in 16 patients (22.8%) only.

Patients' characteristics

The characteristics of the 70 patients included for analysis are shown in Table 1, with no difference between those who underwent FS and those who did not. The mean age was 61.15 ± 10.2 years, and 60 (85.7%) were menopausal at the time of diagnosis. Average BMI was 32.07 ± 5.35. 60 (85.7%) patients had available pre-operative histologic reports showing grade 1 or grade 2 endometrioid endometrial cancer.

Operative and postoperative findings

Operative and postoperative findings were similar between those who underwent FS and those who did not, and are shown in Table 2.

Overall, 43 (61.4%) patients had pelvic lymphadenectomy alone, and two patients (2.8%) had pelvic and para-aortic lymphadenectomy at the time of the initial surgery.

Decision to perform LND was based on physician preference in 31 patients (72%), intraoperative findings of enlarged suspicious LNs in 6 (14%) and on preoperative imaging in 3 (7%). Only 3 patients (7%) underwent LND based on FS results, showing a size >2 cm and/or myometrial invasion (MI) $>50\%$.

Among the 16 patients who underwent intraoperative FS, 5 had at least one high-risk feature (size >2 cm and/or MI $>50\%$). Three underwent pelvic LND based on these results, one had lymphadenectomy at the beginning of the surgery based on physician preference, and one did not undergo any LN assessment.

The only patient who underwent reoperation to complete staging for the presence of a clear cell component on final pathology, had no FS done at initial surgery.

None of the patients who underwent lymphadenectomy had any LN involvement on final pathology.

Six patients (8.5%) were upstaged after the surgery due to cervical, vaginal, parametrial or adnexal involvement.

There were three postoperative complications requiring intervention or hospitalisation. One patient had small bowel obstruction one week after the surgery and underwent laparotomy with small bowel resection, two other patients had severe wound infections requiring IV antibiotics. All three patients had pelvic LND, the first one also underwent paraaortic LND.

Accuracy of frozen section results

Table 3 summarises the results of FS and FP regarding histologic type, grade, MI and size. Histologic type and grade were reported in 13 out of the 16 submitted FS specimen (81.2%) with remaining 3 having no gross residual tumour. MI was reported in 11 (68.7%), and size in 4 cases (25%) only. LVSI was never reported on FS. The overall concordance rate was 92.3% for histologic type, 77% for tumour grade, 82% for MI and 100% for tumour size.

Outcomes

Fourteen patients were lost to follow up after the surgery.

24 patients (34%) received adjuvant therapy (brachytherapy in 4, brachytherapy + EBRT in 19 and chemotherapy in 7 patients). There was no difference in the need for adjuvant

treatment whether FS and LND were performed or not (Supplementary Tables 1 and 2).

At a median follow up of 30 months, 8 patients recurred (11.4%). Three of these were local vaginal recurrences; three had diffuse disease involving multiple locations including one in the retroperitoneum. Two recurrences were confined to the retroperitoneum and these occurred in patients who did not undergo any LN evaluation. When stratified by FS and LND status, there were more recurrences in those who did not undergo FS (13% vs 6.7%) and in those who did not undergo LND (19.2% vs 7%), however this did not reach statistical significance for both (Supplementary Tables 1 and 2). There were no deaths due to disease among patients who underwent LND compared to 2 in those who did not, while the majority of the patients were alive with no evidence of disease (64.3%), and there was no difference according to FS and LND status (Supplementary Tables 1 and 2).

5-year PFS and OS were 76% (95% CI, 60% to 92%) and 84% (95% CI, 70% to 98%), respectively (Supplementary figure 1). 5-year PFS was similar between those who had FS 86% (95% CI, 61%-100%) and those who did not 76% (95%CI, 60%-92%), $p = 0.890$ (Supplementary figure 2). When stratified by LND status, there was a trend towards improved PFS among patients who underwent LND compared to those who did not, although this did not reach statistical significance, with 5-year PFS 88% (95% CI, 76%-100%) vs 58% (95% CI, 29%-87%), $p = 0.103$. In addition, among patients who did not have FS, there was a non-significant trend towards improved PFS for those who had LND compared to those who did not, 87% (95% CI, 73%-100%) vs 52% (95% CI, 17%-87%), $p = 0.103$. However, in both analyses, we can see that Kaplan-Meier curves separate starting 39 months and continue to diverge, with a relatively stable survival for those who had LND and declining survival for those who did not (Figures 1(A) and 2(A)).

When considering patients who did not have LND, PFS was higher in those who had FS compared to those who did not, 80% (95% CI, 45%-100%) vs 52% (95% CI, 17%-87%), without reaching statistical significance (p 0.643), but again the Kaplan-Meier curves start progressively diverging starting about 48 months (Figure 3).

For OS analysis, there was again a non-significant trend towards improved survival among patients who underwent LND compared to those who did not, with 5-year OS of 95% (95% CI, 85%-100%) vs 70% (95% CI, 43%-97%), p 0.149 (Figure 1(B)). However, among patients who did not undergo FS, OS was significantly better in those who underwent LND (5-year OS =100%, 100%-100%) versus those who did not (5-year OS =71%, 95% CI, 38%-100%), p 0.045 (Figure 2(B)).

Table 3. Accuracy of frozen section.

	Final Pathology			
Histologic Type	Endometrioid	Non-Endometrioid	Total	Accuracy
Frozen section				
Endometrioid	12	1	13	**92.3%**
Non-endometrioid	0	0	0	(12/13)
Total	12	1	13	

	Final Pathology			
Myometrial Invasion	≤50%	>50%	Total	Accuracy
Frozen section				
≤50%	7	2	9	**81.8%**
>505	0	2	2	(9/11)
Total	7	4	11	

	Final Pathology				
Grade	Grade 1	Grade 2	Grade3	Total	Accuracy
Frozen section					
Grade 1	6	2	1	9	**76.9%**
Grade 2	0	4	0	4	(10/13)
Total	6	6	1	13	

	Final Pathology			
Size	≤2 cm	>2 cm	Total	Accuracy
Frozen section				
≤2 cm	0	0	0	**100%**
>2 cm	0	4	4	(4/4)
Total	0	4	4	

Discussion

The role of lymphadenectomy in endometrial cancer is controversial. While LN status has a prognostic value and allows guiding adjuvant therapy, two randomised trials (Benedetti Panici et al. 2008; Kitchener et al. 2009) failed to show any

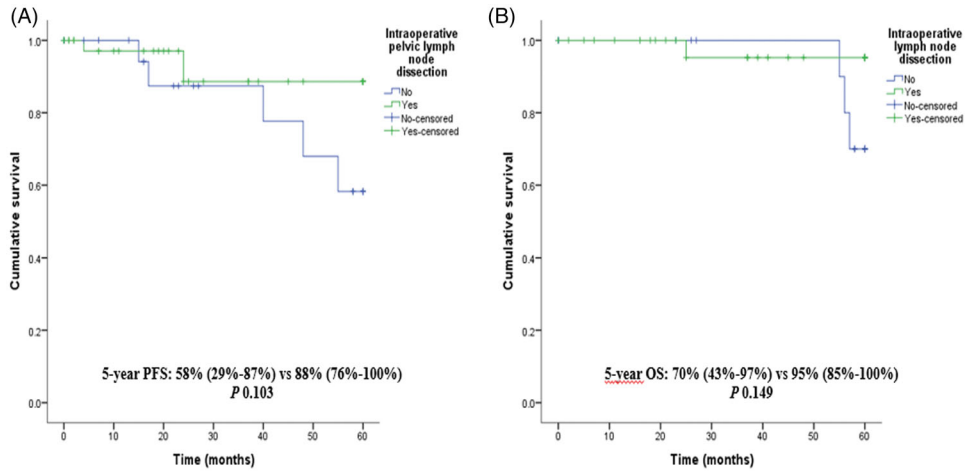

Figure 1. (A) Progression-free survival and (B) Overall survival by lymph node dissection status.

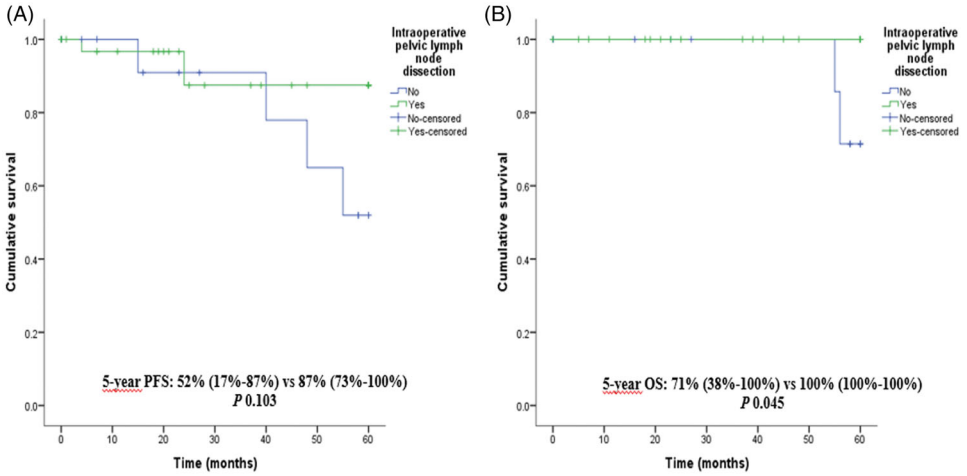

Figure 2. (A) Progression-free survival and (B) Overall survival by lymph node dissection status among patients who did not have frozen section.

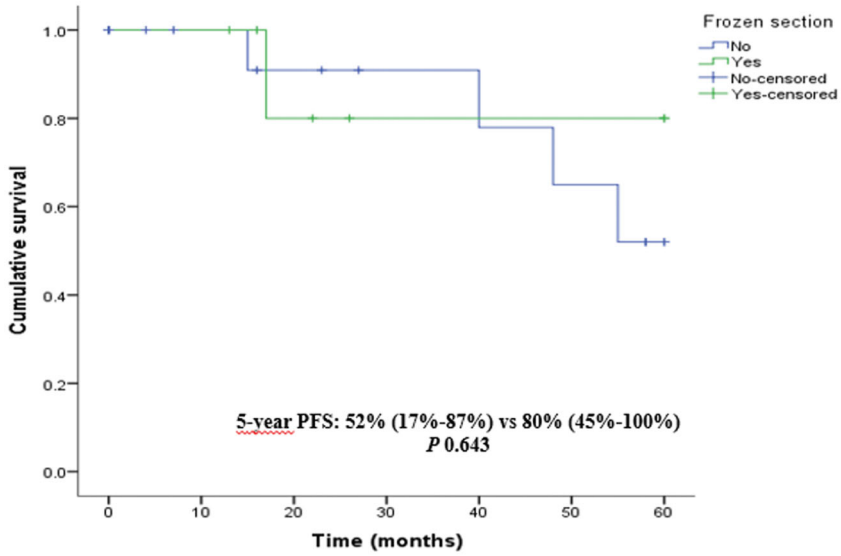

Figure 3. Progression-free survival by frozen section status among patients who did not have lymph node dissection.

survival benefit from systematic lymphadenectomy. In addition, this procedure is not without morbidity and the risk of lymph node metastasis in patients with low-risk features (grade 1 or 2, size <2 cm, MI <50%) is substantially low (Mariani et al. 2000; Chi et al. 2008; Kumar et al. 2012). So far, gynaecologic oncologists have adopted one of three approaches: no lymphadenectomy, systematic comprehensive lymphadenectomy or selective lymphadenectomy based on the above-mentioned criteria. FS can help guide the intraoperative decision and avoid the need for a second surgery and unnecessary adjuvant radiation in unstaged patients. To achieve this purpose, it is essential that FS results accurately reflect the final pathological findings.

Data is conflicting regarding the accuracy and reliability of intraoperative FS findings in apparent early stage endometrial cancer, with some studies considering it a useful tool for guiding intraoperative decision-making (Shim et al. 1992; Kumar et al. 2012; Sala et al. 2014; Wang et al. 2016), whereas others suggested poor correlation with FP (Case et al. 2006; Kitchener et al. 2009).

At our institution, we collected data on 70 patients with apparent early stage endometrial cancer over 20 years. Similar to previous retrospective studies, physician preference was the reason in 72% of the 43 patients undergoing complete pelvic lymphadenectomy in at attempt at avoiding a potential subsequent surgery and possibly improving survival outcomes (Onda et al. 1997; Cragun et al. 2005), although this was not confirmed in two recent randomised trials which concluded that systemic lymphadenectomy significantly improved surgical staging but had no impact on PFS or OS (Benedetti Panici et al. 2008; Kitchener et al. 2009). With three gynaecologic oncologists performing the vast majority of such cases, and considering their expertise and professional vision, the majority of lymphadenectomy was performed based on this factor and in lieu with the highlighted studies above. Although sentinel node biopsy has been introduced as an alternative to lymph node dissection for lymph node status, a negative sentinel node is accepted to confirm pN0, and with the high sensitivity of sentinel lymph node status for lymph node staging in patients with early-stage

endometrial carcinoma, and with the pathologic ability of detecting small metastases which could be missed by standard evaluation, sentinel lymph node biopsy only is associated with substantially lower risk of post-operative morbidity. This is highlighted clearly in the ESGO/ESTRO/ESP guidelines (Concin et al. 2021). However, this is not always possible to perform, especially in institutions which still lack the ability to perform sentinel lymph node mapping technique in early endometrial carcinoma. Thus, in this setting, lymphadenectomy, considering its higher rates of patient's morbidity, is still used and considered the primary care factor for staging endometrial carcinoma.

Of the 16 patients who underwent FS, 5 had at least one high risk feature according to Mayo criteria, based on which 3 patients underwent complete lymphadenectomy. FS is not widely used at our institution as most physicians prefer performing systematic lymphadenectomy and some of them choose to open the specimen themselves in the operating room and visually assess for the depth of MI or the size of the tumour, despite the fact that intraoperative FS was shown to have a better diagnostic performance as compared to intraoperative gross examination for evaluation of MI (Alcazar et al. 2016). This in accordance with a survey of SGO physicians, where only about one third routinely use FS to determine the extent of surgical staging (Soliman et al. 2010).

The overall concordance between the FS and the FP was 92.3% for histological subtype, 77% for tumour grade, 82% for MI and 100% for tumour size. These findings are in agreement with previous studies demonstrating concordance rates of up to 98.7% for histological subtype, 58% to 98% for grade, and 54% to 96.6% for MI (Frumovitz et al. 2004; Turan et al. 2013). Stephan et al. (2014) reported an accuracy of 97.5% for histological subtype, 88% for grade, and 98.2% for MI. Kumar et al. (2012) showed a 100% concordance for tumour size, 86% for histologic type, 97% for grade and 98.9% for MI between FS and FP. This higher concordance between the FS and the FP results as compared to our study is probably due to the technical expertise and the high volume of the FS practice. It should be noted that intraoperative tumour size was described in only 25% of the cases, which is similar to other studies where this parameter was not consistently reported despite being an independent prognostic factor and associated with the risk of extrauterine disease and LN metastases (Khalifa et al. 2017; Strickland et al. 2018).

None of the patients who underwent lymphadenectomy had any LN involvement; this is in contrast with the available literature, where the risk of LN metastasis in apparent early stage endometrial cancer ranges between 5 and 18% (Quinlivan et al. 2001; Cragun et al. 2005; Chi et al. 2008). This can be explained by the limited number of patients overall, and the fact that about a third of the patients did not undergo LN evaluation. Only 6 patients out of 70 (8.5%) were upstaged due to involvement of the stroma of the cervix or adnexal metastases on FP.

The 5-year OS of 84% in our study population with early stage endometrial cancer is consistent with the literature ranging between 75 and 85% (Creutzberg et al. 2000; Sant et al. 2003; Papanikolaou et al. 2006). When stratified by LND status, there was a trend towards lower recurrence and improved PFS and OS at 5 years in favour of performing LND, although this did not reach statistical significance (19% vs 7%, 88% vs 58%, and 95% vs 70% respectively). In addition, among patients who did not have FS, there was a significant improvement in OS and a non-significant trend towards improved PFS for those who had LND compared to those who did not, (100 vs. 71% and 87 vs. 52% respectively). Moreover, among patients who did not undergo LND, PFS was in favour of performing FS. In both analyses, the Kaplan-Meier curves separate starting 39 to 48 months and continue to diverge, with a relatively stable survival for those who had LND and declining survival for those who did not. These findings suggest either a therapeutic benefit of LND although this was contested in the ASTEC and Benedetti-Panici randomised trials (Benedetti Panici et al. 2008; Kitchener et al. 2009), or a retroperitoneal disease that was initially overlooked in those patients in whom neither FS nor lymphadenectomy was performed.

The limitations of our study are inherent to its retrospective nature. In addition, the small sample size and the high percentage of patients who were lost to follow up probably affected the results and might have contributed to many of the non-significant statistical findings. Our centre is a tertiary care referral centre, and thus the limited number of patients with apparent early stage disease in our sample is probably due to the fact that most of these cases are operated by general gynaecologists, with preferential referral of patients with high grade histology and advanced disease.

In conclusion, this study shows a lack of guidelines regarding performing FS and reporting the results at our centre thus calling for better collaboration between pathologists and gynaecologic oncologists. The strong correlation between FS and FP enables the surgeon to intraoperatively decide on performing lymphadenectomy in patients with apparent early stage disease. It is with our total understanding and acknowledgement that sentinel lymph node biopsy is nowadays widely accepted even as a replacement of frozen section analysis as well as lymphadenectomy (Holloway et al. 2017; Concin et al. 2021), to lower the impact of morbidity and probably the unnecessary total lymphadenectomy in certain cases when it comes to early stage endometrial cancer, yet until this newly introduced technique becomes available at our institution.

Disclosure statement

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