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ORIGINAL ARTICLE

Preoperative assessment in endometrial cancer. Is triage for lymphadenectomy possible?

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Summary

Purpose: *We sought to examine whether a preoperative assessment with usual means, available in most hospitals (preoperative histology, pelvic MRI, serum CA-125) can confidently exclude from a full staging surgical procedure low-risk endometrial carcinoma (EC) patients according to ESMO-ESTRO-ESGO criteria (stage I endometrioid EC, grade 1 or 2, myometrial invasion <50% and negative lymphovascular space invasion).*

Methods: *We retrospectively identified all EC patients that underwent total hysterectomy with bilateral salpingo-oophorectomy (TH-BSO) plus lymph node dissection (LND) as primary treatment for endometrioid tumors from January, 2000 to December, 2010. Extensive review was made through patients' medical records. Having set the final pathology report as the "gold standard", we applied the ESMO-ESGO-ESTRO criteria to classify patients into risk categories (low-risk and non-low risk). We also evaluated preoperative risk status using combined data from preoperative biopsy, pelvic MRI and serum CA-125. We classified patients according to the following criteria: grade 1 or 2 on preoperative histology, myometrial invasion on MRI <50% and serum CA-125 <35 IU/ml, in low risk group. Receiver operating characteristic (ROC) curves were plotted. The area under the ROC curve (AUC), quantifying the overall ability of the combined preoperative assessment to discriminate between patients at low and non-low risk, was the primary outcome of our study. False negative rate was the secondary outcome.*

Results: *Preoperative data on histology, MRI and CA-125 levels were available for 292 patients. The sensitivity and specificity of combined preoperative assessment to discriminate between low- and non-low risk EC patients according to ESMO-ESTRO-ESGO criteria were 96.1% and 73.6% respectively. AUC of the corresponding ROC curve was 0.849. False negative rate was 3.8% (9/235). Among the 9 patients falsely classified as low-risk, one patient had nodal metastasis (1/9, 11.1%) after full staging.*

Conclusion: *A selective LND strategy for EC patients based on preoperative assessment is possible and would probably be cost-effective, while not jeopardizing patients' survival or patient quality of life (QoL).*

Key words: *CA-125, endometrial cancer, ESMO-ESGO-ESTRO criteria, low-risk endometrial cancer, pelvic lymph node dissection, pelvic MRI*

Introduction

EC is one of the most common gynecologic cancers in Europe and North America and the sixth most frequent malignancy worldwide with approximately 300,000 new cases annually. After the age of 75 years the cumulative risk of EC has been estimated as high as 1.6% [1]. EC for the most part is diagnosed at an early stage with disease confined to the uterus (80% in stage I), presenting 5-year survival rates of over 95%. Yet, much lower 5-year survival rates are seen with regional spread or distant disease [2].

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An extrafascial TH-BSO has been the standard surgical treatment for EC. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) declared EC a surgically staged disease [3]. Since then, FIGO mandates lymph node dissection of the pelvic (PLND) and para-aortal (PALND) areas through staging system [4], yet controversy still exists regarding their indications, anatomic extent and therapeutic value in the management of EC [2]. Indeed, two randomized trials [5,6], which examined the effect of PLND in clinically early stage EC patients and found no survival benefit, seriously questioned the therapeutic value of lymphadenectomy *per se*. Current FIGO guidelines advocate complete pelvic lymphadenectomy and resection of any enlarged para-aortic nodes for high-risk patients, while remaining ambiguous on the optimal surgical treatment of low-risk EC. As a minimum, any enlarged or suspicious lymph nodes should be removed in all patients [4]. The rationale supporting the full staging of EC patients is to identify the high-risk population with positive nodes, who would benefit from chemotherapy [7]. Moreover, patients with surgically proven low-risk features for recurrence can avoid morbidity associated with adjuvant therapy, mainly radiotherapy.

Since 1988 the percentage of patients undergoing lymph node staging has significantly increased [8]. Concurrently, stratification of EC patients into risk categories so that surgical and adjuvant treatment can be tailored on the basis of the estimated risk of recurrence has been attempted. In 2000, authors from the Mayo Clinic identified a group of patients at minimal risk for LN metastasis (grade 1 or 2 endometrioid corpus cancer with greatest surface dimension ≤2 cm, myometrial invasion ≤50%, and no intraoperative evidence of macroscopic disease), who should be treated optimally with hysterectomy only [9]. Since 1999, patients with such low-risk EC have preferably not undergone LND at the Mayo Clinic [10]. Frozen section (FS) has been the linchpin in the Mayo protocol for the surgical management of EC and was found to provide highly reliable data to guide intraoperative treatment decisions at institutions with sufficient pathologic expertise [11]. Prospectively, in patients with low-risk EC as defined by the Mayo criteria, LND was found to dramatically increase morbidity and cost of care without discernible benefits [10].

Recently a cost-effectiveness analysis of the Mayo algorithm for the surgical management of EC was published. The authors concluded that a selective LND approach based on intraoperative risk factors through FS was less cost-effective than routine LND, even when the impact of lymphedema was considered [12]. On the contrary, a selective LND strategy based on a preoperative prediction model was shown to be more cost-effective than routine LND for EC patients in the US and Korea [13]. This model, developed by the Korean Gynecologic Oncology Group (KGOG), used preoperative data from pelvic MRI and serum CA-125 levels in order to identify a low-risk group among patients with a preoperative histologic diagnosis of endometrioid-type EC [14].

In 2015 the ESMO-ESTRO-ESGO guidelines introduced a new risk classification for EC. Patients with stage I endometrioid EC, grade 1 or 2, myometrial invasion <50% and negative lymphovascular space invasion (LVSI) are at low risk of LN involvement and recurrence, thus neither LND, nor adjuvant therapy is recommended [2].

Our retrospective study was designed in order to answer the following clinically significant query: can preoperative assessment with usual means, available in most hospitals (preoperative histology, pelvic MRI, serum CA-125) confidently exclude from a full staging surgical procedure low-risk EC patients according to ESMO-ESTRO-ESGO criteria? If this is the case, a selective LND strategy based on preoperative assessment would be cost-effective, while not jeopardizing patients' survival or QoL.

Methods

We retrospectively identified all women who were treated for cancer of the uterine corpus at the Department of Obstetrics-Gynaecology of Aschaffenburg–Hospital Clinicum, of the University Würzburg in Germany from January, 2000 to December, 2010. Patients with uterine sarcomas or non-endometrioid endometrial tumors and those with endometrioid tumors who did not receive a primary surgical treatment with TH-BSO plus LND for any reason were excluded. The extent of LND performed was not used as an exclusion criterion. Multiple LN samplings or systematic PLND ± PALND had been performed according to surgeon's preference with consideration of patients' preoperative risk for nodal disease, intraoperative findings, as well as each patients' medical comorbidities. Thus, the study population consisted of EC patients that received TH-BSO plus LND as primary treatment for endometrioid tumors.

An extensive search was made through patients' medical records, followed by a detailed review of postoperative and preoperative findings. Data extracted from final pathology reports were tumor grade (three grades according to 1988 FIGO criteria), depth of myo-

metrial invasion (<50% or ≥50%), LVSI (positive or negative), number of LN retrieved and presence of LN metastasis. Surgical stage was redefined according to 2009 FIGO staging system [15]. Preoperative data that were extracted included information on histological diagnosis, pelvic MRI and serum CA-125 levels. The included patients had a preoperative diagnosis of endometrioid tumor by either endometrial biopsy or dilatation and curettage (D&C), with tumor grade determined as above. Radiologic reports from conventional pelvic MRIs (T1-weighted and T2-weighted images with intravenous injection of contrast media) taken within a month before surgery were used to extract data on myometrial invasion (<50% or ≥50%). Preoperative serum CA-125 was measured by radioimmunoassay. A uniform CA-125 cut-off level (>35 IU/ml) was selected [14,16], because most clinicians are more familiar with its use, in comparison with other cut-off values that have been proposed in bibliography. Preoperative and postoperative histological specimens were examined by attending pathologists and MRI scans were evaluated preoperatively by attending radiologists at our institution. In this study we did not conduct a central postoperative review of preoperative pathology and radiology findings, hence we may consider them to be blinded with respect to final pathology report.

Having set the final pathology report as the "gold standard" throughout our analysis, we applied the ESMO-ESGO-ESTRO criteria to classify patients into risk categories (low-risk and non-low risk). We also evaluated preoperative risk status using combined data from preoperative biopsy, pelvic MRI and serum CA-125. Patients were considered preoperatively to be at low risk when all of the following criteria were met: grade 1 or 2 on preoperative biopsy, superficial myometrial invasion on pelvic MRI <50% and low serum CA-125 <35 IU/ml, otherwise they were categorized as non-low risk. The accuracy, sensitivity and specificity of preoperative findings were evaluated for each modality separately and in combination. The area under the receiver operating characteristic (ROC) curve (AUC) quantifies the overall ability of a test to discriminate between two states, here between individuals at low and non-low risk. AUC for the combined preoperative risk evaluation of EC patients by preoperative biopsy, pelvic MRI and serum CA-125 was the primary outcome of our study. False negative rate, that is the percentage of non-low risk patients falsely classified as low-risk, was the secondary outcome. In contrast to positive and negative predictive values (PPV, NPV), which depend critically on the prevalence of the "abnormality" among the study population, both primary and secondary outcomes selected for this study are only test-dependent and allow for comparison with other studies [17].

Statistics

The agreement between preoperative and postoperative findings was assessed by the Landis and Koch kappa statistic. In order to assess the performance of preoperative tests (separately and in combination) in predicting non-low risk uterine endometrioid cancer ROC curves were plotted and the corresponding AUCs were estimated. Additionally, the association of high serum CA-125 levels with postoperative findings (tumor grade, depth of myometrial invasion and LVSI status) was evaluated by univariate logistic regression analysis. All statistical tests were two-sided and the level of statistical significance was set at 0.05. Data analysis was performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY.

Results

From January 2002 to December 2010, 475 women were treated for cancer of the uterine corpus in our institution. Some patients were excluded from the study for the following reasons: uterine sarcomas (n=24), serous carcinomas (n=30), clear cell carcinomas (n=10), not a primary surgical treatment (n=10) and a primary surgical treatment with no LND performed (n=66). 335 women fulfilled the inclusion criteria and were included in the study. The clinico-pathological characteristics and preoperative assessment of the included patients are listed in Table 1.

On final pathology report 65 patients (19.4%) were low-risk and 270 (80.6%) were intermediate to high risk (non-low risk) according to ESMO-ESTRO-ESGO criteria. 115 patients (34.3%) underwent PLND plus PALND in their initial surgery, while 220 patients (65.6%) underwent PLND only. A median number of 25 (range 2-59) PLN was retrieved and the median number of PALN retrieved was 13 (range 3-51). LN metastasis was present in 36 patients (10.7%). No metastatic LN was found in low-risk patients, thus the rate of nodal disease in non-low risk patients was 13.3%. 29 patients (8.6%) had metastatic disease involving only PLN and 5 patients (1.5%) had metastatic disease involving both PLN and PALN. Isolated PALN metastasis was seen in 2 patients (0.6%).

Preoperative histological diagnosis was available in 327 cases (97.6%). Compared with the final pathology report, preoperative diagnosis of grade had an accuracy rate of 79.5% (260/327). Kappa statistic was estimated to be 0.677. Clinically significant discordance (that is grades 1 and 2 to grade 3 and *vice versa*) was noted in 4.9% of cases (16/327) and 3% of patients (10/327) were upstaged by final pathology. The sensitivity and specificity of preoperative biopsy to discriminate between grades 1, 2 and grade 3 were 86.3% and 97.6% respectively.

Table 1. Clinicopathological characteristics and preoperative assessment of 335 patients with uterine endometrioid cancer, who underwent surgical staging with pelvic ± paraortic lymph node dissection

Clinicopathological characteristics (N = 335)	*N (%)*
Age at diagnosis, years, median (range)	65 (44-82)
BMI, median (range)	33.5 (17.1-42.2)
FIGO stage (2009)	
IA	173 (51.6)
IB	94 (28.0)
II	15 (4.4)
IIIA	5 (1.5)
IIIB	6 (1.8)
IIIC	36 (10.7)
IV	6 n(1.8)
ESMO–ESGO–ESTRO risk group (final pathology)	
Low risk	65 (19.4)
High risk	270 (80.6)
Tumor grade (preoperative biopsy)	
1	110 (32.8)
2	148 m(44.2)
3	69 (20.6)
Missing information	8 (2.4)
Tumor grade (final pathology)	
1	95 (28.3)
2	167 (49.8)
3	73 (21.8)
Myometrial invasion (MRI), %	
<50	131 (39.1)
≥50	179 (53.4)
Missing information	25 (7.5)
Myometrial invasion (final pathology), %	
<50	173 (51.6)
≥50	162 (48.4)
Preoperative serum CA-125, IU/ml	
Low <35	246 (73.4)
High >35	67 (20.0)
Missing information	22 (6.5)
Lymphovascular space invasion (final pathology)	
Present	241 (71.9)
Absent	94 (28.1)
Surgical procedures	
TH + BSO + PLND	220 (65.6)
TH + BSO + PLND + PALND	115 (34.3)
Number of PLN retrieved	25 (2-59)
Number of PALN retrieved	13 (3-51)
Presence of LN metastasis	36 (10.7)

PLND: pelvic lymph node dissection, PALND: paraaortic lymph node dissection, BMI: body mass index, MRI: magnetic resonance imaging, TH: total hysterectomy, BSO: bilateral salpingoophorectomy, PLN: pelvic lymph nodes, PALN: paraaortic lymph nodes, LN: lymhph node

Table 2. Evaluation of risk status by combined use of preoperative biopsy, MRI and serum CA-125 according to ESMO–ESGO–ESTRO criteria

		Preoperative assessment (preoperative biopsy, MRI, CA-125)		
		Low risk	*High risk*	*Total*
ESMO–ESGO–ESTRO risk group (final pathology)	Low risk	42	15	57
	High risk	9	226	235
	Total	51	241	292

Preoperative pelvic MRI was available in 310 cases (92.5%). Compared with the final pathology report, preoperative diagnosis of the depth of myometrial invasion had an accuracy rate of 78.3% (243/310). Kappa statistic was estimated to be 0.568. 7.4% of patients (23/310) had deep myometrial invasion ≥50% in the final pathology, which had been undiagnosed by preoperative MRI. The sensitivity and specificity of preoperative MRI to discriminate between superficial and deep myometrial invasion were 85.1% and 71.8% respectively.

Data on preoperative serum CA-125 levels were available in 313 cases (93.4%). Although the sensitivity of high serum CA-125 levels >35 IU/ml to discriminate between low- and non-low risk EC was only 24.8%, specificity was high, 91.0%. Moreover, in univariate logistic regression analysis, the presence of high serum CA-125 levels was associated with tumor grade 3 vs grades 1, 2 (OR 2.10, 95% CI 1.11 to 3.95, p=0.02), with deep myometrial invasion (OR 1.97, 95% CI 1.13 to 3.45, p=0.02) and most importantly with LVSI (OR 4.22, 95% CI 2.39 to 7.46, p<0.001) in final pathology.

A preoperative assessment combining preoperative biopsy, pelvic MRI and serum CA-125 levels was available for 292 patients (87.1%). Based on preoperative assessment, that is grade 1 or 2 on preoperative biopsy, superficial myometrial invasion on pelvic MRI and low serum CA-125 <35 IU/ml, 51 patients (17.4%) were classified as low-risk. The rest 241 patients (82.5%) were classified as non-low risk. The evaluation of risk status by combined use of preoperative biopsy, MRI and serum CA-125 according to ESMO–ESGO–ESTRO criteria is presented in Table 2. Compared with the final pathology report, the combined preoperative risk evaluation had an accuracy rate of 91.8% (268/292). Kappa statistic was estimated to be 0.728. False negative rate, that is the percentage of non-low risk patients falsely classified as low-risk, was 3.8% (9/235). The sensitivity and specificity of the combined preoperative assessment to discriminate between low- and non-low risk EC patients according to ESMO-ESTRO-ESGO criteria were 96.1% (95% CI 93.7% to 98.6%) and 73.6% (95% CI 62.2% to 85.1%) respectively. The corresponding ROC curve is presented in Figure 1. The area under the ROC curve (AUC) quantifies the overall ability of a test to discriminate between two states, here between individuals at low and non-low risk. AUC was 0.849 for the combined preoperative risk evaluation of EC patients, significantly improved in comparison with single use of preoperative biopsy, pelvic MRI and serum CA-125 (Table 3).

The etiology of false positive results (15/292) was elevated serum CA-125 (4/292), deep myometrial invasion in pelvic MRI (7/292) or both (2/292) and tumor grade 3 in the preoperative biopsy (2/292). The etiology of false negative results (9/292) was tumor grade 3 on the final pathology report (2/292), deep myometrial invasion on the final pathology report (3/292) or both (1/292) and positive LVSI (3/292). Among the patients falsely classified as low-risk, one 62-year-old patient with grade 3 tumor and deep myometrial invasion on the final hysterectomy specimen had nodal me-

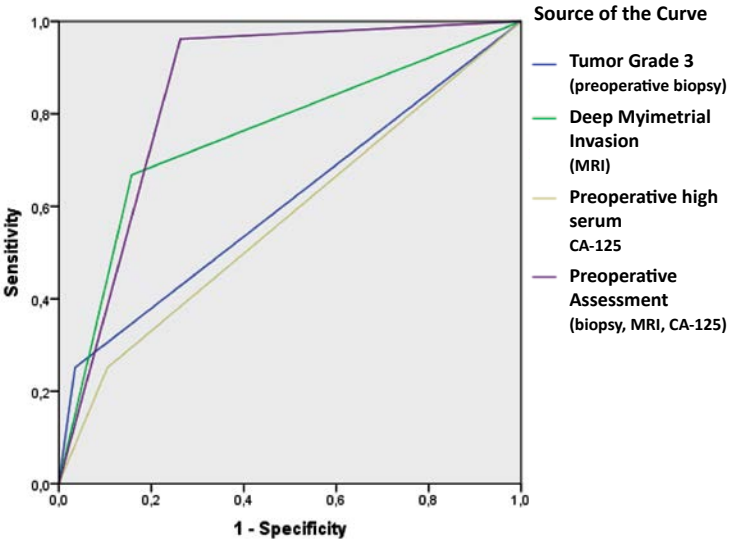

Figure 1. Receiver operating characteristic (ROC) curves for the performance of preoperative tests in predicting non-low risk uterine endometrioid cancer according to ESMO–ESGO–ESTRO criteria.

Table 3. Performance of preoperative biopsy, MRI, serum CA-125 and combined preoperative assessment for the prediction of non-low risk uterine endometrioid cancer according to ESMO–ESGO–ESTRO criteria. Area under the curve (AUC) expresses the discrimination ability of the test (95% confidence interval/CI)

	Sensitivity (%)	*Specificity (%)*	*AUC*	*95% CI*	*p value*
Tumor grade 3 (preoperative biopsy)	25.1	96.5	0.608	0.535, 0.681	0.01
Myometrial invasion ≥50% (MRI)	66.8	84.2	0.755	0.689, 0.822	<0.001
Serum CA-125 >35 IU/ml	24.8	91.0	0.579	0.507, 0.651	0.04
Preoperative assessment (biopsy, MRI, CA-125)	96.2	73.7	0.849	0.779, 0.919	<0.001

tastasis (1/9, 11.1%) and 2 metastatic PLN were retrieved after receiving full staging with PLND and PALND.

Discussion

Our retrospective study was designed to answer the following clinically significant query: can preoperative assessment with usual means, available in most hospitals, confidently exclude from a full staging surgical procedure low-risk EC patients? This question has emerged with the accumulation of evidence from previous studies, which examined survival, QoL outcomes and cost-effectiveness with different treatment approaches regarding LND for low-risk EC patients.

Dowdy et al. performed a prospective assessment of survival, morbidity and cost associated with LND in low-risk EC patients, as defined by the Mayo criteria [10]. This low- risk group accounted for 34.1% of the endometrioid type EC patients. They found that the inclusion of LND significantly and unfavorably impacted operating room time, blood loss, length of hospital stay and 30-day morbidity. The overall, recurrence-free and cause-specific survivals were not significantly impacted by LND, while the addition of LND significantly increased cost [10]. Although data on QoL or long-term complications, such as lymphedema, were not included in this study, a subsequent study estimated that the attributable risk of developing lower-extremity lymphedema was 23% for EC patients undergoing LND [18]. In the same study lymphedema was associated with reductions in multiple QoL domains [18]. Dowdy et al. supported a selective LND strategy for EC patients based on intraoperative findings. However, in this cost-effectiveness analysis the cost of FS, which is an integral part of Mayo algorithm, was not taken into account [10]. Clements et al. applied the Mayo criteria, to describe an EC population, in which theoretically LND would be omitted, following intraoperative assessment with FS [12]. In their cost-effectiveness analysis a selective LND strategy was found to be less cost-effective than routine LND for all EC patients, even when the impact of lymphedema was considered. The additional costs in the selective strategy were predominantly attributable to the cost of FS. Since FS is performed on 75% of the patients in this strategy (patients with high grade or non-endometrioid histological diagnosis preoperatively undergo LND without intraoperative assessment), but only 30% of patients evaluated with FS have LND omitted, the majority of patients in the selective arm ultimately accrue both the costs of FS as well as the costs and complications of LND [12]. These findings seem to support LND for all EC patients. However, Clements et al. did not include surgical complications, length of hospital stay nor QoL data in their analysis. In contrast to intraoperative assessment, a preoperative prediction model using pelvic MRI and serum CA-125, developed by KGOG [14], served as the basis for a selective LND strategy among endometrioid-type EC patients in the cost-effectiveness analysis performed by Lee et al. [13]. Their analysis indicated that, when the QoL benefit gained by avoiding lymphedema is considered, selective LND is less costly and more effective than routine LND in US and Korea. Additional costs under this selective strategy were predominantly attributable to the cost of preoperative testing (CA-125 and MRI). Approximately 51% of endometrioid EC patients would have avoided LND according to this preoperative prediction model. Since futile LND was significantly less common under this selective LND strategy, the cost of CA-125 and MRI was completely compensated for by the more appropriate selection of LND candidates and the subsequent limitation of cost for lymphedema care [13]. Combining the aforementioned studies we may conclude that three key features should characterize a selective LND approach for EC patients in order for it to be cost-effective, while not jeopardizing patients' survival or QoL. First, it should

use information available preoperatively, rather than an intraoperative assessment based on FS. Second, in order to minimize mortality from unstaged advanced disease, high sensitivity and low false negative rate are essentially required. The specificity of the classification method is also important for reducing LND-related morbidity in low-risk patients. Third, a considerable proportion of patients should forego LND under this strategy.

Traditionally, grade 1 and 2 endometrioid EC with myometrial invasion ≤50% has been considered low-risk [19]. Among this subset of patients the rate of nodal metastasis is 3-6% [9,20,21]. During the past decade, LVSI status has become gradually more important as an independent risk factor for patients with early stage EC, associated with nodal metastasis, disease recurrence and survival [19,22]. The presence of LVSI is a strong prognostic marker for survival and recurrence even in patients with otherwise low-risk features [9,23]. Absence of LVSI has a negative predictive value (NPV) of 95.6% for nodal metastasis [23]. According to data by Mariani et al. nodal metastasis among patients with traditionally low-risk features and absence of LVSI would be 3% [9]. Patients with stage I endometrioid EC, grade 1 or 2, myometrial invasion <50% and negative LVSI (low-risk according to ESMO–ESGO–ESTRO criteria) represent a considerable proportion of EC patients who receive a primary surgical treatment, 40-51% [9,21], while among endometrioid-type patients the corresponding value is 47.7% [21]. Yet, obtaining information on LVSI status intraoperatively through FS is difficult [9,22]. In one study FS results on LVSI were found in disagreement with the final pathology in 32% [24]. On the other hand, tumor size added to traditionally low-risk features, may be easily used intraoperatively to classify patients, as proposed by the Mayo criteria [9-11]. At a cut-off level of 2 cm nodal metastasis is minimal, ranging from 0.8% to 1.8% in various studies [10,19,24,25]. However, patients with such low-risk criteria represent only 20-27.6% of EC patients who receive a primary surgical treatment [9,10] and 21-40% of endometrioid-type patients [10,25,26].

Our goal was to retrospectively investigate a relatively large population of EC patients with low-risk features (node metastasis, local recurrence, absence of LVSI) according to ESMO–ESGO–ESTRO criteria and to compare them preoperatively and intraoperatively. Using these criteria, 19.4% of our patients were classified as low-risk and 80.6% high-risk according to the final histological report. Probably, the unexpected high proportion of high risk patients in our study was a bias because of the inclusion criteria protocol. All included patients had received LND, which had been performed according to surgeon's preference with consideration of patients' preoperative risk for nodal disease among others. It is highly possible that a great proportion of patients with preoperative low-risk features did not undergo LND in their primary surgery and thus, they were excluded. In the present study preoperative evaluation of risk status used combined data from the preoperative biopsy, pelvic MRI and serum CA-125. The same modalities have been used in combination for the prediction of LN metastasis in EC patients in previous reports [14,27]. In bibliography, high preoperative CA-125 >35 IU/ml has been correlated with advanced stage, high grade and deep myometrial invasion [16]. Moreover, elevated CA-125 is a prognostic factor for LN metastasis [27,28]. Although some authors advocate the use of age groups with different cut-off values for elevated CA-125, as its serum concentration is affected by ovarian hormones and ageing [27], in the present study a uniform CA-125 cut-off level (>35 IU/ml) was selected beforehand as elsewhere [14,16], for simplicity reasons and because most clinicians are more familiar with its use. In our study high serum CA-125 >35 IU/ml showed high specificity in discriminating non-low risk EC (91.0%) and it was associated with high tumor grade, deep myometrial invasion and presence of LVSI in the final pathology.

LVSI association is very difficult to be assessed intraoperatively as previously reported [28]. In this study the sensitivity and specificity of preoperative biopsy to differentiate between grades 1,2 and grade 3 were 86.3% and 97.6%, respectively.

The estimated specificity is comparable with previous reports (97-99%), while the sensitivity is higher than reported (58-64%) [27,29]. We are uncertain for the etiology of this finding. As non-endometrioid type EC is considered by definition high-risk, requiring surgical management with full staging, we only included endometrioid-type tumors. Furthermore, the majority of preoperative specimens were obtained through D&C, which is generally considered more accurate than pipelle endometrial sampling. Finally, it may reflect a tendency of attending pathologists at our institution towards preoperative upgrading. In previous reports the sensitivity and specificity of preoperative MRI to discriminate between superficial and

deep myometrial invasion varied between 58% to 85% and 74% to 92% respectively [27,29-31]. In our study the corresponding values were 85.1% and 71.8%.

The sensitivity and specificity of the combined preoperative assessment to discriminate between low- and non-low risk EC patients according to ESMO-ESTRO-ESGO criteria were 96.1% and 73.6% respectively. AUC of the corresponding ROC curve was 0.849. False negative rate was 3.8% (9/235). Among the 9 patients falsely classified as low-risk, one patient had nodal metastasis (1/9, 11.1%) after full staging. Among the 57 low-risk patients according to ESMO-ESTRO-ESGO criteria (true negatives) no metastatic LN was found. Considering the test-dependent sensitivity and specificity found in our study, we further used the reported 52.3% prevalence of non-low risk tumors among patients with endometrioid-type histology to estimate predictive values [17,21]. The combined preoperative assessment presented here has a NPV of 94.6% for non-low risk tumors among patients with endometrioid-type histology. The corresponding PPV is 80.0%. Using the same prevalence data, we estimated that with the false negative rate of 3.8% (surgically undertreated patients) and the false positive rate of 17.6% (surgically overtreated patients) over 40% of endometrioid-type patients would forego LND under this selective strategy based on information obtained preoperatively. We found the overall performance of the combined preoperative assessment evaluated here satisfactory, with high sensitivity, acceptable specificity and a low, but not negligible, false-negative rate. The few surgically undertreated patients under this strategy are potential candidates for a second full-staging surgical procedure, which could be minimally invasive, or for a more aggressive treatment regimen postoperatively.

Previous reports have used the same modalities in combination for the direct prediction, though, of LN metastasis in EC patients [14,27]. In the prediction model evaluated by Todo et al. [27], which included an MRI substitute for tumor volume and stratified by age CA-125 cut-off values, 51.4% (110/214) of EC patients of different histologic types were classified as having no risk factors for PLN metastasis. The false negative rate was 3.8% (4/104). In the more elaborated preoperative prediction model developed by KGOG [14], which included the extra MRI parameters of LN enlargement and extension beyond the uterine corpus, 43-53% of endometrioid-type EC patients were classified as part of a low-risk group. The false negative rate was 1.4-1.7%. AUC of the corresponding ROC curve was 0.85. Our results are comparable with those studies.

The accuracy of histologic grade and depth of myometrial invasion obtained intraoperatively through FS varies between studies. Some have demonstrated that both correlate poorly with final pathology [24,32,33]. In these studies the accuracy rate between FS and final pathology for grade was 58- 65% and for myometrial invasion it was 67-72%. False negative rate was also high, 6.6-28% [24,32]. More recent studies report that FS is a reliable method for guiding intraoperative decision making with regard to LND performance [11,34,35]. In the study by Stephan et al., despite the high accuracy rate between FS and final pathology for grade and depth of invasion (88% and 98.2% respectively) clinically significant discordance, which would alter surgical management, had a 5.2% rate [34]. Sala et al. showed that by applying the Mayo criteria, which include tumor size in FS specimens, high specificity and sensitivity is achieved (estimated AUC 0.880), while the false negative rate is as low as 1% [35]. With the same criteria applied, the false negative rate was 1.6% in the prospective study by Kumar et al, where tumor size proved the most reliable variable with an accuracy rate of 100% between FS and final pathology [11]. All authors admit, however, that for such highly reliable FS results, sufficient pathologic expertise within a high-volume center is needed. For those centers, given the results of our study (AUC 0.849, false negative rate 3.8%), FS is more accurate than combined preoperative assessment in the identification of a smaller patient population with lower risk for LN metastasis. However, since the difference is not tremendous, the performance of combined preoperative assessment can be considered acceptable for guiding preoperative decisions regarding LND.

The present study presents certain limitations, mostly due to its retrospective nature. Selection bias is evident in our study by the unexpected high proportion of non-low risk patients, which differs from that reported in the bibliography [9,21]. The major reason for this seems to be the inclusion criteria applied (only patients who received LND). Selection bias, could originate secondarily from missing data, a common disadvantage in all retrospective studies which combine a great number of information for the primary outcome. Additionally, the relatively small sample size in the subgroup of low-risk patients could

explain the absence of low-risk patients with nodal metastasis from our study population, since it is known that nodal metastasis is present at a low rate among low-risk patients [9,21]. However, our study was not designed to report on disease prevalence. Both primary and secondary outcomes remain valid, since they are only test-dependent, therefore allowing for comparison with other studies irrespectively of disease prevalence [17]. Data on tumor size and FS were available in approximately 40% of the cases, yet their use would further limit the sample size, especially in the low-risk subgroup. Only an indirect comparison was attempted instead here by using previous reports. An advantage of our study is that preoperative pathology and radiology findings were blinded with respect to the final pathology, since a central postoperative review was not conducted. To our knowledge, this is the first study on preoperative evaluation of risk status using the current ESMO-ESGO-ESTRO criteria, which have included LVSI status, as the "gold standard". The greatest strength of our study, however, is that only usual means, available in most hospitals, were used in a simple manner without algorithms, scores etc. We believe that the methodology followed in our study reflects common practice in most hospitals, where the availability and reliability of FS is under question. That is why our conclusions can be readily applicable by most gynecologists with various backgrounds who perform surgical procedures for uterine cancer worldwide.

Conclusion

The accumulation of evidence from studies, which examined the role of LND in the surgical management of low-risk EC in terms of survival, QoL and cost-effectiveness are in favor of a selective LND strategy, based on preoperative data, which should essentially exclude a considerable proportion of patients. In the present study we evaluated the performance of preoperative assessment with usual means, available in most hospitals, in identifying intermediate to high risk EC patients according to current ESMO–ESGO–ESTRO criteria. We showed that by combining information from preoperative biopsy, pelvic MRI and serum CA-125 high sensitivity (96.1%), acceptable sensitivity (73.6%) and a low false negative rate (3.8%) are achieved. About half of endometrioid-type EC patients, who are at low risk of nodal metastasis and recurrence, can be excluded from a full staging surgical procedure based on preoperative data. Thus, a selective LND strategy for EC patients based on preoperative assessment is possible and would be cost-effective, while not jeopardizing patients' survival or patient QoL.

Conflict of interests

The authors declare no confict of interests.

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