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Assessment of different pre- and intra-operative strategies to predict the actual ESMO risk group and to establish the appropriate indication of lymphadenectomy in endometrial cancer

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Summary

Purpose of investigation: The objective of this study was to evaluate the best pre- and intra-operative strategy to determine the European Society for Medical Oncology (ESMO) risk group. *Materials and Methods:* Twelve algorithms, integrating endometrial biopsy for histological type and tumour grade, and ultrasound and/or magnetic resonance imaging (MRI) ± intra-operative examination for determination of myometrial invasion, were built. The diagnostic values of each algorithm to predict high- and low-risk group were calculated. *Results:* For the prediction of high-risk group, the best algorithm was endometrial biopsy and ultrasound, combined with MRI in case of myometrial invasion < 50% ± intra-operative examination in case of myometrial invasion < 50% on MRI. For the prediction of low-risk group, the two best algorithms were endometrial biopsy and ultrasound or MRI, combined with MRI or ultrasound in case of myometrial invasion < 50% and intra-operative examination in case of discrepancy between both exams. *Conclusion:* The present study suggests that the best strategy to predict actual ESMO risk group is endometrial biopsy and transvaginal ultrasound ± MRI and intra-operative examination in case of myometrial invasion < 50% on ultrasound.

Key words: Endometrial cancer; Lymphadenectomy; Ultrasound; MRI; Intra-operative examination.

Introduction

Endometrial cancer is the most common pelvic gynaecological cancer in industrialized countries. With 75% of cases diagnosed at Stage I, this cancer is associated with a good prognosis. Its treatment relies first on surgery, which includes at least a total hysterectomy with bilateral salpingo-oophorectomy. The European guidelines recommend pelvic and para-aortic lymphadenectomy in Stage I at high ± intermediate-risk, and Stage II and III cancers [1]. Pre- and intra-operative assessment, which includes endometrial biopsy, transvaginal ultrasound, MRI, and intra-operative examination of the surgical specimen, seems crucial to adequately determine the surgical procedure and to avoid not only the risk of useless lymphadenectomy, but also a second surgical procedure.

The European Society for Medical Oncology (ESMO) classified Stage I tumours according to their risks of recurrence and this classification is used to tailor the therapeutic strategy, including the indication of lymphadenectomy; this evaluation is based on histological type, tumour grade, and myometrial invasion [2]. However, the best diagnostic strategy to determine the ESMO risk group has never been investigated.

The primary objectives of this study were to evaluate the best pre- and intra-operative strategy including endometrial biopsy, transvaginal ultrasound, MRI, and intra-operative examination for the determination of the actual ESMO risk group confirmed by final histology of the hysterectomy specimen. The authors also evaluated the indication of lymphadenectomy on the pre- and intra-operative analysis compared with final histology.

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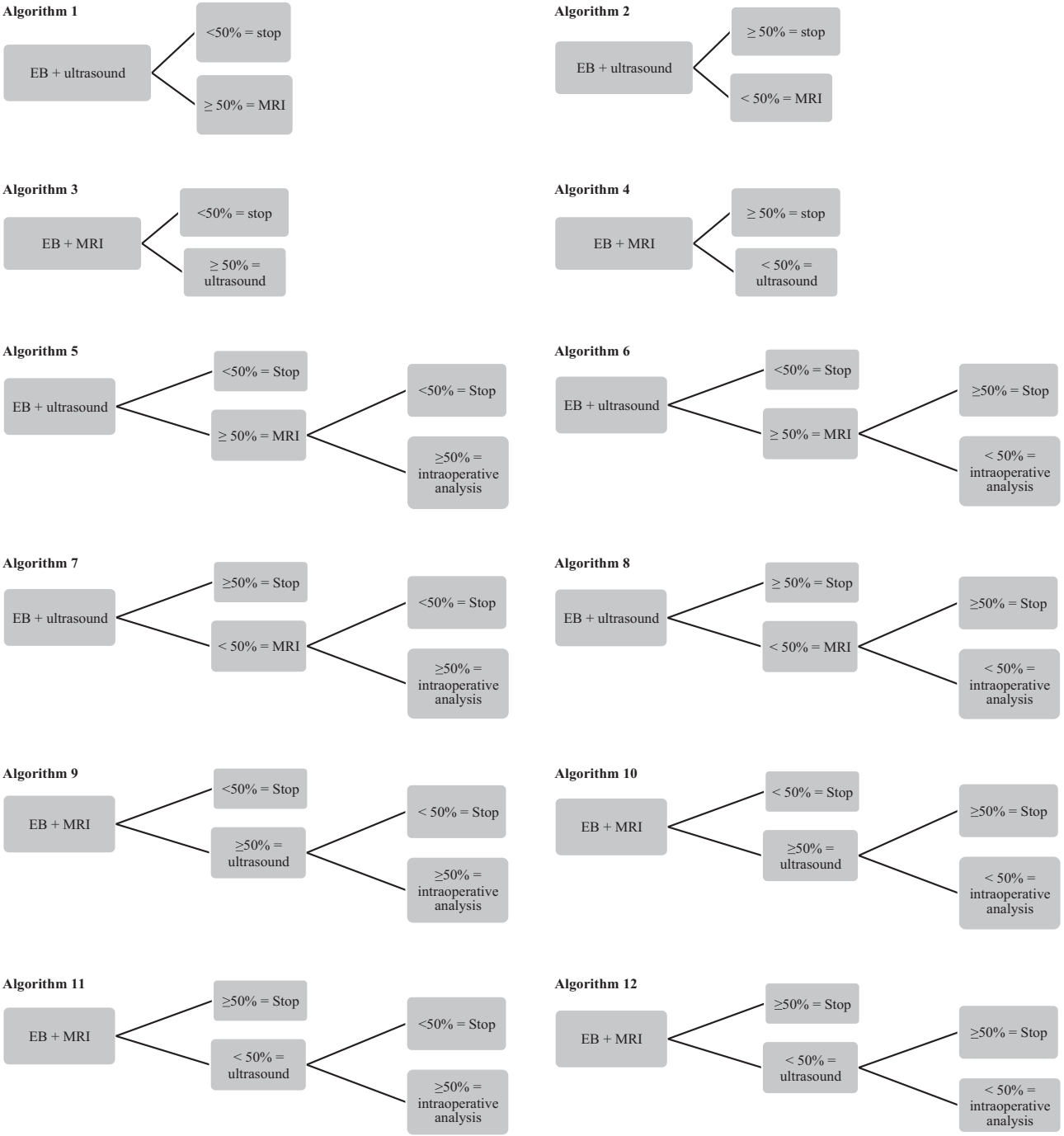

Figure 1. — Description of the 12 algorithms.

Materials and Methods

The authors conducted a retrospective study between January 2006 and December 2011 in the Gynaecological Oncology Department of the European Georges-Pompidou Teaching Hospital, Paris, France on patients with endometrial cancer, irrespective of histological type and FIGO Stage. To be included in the study, patients had to have received a pre- or intra-operative assessment of type and tumour grade on endometrial biopsy and of myometrial invasion on transvaginal ultrasound and/or pelvic MRI ± intraoperative examination of the hysterectomy specimen, and to have been operated on in our department.

Pre-operative assessment included endometrial biopsy, transvaginal ultrasound, and MRI. The endometrial biopsy was reviewed by one of the referral pathologists. Transvaginal ultrasound and/or MRI were performed either in the imaging department or outside. In the present institution, MRI was performed

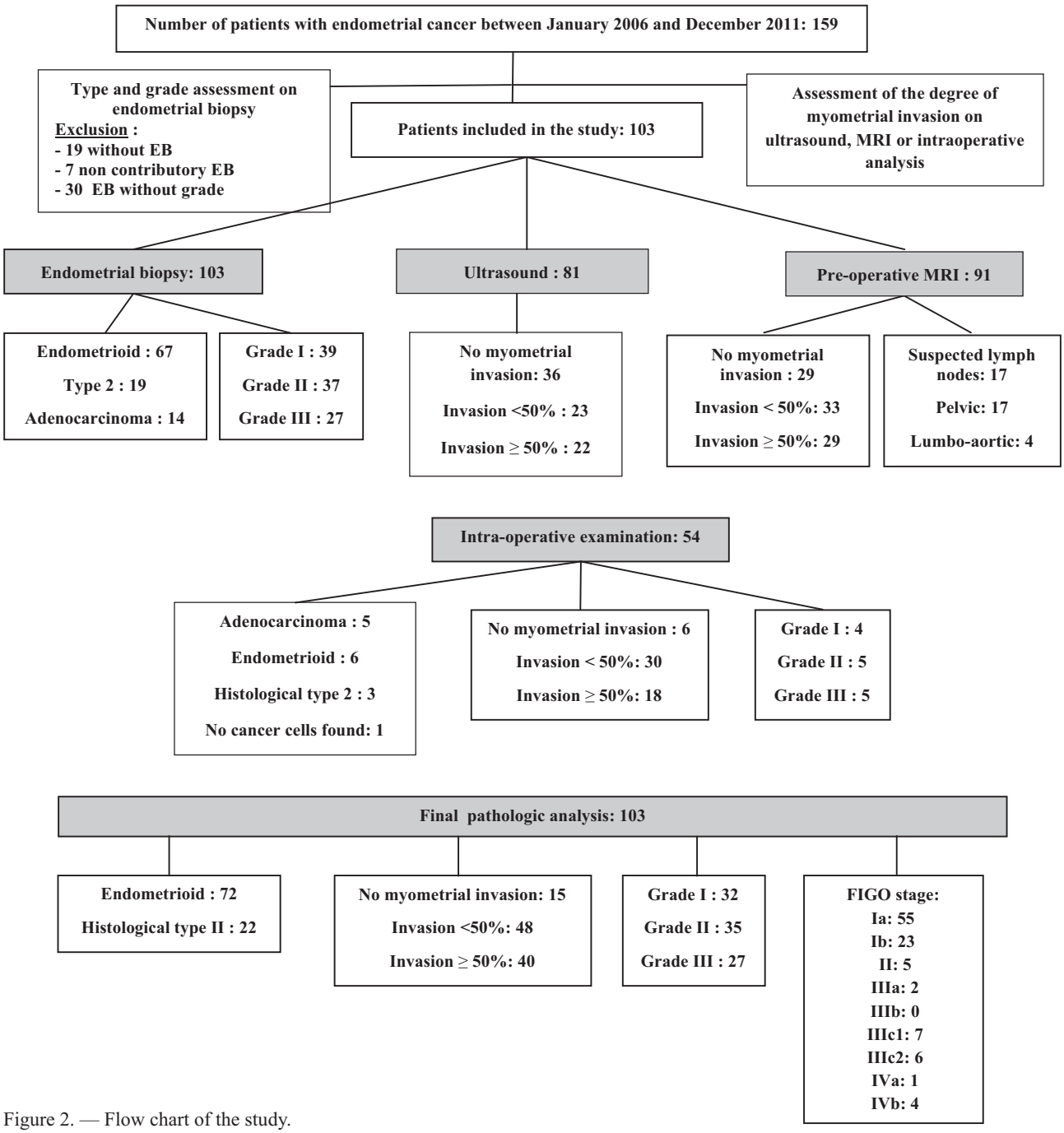

Figure 2. — Flow chart of the study.

using a 1.5 T MR. A pelvic phased array coil was used for all patients. The following sequences were routinely obtained: sagittal and axial T2-weighted imaging, T2-weighted imaging in a coronal oblique plane perpendicular to the endometrial cavity, axial diffusion weighted imaging, axial T1-weighted imaging, fat suppressed T1-weighted imaging in the axial or sagittal plane before and 30, 90, and 150 seconds after administration of a gadolinium chelate. If MRI was done outside the present institution, the authors' referral radiologists reviewed the available sequences.

The surgical procedure included at least a total hysterectomy with bilateral salpingo-oophorectomy, and peritoneal washings. Intra-operative examination (gross examination and frozen section) of the hysterectomy specimen was performed if possible and take into consideration for surgery. Prior to 2009, pelvic ± para-aortic lymphadenectomy was carried out systematically regardless of the level of risk. Since 2009, it was systematically indicated in high-risk tumours and optional in intermediate-risk tumours. In case of serous papillary type, omentectomy was also performed.

The present authors sought to determine which pre- and/or

intra-operative strategy was the best to predict the actual ESMO risk group confirmed on the hysterectomy specimen. For this, they designed 12 algorithms integrating information of endometrial biopsy for histological type and tumour grade, and ultrasound and/or MRI ± intra-operative examination to determine myometrial invasion (Figure 1). Diagnostic values to predict high and low-risk groups were calculated for each algorithm.

Classification of ESMO risk group for Stage I tumours was based on ESMO Clinical Practice Guidelines [2]. Stages II, III, and IV were considered as high-risk tumours.

Pelvic and para-aortic lymphadenectomy was indicated in case of intermediate-risk (except for Stage IB grade 1) and high-risk groups, as recommended by the European and French guidelines [1]. The indication of lymphadenectomy on pre- and intra-operative assessment for each algorithm was compared with the indication on final histological result. To note, the present authors did not consider lymphovascular space involvement on final histology, as this information could not be obtained by pre- and intra-operative assessment. The number of cases with inadequate indication of lymphadenectomy, and conversely the number of cases without pre-operative indication of lymphadenectomy, whereas it would have been indicated by final histology, were examined.

Diagnostic strategies were evaluated using area under the curve (AUC). For each algorithm, sensitivity, specificity, AUC, Cohen's kappa, positive likelihood ratio (Lr+), and negative likelihood ratio (Lr-) were calculated with their 95% CI. Therefore, diagnostic value of pre- and intra-operative tests for the prediction of tumour grade, histological type, and myometrial invasion were evaluated, integrating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Lr+, and Lr-. Statistical analysis was performed using Stata 13.0.

Results

During the study period, 159 patients were operated for endometrial cancer in the present department. Of these patients, 103 met the inclusion criteria and were included in the analysis. The population and tumours characteristics are shown in Figure 2.

Preoperative biopsy found endometrioid adenocarcinoma in 67 cases (65%), type II in 19 cases (18.4%), unspecified adenocarcinoma in 14 cases (13.6%), mucinous adenocarcinoma in one case, and Müllerian mixed adenocarcinoma in one case. There were 39 Grade 1 (37.9%), 37 Grade 2 (36%), and 27 Grade 3 tumours (26.1 %).

Eighty-one (79%) patients had transvaginal ultrasound, which showed myometrial invasion < 50% in 59 cases (73%), and ≥ 50% in 22 cases (27%). Cervical stroma involved in four patients.

Pelvic MRI was available for 91 patients (88%) and found myometrial invasion < 50% in 62 cases (68%) and ≥ 50% in 29 cases (32%). MRI showed a cervical involvement in seven cases (7.7%): three endocervical lesions and four stromal lesions. Seventeen out of 91 patients (18.7%) had suspicious lymph nodes (nodes > ten mm in minor axis). They were located in the pelvic area in 17 cases (100%), and the para-aortic area in four cases (23.5%).

Intra-operative examination of specimen of hysterectomy was performed in 54 cases (52.4%) and found myometrial invasion < 50% in 36 cases (66.6%) and ≥ 50% in 18 cases (33.3%). The histological type was specified in 15 cases (28%): endometrioid adenocarcinoma in six cases (40%), unspecified adenocarcinoma in five cases (33.3%), type II in three cases (20%), and no cancer found in one case (6.7%). Tumour grade was noted in 14 cases (26%): four

Table 1. — *Population and tumour characteristics on final histology (n=103).*

Median age (IQR)	65 (57-73)
Median BMI (IQR)	24.5 (21.7-27.7)
Histological analysis	
Myometrial invasion	
No myometrial invasion	15/103 (14.6%)
< 50%	48/103 (46.6%)
≥ 50%	40/103 (38.8%)
Histological type	
Endometrioid	72/103 (70%)
Type II histological	22/103 (21.4%)
Serous	5/103 (4.8%)
Clear cell	4/103 (3.9%)
Carcinosarcoma	2/103 (1.9%)
Mixed	11/103 (10.7%)
No cancer cells found	8/103 (7.8%)
Adenocarcinoma without accuracy	1/103 (1%)
Tumour grade	
1	32/94 (34%)
2	35/94 (37.2%)
3	27/94 (28.7%)
Cervical invasion	13/103 (12.6%)
Endocervix	5/103 (4.9%)
Cervical stroma	8/103 (7.8%)
Metastatic pelvic lymph nodes	10/78 (12.8%)
Metastatic para-aortic lymph nodes	7/34 (20.6%)
FIGO stage	
IA	55/103 (53.4%)
IB	23/103 (22.3%)
II	5/103 (4.9%)
IIIA	2/103 (1.9%)
IIIB	0/103 (0%)
IIIC1	7/103 (6.8%)
IIIC2	6/103 (5.8%)
IVA	1/103 (1%)
IVB	4/103 (3.9%)
ESMO risk group	
Low-risk	53/103 (51.5%)
Intermediate-risk	24/103 (23.3%)
High-risk	26/103 (25.2%)
Positive peritoneal cytology	5/97 (5.2%)
Emboli	40/103 (38.8%)

Abbreviations: n: total number of patients; IQR: interquartile; %: percentage; BMI: body mass index.

Table 2. — *Diagnostic values of the 12 algorithms for the detection of high-risk groups.*

Algorithms	Kappa	Sensitivity	Specificity	PLR	NLR	Area under the curve	n patients
1	0.484	70.8% (48.9- 87.4)	90.6% (80.7- 96.5)	7.56 (3.38- 16.9)	0.322 (0.172- 0.603)	0.807 (0.708- 0.907)	88
2	0.533	80% (56.3- 94.3)	90.3% (80.1- 96.4)	8.27 (3.75-18.2)	0.221 (0.0918- 0.534)	0.852 (0.754- 0.949)	82
3	0.47	73.7% (48.8- 90.9)	92.3% (83- 97.5)	9.58 (3.96- 23.2)	0.285 (0.134- 0.607)	0.83 (0.723- 0.937)	84
4	0.495	70% (45.7-88.1)	91.9% (82.2- 97.3)	8.68 (3.57- 21.1)	0.326 (0.166- 0.64)	0.81 (0.701-0.918)	82
5	0.465	62.5% (40.6-81.2)	90.6% (80.7- 96.5)	6.67 (2.93- 15.2)	0.414 (0.245- 0.698)	0.766 (0.66- 0.871)	88
6	0.487	70.8% (48.9- 87.4)	89.1% (78.8- 95.5)	6.48 (3.08- 13.6)	0.327 (0.175- 0.614)	0.799 (0.699- 0.9)	88
7	0.541	78.9% (54.4- 93.9)	90.3% (80.1- 96.4)	8.16 (3.68- 18.1)	0.233 (0.0972- 0.559)	0.846 (0.745- 0.948)	81
8	0.55	80% (56.3- 94.3)	90.3% (80.1- 96.4)	8.27 (3.75- 18.2)	0.221 (0.0918- 0.534)	0.852 (0.754- 0.949)	82
9	0.47	73.7% (48.8- 90.9)	92.3% (83- 97.5)	9.58 (3.96- 23.2)	0.285 (0.134- 0.607)	0.83 (0.723- 0.937)	84
10	0.499	77.8% (52.4- 93.6)	92.3% (83- 97.5)	10.1 (4.2- 24.3)	0.241 (0.101- 0.573)	0.85 (0.746- 0.954)	83
11	0.505	70% (45.7- 88.1)	91.9% (82.2- 97.3)	8.68 (3.57- 21.1)	0.326 (0.166- 0.64)	0.81 (0.701- 0.918)	82
12	0.507	70% (45.7- 88.1)	91.9% (82.2- 97.3)	8.68 (3.57- 21.1)	0.326 (0.166- 0.64)	0.81 (0.701- 0.918)	82

Abbreviations: Lr+: positive likelihood ratio; Lr-: negative likelihood ratio; n: number.

Table 3. — *Diagnostic values of the 12 algorithms for the detection of low-risk groups.*

Algorithms	Kappa	Sensitivity	Specificity	Lr+	Lr-	Area under the curve	n patients
1	0.484	65.9% (49.4- 79.9)	87.2% (74.3- 95.2)	2.55 (1.65- 3.96)	0.194 (0.0889- 0.423)	0.765 (0.678- 0.853)	88
2	0.533	84.2% (68.7- 94)	72.7% (57.2- 85)	4.61 (2.16- 9.81)	0..324 (0.196- 0.535)	0.785 (0.696- 0.873)	82
3	0.47	62.2% (44.8- 77.5)	85.1% (71.7- 93.8)	2.25 (1.46- 3.46)	0.24 (0.116- 0.496)	0.736 (0.642- 0.831)	84
4	0.495	84.2% (68.7- 94)	72.7% (57.2- 85)	4.61 (2.16- 9.81)	0.324 (0.196- 0.535)	0.785 (0.696- 0.873)	82
5	0.465	60.5% (43.4- 76)	89.4% (76.9- 96.5)	2.26 (1.51- 3.4)	0.176 (0.0738- 0.418)	0.749 (0.659- 0.84)	85
6	0.487	68.3% (51.9- 81.9)	87.2% (74.3- 95.2)	2.75 (1.73- 4.37)	0.187 (0.086- 0.406)	0.778 (0.691- 0.864)	88
7	0.541	80% (63.1- 91.6)	78.6% (63.2- 89.7)	3.93 (1.99- 7.76)	0.268 (0.147- 0.489)	0.793 (0.701- 0.885)	77
8	0.55	100% (89.7- 100)	54.8% (36- 72.7)		0.452 (0.306- 0.666)	0.774 (0.685- 0.863)	65
9	0.47	62.2% (44.8- 77.5)	85.1% (71.7- 93.8)	2.25 (1.46- 3.46)	0.24 (0.116- 0.496)	0.736 (0.642- 0.831)	84
10	0.499	67.6% (49.5- 82.6)	82.2% (67.9- 92)	2.54 (1.53- 4.21)	0.263 (0.134- 0.514)	0.749 (0.652- 0.847)	79
11	0.505	81.6% (65.7- 92.3)	77.3% (62.2- 88.5)	4.19 (2.11- 8.35)	0.279 (0.158- 0.49)	0.794 (0.706- 0.883)	82
12	0.507	84.2% (68.7- 94)	72.7% (57.2- 85)	4.61 (2.16- 9.81)	0.324 (0.196- 0.535)	0.785 (0.696- 0.873)	82

Abbreviations: Lr+: positive likelihood ratio; Lr-: negative likelihood ratio; n: number.

Grade 1 (28.6%), five Grade 2 (35.7%), and five Grade 3 (35.7%). Tumour characteristics on final histology are summarized in Table 1.

With a follow-up of five years, ten patients (9.7%) experienced a recurrence. Seven cases of deaths occurred (6.8%), including five related to disease progression.

Diagnostic values of the 12 algorithms are summarized in Tables 2 and 3. The Cohen's kappa coefficient, index of interobserver agreement was approximately 0.55 for all the algorithms. Strategies to obtain the best agreement between ESMO risk group estimated by the pre- and intra-operative assessment and actual ESMO risk group confirmed on final histology were:

– To predict the actual high-risk group: endometrial biopsy and ultrasound, combined with MRI in case of myometrial invasion < 50% (Algorithm 2), and endometrial biopsy and ultrasound, combined with MRI in case of myometrial invasion < 50%, and intra-operative examination if myometrial invasion was < 50% on MRI (Algorithm 8).

– To predict the actual low-risk group: endometrial biopsy and ultrasound, combined with MRI in case of myometrial invasion < 50%, and intra-operative examination in case of discrepancy between both tests (Algorithm 7), and endometrial biopsy and MRI, combined with ultrasound in case of myometrial invasion < 50%, and intra-operative examination in case of discrepancy between both tests (Algorithm 11).

According to the different algorithms, lymphadenectomy was indicated on the results of pre- and intra-operative assessment in, respectively, 29.7% to 55.4% of cases, and was finally indicated according to the final histology in 46 patients (44.6%). Lymphadenectomy was indicated by pre- and intra-operative risk assessment, but this indication was not confirmed by post-operative analysis in 4.5% to 12.3% of cases. It was not indicated on pre- and intra-operative risk assessment, but this non-indication was reversed by post-operative analysis in 4.6% to 16.7% of cases. Lymphadenectomy was not performed, as indicated on the actual risk group determined on the hysterectomy specimen,

Table 4. — *Concordant indications of lymphadenectomy between pre-and intra-operative and post-operative assessments based on 12 algorithms.*

	1	2	3	4	5	6	7	8	9	10	11	12
Lymphadenectomy indicated preoperatively and postoperatively	24/88 (27.2%)	26/82 (31.7%)	20/84 (23.8%)	27/82 (33%)	23/85 (27%)	25/88 (28.4%)	22/76 (28.9%)	27/65 (41.5%)	20/84 (23.8%)	19/78 (24.3%)	27/82 (33%)	28/65 (43%)
Lymphadenectomy indicated preoperatively but not postoperatively	4/88 (4.5%)	7/82 (8.5%)	5/84 (6%)	7/82 (8.5%)	4/85 (4.7%)	4/88 (4.5%)	4/76 (5.2%)	8/65 (12.3%)	5/84 (6%)	5/78 (6.4%)	6/82 (7.3%)	8/65 (12.3%)
Lymphadenectomy not indicated preoperatively but indicated postoperative	14/88 (15.9%)	8/82 (9.8%)	14/84 (16.7%)	8/82 (9.7%)	12/85 (14.1%)	13/88 (14.8%)	9/76 (11.8%)	3/65 (4.6%)	14/84 (16.7%)	12/78 (15.4%)	8/82 (9.8%)	3/65 (4.6%)
Lymphadenectomy not indicated preoperatively and postoperatively	46/88 (52.2%)	41/82 (50%)	45/84 (53.6%)	40/82 (48.8%)	46/85 (54.1%)	46/88 (52.3%)	41/76 (54%)	27/65 (41.5%)	45/84 (53.6%)	42/78 (53.8%)	41/82 (50%)	26/65 (40%)
Concordance between the indication of lymphadenectomy in pre-and postoperative	70/88 (79.5%)	67/82 (81.7%)	65/84 (77.3%)	67/82 (81.7%)	69/85 (81.1%)	71/88 (80.6%)	63/76 (82.9%)	54/65 (83%)	65/84 (77.3%)	61/78 (78.2%)	68/82 (82.9%)	54/65 (83%)

in only seven patients. According to the different algorithms, lymphadenectomy was unnecessarily performed in 4.5% to 7.7%. Therefore, pre- and intra-operative analysis was concordant for the indication of lymphadenectomy to post-operative analysis in 77.3% to 83%. Algorithms 8 and 12 had the best agreements with a concordance of 83% (Table 4).

For the diagnosis of tumour grade, the endometrial biopsy and intra-operative examination had a sensitivity of 70% and 83%, a specificity of 91% and 92%, a PPV of 76% and 83%, a NPV of 88% and 92%, a Lr+ of 7.81 and 9.9, and a Lr- of 0.33 and 0.18, respectively.

For the diagnosis of histological type, the endometrial biopsy and intra-operative examination had sensitivity of 60% and 75%, specificity of 90% and 100%, PPV of 63% and 100%, NPV of 89% and 91%, Lr+ of 6.12 and zero, and Lr- of 0.44 and 0.25, respectively.

For the prediction of myometrial invasion, sensitivity, specificity, PPV, NPV, Lr+, and Lr- of ultrasound were, respectively, 42.8%, 81.1%, 54.5%, 72.9, 2.26, and 0.70. Sensitivity, specificity, PPV, NPV, Lr+, and Lr- of MRI were, respectively, 52.9%, 80.7%, 62%, 74.2%, 2.74 and 0.58.

Finally, sensitivity, specificity, PPV, NPV, Lr+, and Lr- of intra-operative examination were, respectively, 70.5%, 83.7%, 66.6%, 86.1%, 4.32 and 0.35.

Discussion

To the present authors knowledge, this study is the first to evaluate the pre- and intra-operative strategy to predict the actual ESMO risk group. This is also the first to investigate the concordance between the indication of lymphadenectomy in pre- and intra-operative and post-operative assessments based on algorithms. However, this appears crucial in the management of endometrial cancer and makes this study of high clinical relevance.

Regarding the prediction of high-risk group, the authors showed that endometrial biopsy and ultrasound, combined with MRI in case of myometrial invasion < 50%, is the best strategy. For low-risk group, strategies with ultrasound and MRI had similar results. The present authors can notify that the index of interobserver agreement is not good for all the algorithms (< 0.6).

The concordance for indication of lymphadenectomy between pre- and intra-operative analysis and post-operative analysis ranged from 77% to 83% according to the algorithms. Regarding the correlation between pre- and intra-operative and post-operative tests for the indication of lymphadenectomy, strategies with ultrasound and MRI had the same results. In both cases, if the myometrial invasion was < 50%, the three exams (ultrasound, MRI, and intra-operative examination) should be performed.

The assessment of ESMO risk group is the cornerstone of the management of endometrial cancer, as it determines the indication of pelvic ± para-aortic lymphadenectomy. Indeed, several trials showed no benefit to perform lymphadenectomy in patients at low-risk [3-7]. Conversely, the indication is formal in case of high-risk and implies performing not only pelvic but also para-aortic lymphadenectomy [5, 6, 8].

Restricting lymphadenectomy to high risk populations is essential, as this procedure is associated with post-operative complications, namely lymphatic ones [4, 9]. Therefore, lymphadenectomy should be appropriately indicated, especially in patients with significant comorbidities. Nodal involvement risk is mainly related to myometrial invasion, type, and tumour grade [10]. The prevalence of nodal involvement increases from 3% in case of myometrial invasion < 50% to 46% in case of myometrial invasion ≥ 50% [11, 12]. The present study is the first to evaluate optimal strategies to tailor this procedure to high-risk patients.

Pre-operative assessment of ESMO risk group relies on endometrial biopsy, transvaginal ultrasound, MRI, and intra-operative examination of the surgical specimen, and is crucial to establish the indication of lymphadenectomy. The isolated diagnostic values of these tests have been widely studied. A meta-analysis reported a sensitivity of 78% for endometrial biopsy in the general population for the prediction

of histological type and tumour grade [13]. Regarding transvaginal ultrasound, the sensitivity for the prediction of myometrial invasion is reported from 37% to 94%, specificity from 64% to 100%, PPV from 51% to 100%, and NPV from 33% to 96% [14-19]. Finally, pelvic MRI is currently considered as a gold standard in pre-operative assessment of endometrial cancer. However, the literature reports highly variable accuracy. Dynamic contrast material-enhanced (DCE) MRI appears better than T2-weighted MRI to assess myometrial invasion and cervical invasion [12, 20]. Moreover, diffusion-weighted (DW) MRI has superior diagnostic accuracy in the assessment of myometrial invasion and significantly higher staging accuracy compared with DCE MRI. Beddy *et al.* reported that diagnostic accuracy, sensitivity, and specificity were, respectively, 90%, 84%, and 100% for DW MRI and 71%, 61%, and 88% for DCE MRI [21]. A recent review of the literature reported a sensitivity of MRI for myometrial invasion estimated between 33% and 100% and a specificity between 72% and 100% [22]. If the MRI sensitivity appears better than ultrasound in throughout the literature, recent studies have shown that the performance of ultrasound is equivalent to that of MRI due to improved technology, when conducted by a trained operator, specialized in imaging pelvis [19, 23-26]. This improved diagnostic value of transvaginal ultrasound can be explained by two arguments. Firstly, there is an improvement of the new technologies with more powerful equipment, especially the use of endovaginal probes with higher frequency (5 MHz to 9 MHz), which allows a better resolution and therefore an easier segregation between tissues, in particular between the endometrium and myometrium [25]. In addition, the new FIGO classification does not more classify myometrial invasion into three categories but two (lower, or upper or equal to 50%). Indeed, poor diagnostic value of transvaginal ultrasound are found especially with the old classification FIGO [27]. Teefey *et al.* described a correlation between transvaginal ultrasound and histological analysis in 53% of cases if the classification of myometrial invasion was made into 3 groups, and 80% if the classification were in 2 groups [28]. The main advantages of transvaginal ultrasound compared to MRI is simple, quick, low-cost, and minimally invasive. However, it is undoubtedly operator-dependent, hence the heterogeneity of results in the literature.

Regarding intra-operative examination, sensitivity and specificity range respectively between 77.8 to 91.2% and 93.1 to 99.5% for tumour grade, 60 to 91.5% and 88.3 to 98.3% for myometrial invasion [29]. Stephan and al evaluated histological type and found 90% sensitivity, 100% specificity, 100% PPV, and 57% NPV [30].

A few limitations should be discussed. First, this is a retrospective and monocentric study. Secondly, these results have to be confirmed, as the diagnostic values of pre-operative tests were poor in our study, compared with the literature. For endometrial biopsy, 9% of presumed endometrioid adenocarcinoma on endometrial biopsy was type II adenocarcinoma on final histology. In six of eight cases (75%), there was a mixed adenocarcinoma (endometrioid and type II adenocarcinoma). Therefore, the present authors can assume that the biopsy was not performed on type II contingent. As far as ultrasound was concerned, the poor diagnostic value may be explained by the fact that all transvaginal ultrasounds were not carried out by a single referral pelvic sonographer. Moreover, radiologists were not always aware of the diagnostic of endometrial cancer, which may decrease the sensitivity of ultrasound. Regarding MRI, all MRIs performed outside the present institution have not been systematically performed again even if DCE and DW MRI were missing. For intra-operative examination, the present results are concordant with the literature, and this test had the best diagnostic value. Nevertheless, data on tumour grade were available only in 14 cases and those on histological type only in 15 cases. Thirdly, all patients did not systematically undergo the three tests. Therefore, the indication of lymphadenectomy was based on ESMO risk groups, although other factors may be involved in decision making, as tumour size, serum CA 125 level, and lymphovascular space invasion. At last, the very low median BMI raises concerns about the external validity to other populations.

Conclusion

The present results show that the best strategy to predict ESMO risk group and lymphadenectomy indication appears to be endometrial biopsy and transvaginal ultrasound, combined with pelvic MRI and intra-operative examination in case of myometrial invasion < 50%. Further prospective studies are required to confirm these results.

References

[1] National Institute of Cancer: "Professional guidelines for clinical practice: endometrial cancer. 2010".

[2] Colombo N., Preti E., Landoni F., Carinelli S., Colombo A., Marini C., Sessa C.: "Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Ann. Oncol.*, 2013, *24*, vi33.

[3] Benedetti Panici P., Basile S., Maneschi F., Alberto Lissoni A., Signorelli M., Scambia G., *et al.*: "Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial". *J. Natl. Cancer. Inst.*, 2008, *100*, 1707.

[4] Kitchener H., Swart AMC., Qian Q., Amos C., Parmar MKB.: "Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study". *Lancet*, 2009, *373*, 125.

[5] Mariani A., Webb MJ., Keeney GL., Podratz KC. "Routes of lymphatic spread: a study of 112 consecutive patients with endometrial cancer". *Gynecol. Oncol*., 2001, *81*, 100.

[6] Kim HS., Suh DH., Kim M-K., Chung HH., Park NH., Song YS. "Systematic lymphadenectomy for survival in patients with endometrial cancer: a meta-analysis". *Jpn. J. Clin. Oncol*., 2012, *42*, 405.

[7] May K., Bryant A., Dickinson HO., Kehoe S., Morrison J.: "Lymphadenectomy for the management of endometrial cancer". *Cochrane Database Syst Rev*., 2010, *1*, CD007585.

[8] Todo Y., Kato H., Kaneuchi M., Watari H., Takeda M., Sakuragi N.

"Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis". *Lancet*, 2010, *375*, 1165.

[9] Achouri A., Huchon C., Bats AS., Bensaid C., Nos C., Lécuru F.: "Complications of lymphadenectomy for gynecologic cancer". *Eur. J. Surg. Oncol.*, 2013, *39*, 81.

[10] Creasman W.T., Odicino F., Maisonneuve P., Quinn M.A., Beller U., Beneder J.L., *et al.*: "Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer". *Int. J. Gynaecol. Obstet.,* 2006, *95*, S105.

[11] Beddy P., O'Neill AC., Yamamoto AK., Addley HC., Reinhold C, Sala E.: "FIGO staging system for endometrial cancer: added benefits of MR imaging". *Radiographics*, 2012, *32*, 241.

[12] Manfredi R., Mirk P., Maresca G., Margariti PA, Testa A., Zannoni GF., *et al.*: "Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning". *Radiology*, 2004, *231*, 372.

[13] Dijkhuizen F.P., Mol B.W., Brölmann H.A., Heintz A.P.: "The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis". *Cancer*, 2000, *89*, 1765.

[14] Miklos P., Klacko M., Babala P., Masak L., Ondrus D., Waczulikova I.: "Transvaginal ultrasound examination of myometrial infiltration by endometrial cancer". *Bratisl. Lek. Listy*., 2014, *115*, 14.

[15] Ortoft G., Dueholm M., Mathiesen O., Hansen ES., Lundorf E., Moller C., *et al.*: "Preoperative staging of endometrial cancer using TVS, MRI, and hysteroscopy". *Acta Obstet. Gynecol. Scand*., 2013, *92*, 536.

[16] Antonsen SL., Jensen LN., Loft A., Berthelsen AK, Costa J., Tabor A., *et al.*: "MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer - a multicenter prospective comparative study". *Gynecol. Oncol*., 2013, *128*, 300.

[17] Akbayir O., Corbacioglu A., Numanoglu C., Numanoglu C., Goksedef B.P.C., Guraslan H., *et al.*: "Combined use of preoperative transvaginal ultrasonography and intraoperative gross examination in the assessment of myometrial invasion in endometrial carcinoma". *Eur. J. Obstet. Gynecol. Reprod. Biol*., 2012, *165*, 284.

[18] Savelli L., Testa A.C., Mabrouk M., Zannoni L., Ludovisi M., Seracchiolo R., *et al.*: "A prospective blinded comparison of the accuracy of transvaginal sonography and frozen section in the assessment of myometrial invasion in endometrial cancer". *Gynecol. Oncol*., 2012, *124*, 549.

[19] Köse G., Aka N., Api M.: "Preoperative assessment of myometrial invasion and cervical involvement of endometrial cancer by transvaginal ultrasonography". *Gynecol. Obstet. Invest.*, 2003, *56*, 70.

[20] Frei K.A., Kinkel K., Bonél H.M., Lu Y., Zaloudek C., Hricak H.: "Prediction of deep myometrial invasion in patients with endometrial cancer: clinical utility of contrast-enhanced MR imaging-a meta-analysis and Bayesian analysis". *Radiology*, 2000, *216*, 444.

[21] Beddy P., Moyle P., Kataoka M., Kataoka M., Yamamoto AK., Joubert I., *et al.*: "Evaluation of depth of myometrial invasion and overall staging in endometrial cancer: comparison of diffusion-weighted and dynamic contrast-enhanced MR imaging". *Radiology*, 2012, *262*, 530.

[22] Haldorsen IS., Salvesen HB. "Staging of endometrial carcinomas with MRI using traditional and novel MRI techniques". *Clin. Radiol.*, 2012, *67*, 2.

[23] Berretta R., Merisio C., Piantelli G., Piantelli G., Rolla M., Giordano G., Melpignano M., Nardelli GB. "Preoperative transvaginal ultrasonography and intraoperative gross examination for assessing myometrial invasion by endometrial cancer". *J. Ultrasound Med.*, 2008, *27*, 349.

[24] Akbayir O., Corbacioglu A., Numanoglu C., Numanoglu C., Guleroglu FY., Ulker V., *et al.*: "Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound". *Gynecol. Oncol*., 2011, *122*, 600.

[25] Savelli L., Ceccarini M., Ludovisi M., Fruscella E., De laco P.A., Salizzoni E., *et al.*: "Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging". *Ultrasound Obstet. Gynecol.*, 2008, *31*, 560.

[26] Ozdemir S., Celik C., Emlik D., Kiresi D., Esen H.: "Assessment of myometrial invasion in endometrial cancer by transvaginal sonography, Doppler ultrasonography, magnetic resonance imaging and frozen section". *Int. J. Gynecol. Cancer*, 2009, *19*, 1085.

[27] Yamashita Y., Mizutani H., Torashima M., Takahashi M., Miyazaki K., Okamura H., *et al.*: "Assessment of myometrial invasion by endometrial carcinoma: transvaginal sonography vs contrast-enhanced MR imaging". *AJR Am. J. Roentgenol.*, 1993, *161*, 595.

[28] Teefey S.A., Stahl J.A., Middleton W.D., Huettner P.C., Bernhard L.M., Brown J.J., *et al.*: "Local staging of endometrial carcinoma: comparison of transvaginal and intraoperative sonography and gross visual inspection". *AJR Am. J. Roentgenol.*, 1996, *166*, 547.

[29] Turan T., Oguz E., Unlubilgin E., Tulunay G., Boran N., Demir O.F., Kose M.F.: "Accuracy of frozen-section examination for myometrial invasion and grade in endometrial cancer". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2013, *167*, 90.

[30] Stephan J-M., Hansen J., Samuelson M., McDonald M., Chin Y., Bender D., *et al.*: "Intra-operative frozen section results reliably predict final pathology in endometrial cancer". *Gynecol. Oncol.*, 2014, *133*, 499.

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