CÁNCER DE ENDOMETRIO DE RIESGO INTERMEDIO- UNA ENTIDAD CLÍNICA HETEROGÉNEA

INTERMEDIATE RISK ENDOMETRIAL CANCER- A HETEROGENEOUS CLINICAL ENTITY

TESIS DOCTORAL EN MEDICINA

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ABSTRACT

Objective

Risk models in endometrial cancer define prognosis and indicate adjuvant therapy. The currently most used classification was updated in 2016 in collaboration with the European Society of Medical Oncology (ESMO), the European Society of Gynecologic Oncology (ESGO) and European Society of Radiotherapy (ESTRO). A high-intermediate risk group was introduced within the intermediate risk group. The objective of this doctoral thesis is to evaluate the clinical relevance of the current subclassification of intermediate risk endometrial cancer in two regards: association with lymph nodal involvement, and oncological outcome.

Methods

A multicenter retrospective study was carried out at 5 international tertiary institutions. Patients diagnosed with intermediate risk endometrial cancer on the basis of definitive pathology findings were included. Patients were stratified into intermediate and high-intermediate risk groups. Incidence of nodal metastases, disease-free and overall survival were compared between the two risk groups in univariate and multivariate analysis.

Results

Four hundred seventy-seven patients were included. Three hundred twenty-five (68%) patients were identified as intermediate and 152 (32%) patients as high-intermediate endometrial cancer patients. Nodal metastases were found in 18 patients (11.8%) with high-intermediate risk endometrial cancer group and 16 patients (4.9%) in intermediate risk group ($p=0.006$). Lymphovascular space invasion (LVSI) was found to be a strong predictive factor of lymph node involvement ($p<0.001$). High-intermediate risk, compared to intermediate risk was found to be an independent factor of disease-free survival (hazard ratio: 1.76; 95% confidence interval: 1.00-3.08; $p=0.050$) and overall survival (hazard ratio: 1.99; 95% confidence interval: 1.10-3.60; $p=0.022$) on multivariate analysis.

Conclusions

The doctoral thesis results validate the clinical significance of intermediate risk endometrial cancer subclassification. Prognosis of high-intermediate risk endometrial cancer is significantly poorer. The prevalence of lymph node metastases is higher in this group of patients.

I. RESUMEN

Objetivo:

Los modelos de riesgo en el cáncer de endometrio permiten definir el pronóstico de la enfermedad y ayudan en la indicación de la terapia adyuvante. La clasificación más usada actualmente fue publicada en el año 2016 en colaboración con la Sociedad Europea de Oncología Médica (ESMO), la Sociedad Europea de Ginecología Oncológica (ESGO) y la Sociedad Europea de Radioterapia (ESTRO).

El objetivo de esta tesis doctoral es evaluar la relevancia clínica de la última subclasificación del cáncer de endometrio de riesgo intermedio en relación a su asociación con la afectación ganglionar y con el pronóstico oncológico.

Métodos

Se realizó un estudio retrospectivo multicéntrico en 5 instituciones terciarias a nivel internacional. Se incluyeron pacientes diagnosticadas de cáncer de endometrio de riesgo intermedio sobre la base de los hallazgos anatomopatológicos definitivos de las piezas quirúrgicas. Las pacientes se subclasificaron en grupos de riesgo intermedio e intermedio-alto. Se comparó la incidencia de metástasis ganglionares, la supervivencia libre de enfermedad y la supervivencia global entre los dos grupos de riesgo en un análisis univariante y multivariante.

Resultados

Se incluyeron 477 pacientes que cumplieron con los criterios establecidos. 325 (68%) pacientes se identificaron como casos de riesgo intermedio y 152 (32%) pacientes como casos con cáncer de endometrio de riesgo intermedio-alto. Se encontraron metástasis ganglionares en 18 pacientes (11,8%) con cáncer de endometrio de riesgo intermedio-alto y en 16 pacientes (4,9%) en el grupo de riesgo intermedio (p=0,006). La invasión del espacio linfovascular (LVSI) fue un factor predictivo importante de la afectación de los ganglios linfáticos (p< 0,001). En el estudio multivariante, el riesgo intermedio-alto fue un factor independiente de supervivencia

libre de enfermedad (Hazard ratio: 1,76; intervalo de confianza del 95%: 1,00 a 3,08; p = 0,050) y supervivencia global (Hazard ratio: 1,99; intervalo de confianza del 95%: 1,10 -3,60; p = 0,022).

Conclusiones

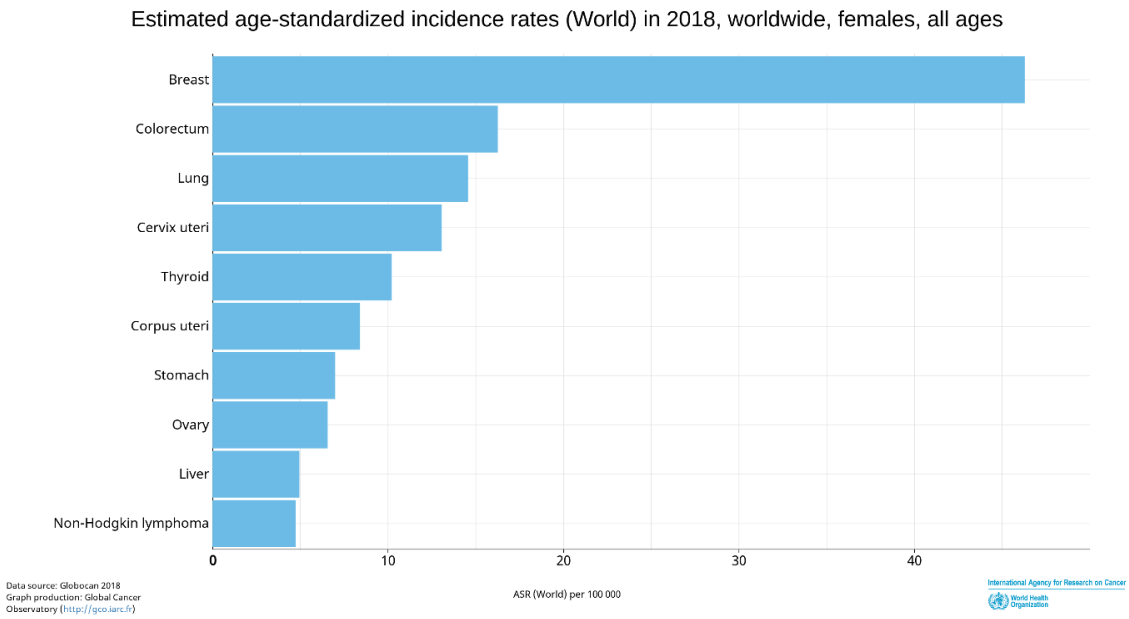
Este trabajo valida la importancia clínica de la subclasificación del cáncer de endometrio de riesgo intermedio. El pronóstico del cáncer de endometrio de riesgo intermedio-alto es significativamente peor. La prevalencia de metástasis ganglionares es mayor en este grupo de pacientes.

II. INTRODUCTION

1. EPIDEMIOLOGY OF ENDOMETRIAL CANCER

Endometrial cancer is the most common female genital tract neoplasm in the Western world. In 2015, around 5,410 new cases were diagnosed in Spain, representing an incidence of 5.9 per 100,000 women, with a 5-year prevalence of 7.6 per 100,000 [1]. Regarding world incidence, presented in Figure 1, it is the sixth most common cancer in women (4.8% of cancers in women) with an estimated incidence of 382,069 cases in 2018. The cumulative risk of developing the disease at 75 years is 1.01% [2]. It is the 14th cancer in terms of mortality in the world (89,929 deaths) [2]. The cumulative risk of death up to age 75 is 0.2%. In Spain the mortality rate is estimated at 3.1 per 100,000 [1].

The increase in incidence of endometrial cancer in recent years in Europe and North America is probably related to the older age of the population as well as the higher prevalence of obesity and metabolic syndrome in these regions. Estimations show that the number of cases will increase to 4,213 per 100,000 by 2030 in the United States [3].



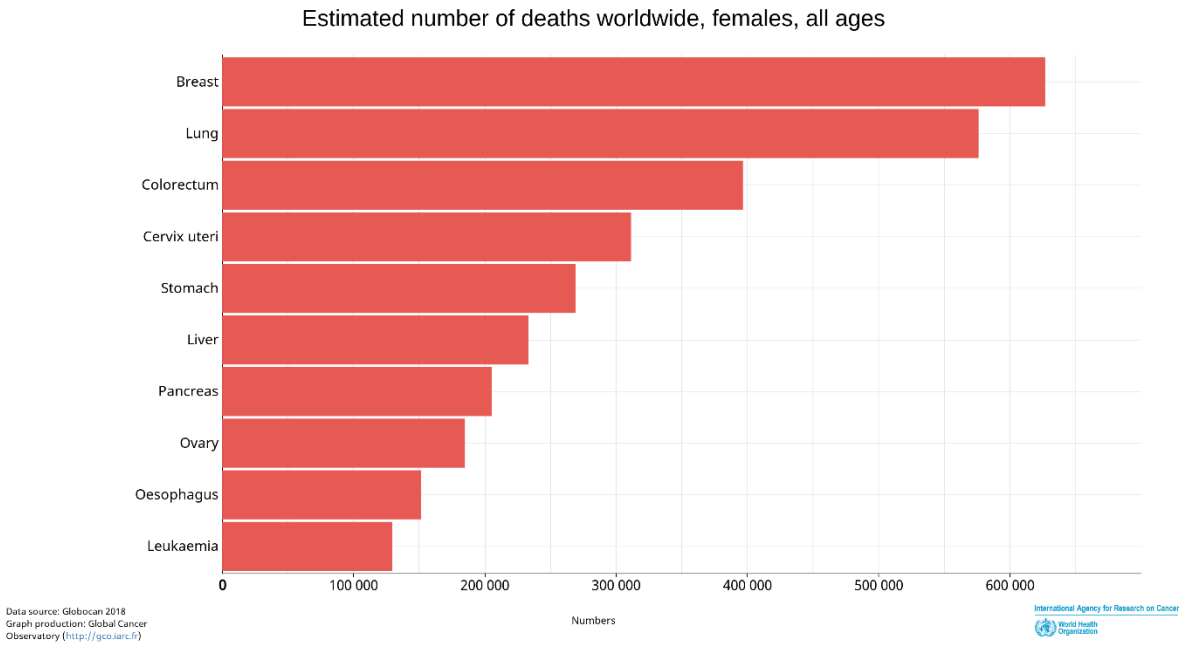


Figure 1 A, B. A: Estimated age-standardized cancer incidence rates in 2018, females, all ages, after GLOBOCAN 2018. B: Estimated number of cancer related deaths in 2018, females, all ages, after GLOBOCAN 2018 [2].

Although endometrial cancer is traditionally associated with postmenopausal bleeding, 14% of cases are diagnosed in premenopausal women, (5% in those under 40 years of age) [4]. The main risk factors include exposure to exogenous oestrogens, family or genetic risk, obesity, nulliparity, early menarche, late menopause, and the use of tamoxifen. The relationship between diabetes mellitus and endometrial cancer remains controversial, as obesity is probably a major confounding factor.

Treatment with Levonorgestrel intrauterine device (IUD), depot progestogens and the use of hormonal contraceptives seems to be protective, especially in patients with hypoestrogenism secondary to chronic anovulation [5].

No screening strategy has been developed for endometrial cancer prevention. This concerns as well patients with hereditary non-polyposis colon cancer or Lynch syndrome where the efficacy of screening has neither been proven. Prophylactic hysterectomy is currently the most efficient prevention measure [6].

2. CLINICAL PRESENTATION AND DIAGNOSIS

Majority of patients (about 90%) presents with abnormal uterine bleeding (postmenopausal bleeding, hypermenorrhea or menometrorrhagia). Abnormal vaginal discharge or pyometra may also occur. Advanced endometrial cancer may have symptoms similar to patients with advanced ovarian cancer such as abdominal pain and distention and constitutional symptoms (weight loss, anaemia). Rarely, patients are diagnosed after an abnormal cervicovaginal Pap smear result.

Pelvic ultrasonography is a standard procedure when abnormal uterine bleeding occurs (Figure 2A). In case of increased endometrial thickness, endometrial sampling is indicated. The cut-off of endometrial thickness is not clear and ranges between 3 and 5 mm in postmenopausal women. A review of 13 studies showed that 5 mm endometrial thickness cut-off has a sensitivity of 90% and specificity of 54%, compared to 98% and 54% when a 3 mm cut-off was used [7]. Diagnosis can be made on a basis of simple office Pipelle endometrial sampling, which is sufficient for preoperative assessment and treatment planning. When the Pipelle biopsy result is inconclusive, hysteroscopy with biopsy is recommended [1] (Figure 2B).

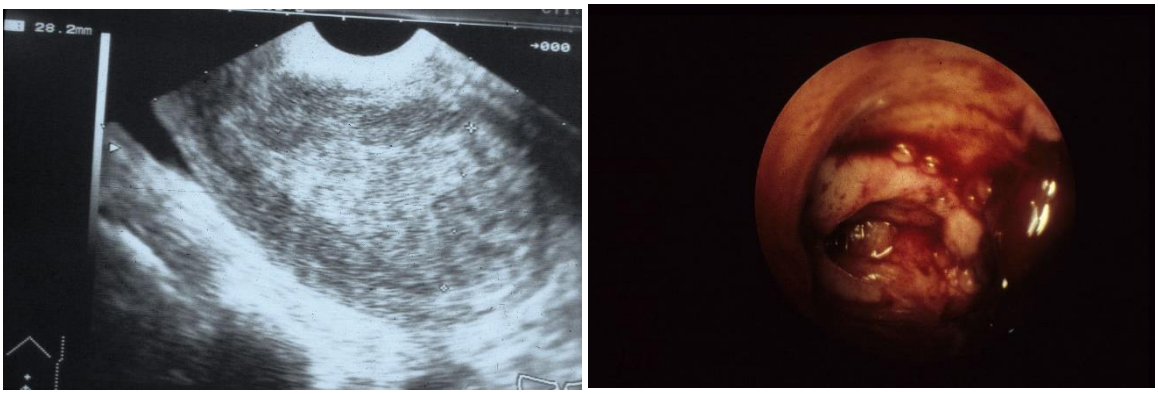


Figure 2 A, B. A: Transvaginal Ultrasound, increased endometrial thickness. B: Hysteroscopic image of endometrial cancer.

3. CLASSIFICATIONS

A) Histological classifications

According to classical Federation of Gynecology and Obstetrics (FIGO) classification (after Bokhman dualistic model [8]) endometrial cancer is traditionally classified as:

- Type 1 – endometrioid, the most common and usually diagnosed at early stages. This type presents a relatively good prognosis. It may arise from complex atypical hyperplasia. Type 1 is endometrioid, diploid and linked to excess of oestrogen stimulation.

- Type 2 – non-endometrioid, less common and less hormone sensitive. Typically, more aggressive, aneuploid, TP53-mutated. It presents a poorer prognosis.

Within type 1 endometrial cancer, the PIK3CA pathway alterations are frequently observed (90% of cases). In 20% of type 1 tumors KRAS mutation is also present. FGFR2 mutations are reported in 12% of tumors [9].

Type 2 endometrial cancers include a wide range of pathological subtypes and have a variety of genomic and molecular features and alterations. Details are represented in table I.

This traditional classification has been currently replaced by endometrioid and non-endometrioid endometrial cancer.

	Endometrioid	Serous	Carcinosarcoma	Clear-cell
Bokhman Subtype	I	II	II	II
TP53 mutation	Rare	>90 %	60-90%	35%
PI3K alterations	PTEN mutation (75–85%) PIK3CA mutation (50–60%) PIK3R1 mutation (40–50%)	PTEN mutation (11%) PIK3CA amplification (45%) PIK3CA mutation (35%) PIK3R1 mutation (12%)	PTEN mutation (19%) PIK3CA mutation (35%) PIK3CA amplification (14%)	PTEN loss (80%) PIK3CA mutation (18%)
KRAS mutation	20-30%	3%	17%	0%
ERBB Alterations	No	ERBB2 amplification (25–30%)	ERBB2 amplification (13–20%) ERBB3 amplification or mutation (13%)	ERBB2 mutation (12%) ERBB2 amplification (16%)
FGFR Amplification/ mutation	FGFR mutation 12 %	FGFR2mutation (5%), frequent FGFR1 and FGFR3 amplification	FGFR3 amplifi-cation (20%)	
Wnt/β-catenin)	CTNNB1 mutation (25%)	CTNNB1 mutation (3%)		

Table I. Molecular classification of endometrial cancers by histology [9].

Endometrial adenocarcinoma can be also classified according the degree of differentiation. Grade 1 comprises less than 5% of a non-squamous or non-morular solid growth pattern. Grade 2 is defined as 6%–50% of a non-squamous or non-morular solid growth pattern. Grade 3 is characterized by greater than 50% of a non-squamous or non-morular solid growth pattern. If an important nuclear atypia is present, it may increase the grade of tumor. Serous and clear-cell carcinomas are considered high-grade tumors by definition by the majority of authors [10].

The WHO (World Health Organization) and the International Society of Gynecological Pathology classification of tumours identifies seven histopathological types of endometrial carcinoma: 1) endometrioid carcinoma (adenocarcinoma; adenocarcinoma-variants [with squamous differentiation; secretory variant; villoglandular variant; and ciliated cell variant) 2) serous carcinoma, 3) clear cell carcinoma, 4) mixed carcinoma, 5) mucinous adenocarcinoma, 6) undifferentiated carcinoma, 7) carcinosarcoma, 8) neuroendocrine carcinomas, and 9) other unusual types [11].

These types differ as for precursor lesions, molecular features and natural history. Serous and clear cell carcinomas are considered as aggressive histologic types. Patients with these types of tumors are often diagnosed at advanced stage (FIGO III-IV in 33-41% of cases).

Carcinoma of the endometrium comprises also mixed epithelial and mesenchymal tumors which include: adenomyoma, atypical polypoid adenomyoma, adenofibroma and adenosarcoma. These histotypes are not concerned in this introduction.

Although the classification proposed by Bokhman in 1983 is frequently used in clinical decision-making, it has been observed that its prognostic value does not apply to all cases. It is estimated that 20% of endometrioid carcinomas will recur, while up to 50% of type 2 carcinomas will never relapse. Consequently, it seems that endometrial carcinoma comprises a great variety of clinical entities where genetic factors and molecular characteristics could play a primary role.

b) Molecular classification

To overcome these problems The Cancer Genome Atlas Research Network (TCGA) performed integrated genomic, transcriptomic and proteomic characterization of 373 endometrial cancer patients [12]. As a result of this work published in 2013 in Nature, a new molecular classification of endometrial cancer was proposed. Their results classified endometrial cancers into four categories: somatic inactivating mutations in polymerase Ɛ exonuclease (POLE ultramutated, 7%), microsatellite instability hypermutated (MSI hypermutated, 28%), copy-number low (non-specific molecular profile, 39%) and copy-number high (serous-like, frequent TP53 mutations, 26%). Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. These results gave evidence that the genomic features of endometrial carcinomas permit a reclassification that may affect surgical management, provide guidance for post-surgical adjuvant therapy and disease surveillance.

The POLE ultramutated group is characterized by an excellent prognosis, whereas the TP53 mutated group typically indicates poor prognosis tumors.

These findings were analyzed in a large randomized trial population (PORTEC group), which confirmed a prognostic capacity of these subgroups [13].

Following these studies, another group developed a simplified, pragmatic, molecular classifier, called Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), which identifies four molecular analogues subtypes to the four genomic subtypes described in TCGA. Mismatch repair deficient (MMR-D), showing loss of one or more mismatch repair protein(s), corresponds to the MSI-H/hypermutated subtype. DNA polymerase epsilon (POLE), with mutations in the exonuclease domain in exons 9–14, corresponds to the ultramutated subtype. P53 abnormal (p53abn) demonstrating aberrant p53 immunohistochemical staining, corresponds to the copy number high subtype. Finally, p53 wild-type (p53wt) corresponds to the copy number low subtype [14, 15].

In contrast to the TCGA methods that depend on fresh-frozen material and require costly and complex methodologies, ProMisE can be achieved on formalin-fixed, paraffin-embedded material using methods easily adopted in pathology labs at most cancer centres.

The usefulness of TCGA approach has been confirmed particularly in high-grade endometrioid carcinoma, and serous carcinoma. POLE mutated high-grade endometrioid carcinoma, have an excellent prognosis. P53 abnormal tumors are characterized by poor outcome. This is the situation of the majority of serous carcinomas (95%). Endometrioid carcinoma with MSI or NSMP, have an intermediate prognosis and they represent the vast majority of low-grade endometrioid carcinoma.

In summary, TCGA molecular surrogate is particularly of interest in high-grade endometrioid carcinoma and tumors in the grey zone between endometrioid carcinoma and serous carcinoma. The decision to implement the molecular-based surrogate in all endometrial cancers, or just in high-grade tumors, or in any of them depends on the available resources. If molecular classification tools are not available, endometrial cancer characterization should be based on traditional pathological features. There is still room for other biomarkers that may be potentially useful in the big group of low-grade endometrioid carcinoma with NSMP, such as L1CAM expression or mutations in CTNNB1. However, in this group, appropriate pathologic staging and assessment of lymphovascular space involvement (LVSI), seems to be particularly useful.

c) New biomarkers

L1 cell adhesion molecule (L1CAM) was found to be a promising biomarker for identification of patients with poor outcome, which has been confirmed in subsequent studies. Other prognostic biomarkers in endometrial cancer are: markers of the p53 pathway, hormone receptor expression, and microsatellite instability [16, 17].

Pathological information has been used to estimate risk of nodal metastasis and define prognosis (recurrence, survival) in endometrial cancer. These prognostic factors are widely used to classify patients into risk groups to guide surgical management and adjuvant treatment.

4. PREOPERATIVE ASSESMENT

Preoperative evaluation of endometrial cancer using modern imaging methods is universally recommended before surgical treatment. The preoperative imaging issues to evaluate the extent of myometrial, cervical invasion and the presence of extrauterine disease.

Magnetic resonance imaging (MRI) is the standard method used in preoperative assessment with highest interobserver concordance [18]. Transvaginal ultrasound is found to have similar sensibility and specificity in experienced hands [19]. In contrast, computerised tomography is not useful to assess the extent of uterine disease (myometrial or cervical invasion) but it can be used to determine extrauterine disease (regional metastatic lymph nodes or metastatic distant disease). The use of PET-CT in early stage endometrial cancer is questionable. Its utility and prognostic value is proven in advanced endometrial cancer [20].

The role of preoperative assessment is to establish a recurrence risk group, on basis of myometrial invasion and cervical involvement to predict the risk of lymph node metastasis and to plan a surgical strategy.

5. STAGING CLASSIFICATIONS

Multiple risk models have been created on the basis of pathologic information to define prognosis and estimate risk of nodal metastasis in endometrial cancer. FIGO 2009 and TNM classifications are the most widely used (Table II, III) [21, 22]. They are based on presence or absence of local or metastatic disease based on surgical staging. FIGO/TNM classifications include the assessment of the extent of myometrial invasion. Deep endometrial invasion is an additional factor predictive of nodal involvement and survival. In the GOG trial published in 1991, authors found 94% 5-year survival when the tumor was confined to endometrium, 91%, 84% and 56 % when the myometrium was invaded <33%, 33-66% and >66%, respectively [23].

FIGO stage is one of the strongest predictors of outcome in patients with endometrial cancer. For example, patients with nodal metastases in endometrial cancer have poorer prognosis when compared with negative nodes patients. FIGO publication showed 57% 5-year survival in patients with stage IIIC disease when compared to 74-91% in patients without lymph node involvement.

FIGO Stage	
I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus (A)
III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae (B)
IIIB	Vaginal involvement and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes)

Table II. Current FIGO 2009 staging classification for cancer of the corpus uteri [21].

A: Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

B: Positive cytology has to be reported separately without changing the stage.

FIGO Stage	Union for International Cancer Control (UICC)		
	T (tumor)	N (lymph nodes)	M (metastasis)
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T3	N0–N1	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC1	T1–T3	N1	M0
IIIC2	T1–T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

Table III. Cancer of the corpus uteri: FIGO staging compared with the TNM classification [22].

Different risk models have been created to adjust more accurately the risk stratification systems. These classifications add other prognostic factors not included in FIGO/TNM classification such as age, grade and type of tumor, tumor size and the presence of LVSI.

The European Society of Medical Oncology (ESMO) [24] and more recently together with the European Society of Gynecologic Oncology (ESGO) and the European Society of Radiation Oncology (ESTRO), a risk classification system has been published (Table IV, V), which is the one most commonly used in Europe to tailor adjuvant treatment and also to plan surgical management on the basis of preoperative information [25].

Risk group	Description
Low	Stage I endometrioid, grade 1 or 2, <50% myometrial invasion, LVSI negative
Intermediate	Stage I endometrioid, grade 1 or 2, ≥ 50% myometrial invasion, LVSI negative
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status Stage I endometrioid, grade 1 or 2, LVSI unequivocally positive, regardless of depth of invasion
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status Stage II Stage III endometrioid, no residual disease Non endometrioid (serous or clear cell or undifferentiated carcinoma or carcinosarcoma)
Advanced	Stage III residual disease and stage IVA
Metastatic	Metastatic Stage IVB

Table IV. Risk groups according to ESGO/ESMO/ESTRO 2016 classification [25].

Risk group	Description
Low	Stage I endometrioid, grade 1 or 2, <50% myometrial invasion
Intermediate	Stage I endometrioid, grade 1 or 2, ≥ 50% myometrial invasion Stage I endometrioid, grade 3, <50% myometrial invasion
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion Non endometrioid (serous or clear cell or undifferentiated carcinoma or carcinosarcoma)

Table V. Risk groups according to ESGO 2010 classification [24].

6. DEFINITIONS OF INTERMEDIATE RISK ENDOMETRIAL CANCER

a) Intermediate risk classifications based on traditional pathological features

When looking back into literature, the risk classifications have substantially changed in the last 20 years. Regrettably, the definition of intermediate risk and high-intermediate risk endometrial cancer is not universal. These differences in definition make it difficult to extrapolate the results of studies addressing the prognosis of intermediate low and high risk endometrial cancer patients. For example, in GOG 99 high-intermediate risk patients were defined as: 1) moderate to poorly differentiated tumors, presence of LVSI and outer third myometrial invasion; 2) age 50 or greater with any two risk factors listed above; or 3) age of at least 70 with any risk factor listed above. Intermediate low-risk was defined as age ≤50 and ≤2 risk factors; age 50-69 and ≤1 risk factor or age ≥70 years without risk factors [26]. In contrast, The PORTEC-1 definition of high-intermediate risk is two of the following three factors: age >60, more than one half myometrial invasion, and grade 3 disease. Intermediate low was defined as 1) stage I, grade 1, myometrial invasion ≥50%; 2) stage I, grade 2 or 3) stage I, grade 3, myometrial invasion <50%. The latter definition was further used in ESMO 2010 for the definition of intermediate risk [24, 27]. An interesting review both on PORTEC 1 and GOG 99 classification of high/intermediate risk patients showed that adjuvant radiation was associated with an overall survival benefit in patients meeting GOG-99 criteria only; however, no survival benefit was seen in patients meeting PORTEC-1 criteria only. The authors proposed a new classification on these findings [28].

One study compared the accuracy of different risk stratification, demonstrating that none of the five major risk systems shows high accuracy to stratify recurrence risk and nodal metastases in early-stage endometrial cancer [29].

Different international societies add different criteria to consider high-intermediate risk patients and need for adjuvant brachytherapy. The National Comprehensive Cancer Network (NCCN) includes extensive LVSI, age, tumor size and lower uterine segment invasion as additional risk factors [30]. The new NCCN criteria classified patients as high-intermediate group based on GOG 249 study. High intermediate group is defined as: age 50-69 years with two risk factors or <50 years with 3 risk factors. The American Society for Therapeutic Radiation Oncology guidelines specify age >60 and LVSI as adverse risk factors [31].

b) Molecular classification

New NCCN guidelines mention the molecular classification in recommendations. According to these guidelines, molecular testing is counselled to all endometrial cancer patients, especially in patients with high-grade endometrioid cancer. Schematic proposition of implementation of molecular testing after Murali et al., is presented in the Figure 3 [32].

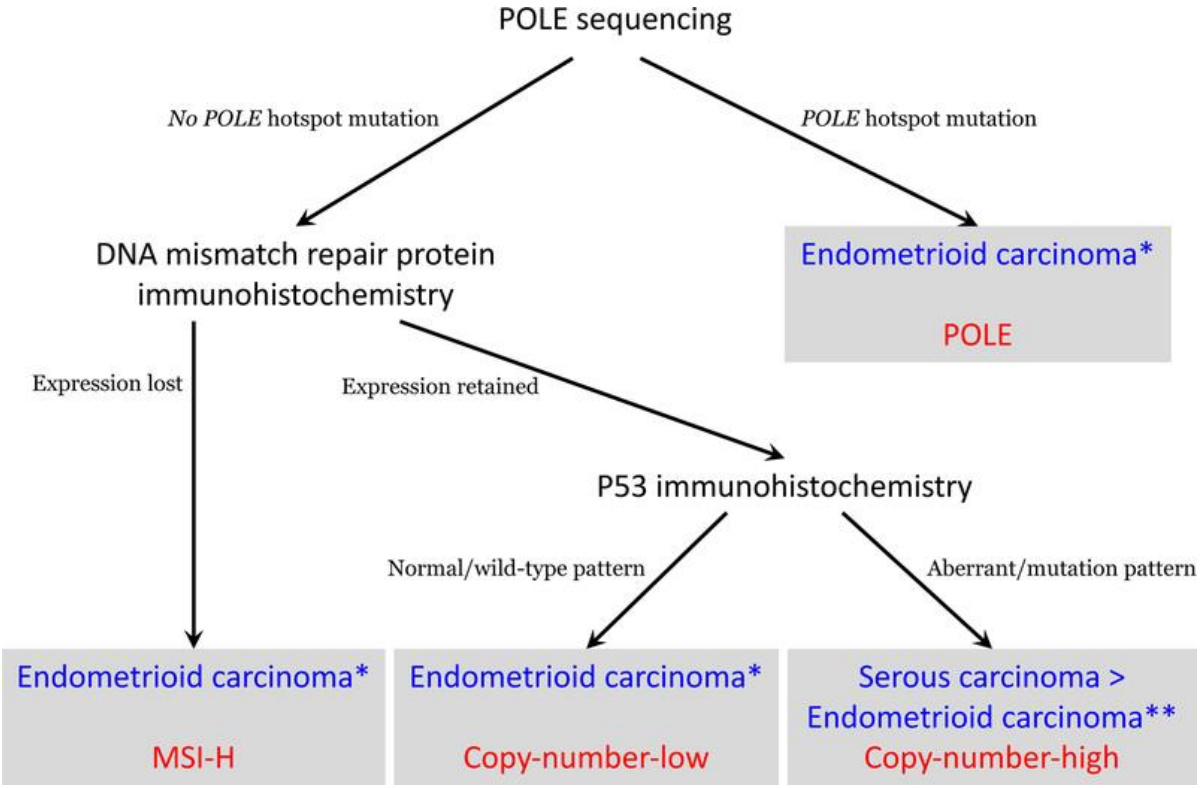


Figure 3. Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas (blue=histotype; red=TCGA genomic class) [32].

MSI-H: microsatellite instability high; *May also apply to clear cell carcinomas; **This algorithm does not distinguish between histotypes of TP53-mutated copy-number-high tumors, i.e., high-grade endometrioid carcinoma, serous carcinoma, or clear cell carcinoma

Holding all the new molecular local predicting factors markers that could potentially permit to classify patients into risk groups, the question of interest of lymph node dissection may again be put forward.

However, for the moment it is uncertain whether preoperative ProMisE/TCGA classification (using biopsy or curettage specimen) can be used to select patients to different

types of staging surgery. For example, patients with *POLE*-mutant tumors might not need comprehensive surgical staging. Similarly, patients with serous and serous-like carcinomas may not benefit from comprehensive surgical staging, since nearly all will require adjuvant chemotherapy and it is possible that full surgical staging may only be applicable to the remaining categories.

None of the international societies considers the TCGA biomarkers in prognostic risk group stratification to guide adjuvant treatment so far. This is probably due to lack of prospective data that would support the real benefit of this classification.

c) ESGO/ESMO/ESTRO 2016 CLASIFICATION

In 2016 a joint consensus of European Societies (ESGO, ESMO and ESTRO) has decided to change the risk stratification system. The subclassification of intermediate risk endometrial cancer was introduced and a new definition of high-intermediate group was added. High-intermediate risk was described as: 1) stage I endometrial, grade 3, myometrial invasion <50%, independently of LVSI or 2) stage I endometrial grade 1-2, LVSI invasion unequivocally positive, independently of myometrial invasion [25]. This new subclassification into standard intermediate and high-intermediate risk was supported by retrospective reports, which documented adverse prognosis of LVSI positive and grade 3 tumors. LVSI with an emphasis on 'extensive' was incorporated as an important prognostic factor [33-37]. The presence of extensive LVSI classifies patients into high-intermediate risk group.

The introduction of extensive LVSI in the risk stratification has been an important point, as this histologic feature strongly impacts prognosis in early stage endometrial cancer and should be precisely reported in the pathological report. Research based on PORTEC 1 and 2 cases highlighted the importance of quantifying the number of vessels involved with LVSI as focal or substantial/extensive. Substantial LVSI, in contrast to focal or no LVSI, was found to be the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival [38]. Examples of focal and extensive LVSI are represented in Figure 4 A, B.

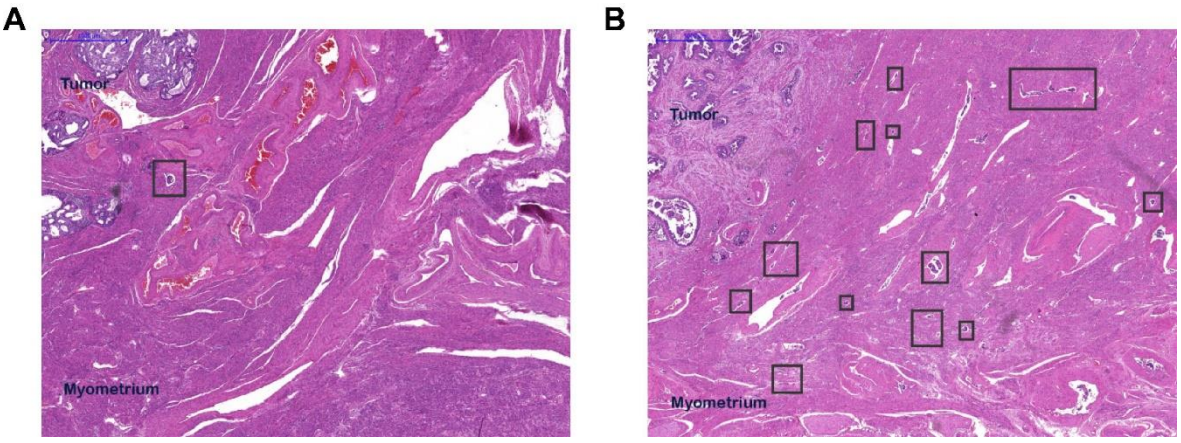


Figure 4 A, B. A: focal lymphovascular space invasion (LVSI). B: Representative examples of substantial LVSI. Black boxes indicate foci of LVSI. (Bosse et al. [38]).

7. SURGICAL MANAGEMENT OF INTERMEDIATE AND HIGH-INTERMEDIATE ENDOMETRIAL CANCER

As a transitional risk group between low and high risk endometrial cancer, the management of intermediate risk endometrial cancer patients is frequently an issue of controversy. The debate is frequently focused on the indication of lymph node dissection and adjuvant treatment.

There is a universal consensus that total hysterectomy with bilateral salpingo-oophorectomy is the standard treatment for apparent stage I endometrial cancer and is effective in most cases [25].

The majority of international guidelines already agree that patients classified as ESMO low risk tumors (FIGO IA, grade 1 and 2 without LVSI) for recurrence could benefit from the conservative staging procedures without lymph node dissection and no adjuvant treatment is recommended [1, 25].

On the contrary, in high risk endometrial cancer (Stage IB grade 3 endometrioid type with positive LVSI or non-endometrioid disease of all stages) comprehensive surgical staging including hysterectomy with bilateral salpingo-oophorectomy, pelvic washing, and pelvic and para-aortic lymph node dissection is recommended.

This opinion is based on prognostic significance of lymph nodes involvement known from decades and has given the idea of full lymph node staging in order to improve survival.

However, there is only one retrospective study that evidenced a survival improvement of complete surgical staging [39, 40]. However, non-randomized studies support these data [41, 42].

Our group has published a matched pair retrospective multicenter study and has observed the lack of prognostic value of lymphadenectomy in high risk endometrial cancer [43].

8. ADJUVANT TREATMENT IN INTERMEDIATE AND HIGH-INTERMEDIATE ENDOMETRIAL CANCER

The therapeutic role and the modalities of adjuvant treatment in endometrial cancer are also controversial. The publication of the Dutch PORTEC group trial has resulted in reduction of adjuvant radiotherapy in early stage endometrial cancer. The PORTEC 1 study showed no benefit in overall survival for patients with low or intermediate risk endometrial cancer, whether they received adjuvant radiation therapy or not [27]. PORTEC 2 study compared vaginal brachytherapy versus external beam radiotherapy for patients with high-intermediate risk endometrial cancer (PORTEC risk stratification) and found no differences in disease-free survival. Toxicity and quality-of-life profile were more favourable in the brachytherapy arm [44].

The results of these trials have been universally implemented. In consequence, in 85% of patients with early stage endometrial cancer routine adjuvant radiotherapy has been abandoned. Of note, lymphadenectomy was not done routinely in the PORTEC trials. The authors of PORTEC 1 suggest that these results should not motivate surgeons to perform more lymph node dissections in order to find microscopic disease, as this increases morbidity without benefit on overall survival [45].

The ASTEC/EN.5 trial has analysed intermediate or high risk of recurrence patients, randomised to either adjuvant brachytherapy and external beam radiotherapy (EBRT) or brachytherapy alone. Only 31% and 28% of patients in each group, respectively, underwent lymphadenectomy (pelvic or pelvic and para-aortic). This study has shown no evidence of benefit for external beam radiotherapy for early endometrial cancer in terms of overall, disease-specific, and disease-specific recurrence-free survival [46].

Finally, the GOG 99 trial studied specifically intermediate risk endometrial carcinoma. The authors concluded that adjuvant EBRT decreases the risk of recurrence, but should be limited to high-intermediate risk patients. In absolute terms, EBRT patients in the group of high-intermediate risk resulted in a 19% improvement in cumulative incidence of recurrence at 24 months when compared to the control group. Overall survival seemed to be better in the radiotherapy arm (92% versus 86%, respectively). However, it did not reach statistical significance. Of note more than 50% of the deaths reported in GOG 99 were not cancer related [26].

A meta-analysis on the effect of external beam radiotherapy on overall survival in intermediate risk and high risk early-stage disease, including Cochrane and ASTEC/EN.5 results, showed a non-significant hazard ratio of 1.04 (95% confidence interval 0.84–1.29; p=0.38) [46]. Based on this finding, the European consensus panel recommends external beam radiotherapy only in the subgroup of high-intermediate risk patients with unknown nodal status [25].

This leads to another challenging discussion on endometrial cancer adjuvant treatment. If 5-year overall survival rates range around 90% and the disease affects elderly patients, it is extremely difficult to prove that any treatment will improve the overall survival.

Still importance on DFS improvement with radiotherapy is not negligible as it may improve the quality of life. This is documented in patient's preference study that showed patient choice towards a treatment to prevent the relapses [47].

According to European guidelines and based on strong evidence supported by the results of PORTEC group trials patients with low risk endometrial cancer features are not candidates for adjuvant radiation therapy. These patients managed with surgery only have 95% probability of relapse-free survival at 5 years.

EBRT is still indicated for patients characterized as high risk of recurrence.

For intermediate risk endometrial cancer adjuvant brachytherapy is currently a standard treatment. This therapy is recommended to decrease vaginal recurrence. No adjuvant treatment is an option, especially for patients aged <60 years.

Randomized clinical trials have shown very good vaginal control with adjuvant brachytherapy, and only 2% vaginal recurrence. Overall survival rates are comparable to EBRT arm in intermediate risk endometrial cancer patients. These results were confirmed in the 10-year analysis of the PORTEC-1 trial [45].

A Danish gynecologic oncology group presented a nationwide prospective study and demonstrated that postoperative radiotherapy could be omitted in low and intermediate risk stage I patients without loss of survival. For this reason, European guidelines mention an omission of treatment as an option, especially for patients younger than 60 years [48].

In the 10-year analysis of PORTEC 2 trial, it has been shown that patients that presented with substantial LVSI, p53abn or L1-CAM overexpression had a hardly higher risk of pelvic relapse with brachytherapy than those who were managed with EBRT [49].

In high-intermediate group, European guidelines recommend external-beam radiotherapy for patients with unknown lymph node status.

NCCN guidelines recommend vaginal brachytherapy as a preferred option for intermediate risk endometrial cancer, or observation, if no other adverse risk factors are present (age > 60, LVSI). In case of high-intermediate risk vaginal brachytherapy is still preferred, however, external beam radiotherapy can be considered [30].

9. CONTROVERSIES ON SURGICAL STAGING: THE ISSUE OF LYMPH NODE DISECTION

The role of staging procedure in any malignant tumor is to define similar patients' populations referring to prognosis and therapy. In endometrial cancer, surgical staging has been introduced in 1988 after the publication of the Gynecologic Oncology Group (GOG) study [50]. That year, the International Federation of Gynecology and Obstetrics (FIGO) and GOG recommended systematic surgical procedure that included hysterectomy with bilateral oophorectomy (TH&BSO), pelvic washing, and pelvic and para-aortic lymph node dissection (LND) in patients who presented risk factors including unfavorable histology and myometrial invasion. However, systematic LND has been lately a reason of debate. The doubts are more than justified considering the generally underestimated, serious consequences and possible complications of the LND just to stratify the patient, if in fact there is no impact on overall survival.

a) Tumor characteristics predictive of nodal involvement

Pathological information has been used to estimate risk of nodal metastasis and define prognosis (recurrence, survival) in endometrial cancer. These prognostic factors are widely used to classify patients into risk groups to guide surgical management and adjuvant treatment.

The grade of histologic differentiation is a known factor of tumor spread. It is directly related to myometrial invasion, risk of nodal involvement and in consequence overall survival. The relative risk of death for patients with grade 3 compared to grade 1 in PORTEC trial was 4.9 vs. 0.45, respectively [27].

Deep endometrial invasion is an additional factor predictive of nodal involvement and survival. In the GOG trial published in 1991, authors found 94% 5-year survival when the tumor was confined to endometrium, 91%, 84% and 56 % when the myometrium was invaded <33%, 33-66% and >66% respectively [23].

LVSI is defined as the presence of viable tumour cells within endothelium-lined spaces, typically as clusters of cells that appear “free-floating” and often conform to the shape of the space. It is found in around 10-15% of FIGO stage I endometrial cancers. The presence of LVSI is a well-known prognostic factor in endometrial cancer and should always be recorded in the pathology report. A recently published novel LVSI classification based on PORTEC 1 trial points out the importance to quantify the number of vessels involved with LVSI as focal or substantial/extensive. According to the authors substantial LVSI, in contrast to focal or no LVSI, was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival [38]. The reproducibility of this new LVSI classification has been validated in an ancillary study by Peters et al. [51].

Involvement of more myometrial vessels and more distant vessels is closely related to the probability of lymph node metastasis and a shorter disease-free and overall survival [52].

LVSI confined to rare vessels are of questionable prognostic value and classified by some pathologists as “indeterminate,” corresponding to the definition of “focal”.

The pseudo LVSI artifacts mimicking LVSI has also been found due to processing or uterine manipulation during laparoscopic surgery. Although the differential diagnosis is sometimes extremely difficult the effort should be made to distinguish true LVSI from such mimics, since the pseudo LVSI is not a prognostic factor [53].

Finally, LVSI as an important prognostic factor, with an emphasis on 'extensive' has been added to the ESGO/ESMO/ESTRO risk stratification. The presence of extensive LVSI, classifies patients into high-intermediate risk group.

While conventional pathology remains the standard for the diagnosis of endometrial cancer, its main problem is the inter-observational reproducibility. Various studies have shown that a high-grade endometrial cancer diagnosis is not highly reproducible. Some pathologists have observed even 10% of discordance in pathological diagnosis in high-grade endometrial tumors [54, 55].

Another issue is the limitation of prognostic value of standard pathology. Interestingly, not all high-grade tumors relapse and not all low-grade tumors show good prognosis.

b) Risk and complications related to lymph node dissection.

Potential risks of lymph node dissection must be taken into account in the risk/benefit balance.

Intraoperative and postoperative morbidity has been described in around 8% of para-aortic lymph node dissections (LND) [41, 56].

The most common intraoperative complications are vascular injuries, occurring up to 5% of cases. These can lead to conversion to laparotomy when major vessels are involved. Acute arterial dissection is a rare serious vascular complication described in the literature [57]. Deep venous thrombosis and/or pulmonary embolism have been reported in approximately 0-8% in modern series. Lymphocele is directly associated with an increased risk of thromboembolic events.

Ureteral and bowel injuries are infrequent complications that have also been reported in lymphadenectomy. Severe nerve injuries are rarely reported in the literature. The most

frequent neuronal complication concerns the obturator nerve. In this case, usually we speak about a nerve contusion or so called neuropraxia. Recovery is expected to occur within 6 weeks. In more severe cases the functional recovery occurs within 6-12 month. The injury of obturator nerve can be a cause of pain, sensory loss to the medial thigh and inconstant loss of adductor muscle function. Long-term motor consequences, even if complete division occurs, are extremely rare. This is due to dual innervation of several adductors' muscles and presence of an accessory obturator nerve [58].

Long-term complications associated to LND are mainly lymphocele and lower limb lymphedema. The exact incidence of these complications is unknown and usually underestimated. Lymphoceles are lymph-filled collections without a distinct epithelial lining, caused by the disruption of efferent lymphatics during LND. The incidence of lymphocele formation ranges from 1 to 58%. Most lymphoceles are asymptomatic and resolve spontaneously with the development of new lymphatic vessels. Symptomatic lymphoceles are described in 5-34.5% of cases. Signs are habitually related to compression to adjacent organs, infection, or discharge related to spontaneous drainage [59-61]. Lymphedema is defined as a chronic, dynamic condition in which protein rich fluid accumulates in the superficial tissues. It occurs in 12% up to 40% of patients surgically staged for endometrial cancer. This difficult condition may cause discomfort, heaviness but also reduced mobility in these patients. It is related to reductions in both physical and mental quality of life 3-5 years after cancer treatment [62-66].

Adjuvant radiotherapy, extensive nodal dissection (higher node count), and removal of circumflex iliac nodes to the distal external iliac nodes, are described as the main risk factors of lymphedema [67].

A recently published large prospective trial (GOG 244) assessed the incidence of lymphedema by regular measuring of the leg volume with a follow up of 48 months. The authors observed lymphedema defined by volume change >10% - in 34% of endometrial cancer patients fully staged with pelvic and para-aortic LND. Advanced age and node count over 8, were found as the main risk factors. Increase risk of lymphedema was not associated with radiation, advanced stage or other commonly reported risk factors [68].

Other authors use the Lymphedema PRO e-mail surveys. This is the case of Leitao et al. study [69] that compared the prevalence of patient-reported lower-extremity lymphedema in patients with newly diagnosed endometrial carcinoma who underwent full surgical staging (para-aortic and pelvic lymphadenectomy) when compared with sentinel lymph node biopsy. The authors observed a prevalence of lymphedema in order of 41% in the lymphadenectomy group compared to 27% in the sentinel lymph node group that surprisingly is comparable to the group without any lymph node mapping. It suggests that the incidence of this complication is probably overestimated in this article. Authors concluded that sentinel lymph node mapping over lymphadenectomy is independently associated with a significantly lower prevalence of patient-reported lower-limb lymphedema.

The results were confirmed in a prospective multicentric trial publication on cervical cancer–SENTICOL 2 presented at SGO meeting in 2017, yet unpublished [70].

c) Therapeutic value of lymphadenectomy

THE POTENTIAL OF SURGICAL RESECTION OF NODAL DISEASE

Some historical publications pointed out the therapeutic value of surgical excision of positive lymph nodes. These data have not been confirmed in previously mentioned prospective trials [41, 42]. However, a few retrospective works suggested that full lymph node dissection have a positive impact on patient's survival. The question remains tough controversial. A control case study published in 1996 suggested that patients who underwent pelvic node sampling had better outcome [71]. Different publication showed improved prognosis in patients with positive lymph nodes or with high-grade tumors [72, 73].

The SEPAL study showed also better outcome in patients undergoing pelvic and para-aortic lymphadenectomy versus pelvic lymphadenectomy only. However, also in this retrospective study adjuvant therapy was not comparable in the two groups. In patients who underwent both pelvic and para-aortic lymphadenectomy, 77% received chemotherapy and only 45% in the pelvic lymphadenectomy group [74].

Therefore, for the moment, there is no definitive evidence that lymphadenectomy has a therapeutic value. According to the available evidence its role is mainly prognostic and

serves as information to guide further adjuvant treatment. Consequently, if the same prognostic information can be obtained by SLN biopsy alone, the patient could be spared the risks associated with comprehensive LND.

THE ROLE OF LYMPH NODE DISSECTION IN TAILORING ADJUVANT TREATMENT

The information provided by the lymph nodal assessment is traditional a major argument in favour of adjuvant treatment. Lymph node involvement has been the most important prognostic information in patients with endometrial cancer. However, this paradigm has recently lost in importance.

The authors of PORTEC-1 trial suggest that 9% prevalence of microscopic lymph nodes disease in early stage endometrial cancer patients probably do not justify the morbidity of systematic lymph node dissection. In none of the previously mentioned randomised studies on radiotherapy in endometrial cancer, lymph node status has been taken into account.

Even if the decision on radiotherapy is a minor question facing the results of PORTEC, ASTEC/EN.5 and GOG 99 trials, still the decision on adjuvant chemotherapy could be influenced by the nodal status and impact survival. Positive lymph node is still standing indication for adjuvant therapy. These recommendations are supported by the PORTEC 3 trial, and the recently published GOG 258 trial [75, 76].

PORTEC 3 trial randomized patients with high-risk Stage I–II (32% grade 3 and 29% serous or clear cell cancer) or with Stage III (45%) endometrial cancer to either pelvic EBRT alone or EBRT with two concurrent cycles of cisplatin in weeks 1 and 4 of EBRT, followed by four cycles of carboplatin and paclitaxel. In this study women with Stage III disease had the highest absolute benefit of chemoradiotherapy, with 5-year failure-free survival of 69% versus 58% for radiotherapy alone (P=0.03) [75].

In the randomized GOG-258 trial for Stage III and Stage IV (residual disease <2 cm allowed), 813 patients were randomized to receive either chemoradiotherapy as used in PORTEC-3 or six cycles of carboplatin and paclitaxel without radiotherapy. This last study showed non-inferior DFS and OS in patients FIGO stage III and IV that received only adjuvant chemotherapy [76]. Results of GOG 258 and PORTEC 3 again pose a challenge in the discussion about the relevance of lymph node dissection. According to current guidelines, for patients

with Stage III endometrial cancer, the combination of adjuvant chemotherapy and EBRT seems most effective to increase the DFS.

Despite of this evidence there is no proof that the abstention of adjuvant treatment in patients with positive lymph nodes has a negative impact on survival. As for our knowledge and after a thorough bibliographic research there is no trial that compared adjuvant treatment versus no treatment in patients with lymph node disease. In other words, knowledge of the presence or absence of lymph node metastasis may change treatment approaches and indicate different management, but the impact of those changes on overall survival is not clear at all. However, the fact is that if combined treatment -radiation therapy with chemotherapy - is more effective than radiation therapy in stage IIIC endometrial cancer patients (as revealed in the PORTEC 3 trial), this fact would appeal for a therapeutic effect of chemotherapy. The evidence is even stronger with the results of GOG 258 trial. These results speak in favour for lymph node dissection in groups with high risk of lymph node involvement.

Going further in the discussion, the decision about adjuvant treatment could theoretically be guided only on the basis of local pathological risk factors (grade, type, LVSI), independently of nodal status. Actually, it is unknown if adjuvant therapies given to lymph node positive or patients with unknown node status perform similarly.

This is probably even more valid if molecular prognostic factors are used in complement of the traditional pathologic characteristics. The potential of biomarkers in tailoring adjuvant therapy was suggested already in two promising papers [16, 77] and is being investigated in the PORTEC 4a trial. [78]. This prospective phase III trial investigates the role of an integrated clinicopathological and molecular risk profile to determine if patients with high-intermediate risk features should receive no adjuvant therapy, vaginal brachytherapy or external beam radiotherapy. Awaiting the results of this study, the current ESGO/ESMO/ESTRO subclassification of intermediate risk has to be taken into account for adjuvant treatment planning. The same will remain valid in the future in settings where molecular biology resources are not available.

Taking into consideration the difficulty in assessing LVSI preoperatively and the controversy regarding full lymph node dissection, the current development of the SLN

technique is likely to be the best staging compromise in intermediate risk cancer patients [79] (see below).

d) Evidenced based lymphadenectomy (prospective/retrospective)

There are two prospective randomized studies analyzing the role of LND in endometrial cancer [41, 42]. Both Benedetti Panici group and ASTEC study concluded that apparently there is no survival benefit of LND neither in low risk nor intermediate/high risk endometrial cancer.

Both studies recruited a large number of patients, and investigators observed a large number of events to establish the survival outcome. However, both studies were widely criticized. The main drawback of the ASTEC study was the absence of routine para-aortic LND in the lymphadenectomy group, the low mean number of nodes retrieved when LND was performed and the mathematical model used in the analysis. Another major criticism was the high proportion of low-risk patients that might have biased the results. In the Benedetti Panici trial, which randomized only intermediate and high risk patients, para-aortic LND was performed only in a small (26%) proportion of patients from LND group. This trial, showed no statistically significant differences for vaginal recurrence (2.6% for LND group vs. 2.4% for no LND group), lymph node recurrence (1.5% vs. 1.6%), and intraperitoneal relapse (3% vs. 2.8%) between the two arms of the study.

A secondary analysis of this randomized study was further performed. The authors found a poorer prognosis in obese and elderly patients whether or not they underwent lymphadenectomy and irrespective of the presence of nodal metastasis [80].

The survival results of these prospective trials were combined in a Cochrane group meta-analysis [81]. The conclusion of this review indicated no significant differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy. In this meta-analysis the hazard ratio was 1.07 (95% confidence interval 0.81 to 1.43) for overall survival and hazard ratio 1.23 for recurrence-free survival (95% Confidence Interval 0.96 to 1.58).

The evidence from these randomized clinical trials did not show a clear benefit of LND for women with early-stage endometrial cancer. The authors of the Cochrane meta-analysis

suggested that it is questionable whether additional trials in this area are justified. However, the authors of this analysis evoked the need of studies for intermediate risk patients independently.

Indeed, a new clinical trial was opened to recruitment 2 years ago and is ongoing. The Endometrial Cancer Lymphadenectomy Trial (ECLAT), (NCT03438474) aims to assess whether or not systematic pelvic and para-aortic LND have a significant impact on overall survival in patients with high risk endometrial cancer. The results of this trial are expected by the end of 2029 [82].

LND in intermediate/high risk endometrial cancer has been also studied in numerous retrospective trials, showing controversial results in relation to its survival benefit [83, 84].

Similarly, differences between pelvic and para-aortic LND compared to pelvic LND alone have been studied, again with controversial results [85, 86]. The SEPAL study concluded that comprehensive para-aortic LND had survival benefits (DFS and OS) for patients with intermediate and high risk endometrial cancer compared to pelvic LND alone. The median lymph node count was 34 in pelvic LND group and 82 on pelvic and para-aortic group. FIGO stage IIIC disease was found in 16% of patients. The considerable node count could speak in favor of therapeutic role of LND. However, the outcome of no-LND group was not reported, which makes a definitive conclusion impossible. Another recently published retrospective study concluded that the combination of pelvic/para-aortic lymphadenectomy significantly reduces the mortality in patients with intermediate risk compared to the patients who underwent no lymphadenectomy (hazard ratio 0.50, 95% confidence interval 0.43-0.81, $p<0.0001$) [74].

Another large multicentric retrospective study that included 27,063 patients with early stage endometrial cancer compared the outcome of women with or without lymphadenectomy. The authors concluded that lymphadenectomy is associated with an improved survival in stage I grade 3 and more advanced endometrioid uterine cancers [87].

In contrast, the multicentric retrospective study published by Coronado et al. did not find any benefit for survival in intermediate risk endometrial cancer [88]. The results were

though limited by a low number of nodes removed, a low number of positive nodes and the absence of systematic para-aortic dissection.

A similar multicentric study from the French FRANCOGYN Research Group was recently published, confirming those results [89].

e) Anatomical and pathological basis of LND in endometrial cancer

The anatomy of lymphatic drainage of the uterus has been explored by Burke in his pivotal study on sentinel lymph node in endometrial cancer. In this study, the authors found bilateral lymphatic channels in the infundibulo-pelvic and broad ligaments. Interestingly, the authors did not identify para-aortic blue nodes below the level of the inferior mesenteric artery. This would suggest that the para-aortic lymphatic channels from the uterus go parallel to the ovarian vessels. The authors found also a great variation of the localization of pelvic nodes that would suggest heterogeneity of lymphatic routes [90].

Until the date we know that there are two pelvic lymph node spread pathways in endometrial carcinoma. The major route of drainage passes ventrally to the uterine vessels and internal iliac artery before entering the nodes in the proximal obturator fossa (at the bifurcation common iliac vessels) or on the medial surface of the external iliac vein. The other turns cephalad, rather than laterally in the parametrium, and enters the presacral nodes. The presence of this second drainage is not constant. Some authors named the two routes as upper and lower paracervical pathway, where the lower pelvic pathway drains to the SLN on the sacral promontory [91].

f) The role of para-aortic lymphadenectomy.

Following the anatomical condition of lymphatic pathways, para-aortic lymphadenectomy should be performed up to the level of left renal vein. Thirty-five % of isolated aortic metastases are described to be located in the supramesenteric area [92]. The same study observed that 77% of patients in this group with any para-aortic node involvement had metastases above the inferior mesenteric artery. According to the pivotal study published in 1988 by Creasman, the overall probability of finding an isolated positive para-aortic lymph node is approximately 2% in apparently early stages of endometrial cancer with no pelvic

nodal disease. However, when it comes to high risk patients (type 2, grade 3; myometrial invasion >50%; primary tumor diameter >2 cm), the incidence of isolated positive para-aortic nodes was 16% [50, 92]. The same study observed that 77% of patients in this group with any para-aortic node involvement had metastases above the inferior mesenteric artery.

When lymph nodes are found positive, the para-aortic nodes are involved in 50% of cases [93-95].

Recently published retrospective evidence is quite confusing. Some authors clearly state that para-aortic LND up to the level of left renal vein should always be performed in intermediate high risk patients, with a yield of 16% patients with para-aortic metastasis [92]. Other authors suggested to skip this procedure in the absence of pelvic node metastasis and deep myometrial invasion [96].

Better outcome of patients undergoing para-aortic LND was found in some retrospective trials maybe due to selection bias of patients. Those without important comorbidities would more often be subjected to the full staging procedure [97].

Therefore, probably only high risk patient might benefit from para-aortic lymph node dissection. Some authors consider only the combination of 2 risk factors (grade 3; myometrial invasion >50%; primary tumour diameter >2 cm) to indicate performing the para-aortic lymph node dissection.

After the publication of the GOG 258 study in June 2019 not only the role of radiation therapy has been brought into question [76]. This clinical trial assessed whether 6 months of platinum-based chemotherapy plus radiation therapy (chemoradiotherapy) is associated with longer relapse-free survival (primary end point) than six cycles of combination chemotherapy alone in patients with stage III or IVA endometrial carcinoma Secondary end points included overall survival, acute and chronic toxic effects, and quality of life. The results of the trial revealed that the chemotherapy with external beam radiation was not better than chemotherapy alone with respect to, disease free survival and overall survival.

Interestingly this study questions as well the role of para-aortic lymphadenectomy in the treatment of apparently early stage endometrial cancer.

Anyway, in the era of sentinel lymph node, the discussion may be obsolete. Risk of complications associated with comprehensive lymph node dissection should not be neglected.

g*) Controversy on intermediate risk surgical management*

The most important controversy remains for tumors preoperatively classified as ESMO (ESGO/ESMO/ESTRO) intermediate risk for recurrence. The benefit in DFS and OS of lymphadenectomy in intermediate risk endometrial cancer is not clear and there is no consensus among international scientific societies. Our group has analyzed the impact of lymph node dissection in this group of patients in a match pair study without founding any benefit for survival in these types of tumors [88]. The NCCN panel recommends that lymphadenectomy should be done only in selected patients with endometrial cancer with para-aortic done as indicated for high risk patients [30]. The American College of Obstetrics and Gynecology still recommends comprehensive surgical staging as an initial management intermediate risk endometrial cancer [98], whereas others institutions suggest an individually adjusted LND approach [99].

The French guidelines highlight that there is no convincing data in the literature specifically for the intermediate risk patients. However, they propose the use of sentinel lymph node (SLN), awaiting the results of the national SENTIRAD study [100]. The European consensus of the three societies of Radiotherapy and Oncology (ESTRO), Gynecological Oncology (ESGO), and European Society of Medical Oncology (ESMO) again do not clarify the surgical staging in patients with intermediate risk endometrial cancer [25].

This controversial issue is likely to be concluded by the universal use of SLN mapping in supposed intermediate or high-intermediate patients. Currently, almost all guidelines agree that SLN mapping can be considered as an alternative to full lymphadenectomy, when a strict surgical algorithm is applied [79].

Prospective clinical trials (SENTI-ENDO and FIRES) have established that the method is safe and associated with a lower rate of complications than standard lymphadenectomy [101-103].

SLN in endometrial cancer was first described by Thomas Burke of M D Anderson Cancer Center in 1996 [104]. His group first described 15 patients having the fundus injection of blue dye. A detailed algorithm was then developed by the group of Abu-Rustum from Memorial Sloan Kettering Cancer Center in New York (USA) [105, 106].

A recent meta-analysis reported overall detection rates higher than 80%, with 50% bilateral pelvic node detection rate and 17% para-aortic detection rate. The sensitivity of sentinel lymph node mapping to detect metastases is higher than 90%, reaching almost 100% in this meta-analysis. These low false-negative rates are comparable to those observed in breast cancer (10%) and vulvar cancer (8%), in which SLN is an accepted staging modality [107].

Multiple tracers and their combinations have been used in order to increase the detection rate. According to the present literature it seems that the Indocyanine green (ICG) or the combination of TC 99 and blue dye have the highest detection rate, usually higher than 90% and 80% for bilateral detection [108]. The recently published FILM (Fluorescence Imaging for Lymphatic Mapping) prospective randomised study, compared the detection rate using ICG or blue dye. The results were in favour of the ICG tracer [109]. The authors suggested that the use of blue dye alone should not be implemented for SLN mapping purposes. In addition, the use of ICG is especially useful in obese patients [110]. Figure 5 represents examples of blue dye and ICG tracer.

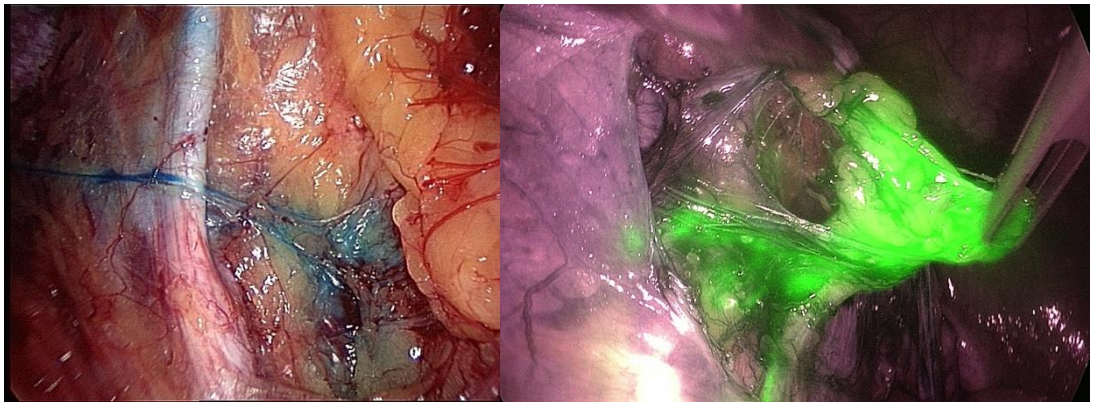


Figure 5. Pelvic sentinel lymph node traced with patent blue (left) and indocyanine green (right).

As far as the injection site is concerned, the majority of authors recommend the cervical injection, superficial and deep at 3 and 9 hours, easily accessible and reproducible [111]. Recently a dual injection has also been studied. It consists of deep fundus transvaginal application and cervical injection. It seems that the use of these method increases the aortic SLN detection. The importance of this finding needs further studies [112].

A learning curve, self-validated by monitoring the detection rate, is necessary, when introducing the SLN technique. All the SLN should be removed with macroscopically or radiologically suspected nodes.

Frozen section examination can be performed by an expert pathologist and is sufficiently reliable to guide further staging [113].

There is no consensus on the value of a complete lymph node dissection in the presence of a positive pelvic sentinel node. The OSNA technique has been evaluated but cannot be used in everyday practice due to false positive cases. [114, 115].

SLN must be subjected to serial sections and immunohistochemistry stains to cytokeratin (AE3 and AE 4). The objective of this ultrastaging procedure is to discover low-volume metastatic disease whose frequency is not negligible [100].

Classically the lymph node metastases are classified by their size [116]. Micrometastases range in size between 0.2 and 2 mm and isolated tumor cells are described as clusters of malignant cells less than 0.2 mm in dimension. While it is possible to identify previously undetected disease with these novel techniques, it is unknown if this low-volume disease is clinically significant. A study on a large series of patients with low-risk features demonstrated that use of ultrastaging doubled the identification of positive lymph nodes from 2.6% to 5.9% [117]. However, retrospective data showed that detection and treatment of isolated tumor cells may not have any impact on patient's survival [118]. Contrary, there is evidence to support the treatment of micrometastases in a similar manner to macrometastases [119].

Finally, the value of SLN is indisputable. Its safety, accuracy and prognostic information support its universal use in patients with intermediate risk endometrial cancer.

III. JUSTIFICATION OF THE PROJECT

Management of women with early-stage endometrial cancer is still controversial and practice routine differs among gynecologic oncologists, countries and continents. The controversies are focused on intermediate risk endometrial cancer. This is principally because there are diverse criteria defining intermediate risk groups for recurrence, non-standardised protocols for surgical staging and different indications for adjuvant therapies.

We have earlier addressed the issue of intermediate risk in a research work based on an earlier version of the risk classification [88]. It seemed necessary to reassess the clinical significance of the more recent stratification, with the introduction of a high-intermediate risk classification, since there are no studies giving strong evidence that the subclassification in two specific risk groups is relevant in real life clinical context [29].

Consequently, we carried out a study comparing the intermediate risk with high-intermediate risk endometrial cancer (according to ESMO/ESGO/ESTRO 2016 classification) regarding nodal metastases rate and oncologic outcome.

IV. HYPOTHESIS

The new risk classification for early-stage intermediate risk, including the high-intermediate risk endometrial cancer could better predict the lymph node involvement and oncological outcome than the old classification, allowing a more accurate tailoring of both surgical and adjuvant treatments. It would imply that the new subdivision would show different prognostic results among intermediate risk subgroups.

V. OBJECTIVES

PRIMARY

The primary aim of the study was to evaluate the oncological outcome according to the current European intermediate risk subclassification of endometrial cancer by comparing the disease-free and overall survival in patients with intermediate and high-intermediate risk endometrial cancer.

SECONDARY

1- To compare lymph node involvement in intermediate and high-intermediate risk endometrial cancer.

2- To analyze the predictive factors of lymph node involvement among the new risk groups.

3- To analyze the factors associated with recurrence and death in intermediate and high-intermediate risk group.

VI. MATERIAL AND METHODS

We conducted a multicenter retrospective study at 4 tertiary Spanish institutions and one French Comprehensive Cancer Center. Data collection included the period from January 2000 to December 2018. One thousand eight hundred sixty-four patients with endometrial cancer were recorded in a database. Only patients who underwent hysterectomy with nodal assessment, either full lymphadenectomy or sentinel lymph node biopsy were included in the study. Patients with FIGO stage II, IIIA, IIIB and IV were excluded. The data of patients with FIGO stage IIIC were incorporated in order to assess the risk of nodal metastases. Patients with FIGO stage IIIC and either one (or more) of the following: cervical stromal invasion, adnexal invasion, uterine serosa invasion were excluded. Out of 576 patients, 99 were excluded due to cervical, adnexa, serosa, parametrial, vesical involvement or metastatic disease. A sample of 477 patients with uterine characteristics of intermediate risk endometrial cancer on definitive pathology, according to the guidelines of the ESMO/ESGO/ESTRO 2016 were identified and reviewed [25]. Patients' selection chart is represented in Figure 6.

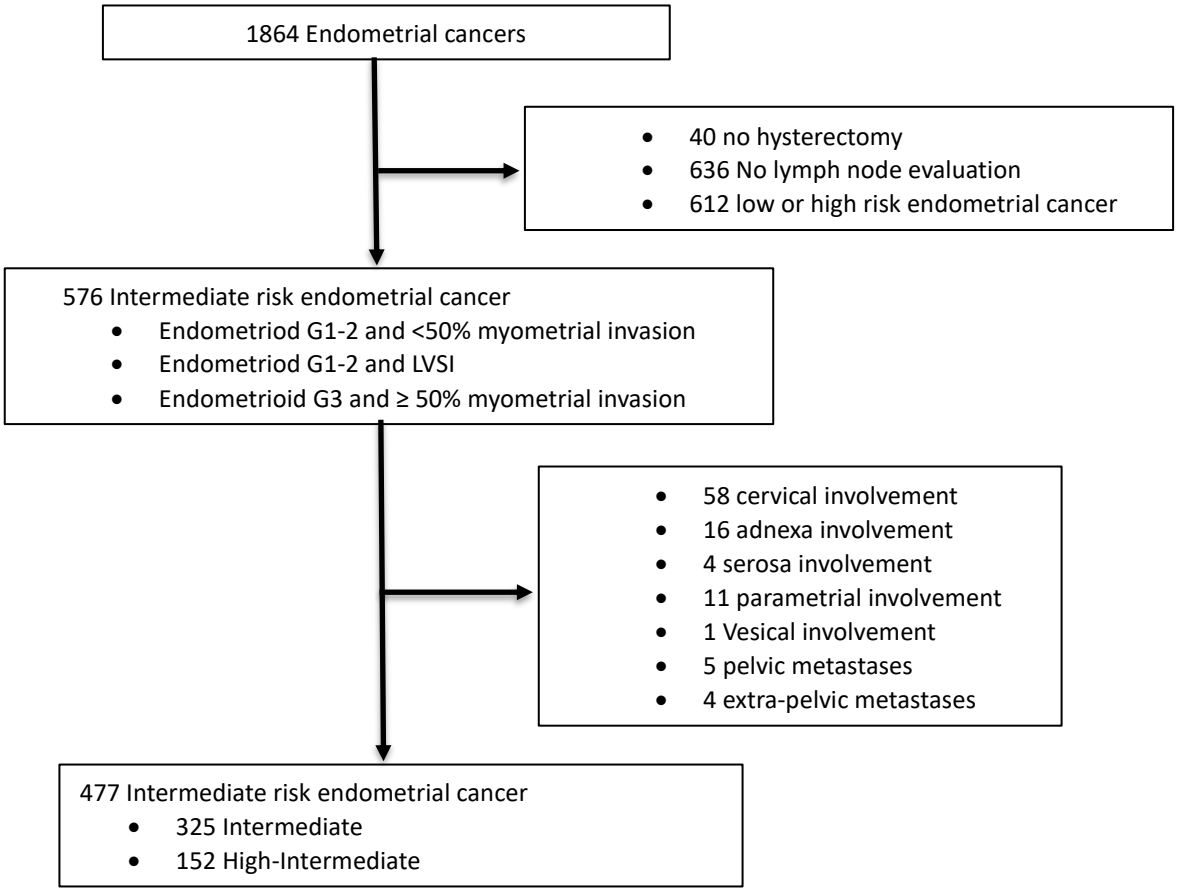


Figure 6. Patients' selection chart.

The intermediate risk subclassification was defined as endometrioid histology with myometrial invasion ≥50%, grades 1–2 and negative LVSI. Patients with grade 1–2 tumours with LVSI unequivocally positive regardless the depth of myometrial invasion, and those with grade 3 tumours with <50% myometrial invasion regardless of LVSI status were categorized as high-intermediate risk (Table VI).

Intermediate risk	Endometrioid histology grade 1–2 and negative LVSI with myometrial invasion ≥50%
High-intermediate risk	Endometrioid histology grade 1–2 tumours with LVSI unequivocally positive regardless the depth of myometrial invasion, grade 3 tumours with <50% myometrial invasion regardless of LVSI status

Table VI. Definition of Intermediate and high-intermediate according to ESGO/ESMO/ESTRO 2016. LVSI (Lymphovascular space invasion).

Both intermediate risk groups were compared as to risk of nodal metastases, disease-free and overall survival. Other patient´s and tumor´s characteristics (grade, myometrial invasion, histologic subtype, maximal tumor size), and adjuvant treatment were recorded.

The protocol of the study was submitted and approved by the Hospital Clínico San Carlos Institutional Review Board (approval number C.P ISM-200503-C.I. 20/407-E) as Spanish reference center and ratified at the remaining Spanish institutions. The samples from the French tumor archives were centralized in the Biological Resources Centres of Institut Bergonié, which the French authorities authorized for scientific research.

All patients underwent hysterectomy with bilateral salpingo-ooforectomy. Lymphadenectomy or sentinel lymph node biopsy were performed at institution discretion based on surgical team experience and institutional protocols. The same oncological team in each center performed all surgical interventions. Sentinel lymph node biopsy was detected

with combined method: blue dye and radiocolloid tracer and more recently with fluorescence imaging using indocyanine green tracer.

Route of surgery (open or minimally invasive) depended on the surgical team and institution experience. In one center also robotic surgery as a minimally invasive approach was used.

Preoperatively, mechanical bowel preparation could be carried out, and prophylactic antibiotics and low molecular weight heparin always administered. Intravenous fluids were maintained until patients tolerated oral fluids, usually within first 24 hours after the surgery. Foley catheter was usually removed the day after the surgery. Serum hemoglobin levels were routinely obtained within 24 hours after the procedure. Patients were discharged home if they demonstrated ability to ambulate independently, tolerated a regular diet, had stable vital signs and pain was under control.

All the pathological specimens were analysed by expert pathologists dedicated to gynecologic oncology. Hysterectomy specimen were oriented, then opened and the tumor was measured in the largest dimension. A sample sections per centimeter of the largest tumor dimension were submitted to microscopical examination. The pathological reports included information about histologic type of tumor and histologic grade. Myometrial thickness, information about the presence of myometrial invasion and its depth was also reported. Information about uterine serosa involvement, lower uterine segment Involvement, cervical stromal involvement, parametrial and vaginal involvement were noted. All reports included information about lymphovascular space invasion, defined as at least one identified focus of lymphatic, vascular invasion, or lymphovascular invasion. Number of lymph nodes and positive lymph nodes were detailed as well.

TNM staging system for endometrial cancer and FIGO were both used as pathologic stage classifications.

Even though there are no controlled studies to support follow-up of patients once the treatment is completed, the follow up visits have been performed every 3-6 months up to 5 years and then every 6-12 months up to 10 years. Each visit included physical examination and

pelvic ultrasound. Chest x-ray, computerized tomography or other more specific tests were recommended according to clinical findings. Patients have been informed about the need to consult in case of abnormal vaginal bleeding, abdominal distention, persistent pelvic pain, fatigue, persistent constipation and unexplained weight loss.

The presence of recurrence, type of therapies, and patient status at last contact were collected during the patient's follow-up. Time to relapse, and type and pattern of recurrence were collected. Recurrence was confirmed by biopsy or unambiguous imaging.

Patients were managed following the guidelines approved by the European Society of Gynecology Oncology and Spanish Society of Obstetrics and Gynecology.

The data were centralised in an encrypted database which is in propriety of Women's Health Institute of the Hospital Clinico San Carlos located at Profesor Martín Lagos Street, 28040 Madrid, Spain.

Statistical analysis

For continuous variables

Continuous variables were expressed as mean and standard deviation. Kolmogorov-Smirnov test was used to assess the normal distribution. To analyze the association between a continuous variable and a qualitative variable with two categories T-test was used in normal distributions or the Mann-Whitney test in non-parametrical distributions. To analyze the association between a continuous variable and a qualitative variable with three or more categories we used the ANOVA or Kruskal-Wallis test.

For qualitative variables

Qualitative variables were expressed with absolute frequencies and percentages. Comparison between two qualitative variables was made by a chi-squared test. In case of small cell comparisons, a Fisher's exact test was used.

For survival analysis

Tumoral recurrence was the dependent variable to assess the disease-free survival. The time to analyze this variable was the result of measure the time between the definitive surgery and the first evidence of recurrence.

Decease due to tumor, for other causes or unknown was considered as dependent variable to assess the overall survival. The time to analyze this variable was the result of measure the time between the definitive surgery and the decease or the patient`s last contact.

The Kaplan–Meier method was used to estimate the survival distribution in the study groups. The Log-rank test was used to calculate the statistical signification between the groups in relation to disease-free and overall survival.

Mantel-Cox´s method was used to identify the factors directly associated with DFS or overall survival. In that cases the dependent variables were recurrence and death. Multivariate modeling using Cox's proportional hazard models was performed to obtain a subset of independent predictors of disease-free and overall survival. We included in the multivariant model the variables associated to recurrence or death in Cox univariate analysis. Hazard ratios with 95% confidence interval were calculated.

All statistical tests were two-sided and statistical significance was defined as *p* value less than 0.05. All computations were performed using IBM SPSS Statistic version 25 (Chicago, IL, USA).

VI. RESULTS

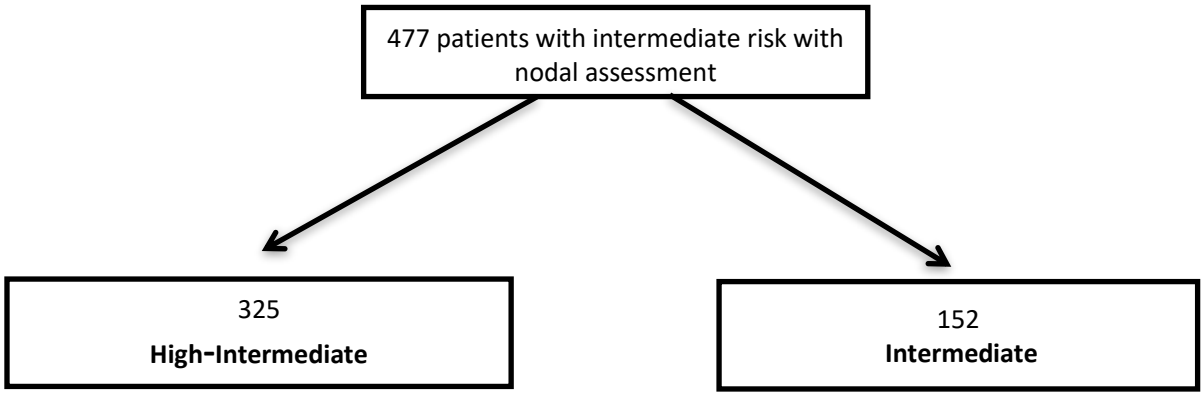


Figure 7. High-intermediate and intermediate risk study group.

A total of 477 patients with intermediate risk endometrial cancer at definitive pathology and who had nodal assessment were included. Of these, 325 (68%) patients were identified as intermediate risk and 152 (32%) patients as high-intermediate risk (Figure 7). Both groups were similar in baseline characteristics (age, body mass index, comorbidities). The median age of the total cohort was 66 years (range, 31-89). Three hundred eighty-seven patients (81.2%) received adjuvant treatment, including brachytherapy (195 patients), external beam radiotherapy (166 patients), and irradiation and chemotherapy (26 patients). Patients' characteristics are presented in Table VII. Comparison of selective features of intermediate risk and high-intermediate risk group is represented in Figure 8.

	Intermediate N=325	High-intermediate N=152	p value*
Age (years)	66.4 ± 9.1	65.1 ± 9.8	0.153
BMI (kg/m2)	29.8 ± 5.7	28.8 ± 5.4	0.077
Associated diseases †	214 (65.8)	91 (59.9)	0.205
Years from menopause	16.3 ± 9.6	15.1 ± 10.2	0.288
Parity	1.9 ± 1.5	1.9 ± 1.3	0.767
Pre-surgical hemoglobin (mg/L)	13.5 ± 1.1	13.4 ± 1.4	0.597
Histologic subtype			0.598
• **Pure endometrioid**	308 (94.8)	147 (96.7)	
• **With mucinous differentiation**	5 (1.5)	1 (0.7)	
• **With squamous differentiation**	12 (3.7)	4 (2.6)	
Histological grade			**< 0.001**
• **G1**	164 (50.5)	31 (20.4)	
• **G2**	161 (49.5)	47 (30.9)	
• **G3**	0 (0)	74 (48.7)	
Myometrial invasion			**<0.001**
• **< 50%**	0 (0)	84 (55.3)	
• **≥ 50%**	325 (100)	68 (44.7)	
Lymphovascular space invasion			**<0.001**
• **No**	278 (85.5)	60 (39.5)	
• **Yes**	0 (0)	86 (56.6)	
• **Unknown**	47 (14.5)	6 (3.9)	
Tumor size (cm)	3.0 ± 1.5	3.3 ± 1.7	**0.046**
Surgical approach			**0.045**
• **Laparotomy**	190 (58.5)	74 (48.7)	
• **Minimally invasive**	135 (41.5)	78 (51.3)	
Lymphadenectomy			**<0.001**
• **Pelvic only**	272 (83.7)	85 (55.9)	
• **Pelvic and para-aortic**	53 (16.3)	67 (44.1)	
Nº nodes removed			
• **Pelvic**	14.1 ± 7.4	14.1 ± 6.7	0.959
• **Pelvic and para-aortic**	12.2 ± 10.0	12.3 ± 9.2	0.935
Lymph nodes status			
• **Negative**	309 (95.1)	134 (88.2)	**0.006**
• **Positive**	16 (4.9)	18 (11.8)	
Adjuvant Treatment			**0.008**
• **None**	67 (20.6)	23 (15.1)	
• **Brachytherapy**	140 (43.1)	55 (36.2)	
• **External beam radiation**	107 (32.9)	59 (38.8)	
• **Irradiation and chemotherapy**	11 (3.4)	15 (9.9)	
Length of follow-up in months	60.1 ± 40.4	48.8 ± 33.5	**0.001**

Table VII. Patient demographics and pathologic details in intermediate risk endometrial cancers. Data are shown as mean ± (standard deviation) or cases (%). BMI: Body Mass index. ASA: American Society of Anesthesiologist. *t test in variables with normal distribution, Mann-Whitney test for the others continuous variables and chi2 test or Fisher's test in discrete variables. †Includes hypertension, diabetes, lung and heart disease.

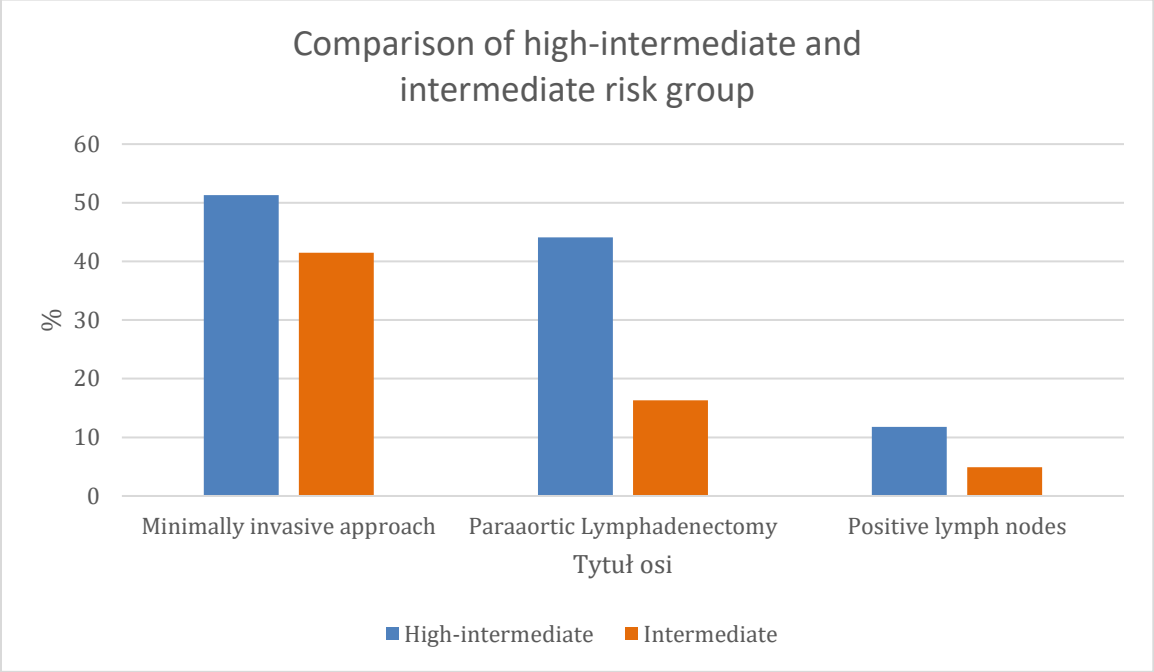


Figure 8. Comparison of intermediate risk and high-intermediate risk group (%).

Thirty-four patients (7.1%) were found to have lymph node metastases in the entire group. In the intermediate risk group 16 patients (4.9%) had lymph node metastases. Nodal disease was found in 18 (11.8%) patients with uterine characteristics of high-intermediate risk endometrial cancer. The difference was statistically significant (p=0.006). LVSI was the only independent pathological feature associated with lymph node involvement (p<0.001). The characteristics of predictor factors of lymph node metastases are reported in Table VIII.

Variables	No lymph node metastases N=443	Lymph node metastases N=34	P value*
Age (years)	66.2 ± 91	63.1 ± 11.3	0.056
Histologic subtype • **Endometrioid** • **Mucinous** • **Squamous**	 421 (95.0) 6 (1.4) 16 (3.6)	 34 (100) 0 (0) 0(0)	0.413
Histological grade • **G1-G2** • **G3**	 371 (83.7) 72 (16.3)	 32 (94.1) 2 (5.9)	0.107
Myometrial invasion • **< 50%** • **≥ 50%**	 77 (17.4) 366 (82.6)	 7 (20.6) 27 (79.4)	0.636
Maximum tumor size (cm)	3.1 ± 1.6	3.4 ± 1.5	0.381
Lymphovascular space invasion* • **No** • **Yes**	 325 (82.5) 69 (17.5)	 13 (43.3) 17 (56.7)	**< 0.001**
Risk stratification • **Intermediate** • **High-intermediate**	 309 (69.8) 134 (30.2)	 16 (47.1) 18 (52.9)	**0.006**

Table VIII. Predictive factors of lymph node metastases in 477 cases of intermediate risk endometrial cancers. Data are shown as cases (%) and mean ± standard deviation. LVSI (Lymphovascular space invasion).

*Only patients with known LVSI status were included in the statistical analysis.

After a median follow up of 53.2 months [interquartile range, 25.9-86.9], 53 (11%) patients recurred, 29 (8.9%) patients in the intermediate group and 24 (15.8%) patients in the high-intermediate risk group. The distribution of recurrences was significantly (p=0.024) different between groups, with 10 pelvic recurrences (34.5% of recurrences), 2 nodal recurrences (6.9%), and 17 distant recurrences (58.6%) in the intermediate risk group compared to 3 pelvic (12.5%), 8 nodal (33.3%) and 13 distant (54.2%) in the high-intermediate risk group. Interestingly, nodal recurrence rate occurred in 0.6% of patients in intermediate risk patients versus 5.2% in the high-intermediate group.

Twenty-seven patients (5.6%) were alive with disease. A total of 47 (9.8%) patients died and, of these, 27 patients died of disease. Cancer related deaths were more common in the high-intermediate group, 15 (9.8%) patients versus 13 (4%) patients in the intermediate group, but this finding did not reach the statistical significance (p=0.056) (Table IX). Oncological outcome of intermediate and high-intermediate risk is also represented in the Figure 9.

	Intermediate N=325	High-intermediate N=152	p value
Recurrence	29 (8.9)	24 (15.8)	0.026
Site of recurrence:	% from recurrences		
• **Pelvis**	10 (34.5)	3 (12.5)	0.024
• **Nodes***	2 (6.9)	8 (33.3)	
• **Spread†**	17 (58.6)	13 (54.2)	
Decrease	28 (8.6)	19 (12.7)	0.173
Cause of decrease:	% from recurrences		
• **Dead for tumor**	13 (46.4)	15 (78.9)	0.056
• **Dead for other causes**	14 (50.0)	3 (15.8)	
• **Cause unknown**	1 (3.6)	1 (5.3)	

Table IX: Recurrence and mortality in 477 intermediate risk endometrial cancers. Data are shown as cases (%).

*Recurrence in nodes as first localization.

†Recurrence in two or more sites, or distant metastases.

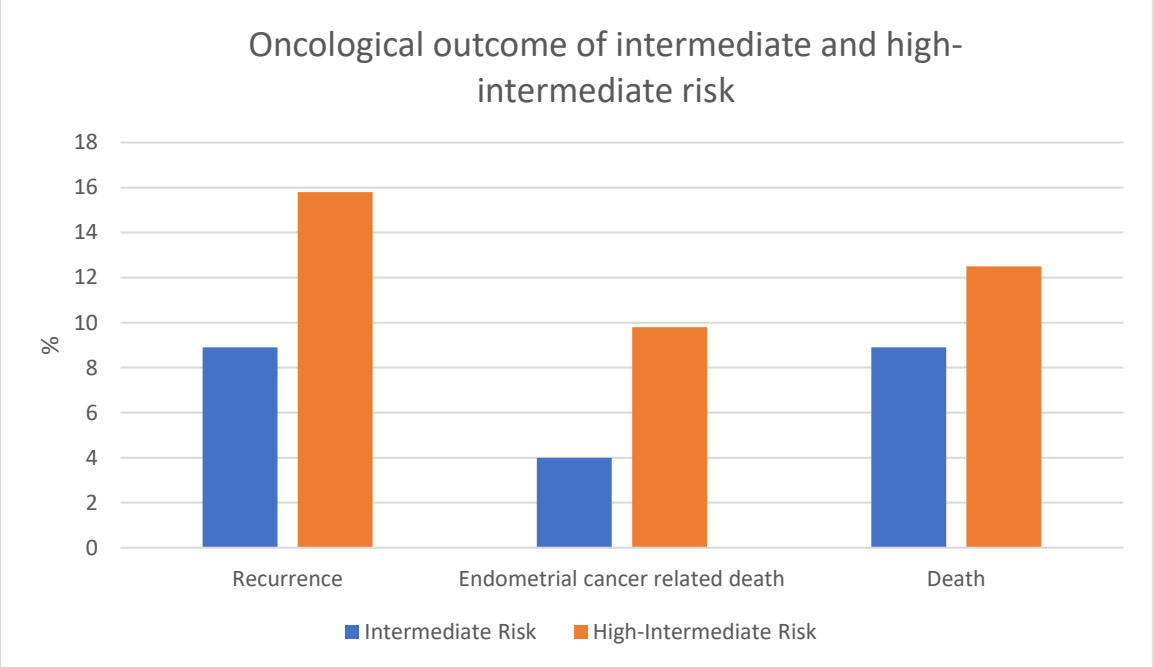


Figure 9. Oncological outcome of intermediate and high-intermediate risk.

Five-year disease-free survival was 90.7% in the intermediate risk group versus 79.5% in the high-intermediate risk group (p=0.006). Five-year overall survival was 92.5% in the intermediate group and 83.7% in the high-intermediate risk group (p=0.042). Disease-free and overall survival were significantly lower in the high-intermediate group with hazard ratio 2.10

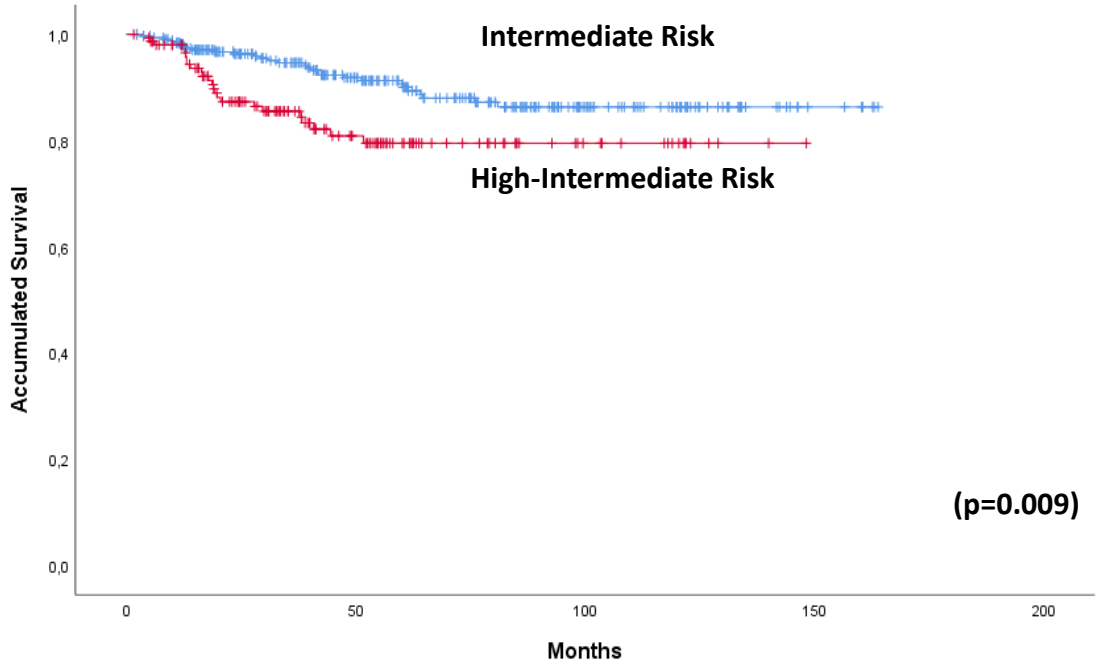
(95% confidence interval 1.22-3.62; p=0.009) and hazard ratio 1.82 (1.01-3.28; p=0.045), respectively (Figure 10).

In the univariant analysis high-intermediate risk was an independent factor of disease-free (hazard ratio: 2.10, 95% confidence Interval: 1.22-3.62; p=0.009) and overall survival (hazard ratio: 1.82; 95% confidence Interval 1.01-3.28; p=0.045). Lymph node involvement was also identified as a factor of recurrence (hazard ratio: 3.68, 95% confidence interval: 1.84-7.36; p<0.001) and death (hazard ratio: 2.36, 95% confidence interval: 1.00-5.57; p=0.050) (Table X).

	Disease-free survival		Overall Survival	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Age (linear increment per year)	1.02 (0.99-1.05)	0.176	1.05 (1.01-1.08)	**0.011**
Risk Stratification:				
• **Intermediate**	1		1	
• **High-intermediate**	2.10 (1.22-3.62)	**0.009**	1.82 (1.01-3.28)	**0.045**
Lymphovascular space invasion:				
• **No**	1		1	
• **Yes**	1.83 (0.98-3.43)	0.062	1.87 (0.97-3.60)	0.062
Positive lymph nodes:				
• **No**	1		1	
• **Yes**	3.68 (1.84-7.36)	**<0.001**	2.36 (1.00-5.57)	**0.050**
Histological Subtype:				
• **Endometrioid**	1		1	
• **Mucinous**	-	-	-	-
• **Squamous**	1.66 (0.52-5.32)	0.395	2.32 (0.83-6.48)	0.107
Histological Grade:				
• **G1**	1		1	
• **G2**	1.14 (0.63-2.08)	0.662	1.06 (0.57-1.95)	0.862
• **G3**	1.69 (0.79-3.60)	0.173	1.04 (0.42-2.57)	0.939
Myometrial invasion:				
• **< 50%**	1		1	
• **≥ 50%**	0.59 (0.31-1.12)	0.107	0.95 (0.43-2.13)	0.905

Table X. Univariate analysis of disease-free survival and overall survival in 477 intermediate risk endometrial cancers. HR= Hazard Ratio. CI = confidence interval.

A- Disease-free Survival



B- Overall Survival

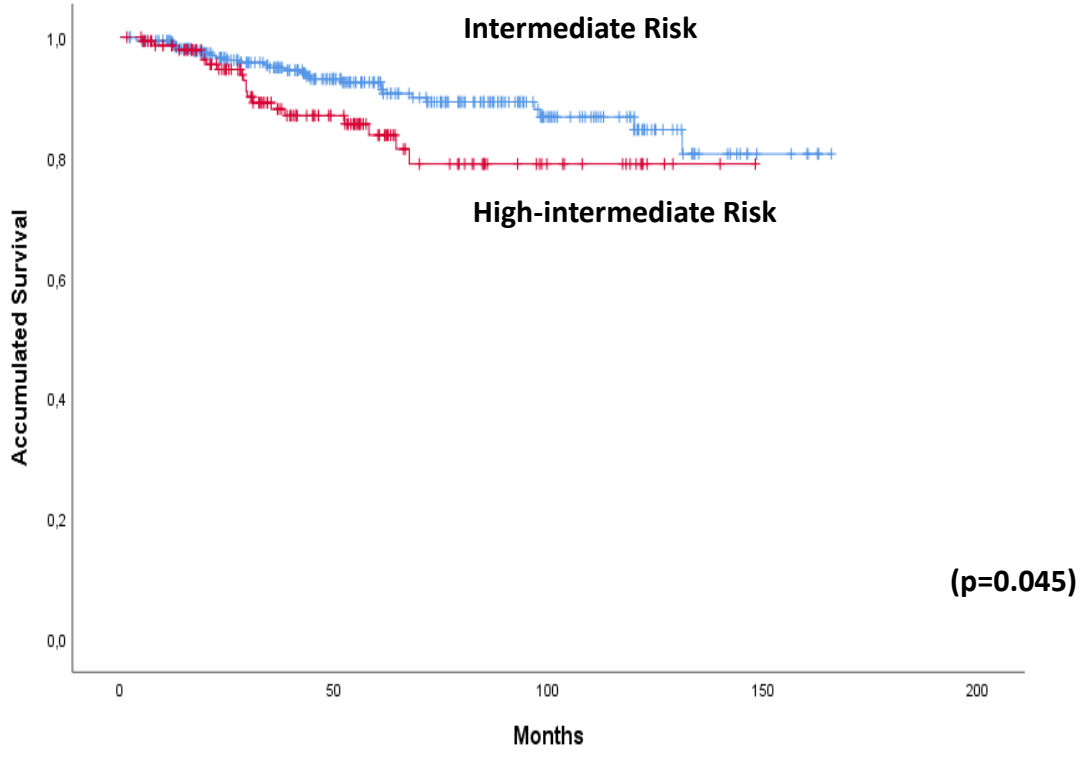


Figure 10 A, B: Kaplan-Meier estimate of disease-free survival and overall survival in intermediate and high-intermediate endometrial cancer respectively.

The multivariate analysis found that high-intermediate risk was an independent factor of disease-free survival (adjusted hazard ratio: 1.86, 95% confidence Interval: 1.02-3.39; p=0.043) and overall survival (adjusted hazard ratio: 1.99; 95% confidence Interval 1.10-3.60; p=0.022). In addition, lymph node involvement was also identified as an independent factor of recurrence (hazard ratio: 3.06, 95% confidence interval: 1.39-6.72; p=0.005). When risk stratification, was removed from the model, age (hazard ratio: 1.04, 95% confidence Interval: 1.01-1.07; p=0.038) and LVSI (hazard ratio: 1.93, 95% confidence Interval: 1.01-3.73; p=0.049) were found to be independent factors for disease-free survival (Table XI). Kaplan-Meier estimate of disease-free survival and overall survival for patients with different lymphovascular space invasion and lymph node status are represented in Figures 11-14.

	Disease-free survival		Overall Survival	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Age (linear increment per year)	-	-	1.05 (1.01-1.09)	**0.007**
Risk Stratification:				
• **Intermediate**	1		1	
• **High-intermediate**	1.76 (1.00-3.08)	**0.050**	1.99 (1.10-3.60)	**0.022**
Positive lymph nodes:				
• **No**	1		-	-
• **Yes**	3.06 (1.39-6.72)	**0.005**		
Lymphovascular space invasion*:				
• **No**	1		-	-
• **Yes**	1.93 (1.01-3.73)	**0.049**		

Table XI. Multivariate analysis of disease-free survival and overall survival in 477 intermediate risk endometrial cancers. HR= Hazard Ratio. CI = confidence interval.

* Lymphovascular space invasion is a significant variable when risk stratification is removed from the model, as lymphovascular space invasion is included in the definition of high-intermediate risk.

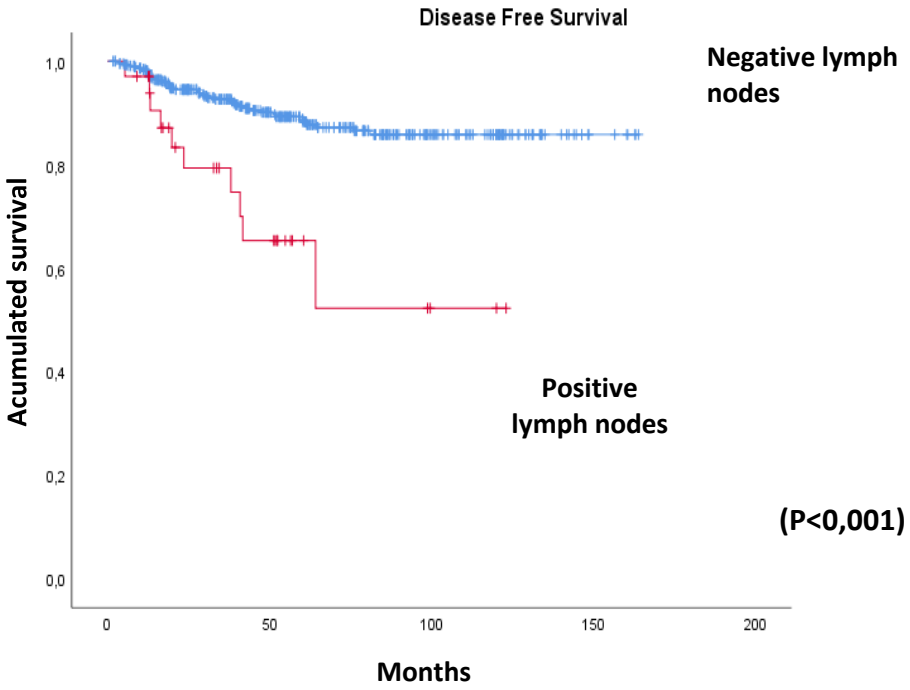


Figure 11. Impact of positive lymph nodes on disease-free survival (p<0.001).

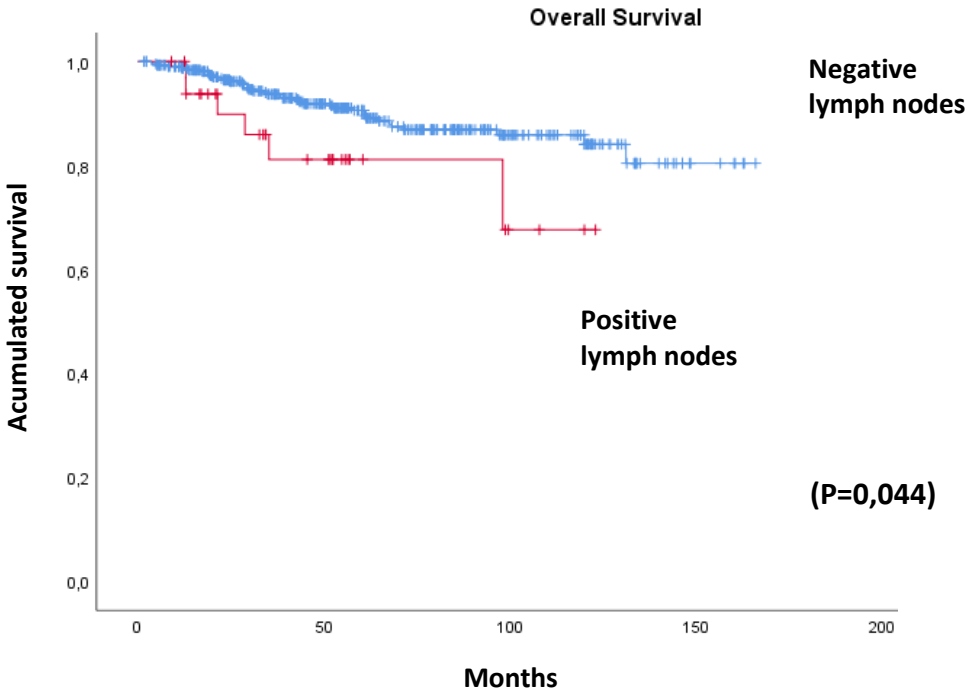


Figure 12. Impact of positive lymph nodes on overall survival.

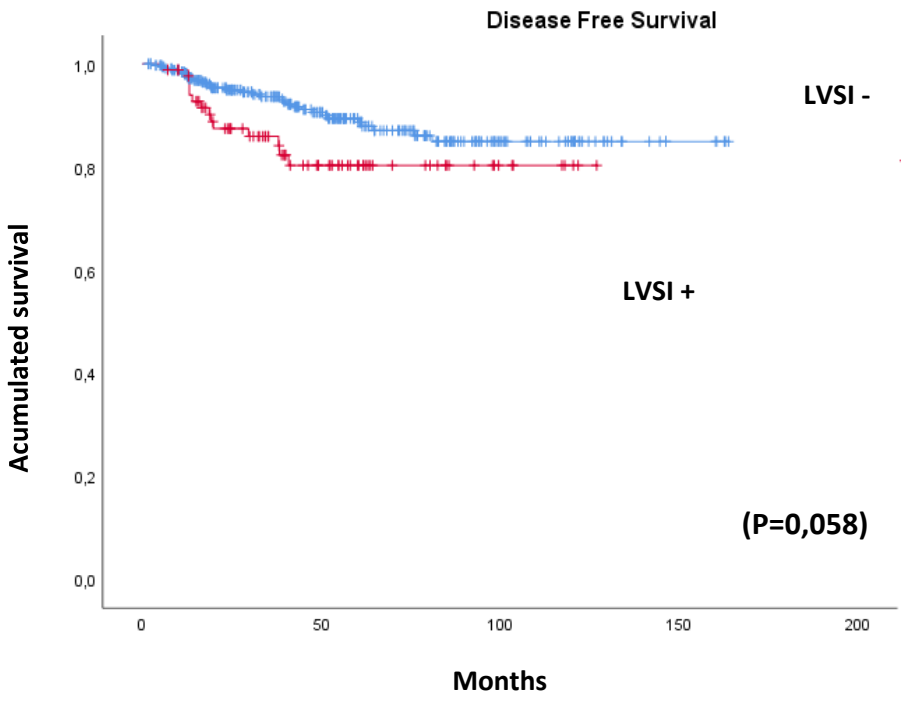


Figure 13. Impact of Lymphovascular space invasion (LVSI) on disease-free survival.

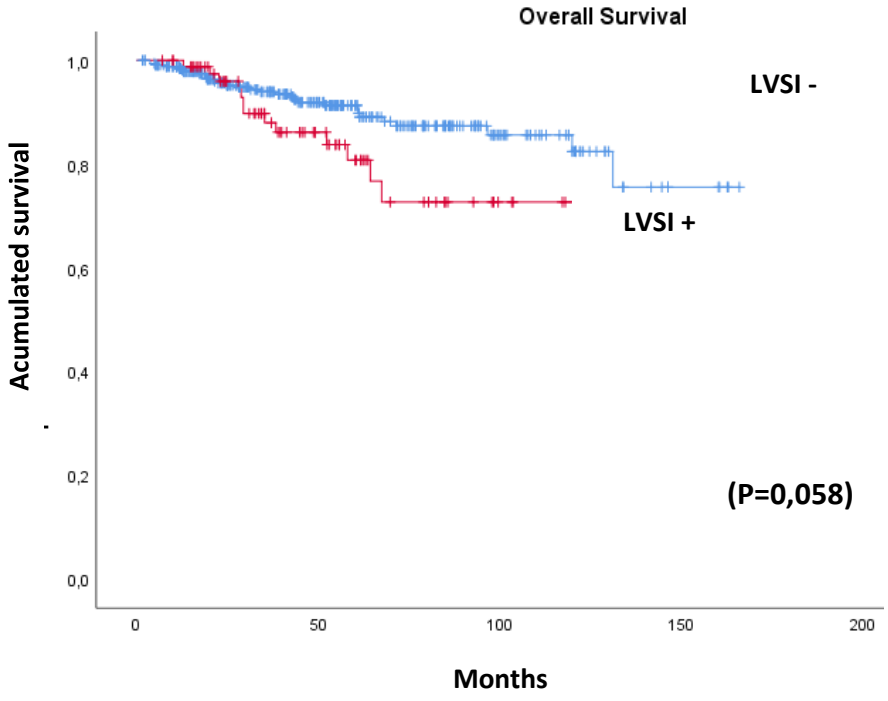


Figure 14. Impact of Lymphovascular space invasion (LVSI) on overall survival.

VII. DISCUSSION

Our study shows that the current European risk stratification is effective in defining the risk of lymph node disease and prognosis in intermediate risk group. The subclassification of risk into standard intermediate and high-intermediate has been validated in our series. Within the wider intermediate risk group, patients have different risk of nodal disease and different prognosis. The current subclassification partially reflects and reduces this heterogeneity. The prevalence of nodal disease is significantly higher and nodal recurrences are more frequent in the high-intermediate group. Prognosis is substantially poorer in high-intermediate risk cancer patients. The former intermediate risk endometrial cancer is therefore not a homogeneous group, and the subclassification is fully justified to guide adjuvant therapy.

The risk classifications substantially changed in the last 20 years. The definition of intermediate risk and high-intermediate risk endometrial cancer is not universal. These differences in definition make it difficult to extrapolate the results of studies addressing the prognosis of intermediate low and high risk endometrial cancer patients.

One study compared the accuracy of five major risk stratification systems in classifying the risk of recurrence and nodal metastases in early-stage endometrial cancer. The authors found that none of the five major risk stratification systems showed high accuracy in stratifying the risk of recurrence or nodal metastases in patients with early-stage endometrial cancer, although the current European classification emerged as having the highest power of discrimination [28].

Our study suggests that the current European risk stratification is effective in defining the risk of lymph node disease and prognosis. To our knowledge this is the first study that evaluates the role of the subclassification of intermediate risk endometrial cancer in a large multicentric cohort with multivariate analysis.

In relation to our results, it remains necessary to discuss in what regard they are relevant for clinical practice. Without any doubt, the finding of high-intermediate features at definitive pathology orientates state-of-the-art adjuvant treatment, and forms the basis of future clinical trials.

However, there are still several clinically relevant topics open for in depth discussion. First, the preoperative risk assessment is incomplete or inaccurate in several regards: the LVSI status is unknown before definitive pathology of the operating specimen, the pathologic grading on endometrial biopsy specimens may not reflect the final pathology and the estimation of myometrial invasion by imaging may be inaccurate.

The preoperative work-up using diagnostic pathology examination and radiological assessment may fail in nearly 40 % of cases. In consequence, this may lead to suboptimal initial surgical management of patients with endometrial cancer.

Histotype and grade, key parameters in the classical stratification systems of endometrial cancer, have been shown to have important rate of preoperative misdiagnosis.

The most widely used histologic grading system for endometrial carcinoma is the three-tiered FIGO classification. Based on the data presented by Creasman the frequency of pelvic lymph node metastases is found in 3%, 9%, and 18% in grade 1, 2, and 3 endometrial cancer and of para-aortic involvement 2%, 5%, and 11% in grade is 1, 2, and 3, respectively [50]. Erroneous preoperative grade assessment count for 30-40% when compared with final histology [120].

In order to unify the classification, a binary grading system (high grade/low grade) was proposed based on the amount of solid growth, the pattern of myometrial invasion, and the presence of tumor cell necrosis. The interobserver agreement of both systems was analysed in several studies finding at first promising results that were finally not confirmed in further studies [121-124].

However, the overall reported reproducibility using the FIGO system is 64.5-70% [80, 84]. In some publication concordance for grade 3 tumors was significantly higher than that for grade 1 or 2 [125, 126].

An interesting publication by Eltabbakh et al. found that approximately 30% of women with endometrial carcinoma whose preoperative endometrial biopsy shows grade 1 tumors have grade 2 or 3 in the hysterectomy specimen [120].

The reproducibility of diagnosis of endometrial hyperplasia, atypical hyperplasia and well-differentiated carcinoma were also assessed in several studies. The reported results show that the interobserver agreement ranges from 76% to 89% [54, 55, 127-129].

Erroneous pathological diagnosis may lead to suboptimal initial surgical management of patients with endometrial cancer. Therefore, some authors recommend to always perform a full staging procedure regardless the initial preoperative grade and stage [130].

Interestingly the concordance in molecular tumor alterations between preoperative (hysteroscopy, curettage) and postoperative (surgical specimen) findings is high [131, 132].

Preoperative evaluation of endometrial cancer using modern imaging methods is another element, universally recommended before surgical treatment. Out of possible imaging methods magnetic resonance imaging (MRI) used to be described as the most accurate in describing local-regional stage of endometrial carcinoma. MRI is superior to computed tomography for visualizing uterine and pelvic tissues. [133-135].

However, more recent works, like those from Prague group led by Daniela Fischerova, report comparable accuracy of ultrasound to that of MRI in depicting myometrial and cervical infiltration by endometrial cancer when performed by an expert [136].

The group from Prague established a detailed ultrasound protocol to correctly assess stage of endometrial cancer. These authors report underestimation of myometrial invasion in 8.6%. Cervical Stromal invasion was underestimated in 10.5% of cases. Myometrial invasion was overestimated in 15.7% cases, and cervical invasion in 4.8%. The global accuracy in this study was influenced by tumor size, density of tumor vascularization, tumor vessel architecture and histological grading, while it was not significantly affected by BMI, uterine position and image quality [136].

Revision of the FIGO staging system in 2009 simplified stage I disease to only two categories (i.e. FIGO stage IA: no or less than half myometrial invasion; FIGO stage IB: invasion equal to or more than half of the myometrium) and left only cervical stromal invasion as a distinct stage (FIGO stage II), while endocervical glandular involvement only should be

considered as FIGO stage I and no longer as stage II. The simplified FIGO staging system may have contributed to higher preoperative diagnostic accuracy [137, 138].

In order to overcome the discordance between the preoperative and definitive pathological assessment, some authors proposed intraoperative evaluation of myometrial invasion performed as gross or frozen section examination. The intraoperative evaluation of myometrial invasion and grade lead the surgical decision whether to perform or not a full staging procedure. The supporters of this method point out its low cost and accuracy when perform by an experienced pathologist. In a recent study published by an Italian group the concordance rate between myometrial invasion in frozen section and final pathology was 89.1%. The same study shows accuracy of intraoperative grading in 91% of cases. The authors finally suggest to use frozen section examination only in ambiguous or inconclusive preoperative diagnosis [139].

These data are not confirmed in different studies that report 30-60% of grade agreement and important underestimation of myometrial invasion agreement [140-143].

In this regard macroscopic of myometrial/cervical invasion may be challenging especially in small, low grade tumors as the invasion line can be heterogeneous or skip metastasis may be present.

The idea of frozen section examination has not been retained in the last ESGO/ESMO/ESTRO recommendations. This opinion is supported by groups of pathologists, who underline the importance of artefact generated during frozen section examination, that interferes with an optimal pre-analytical procedure required for standardized histopathological diagnosis [143].

On the other hand, LVSI status cannot be established at all in the preoperative setting. In other words, the LVSI status component of the ESGO/ESMO/ESTRO classification cannot be used to indicate lymph node dissection.

However, as already mentioned, there is no definitive evidence that lymphadenectomy has a therapeutic value. Available randomised data on lymph node dissection did not show any survival benefit in patients with low and intermediate/high risk endometrial cancer while impacting morbidity [41, 42].

The finding of our study is that the risk of lymph node involvement in the standard intermediate group is low, with consequently no obvious benefit of lymph node dissection. While the higher risk in the high-intermediate group, with consequently a potential yield, influence on adjuvant treatment, and therapeutic impact of lymph node dissection, makes the question of performing or not a node dissection in presumed intermediate risk is a very difficult one. The point is then to decide on the basis of relatively inaccurate stratification, or to find a midterm between no node dissection and complete node dissection. Taking into consideration the difficulty in assessing LVSI preoperatively and the controversy regarding full lymph node dissection, the current development of the SLN technique is likely to be the best staging compromise in intermediate risk cancer patients [119]. Prospective clinical trials (SENTI-ENDO and FIRES) have established that the method is safe and associated with a lower rate of complications than standard lymphadenectomy [100-102].

The paradigm of lymph node dissection continues to be challenged. Adjuvant treatment can potentially be guided only by uterine pathologic features and recently introduced molecular markers based on the Cancer Genome Atlas Research Network data [12]. Molecular characteristics have already been incorporated in the NCCN guidelines algorithms [30]. In addition, L1 cell adhesion molecule (L1-CAM) was found to be an independent marker of distant recurrence and overall survival [16].

Awaiting the results of PORTEC 4A study, the current subclassification of intermediate risk has to be taken into account for adjuvant treatment planning. The same will remain valid in the future in settings where molecular biology resources are not available. In addition, the therapeutic role and the modalities of adjuvant treatment in endometrial cancer is also controversial. The publications of the PORTEC group question the prognostic value of external beam radiotherapy [27]. PORTEC 2 study compared vaginal brachytherapy versus external beam radiotherapy for patients with high-intermediate risk endometrial cancer (PORTEC risk stratification) and found no difference in disease-free survival. Toxicity and quality of life profile were more favourable in the brachytherapy arm [44]. Based on these finding, the European consensus panel recommends external beam radiotherapy only in the subgroup of high-intermediate risk patients with unknown nodal status [25].

METHODOLOGICAL ISSUES AND REMAINING UNANSWERED QUESTIONS

The main weakness of this study is its retrospective nature. Consequently, conclusions about the impact of adjuvant treatment cannot be drawn, as clinical protocols changed along years and differed across the centres. The introduction of adjuvant treatments in this model cannot be relevant. This bias is only partially controlled by multivariant character of statistical study. This study could though be a basis for a prospective, multicentric project with standardised criteria for adjuvant treatment and pathological analysis with centralized review.

Another methodological weakness could be related to the lack of power of the study. Lymph node involvement was identified as a significant independent factor of recurrence but not for overall survival. It is likely but not demonstrated, that the same figures would become significant with larger sample size. In spite of these reservations, it remains that the multivariate analysis found high-intermediate risk to be a significant, independent factor of disease-free and overall survival, which was the primary objective of this study.

In addition, we had to remove the risk stratification from the multivariate analysis in order to identify the significant prognostic value of LVSI. This decision was justified by the fact that LVSI is included in the definition of the majority of high-intermediate risk cases, generating redundant information.

Another issue is that the extent of LVSI (focal or extensive), a relatively recently defined distinction, was not recorded in our pathological records. Moreover, centralized pathology review, comparison between centres and quality control between pathologists were not performed. Mention of LVSI when only focal disease was found may potentially have led to inappropriately allocating patients in the high-intermediate risk group, and incorrectly improve the prognosis of this group of patients, decrease the rate of lymph node involvement and expose those patients to unnecessary adjuvant treatment. However, this does not impact the conclusions of this study, as it is likely that not including focal LVSI would have reinforced the impact of extensive LVSI as an independent prognostic factor.

A criticism about the absence of routine para-aortic lymph node dissection in our study could also be raised. However, the risk of isolated aortic node disease when the pelvic nodes are negative is negligible [50]. Even if the risk of aortic lymph node involvement is high when pelvic nodes are positive, there is no evidence that systematic para-aortic lymph node dissection improves survival.

FUTURE PERSPECTIVES

Still many questions require an answer: do we really need the lymph node status to make a decision on adjuvant treatment? Would it be detrimental for our patients to omit lymphadenectomy, if the preoperative record is negative? Isn't it more detrimental to perform a full staging knowing the chance of short- and long-term complications? The results of our study are in favor of some form of lymph node assessment, given the high rate of node-positivity in high-intermediate risk patients. However, the low rate of lymph node involvement in low intermediate risk patients does not justify the full lymph node dissection with its short and long-term complications. As the high intermediate risk is known only after definitive pathology, sentinel lymph node biopsy in all patients seems to be a reasonable compromise. However, this assumption needs to be confirmed in prospective trials.

The results of ECLAT prospective trial will be crucial to find the definitive answer about the utility of para-aortic lymph node dissection in endometrial cancer patients. The answer is expected to arrive by 2028. If this study is negative, possibly ''la belle époque'' of lymphadenectomy in endometrial cancer as a standard procedure of every gynecologic oncologist could be ended.

Meanwhile, the molecular classification could open new perspectives in treatment of endometrial cancer. Its universal use in pre- and postoperative setting could potentially conclude for always the controversy around lymph node dissection.

It is possible that individualised treatment could be a perfect answer in the management of endometrial cancer patients. Choice of the best therapy could be guided by tumor pathological and molecular characteristics, SLN status, but also patient's characteristics. Age and risk of death due to other pathologies should be taken into account.

The individual decision of the patients about the treatment preventing relapse could also be an important item when planning adjuvant treatment. The idea of use of artificial intelligence algorithm in taking this decision could be revolutionary. This philosophic and futuristic discussion in the light of fast-growing research is at our fingertips.

VIII. CONCLUSIONS (ENGLISH)

- Disease-free and overall survival of high-intermediate risk endometrial cancer according to current European intermediate risk subclassification is significantly poorer when compared to intermediate risk endometrial cancer.
- Lymph node involvement is significantly higher in high-intermediate risk group when compared to intermediate risk group and was an independent factor of recurrence.
- Lymphovascular space invasion is the most important predictive factor of lymph node disease.
- The age and presence of lymphovascular space invasion are found to be independent factors associated with recurrence in the whole group of intermediate risk endometrial cancer.
- The age and high-intermediate risk were independent variables of mortality in the multivariate analysis in the whole group of intermediate risk endometrial cancer.

CONCLUSIONES (ESPAÑOL)

- Las pacientes con cáncer de endometrio de riesgo intermedio-alto, según la subclasificación europea actual, presentaron una supervivencia libre de enfermedad y una supervivencia global significativamente peores en comparación con las pacientes con cáncer de endometrio de riesgo intermedio.

- La afectación ganglionar es significativamente mayor en el grupo de riesgo intermedio-alto en comparación con el grupo de cáncer de endometrio de riesgo intermedio. Además, esta afectación ganglionar es un factor de riesgo independiente para la recurrencia de la enfermedad.

- La invasión linfovascular es el factor predictivo más importante asociado con la afectación ganglionar linfática.

- La edad y la presencia de la invasión linfovascular son factores de riesgo independientes asociados con la aparición de recurrencias en las pacientes con cáncer de endometrio de riesgo intermedio de modo general.

- La edad y las características tumorales de riesgo intermedio-alto fueron las variables independientes de supervivencia global en las pacientes con cáncer de endometrio de riesgo intermedio de modo general.

IX. APPENDIX

INSTITUTIONAL REVIEW BOARD

Hospital Clínico San Carlos
SaludMadrid
Comunidad de Madrid

Dictamen Protocolo Favorable
C.P. ISM-200503 - C.I. 20/407-E
21 de mayo de 2020

CEIC Hospital Clínico San Carlos

Dra. Mar García Arenillas
Presidenta del CEIC Hospital Clínico San Carlos

CERTIFICA

Que el CEIC Hospital Clínico San Carlos en su reunión del día 20/05/2020, acta 5.2/20 ha evaluado la propuesta del promotor/investigador referida al estudio:

Título: Análisis de los Carcinomas de Endometrio de Riesgo Intermedio según la nueva clasificación ESGO (estudio CERI).

Código Interno: 20/407-E
Versión Protocolo Evaluada: 03 de mayo de 2020
Versión Hoja Información al Paciente Evaluada: GENERAL / 03 de mayo de 2020

Que en este estudio:

- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Es adecuado el procedimiento para obtener el consentimiento informado.
- La capacidad del investigador y los medios disponibles son adecuados para llevar a cabo el estudio.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto de los postulados éticos.
- Se cumplen los preceptos éticos formulados en la Declaración de Helsinki de la Asociación Médica mundial sobre principios éticos para las investigaciones médicas en seres humanos y en sus posteriores revisiones, así como aquellos exigidos por la normativa legal aplicable en función de las características del estudio.

Es por ello que el Comité **informa favorablemente** sobre la realización de dicho proyecto por el **Dr. Pluvio J. Coronado Martín** del Instituto de Salud de la Mujer José Botella Llusiá del Hospital Clinico San Carlos de Madrid.

Lo que firmo en Madrid, a 21 de mayo de 2020

Hospital Clínico San Carlos
SaludMadrid

Dra. Mar García Arenillas
Presidenta del CEIC Hospital Clínico San Carlos

Clinical relevance of high–intermediate risk endometrial cancer according to European risk classification

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HIGHLIGHTS

- High–intermediate risk patients have poorer disease free and overall survival compared with the standard intermediate risk group.
- High–intermediate classification, including lymphovascular space invasion, was a predictive factor for lymph nodal metastases.
- Subclassification of intermediate risk group is clinically relevant in management algorithms.

ABSTRACT

Objective Risk models in endometrial cancer define prognosis and indicate adjuvant therapy. One of the currently used classifications was designed in 2016 in collaboration with the European Society of Medical Oncology (ESMO), the European Society of Gynecologic Oncology (ESGO), and the European Society of Radiotherapy (ESTRO). A high–intermediate risk group was introduced within the intermediate risk group. The purpose of this study was to evaluate the clinical relevance of this subclassification.

Methods A multicenter retrospective study was carried out at five international tertiary institutions. Patients diagnosed with intermediate risk endometrial cancer on the basis of definitive pathology findings were included. Patients were stratified into intermediate and high–intermediate risk groups. Incidence of nodal metastases, and disease free and overall survival were compared between the two risk groups in univariate and multivariate analysis.

Results 477 patients were included: 325 (68%) patients were identified as intermediate and 152 (32%) as high–intermediate endometrial cancer patients. Nodal metastases were found in 18 patients (11.8%) in the high–intermediate risk endometrial cancer group and 16 patients (4.9%) in the intermediate risk group. Lymphovascular space invasion was found to be a strong predictive factor of lymph node involvement. High–intermediate risk was found to be an independent factor of disease free survival (hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.00 to 3.08; p=0.050) and overall survival (HR 1.99; 95% CI 1.10 to 3.60; p=0.022) in the multivariate analysis.

Conclusions The study validates the clinical significance of the intermediate risk endometrial cancer subclassification. Prognosis for high–intermediate risk endometrial cancer was significantly poorer. The prevalence of lymph node metastases was higher in this group of patients.

INTRODUCTION

Multiple risk models have been created on the basis of pathologic information to define prognosis and to estimate the risk of nodal metastasis in endometrial cancer. In the European setting, the European Society of Medical Oncology, the European Society of Gynecologic Oncology, and the European Society of Radiotherapy (ESMO/ESGO/ESTRO) risk classification is commonly used to tailor adjuvant treatment and plan surgical management.[1] The previous ESMO risk classification was modified in 2016, dividing the intermediate risk into two categories: intermediate risk group and high–intermediate risk group. Lymphovascular space invasion was incorporated as an important prognostic factor.[2] This subclassification into standard intermediate risk and high–intermediate risk was supported by retrospective reports, which documented an adverse prognosis for lymphovascular space invasion positive and grade 3 tumors.[3–7]

Patients with nodal metastases in endometrial cancer have a poorer prognosis compared with patients with negative nodes. The significance of this prognosis has been known from decades, which has supported the implementation of full lymph node staging in clinical practice.[8] However, it is generally considered that lymph node dissection should be reserved for those patients with a high risk of nodal disease. While data from the Gynecologic Oncology Group (GOG) 33 study found a 9% overall prevalence of nodal disease in endometrial cancer, the prevalence was as high as 18% in grade 3 tumors, and 34% when deep myometrial invasion was present.[9]

To our knowledge, there are no studies providing strong evidence that the subclassification in two specific risk groups is relevant in 'real life' clinical context.[10] Consequently, we carried out a study

comparing an intermediate risk endometrial cancer group with a high–intermediate endometrial cancer group (according to the ESMO/ESGO/ESTRO 2016 classification), regarding nodal metastases rate and oncologic outcome.

METHODS

We conducted a multicenter retrospective study between January 2000 and December 2018 at four tertiary Spanish institutions and one French comprehensive cancer center. A sample of 477 patients with uterine characteristics of intermediate-risk endometrial cancer on definitive pathology, according to the guidelines of the ESMO/ESGO/ESTRO 2016, were identified and reviewed.[2] The intermediate risk subclassification was defined as endometrioid histology with myometrial invasion ≥50%, grades 1–2, and negative lymphovascular space invasion. Patients with grade 1–2 tumors with lymphovascular space invasion unequivocally positive, regardless of the depth of myometrial invasion, and those with grade 3 tumors with <50% myometrial invasion, regardless of lymphovascular space invasion status, were categorized as high–intermediate risk.

Only patients who underwent hysterectomy with nodal assessment, either full lymphadenectomy or sentinel lymph node only, were included in the study. Patients with International Federation of Gynecology and Obstetrics (FIGO) stages II, IIIA, IIIB, and IV were excluded. Data of patients with FIGO stage IIIC were incorporated in order to assess the risk of nodal metastases. Patients with FIGO stage IIIC and one (or more) of the following were excluded: cervical stromal invasion, adnexal invasion, and uterine serosa invasion. Both intermediate risk groups were compared for the risk of nodal metastases, and disease free and overall survival. Other patient and tumor characteristics (grade, myometrial invasion, histologic subtype, maximal tumor size) and adjuvant treatment were recorded.

The protocol of the study was submitted and approved by the San Carlos Clínico Hospital Institutional Review Board. Samples from the French tumor archives were centralized in the Biological Resources Centres of Institut Bergonié, which the French authorities authorized for scientific research.

Statistical Analysis

Continuous variables are expressed as mean (standard deviation) and were compared using the t test for normal distributions or the Mann–Whitney test for non-parametric distributions. Quantitative variables are expressed as frequencies and percentages, and were compared with the χ^2 test or Fisher's exact test in small cell comparisons. For survival analysis, the Kaplan–Meier method was used to estimate the survival distribution in the study groups. The log rank test was used to calculate the statistical significance between the groups in relation to disease free and overall survival. Cox's method was used to identify the factors directly associated with survival. Multivariate modeling using Cox's proportional hazard models was performed to obtain a subset of independent predictors of disease free and overall survival. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. All statistical tests were two sided and statistical significance was defined as a p value <0.05. All computations were performed using IBM SPSS Statistic V.25 (Chicago, Illinois, USA).

RESULTS

A total of 477 patients with intermediate risk endometrial cancer at definitive pathology and who had nodal assessment were included. Of these, 325 (68%) patients were identified as intermediate risk and 152 (32%) as high–intermediate risk. Both groups were similar in general characteristics (age, body mass index, comorbidities). The median age of the total cohort was 66 years (range 31–89). A total of 387 (81.2%) patients received adjuvant treatment, including brachytherapy (195 patients), external beam radiotherapy (166 patients), and irradiation and chemotherapy (26 patients). Patient characteristics are presented in Table 1.

Thirty-four patients (7.1%) in the entire group were found to have lymph node metastases. In the intermediate risk group, 16 patients (4.9%) had lymph node metastases. Nodal disease was found in 18 (11.8%) patients with uterine characteristics of high–intermediate risk endometrial cancer. The difference was statistically significant (p=0.006). Lymphovascular space invasion was the only independent pathological feature associated with lymph node involvement (p<0.001). Predictive factors for lymph node metastases are reported in Table 2. After a median follow-up of 53.2 months (range 25.9–86.9), 53 (11%) patients recurred, 29 (8.9%) patients in the intermediate risk group and 24 (15.8%) patients in the high–intermediate risk group. The distribution of recurrences was significantly (p=0.024) different between groups, with 10 pelvic recurrences (34.5% of recurrences), 2 nodal recurrences (6.9%), and 17 distant recurrences (58.6%) in the intermediate risk group compared with 3 pelvic (12.5%), 8 nodal (33.3%), and 13 distant (54.2%) in the high–intermediate risk group. Interestingly, the nodal recurrence rate was 0.6% in patients in the intermediate risk group compared with 5.2% in the high–intermediate risk group.

Twenty-seven patients (5.6%) were alive with disease. A total of 47 (9.8%) patients died and, of these, 27 patients died of disease. Cancer related deaths were more common in the high–intermediate group than in the intermediate group (15 (9.8% of patients) vs 13 (4.0%), respectively) but this finding was not significant (p=0.056).

Five year disease free survival was 90.7% in the intermediate risk group compared with 79.5% in the high–intermediate risk group (p=0.006). Five year overall survival was 92.5% in the intermediate group and 83.7% in the high–intermediate risk group (p=0.042). Disease free and overall survival were significantly lower in the high–intermediate group (HR 2.10, 95% CI 1.22 to 3.62, p=0.009; and HR 1.82, 1.01 to 3.28, p=0.045, respectively) (Figure 1A and B).

A multivariate analysis was performed using the Cox model. This analysis found that high–intermediate risk was an independent factor of disease free survival (adjusted HR 1.86; 95% CI 1.02 to 3.39; p=0.043) and overall survival (adjusted HR 1.99; 95% CI 1.10 to 3.60; p=0.022). In addition, lymph node involvement was also identified as an independent factor of recurrence (HR 3.06; 95% CI 1.39 to 6.72; p=0.005). When risk stratification was removed

Table 1 Patient demographics and pathologic details in intermediate risk endometrial cancers

	Intermediate risk (n=325)	Intermediate–high risk (n=152)	P value*
Age (years)	66.4±9.1	65.1±9.8	0.153
Body mass index (kg/m^2)	29.8±5.7	28.8±5.4	0.077
Associated diseases†	214 (65.8)	91 (59.9)	0.205
Years from menopause	16.3±9.6	15.1±10.2	0.288
Parity	1.9±1.5	1.9±1.3	0.767
Pre-surgical hemoglobin (mg/L)	13.5±1.1	13.4±1.4	0.597
Histologic subtype			0.598
Endometrioid pure	308 (94.8)	147 (96.7)	
With mucinous differentiation	5 (1.5)	1 (0.7)	
With squamous differentiation	12 (3.7)	4 (2.6)	
Histological grade			<0.001
G1	164 (50.5)	31 (20.4)	
G2	161 (49.5)	47 (30.9)	
G3	0 (0)	74 (48.7)	
Myometrial invasion			<0.001
<50%	0 (0)	84 (55.3)	
≥50%	325 (100)	68 (44.7)	
Lymphovascular space invasion			<0.001
No	278 (85.5)	60 (39.5)	
Yes	0 (0)	86 (56.6)	
Unknown	47 (14.5)	6 (3.9)	
Tumor size (cm)	3.0±1.5	3.3±1.7	0.046
Surgical approach			0.045
Laparotomy	190 (58.5)	74 (48.7)	
Minimally invasive	135 (41.5)	78 (51.3)	
Lymphadenectomy			<0.001
Pelvic only	272 (83.7)	85 (55.9)	
Pelvic and para-aortic	53 (16.3)	67 (44.1)	
No of nodes removed			
Pelvic	14.1±7.4	14.1±6.7	0.959
Pelvic and para-aortic	12.2±10.0	12.3±9.2	0.935
Lymph node status			0.006
Negative	309 (95.1)	134 (88.2)	
Positive	16 (4.9)	18 (11.8)	
Adjuvant treatment			0.008
None	67 (20.6)	23 (15.1)	
Brachytherapy	140 (43.1)	55 (36.2)	
External beam radiation	107 (32.9)	59 (38.8)	
Irradiation and chemotherapy	11 (3.4)	15 (9.9)	
Follow-up alive (months)	60.1±40.4	48.8±33.5	0.001

Data are mean±SD or n (%).
*t test for variables with a normal distribution, Mann–Whitney test for other continuous variables, and χ^2 test or Fisher's test for discrete variables.
†Includes hypertension, diabetes, and lung and heart disease.

Table 2 Predictive factors of lymph node metastases in 477 cases of intermediate risk endometrial cancers.

Variable	No lymph node metastases (n=443)	Lymph node metastases (n=34)	P value*
Age (years)	66.2±91	63.1±11.3	0.056
Histologic subtype			0.413
Endometrioid	421 (95.0)	34 (100)	
Mucinous	6 (1.4)	0 (0)	
Squamous	16 (3.6)	0 (0)	
Histological grade			0.107
G1–G2	371 (83.7)	32 (94.1)	
G3	72 (16.3)	2 (5.9)	
Myometrial invasion			0.636
<50%	77 (17.4)	7 (20.6)	
≥50%	366 (82.6)	27 (79.4)	
Maximum tumor size (cm)	3.1±1.6	3.4±1.5	$0.38
Lymphovascular space invasion*			<0.001
No	325 (82.5)	13 (43.3)	
Yes	69 (17.5)	17 (56.7)	
Risk stratification			0.006
Intermediate	309 (69.8)	16 (47.1)	
High–intermediate	134 (30.2)	18 (52.9)	

Data are mean±SD or n (%).
*Only patients with known lymphovascular space invasion status were included in the statistical analysis.

from the model, age (HR 1.04; 95% CI 1.01 to 1.07; p=0.038) and lymphovascular space invasion (HR 1.93; 95% CI 1.01 to 3.73; p=0.049) were found to be independent factors for disease free survival.

DISCUSSION

The subclassification of risk into standard intermediate and high–intermediate has been validated in this series. Within the intermediate risk group, patients had a different risk of nodal disease and prognosis. The current subclassification partially reflects and reduces this heterogeneity. The prevalence of nodal disease was significantly higher and nodal recurrences were more frequent in the high–intermediate group. Prognosis was substantially poorer in high–intermediate risk cancer patients. Intermediate risk endometrial cancer was therefore not a homogeneous group.

When looking at the literature, risk classifications have substantially changed in the past 20 years. Regrettably, the definition of intermediate risk and high–intermediate risk endometrial cancer is not universal. These differences in definition make it difficult to extrapolate the results of studies addressing the prognosis of intermediate low and high risk endometrial cancer patients. For example, in GOG 99, high–intermediate risk patients were defined as: (1) moderate to poorly differentiated tumors, presence of lymphovascular space invasion, and outer third myometrial invasion; (2) age 50 years or older, with any two risk factors listed above; or (3) age at least 70 years with any risk factor listed above. Intermediate low risk was defined as age ≤50 years and ≤2 risk factors; age 50–69 years and ≤1 risk factor; or age ≥70 years with no risk factors.[11]

In contrast, the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 definition of high–intermediate risk is two of the following three factors: age >60 years, more than one half myometrial invasion, and grade 3 disease. Intermediate low was defined as (1) stage I, grade 1, myometrial invasion ≥50%; (2) stage I, grade 2; or (3) stage I, grade 3, myometrial invasion <50%. The latter definition was further used in ESMO 2010[1] for the definition of intermediate risk.[12]

Different international societies add different criteria to consider high–intermediate risk patients and the need for adjuvant brachytherapy. The National Comprehensive Cancer Network (NCCN) includes lymphovascular space invasion, age, tumor size, and lower uterine segment invasion as additional risk factors.[13] The American Society for Therapeutic Radiation Oncology guidelines specify age >60 years and lymphovascular space invasion as adverse risk factors.[14] The ESMO/ESGO/ESTRO[2] definition added a high–intermediate group, described as: (1) stage I endometrial, grade 3, myometrial invasion <50%, independently of lymphovascular space invasion; or (2) stage I endometrial, grade 1–2, lymphovascular space invasion invasion unequivocally positive, independently of myometrial invasion.[2] One study compared the accuracy of different risk stratification, demonstrating that none of the five major risk systems showed high accuracy to stratify recurrence risk and nodal metastases in early stage endometrial cancer.[10] In contrast, our study suggests that the current European risk stratification is effective in defining the risk of lymph node disease and prognosis.

The introduction of extensive lymphovascular space invasion in the risk stratification has been an important point, as this

Table 3 Univariant analysis of disease free survival and overall survival in 477 intermediate risk endometrial cancers

	Disease free survival		Overall survival	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (linear increment per year)	1.02 (0.99 to 1.05)	0.176	1.05 (1.01 to 1.08)	0.011
Risk stratification				
Intermediate	1		1	
High–intermediate	2.10 (1.22 to 3.62)	0.009	1.82 (1.01 to 3.28)	0.045
Lymphovascular space invasion				
No	1		1	
Yes	1.83 (0.98 to 3.43)	0.062	1.87 (0.97 to 3.60)	0.062
Positive lymph nodes				
No	1		1	
Yes		<0.001	2.36 (1.00 to 5.57)	0.05
Histological subtype				
Endometrioid	1		1	
Mucinous	–	–	–	–
Squamous	1.66 (0.52 to 5.32)	0.395	2.32 (0.83 to 6.48)	0.107
Histological grade				
G1	1		1	
G2	1.14 (0.63 to 2.08)	0.662	1.06 (0.57 to 1.95)	0.862
G3	1.69 (0.79 to 3.60)	0.173	1.04 (0.42 to 2.57)	0.939
Myometrial invasion				
<50%	*1*		1	
≥50%	0.59 (0.31 to 1.12)	0.107	0.95 (0.43 to 2.13)	0.905

Multivariate analysis included all variables with a p value <0.10.
*The independent variables of recurrence in the multivariate analysis were intermediate–high (hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.00 to 3.08; p=0.050), and need for brachytherapy (HR 3.46; 95% CI 1.03 to 11.62; p=0.045) and chemoradiation as adjuvant treatment (HR 9.22; 95% CI 2.38 to 35.64; p=0.001).
†The independent variables of mortality in the multivariate analysis were age (linear increment per year HR 1.05; 95% CI 1.01 to 1.09; p=0.007) and the intermediate–high risk (HR 1.99; 95% CI 1.10 to 3.60; p=0.022).

histologic feature strongly impacts prognosis in early stage endometrial cancer and should be precisely reported in the pathological report. Research based on PORTEC-1 and -2 cases highlighted the importance of quantifying the number of vessels involved with lymphovascular space invasion as focal or substantial/extensive. Substantial lymphovascular space invasion, in contrast with focal or no lymphovascular space invasion, was found to be the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis, and overall survival.[15] However, the impact of lymphovascular space invasion makes the current ESMO/ESGO[2] classification not practical in the preoperative context, as the level of lymphovascular space invasion can be reliably established only in the surgical specimen. In other words, the lymphovascular space invasion status component of the classification cannot be used to indicate lymph node dissection. On the other hand, there is no definitive evidence that lymphadenectomy has a therapeutic value.[16] Our group retrospectively analyzed a match pair study of 720 patients with standard intermediate risk endometrial cancer according to the ESMO 2010[1] classification. No benefit in disease free or overall survival of lymph node dissection was found.[17]

The available randomized data on lymph node dissection did not show any survival benefit in patients with low and intermediate/high risk endometrial cancer while impacting morbidity.[18 19] The ongoing AGO/ECLAT (Arbeitsgemeinschaft fuer Gynaekologische Onkologie/Endometrial Cancer Lymphadenectomy Trial) study (NCT 03438474) was opened to recruitment in 2018. The ECLAT trial aims to assess whether systematic pelvic and para-aortic lymph node dissection has a significant impact on overall survival in patients with high risk endometrial cancer.[20] Taking into consideration the difficulty in assessing lymphovascular space invasion preoperatively and the controversy regarding full lymph node dissection, the current development of the sentinel lymph node technique is likely to be the best staging compromise in intermediate risk cancer patients.[21] Prospective clinical trials (Sentinel Node and Endometrial Cancer (SENTI-ENDO) and Determining the Sensitivity of Sentinel LymphNodes Identified With Robotic Fluorescence Imaging (FIRES)) have established that the method is safe and associated with a lower rate of complications than standard lymphadenectomy.[22–24]

The paradigm of lymph node prognostic value continues to be challenged. Adjuvant treatment can potentially be guided only by

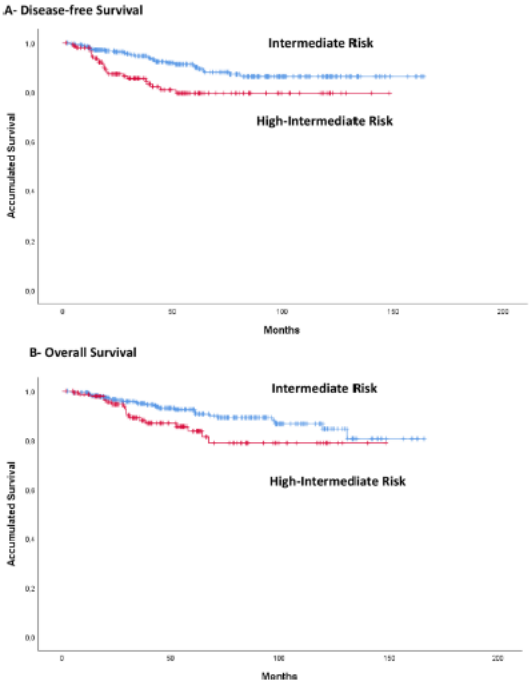

Figure 1 Kaplan–Meier estimate of disease free survival (A) and overall survival (B) in intermediate and high–intermediate endometrial cancer.

uterine pathologic features and recently introduced molecular markers based on the Cancer Genome Atlas Research Network data.[25] Molecular characteristics have already been incorporated in the NCCN guidelines algorithms.[13] In addition, L1 cell adhesion molecule was found to be an independent marker of distant recurrence and overall survival.[26] The potential of biomarkers in tailoring adjuvant therapy is suggested in two manuscripts[27 28] and is being investigated in the PORTEC-4a study (NCT 03469674).[29] This prospective phase III trial is investigating the role of an integrated clinicopathological and molecular risk profile to determine if patients with high–intermediate risk features should receive no adjuvant therapy, vaginal brachytherapy, or external beam radiotherapy. Awaiting the results of this study, the current subclassification of intermediate risk has to be taken into account for adjuvant treatment planning. The same will remain valid in the future in settings where molecular biology resources are not available. In addition, the therapeutic role and the modalities of adjuvant treatment in endometrial cancer are also controversial. The publications of the PORTEC group question the prognostic value of external beam radiotherapy.[12] The PORTEC-2 study compared vaginal brachytherapy with external beam radiotherapy for patients with high–intermediate risk endometrial cancer (PORTEC risk stratification) and found no difference in disease free survival. Toxicity and quality of life profile were more favorable in the brachytherapy arm.[30] A meta-analysis on the effect of external beam radiotherapy on overall survival in intermediate risk and high risk early stage disease, including Cochrane and ASTEC/EN.5 results, showed a non-significant HR of 1.04 (95% CI 0.84 to 1.29; p=0.38).[31] Based on this finding, the European consensus panel recommends external beam radiotherapy only in the subgroup of high–intermediate risk patients with unknown nodal status.[2]

To our knowledge, this is the first study that has evaluated the role of the subclassification of intermediate risk endometrial cancer in a large multicentric cohort with multivariate analysis. The main weakness of this study is its retrospective nature. Consequently, conclusions about the impact of adjuvant treatment cannot be drawn, as clinical protocols changed along the years and differed across the centers. A criticism about the absence of routine paraaortic lymph node dissection in our study could also be raised. However, the risk of isolated aortic node disease when the pelvic nodes are negative is negligible.[9] Another weakness is that the extent of lymphovascular space invasion (focal or extensive), a relatively recently defined distinction, was not recorded in our pathological records. Moreover, centralized pathology review, comparison between centers, and quality control between pathologists were not performed. Mention of lymphovascular space invasion when only focal disease was found may potentially have led to inappropriately allocating patients in the high–intermediate risk group. However, this does not impact the conclusions of this study, as it is likely that not including focal lymphovascular space invasion would have reinforced the impact of extensive lymphovascular space invasion as an independent prognostic factor.

This study provides confirmation that the intermediate risk subclassification designed in 2016 in the ESMO/ESGO/ESTRO classification is clinically relevant. The prognosis of high–intermediate endometrial cancer was significantly poorer compared with low–intermediate risk in spite of more frequent use of adjuvant treatment in this group of patients. The 2016 ESMO/ESGO/ESTRO risk stratification is relevant for adjuvant treatment planning. The prevalence of lymph node metastases was significantly higher in the high–intermediate risk group of patients. The prevalence of nodal metastasis was as high as 11.8% in the high–intermediate risk group in our study. Lymphovascular space invasion is the most important predictive factor of lymph node disease. Mentioning this pathological feature, along with its extent, is a critical component of a definitive pathological report. As lymphovascular space invasion is not known before surgery, evaluation of he lymph node status may be useful. On the other hand, as the prevalence of nodal disease was low in the overall group, especially in the standard intermediate group, the risk–benefit ratio of full lymph node dissection was not favorable, while the universal use of a sentinel lymph node algorithm could be justified.

The introduction of molecular markers into the risk classification can potentially help to more accurately define the prognosis of patients currently classified as having intermediate or high–intermediate risk endometrial cancer. However, the algorithmic concept underlying all stratification models may eventually be replaced in future by a multivariate predictive modeling approach incorporating the independent weight of all the biopathological and clinical prognostic factors.[32]

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REFERENCES

1 Plataniotis G, Castiglione M. ESMO guidelines working group. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:41–5.
2 Colombo N, Creutzberg C, Amant F, *et al*. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *Int J Gynecol Cancer* 2016;26:2–30.
3 Briet JM, Hollema H, Reesink N, *et al*. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. *Gynecol Oncol* 2005;96:799–804.
4 Cohn DE, Horowitz NS, Mutch DG, *et al*. Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? *Gynecol Oncol* 2002;87:243–6.
5 Gadducci A, Cavazzana A, Cosio S, *et al*. Lymph-vascular space involvement and outer one-third myometrial invasion are strong predictors of distant haematogeneous failures in patients with stage I-II endometrioid-type endometrial cancer. *Anticancer Res* 2009;29:1715–20.
6 Gemer O, Arie AB, Levy T, *et al*. Lymphvascular space involvement compromises the survival of patients with stage I endometrial cancer: results of a multicenter study. *Eur J Surg Oncol* 2007;33:644–7.
7 Guntupalli SR, Zighelboim I, Kizer NT, *et al*. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. *Gynecol Oncol* 2012;124:31–5.
8 Creasman WT, Odicino F, Maisonneuve P, *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:S105–4.
9 Creasman WT, Morrow CP, Bundy BN, *et al*. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer* 1987;60:2035–41.
10 Bendifallah S, Canlorbe G, Collinet P, *et al*. Just how accurate are the major risk stratification systems for early-stage endometrial cancer? *Br J Cancer* 2015;112:793–801.
11 Keys HM, Roberts JA, Brunetto VL, *et al*. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2004;92:744–51.
12 Creutzberg CL, van Putten WLJ, Koper PCM, *et al*. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. *Lancet* 2000;355:1404–11.
13 NCCN Clinical practical guidelines in oncology. Uterine neoplasm. version 1.2020, 2020. Available: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf [Accessed 16 Jul 2020].
14 Klopp A, Smith BD, Alektiar K, *et al*. The role of postoperative radiation therapy for endometrial cancer: an ASTRO evidence-based guideline. *Pract Radiat Oncol* 2014;4:137–44.
15 Bosse T, Peters EEM, Creutzberg CL, *et al*. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer-A pooled analysis of PORTEC 1 and 2 trials. *Eur J Cancer* 2015;51:1742–50.
16 Coronado PJ, Fasero M, Baquedano L, *et al*. Impact of the lymphadenectomy in high-risk histologic types of endometrial cancer: a matched-pair study. *Int J Gynecol Cancer* 2014;24:703–12.
17 Coronado PJ, Rychlik A, Martínez-Maestre MA, *et al*. Role of lymphadenectomy in intermediate-risk endometrial cancer: a matched-pair study. *J Gynecol Oncol* 2018;29:e1.
18 Benedetti Panici P, Basile S, Maneschi F, *et al*. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst* 2008;100:1707–16.
19 ASTEC study group, Kitchener H, Swart AMC, *et al*. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* 2009;373:125–36.
20 ClinicalTrials.gov [Internet]. Identifier NCT00287392, Endometrial Cancer Lymphadenectomy Trial (ECLAT)/2018 Feb 19. Available: https://clinicaltrials.gov/ct2/show/NCT03438474 [Accessed 16 Jul 2020].
21 Holloway RW, Abu-Rustum NR, Backes FJ, *et al*. Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations. *Gynecol Oncol* 2017;146:405–15.
22 Ballester M, Dubernard G, Lécuru F, *et al*. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). *Lancet Oncol* 2011;12:469–76.
23 Rossi EC, Kowalski LD, Scalici J, *et al*. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. *Lancet Oncol* 2017;18:384–92.
24 Soliman PT, Westin SN, Dioun S, *et al*. A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. *Gynecol Oncol* 2017;146:234–9.
25 Cancer Genome Atlas Research Network, Kandoth C, Schultz N, *et al*. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013;497:67–73.
26 Bosse T, Nout RA, Stelloo E, *et al*. L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results. *Eur J Cancer* 2014;50:2602–10.
27 Stelloo E, Bosse T, Nout RA, *et al*. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. *Mod Pathol* 2015;28:836–44.
28 Kommoss S, McConechy MK, Kommoss F, *et al*. Final validation of the promise molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol* 2018;29:1180–8.
29 Identifier NCT 03469674, PORTEC-4a: molecular profile-based versus standard adjuvant radiotherapy in endometrial cancer (PORTEC-4a), 2018. Available: https://clinicaltrials.gov/ct2/show/NCT03469674 [Accessed 16 Jul 2020].
30 Nout RA, Smit VTHBM, Putter H, *et al*. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010;375:816–23.
31 ASTEC/EN.5 Study Group, Blake P, Swart AM, *et al*. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet* 2009;373:137–46.
32 Bendifallah S, Daraï E, Ballester M. Predictive modeling: a new paradigm for managing endometrial cancer. *Ann Surg Oncol* 2016;23:975–88.

X. BIBLIOGRAPHY

1. Guías de asistencia práctica. Oncoguía SEGO: Cáncer de Endometrio 2016. Prog Obstet Ginecol 2017;60:274-302.

2. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394-424.

3. Sheikh MA, Althouse AD, Freese KE et al. USA endometrial cancer projections to 2030: should we be concerned? Future Oncol 2014;10:2561–68.

4. Evans-Metcalf ER, Brooks SE, Reale FR et al. Profile of women 45 years of age and younger with endometrial cancer. Obstet Gynecol 1998;91:349–54.

5. Soini T, Hurskainen R, Grénman S et al. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol 2014;124:292–9.

6. Renkonen-Sinisalo L, Bützow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007;120:821–24.

7. Long B, Clarke MA, Del Mar Morillo A et al. Ultrasound detection of endometrial cancer in women with postmenopausal bleeding: Systematic review and meta-analysis. Gynecol Oncol 2020;157:624-33.

8. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983;15 :10–7.

9. Morice P, Leary A, Creutzberg C et al. Endometrial Cancer. Lancet 2016;387:1094-108.

10. Amant F, Mirza M, Koskas M et al. Cancer of corpus uteri. FIGO Cancer reports Int J Gynecol Obstet 2018;143:37-50.

11. Kurman RJ, Carcangiu ML, Herrington S et al. Tumours of the Female Reproductive Organs. WHO classification of tumours. Lyon: IARC Press; 2014.

12. Douglas A. Levine & The Cancer Genome Atlas Research Network Integrated genomic characterization of endometrial carcinoma Nature 2013;497:67–73.

13. Stelloo E, Nout RA, Osse EM et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. Clin Cancer Res 2016; 22: 4215–24.

14. Talhouk A, McConechy MK, Leung S et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017 ;123: 802-13.

15. Kommoss S, McConechy MK, Kommoss F et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Annals of Oncology 2018;29:1180–8.

16. Bosse T, Nout RA, Stelloo E et al. L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results. Eur J Cancer 2014;50:2602-10.

17. van der Putten LJM, Visser NCM, van de Vijver K et al. Added value of estrogen receptor, progesterone receptor, and L1 cell adhesion molecule expression to histology-basedendometrial carcinoma recurrence prediction models: An ENITEC collaboration study. Int J Gynecol Cancer 2018;28:514–23.

18. Savelli L, Ceccarini M, Ludovisi M, et al. Preoperative local staging of endometrial cancer: transvaginal sonography vs magnetic resonance imaging. Ultrasound Obstet Gynecol 2008;31:560–6.

19. Akbayir O, Corbacioglu A, Numanoglu C, et al. Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound. Gynecol Oncol 2011;122:600–3.

20. Lai CH, Lin G, Yen TC et al. Molecular imaging in the management of gynecologic malignancies. Gynecol Oncol 2014;135:156–62.

21. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105:103–4.

22. Union internationale contre le cancer (UICC). TNM: Classification des tumeurs malignes, 7th edn. New York, NY: Wiley-Blackwell,2009.

23. Morrow CP, Bundy BN, Kurman RJ et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40:55-65.

24. Colombo N, Preti E, Landoni F et al. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(SUPPL.6).

25. Colombo N, Creutzberg C, Amant F et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016;27:16-41.

26. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.

27. Creutzberg, CL, van Putten, WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. Lancet 2000;355:1404–11.

28. Li R, Shinde A, Haet E al. A proposal for a new classification of “unfavorable risk criteria” in patients with stage I endometrial cancer Int J Gynecol Cancer 2019;29:1086–93.

29. Bendifallah S, Canlorbe G, Collinet P et al. Just how accurate are the major risk stratification systems for early-stage endometrial cancer? Br J Cancer 2015;112:793–801.

30. NCCN Clinical practical guidelines in oncology. Uterine neoplasm. Version 1.2020. March 06, 2020. Available from:https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf (accessed July 16, 2020).

31. Klopp A, Smith BD, Alektiar K et al. The Role of Postoperative Radiation Therapy for Endometrial Cancer: An ASTRO Evidence-Based Guideline. Pract Radiat Oncol 2014; 4:137-44.

32. Murali R, Delair DF, Bean SM et al. Evolving Roles of Histologic Evaluation and Molecular/Genomic Profiling in the Management of Endometrial Cancer. J Natl Compr Canc Netw. 2018;16:201-9.

33. Briët JM, Hollema H, Reesink N et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol 2005;96:799–804.

34. Cohn DE, Horowitz NS, Mutch DG et al. Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 2002;87:243–6.

35. Gadducci A, Cavazzana A, Cosio S et al. Lymph-vascular space involvement and outer one-third myometrial invasion are strong predictors of distant haematogeneous failures in patients with stage I-II endometrioid-type endometrial cancer. Anticancer Res 2009; 29:1715–20.

36. Gemer O, Arie AB, Levy T et al. Lymphvascular space involvement compromises the survival of patients with stage I endometrial cancer: results of a multicenter study. Eur J Surg Oncol 2007;33:644–7.

37. Guntupalli SR, Zighelboim I, Kizer NT et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol 2012;124:31–5.

38. Bosse T, Peters EE, Creutzberg CL et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer 2015;51:1742-50.

39. Kilgore LC, Partridge EE, Alvarez RD et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol.1995;56:29–36.

40. Chan JK, Cheung MK, Huh WK et al. Therapeutic role of LN resection in endometrioid corpus cancer. Cancer. 2006; 107:1823–30.

41. Panici PB, Basile S, Maneschi F et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: Randomized clinical trial. J Natl Cancer Inst. 2008;100:1707–16.

42. ASTEC study group, Kitchener H, Swart AM, Qian Q et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009; 373:125-36.

43. Coronado PJ, Fasero M, Baquedano L et al. Impact of the lymphadenectomy in high-risk histologic types of endometrial cancer: a matched-pair study. Int J Gynecol Cancer. 2014; 24: 703-12.

44. Nout RA, Smit VTHB, Putter H et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial carcinoma of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. Lancet 2010; 375: 816–23.

45. Creutzberg CL, Nout RA, Lybeert MLM et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2011; 81: 631-8.

46. Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): Pooled trial results, systematic review, and meta-analysis. Lancet. 2009; 373: 137–46.

47. Kunneman M, Pieterse AH, Stiggelbout AM et al. Treatment preferences and involvement in treatment decision making of patients with endometrial cancer and clinicians. Br J Cancer. 2014;111: 674–9.

48. Ortoft, G, Hansen ES, Bertelsen, K et al. Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: the Danish Endometrial Cancer Study. Int J Gynecol Cancer 2013.23,1429-37.

49. Wortman, BG, Creutzberg CL, Putter H et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer 2018;119:1067-74.

50. Creasman WT, Morrow CP, Bundy BN et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60:2035–41.

51. Peters E, Bartosch C, McCluggage WG et al. Reproducibility of lymphovascular space invasion assessment in endometrial cancer. Histopathology 2019;75: 128–36.

52. Kuroki J, Hasegawa K, Kato R, et al. Relationship between the classification of vascular invasion severity and the prognosis of uterine endometrial cancer. Int J Gynecol Cancer 2003;13:47–52.

53. Folkins AK, Nevadunsky NS, Saleemuddin A et al. Evaluation of vascular space involvement in endometrial adenocarcinomas: laparoscopic vs abdominal hysterectomies. Mod Pathol 2010;23:1073–9.

54. Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. Am J Surg Pathol 2013;37:874–81.

55. Han G, Sidhu D, Duggan MA, et al. Reproducibility of histological cell type in high-grade endometrial carcinoma. Mod Pathol 2013;26:1594-604.

56. Querleu D, Leblanc E, Cartron G et al. Audit of preoperative and early complications of laparoscopic lymph node dissection in 1000 gynecologic cancer patients. Amer J Obstet Gynecol 2006;195:1287-92.

57. Angeles MA, Meyrignac O, Martínez-Gómez C et al. Aortic abdominal dissection after retroperitoneal laparoscopic para-aortic lymphadenectomy. Gynecol Oncol Rep 2019;29:25–8.

58. Vasilev SA. Obturator Nerve Injury: A Review of Management Options Gynecol Oncol. 1994;53:152-5.

59. Kim H.Y., Kim J.W., Kim S.H. et al. An analysis of the risk factors and management of lymphocele after pelvic lymphadenectomy in patients with gynecologic malignancies. Cancer Res Treat 2004;36:377–83.

60. Todo Y, Yamamoto R, Minobe S et al. Risk factors for postoperative lower-extremity lymphedema in endometrial cancer survivors who had treatment including lymphadenectomy. Gynecol Oncol 2010;119:60–4.

61. Achouri A, Huchon C, Bats AS et al. Complications of lymphadenectomy for gynecologic cancer. Eur J Surg Oncol 2013;39:81–6.

62. Petru E, Tamussino K, Lahousen M et al. Pelvic and para-aortic lymphoceles after radical surgery because of cervical and ovarian cancer. Am J Obstet Gynecol 1989;161:937–41.

63. Rowlands IJ, Beesley VL, Janda M et al. Quality of life of women with lower limb swelling or lymphedema 3-5 years following endometrial cancer. Gynecol Oncol 2014;133:314-8.

64. Salani R, Preston MM, Hade EM et al. Swelling among women who need education about leg lymphedema a descriptive study of lymphedema in women undergoing surgery for endometrial cancer. Int J Gynecol Cancer 2014;24:1507-12.

65. Lindqvist E, Wedin M, Fredrikson M et al. Lymphedema after treatment for endometrial cancer - a review of prevalence and risk factors. Eur J Obstet Gynecol Reprod Biol 2017;211:112-21

66. Yost KJ, Cheville AL, Al-Hilli MM et al. Lymphedema after surgery for endometrial cancer: prevalence, risk factors, and quality of life. Obstet Gynecol 2014;124:307-15.

67. Beesley VL, Rowlands IJ, Hayes SC et al. Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb lymphedema and lymphedema-specific supportive care needs in women treated for endometrial cancer. Gynecol Oncol 2015; 136:87–93.

68. Carlson JW, Kauderer J, Hutson A et al. GOG 244-The lymphedema and gynecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients. Gynecol Oncol.2020;156:467-74.

68. Leitao MM, Zhou QC, Gomez-Hidalgo NR et al. Patient-reported outcomes after surgery for endometrial carcinoma:Prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy. Gynecol Oncol 2020;156:147-53.

70. Mathevet P, Lecuru F, Magaud L et al. Sentinel lymph node biopsy for early cervical cancer: Results of a randomized prospective, multicenter study (Senticol 2) comparing adding pelvic lymph node dissection vs sentinel node biopsy only.2017 Gynecol Oncol;145:2-3 SGO abstract.

71. Kilgore LC, Partridge EE, Alvarez RD et al. Adenocarcinoma of the endometrium: Survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995;56:29–33.

72. Larson DM, Broste SK, Krawisz BR et al. Surgery without radiotherapy for primary treatment of endometrial cancer. Obstet Gynecol 1998; 91 :355–9.

73. Cragun JM, Havrilesky LJ, Calingaert B et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer J Clin Oncol 2005;23:3668–74.

74. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375:1165–72.

75. de Boer SM, Powell ME, Mileshkin L et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): Final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19:295–309.

76. Matei D, Filiaci V, Randall ME et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med 2019;380:2317-26.

77. Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod Pathol 2015; 28:836–44.

78. ClinicalTrials.gov [Internet]. Identifier NCT 03469674, PORTEC-4a: Molecular Profile-based Versus Standard Adjuvant Radiotherapy in Endometrial Cancer (PORTEC-4a) March 19, 2018 Available from https://clinicaltrials.gov/ct2/show/NCT03469674 (accessed July 16, 2020).

79. Holloway RW, Abu-Rustum NR, Backes FJ et al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol 2017; 146:405-15.

80. Benedetti Panici, P, Basile S, Salerno MG et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol 2014; 210: 363.e1-363.e10.

81. Frost JA, Webster KE, Bryant A et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 2017;10:CD007585.

82. ClinicalTrials.gov [Internet]. Identifier NCT00287392, Endometrial Cancer Lymphadenectomy Tral (ECLAT)/ 2018 Feb 19. Available from: https://clinicaltrials.gov/ct2/show/NCT03438474 (accessed July 16, 2020).

83. Lankveld MA van, Koot NC, Peeters PH et al. Compliance to surgical and radiation treatment guidelines in relation to patient outcome in early stage endometrial cancer. J Eval Clin Pract 2006;12:196–201.

84. Trimble EL, Kosary C, Park RC. Lymph node sampling and survival in endometrial cancer Gynecol Oncol 1998;71:340-3.

85. Tong S-Y, Lee J-M, Lee J-K et al. Efficacy of para-aortic lymphadenectomy in early-stage endometrioid uterine corpus cancer. Ann Surg Oncol 2011;18:1425–30.

86. Eggemann, H, Ignatov T, Kaiser K et al. Survival advantage of lymphadenectomy in endometrial cancer. J Cancer Res Clin Oncol 2016;142:1051-60.

87. Chan JK, Wu H, Cheung MK et al. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. Gynecol Oncol 2007;106:282-8.

88. Coronado PJ, Rychlik A, Martinez-Maestre MA et al. Role of lymphadenectomy in intermediate-risk endometrial cancer: a matched-pair study. J Gynecol Oncol 2018;29: e1.

89. Bougherara L, Azais H, Béhal H et al. Does lymphadenectomy improve survival in patients with intermediate risk endometrial cancer? A multicentric study from the FRANCOGYN Research Group. Int J Gynecol Cancer 2019;29:282-9.

90. Burke TW, Levenback C, Tornos C et al. Intraabdominal lymphatic mapping to direct selective pelvic and para-aortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. Gynecol Oncol 1996;62:169–73.

91. Persson J, Geppert B, Lönnerfors C et al. Description of a reproducible anatomically based surgical algorithm for detection of pelvic sentinel lymph nodes in endometrial cancer. Gynecol Oncol 2017;147:120-5.

92. Mariani A, Dowdy S, Cliby W et al. Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging Gynecol Oncol 2008;109:11–8.

93. Onda T, Yoshikawa H, Mizutani K et al. Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. Br J Cancer 1997;75:1836–41.

94. Hirahatake K, Hareyama H, Sakuragi N et al. A clinical and pathologic study on para-aortic lymph node metastasis in endometrial carcinoma. J Surg Oncol 1997;65:82-7.

95. McMeekin D, Lashbrook D, Gold M et al. Analysis of FIGO Stage IIIc Endometrial Cancer Patients. Gynecol oncol 2001;81:273–8.

96. Baiocchi, G, Faloppa CC, Mantoan H et al. Para-aortic lymphadenectomy can be omitted in most endometrial cancer patients at risk of lymph node metastasis. J Surg Oncol 2017;116: 220-6.

97. Courtney-Brooks, M, Scalici JM, Tellawi AR et al. Para-aortic lymph node dissection for women with endometrial adenocarcinoma and intermediate- to high-risk tumors: does it improve survival? Int J Gynecol Cancer 2014;24:91-6.

98. ACOG. Practice bullet. Endometrial cancer. 2015;125:1007-26.

99. Giede C, Le T, Power P et al. The role of surgery in endometrial cancer. J Obstet Gynaecol Can 2013;35:370–4.

100. Querleu D, Planchamp F, Narducci F et al Clinical practice guidelines for the management of patients with endometrial cancer in France: Recommendations of the Institut National du Cancer and the Société Française d'Oncologie Gynécologique. Int J Gynecol Cancer 2011;21:945-50.

101. Ballester M, Dubernard G, Lécuru F et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 2011;12:469-76.

102. Rossi EC, Kowalski LD, Scalici J et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): A multicentre, prospective, cohort study. Lancet Oncol 2017;18:384–92.

103. Soliman PT, Westin SN, Dioun S, et al. A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. Gynecol Oncol 2017;146:234–9.

104. Burke TW, Levenback C, Tornos C et al. Intraabdominal lymphatic mapping to direct selective pelvic and para-aortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. Gynecol Oncol 1996;62:169–73.

105. Use of the algorithm allows to decrease SLN false negative rate. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol 2009;113:163–9.

106. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol 2012;125:531–5.

107. Bodurtha Smith AJ, Fader AN, Tanner EJ. Sentinel lymph node assessment in endometrial cancer: A systematic review and meta-analysis. Am J Obstet Gynecol 2017;216:459–476.

108. How J, Gotlieb WH, Press JZ et al. Comparing indocyanine green, technetium, and blue dye for sentinel lymph node mapping in endometrial cancer. Gynecol Oncol 2015;137:436-42.

109. Frumovitz M, Plante M, Lee PS, et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol 2018;19:1394-403.

110. Tanner EJ, Sinno AK, Stone RL et al. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. Gynecol Oncol 2015;138:542-7.

111. Abu-Rustum NR. Sentinel lymph node mapping for endometrial cancer: a modern approach to surgical staging. J Natl Compr Canc Netw 2014;12:288-97.

112. Ruiz R, Gorostidi M, Jaunarena I et al. Sentinel node biopsy in endometrial cancer with dual cervical and fundal indocyanine green injection. Int J Gynecol Cancer 2018;28:139-44.

113. Rychlik A, Angeles MA, Migliorelli F et al. Frozen section examination of sentinel lymph nodes can be used as a decisional tool in the surgical management of early cervical cancer Int J Gynecol Cancer 2020;30:358-63.

114. Nagai T, Niikura H, Okamoto S et al. A new diagnostic method for rapid detection of lymph node metastases using a one-step nucleic acid amplification (OSNA) assay in endometrial cancer. Ann Surg Oncol 2015;22:980-6.

115. López-Ruiz ME, Diestro MD, Yébenes L et al. One-step nucleic acid amplification (OSNA) for the detection of sentinel lymph node metastasis in endometrial cancer. Gynecol Oncol. 2016;143:54-9.

116. Edge SB BD, Compton CC. AJCC cancer staging manual. 7th edn. New York: Springer,2010.

117. Kim CH, Khoury-Collado F, Barber EL, et al. Sentinel lymph node mapping with pathologic ultrastaging: a valuable tool for assessing nodal metastasis in low-grade endometrial cancer with superficial myoinvasion. Gynecol Oncol 2013; 131:714–9.

118. St Clair CM, Eriksson AG, Ducie JA, et al. Low-volume lymph node metastasis discovered during sentinel lymph node mapping for endometrial carcinoma. Ann Surg Oncol 2016;23:1653–9.

119. Rossi EC. Current state of sentinel lymph nodes for women with endometrial cancer. Int J Gynecol Cancer 2019;29:613–21.

120. Eltabbakh GH, Shamonki J, Mount SL. Surgical stage, final grade, and survival of women with endometrial carcinoma whose preoperative endometrial biopsy shows well-differentiated tumors. Gynecol Oncol 2005;99:309–12.

121. Scholten NA, Smit VTHBM, Beerman H et al. Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. Cancer 2004;100:764–72.

122. Sagae S, Saito T, Satoh M et al. The reproducibility of a binary tumor grading system for uterine endometrial endometrioid carcinoma, compared with FIGO system and nuclear grading. Oncology 2004;67:344–50.

123. Lax SF, Kurman RJ, Pizer ES et al. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. Am J Surg Pathol 2000;24:1201–8.

124. Taylor RR, Zeller J, Lieberman RW et al. An analysis of two versus three grades for endometrial carcinoma. Gynecol Oncol 1999;74:3–6.

125. Mitchard J and Hirschowitz L. Concordance of FIGO grade of endometrial adenocarcinomas in biopsy and hysterectomy specimens. Histopathology 2003;42:372–8.

126. Wang X, Huang Z, Di W et al. Comparison of D&C and hysterectomy pathologic findings in endometrial cancer patients. Arch Gynecol Obstet 2005;272:136-41.

127. Kendall BS, Ronnett BM, Isacson C et al. Reproducibility of the diagnosis of endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma. Am J Surg Pathol 1998; 22:1012–9.

128. Guan H, Semaan A, Bandyopadhyay S et al. Prognosis and reproducibility of new and existing binary grading systems for endometrial carcinoma compared to FIGO grading in hysterectomy specimens. Int J Gynecol Cancer 2011;21:654–60.

129. Grevenkamp F, Kommoss F, Kommoss F et al. Second opinion expert pathology in endometrial cancer: potential clinical implications. Int J Gynecol Cancer 2017;27:289–96.

130. Erdemoglu E, Yalcin Y, Bozkurt KK et al. Surgical staging of low-risk Stage IA endometrioid endometrial cancers. Eur J Gynaecol Oncol 2017;38:80-4.

131. Stelloo E, Nout RA, Naves LC et al. High concordance of molecular tumor alterations between pre-operative curettage and hysterectomy specimens in patients with endometrial carcinoma. Gynecol Oncol 2014;133:197–204.

132. Talhouk A, Hoang LN, McConechy MK et al. Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: earlier prognostic information to guide treatment. Gynecol Oncol 2016;143:46–53.

133. Manfredi R, Mirk P, Maresca G et al. Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. Radiology 2004;231:372-8.

134. Kinkel K, Kaji Y, Yu KK et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology 1999;212:711–8.

135. Hardesty LA, Sumkin JH, Hakim C et al. The ability of helical CT to preoperatively stage endometrial carcinoma. AJR Am J Roentgenol 2001;176:603–6.

136. Fischerova D, Frühauf F, Zikan M et al. Factors affecting sonographic preoperative local staging of endometrial cancer. Ultrasound Obstet Gynecol 2014;43:575-85.

137. Beddy P, O'Neill AC, Yamamoto AK et al. FIGO staging system for endometrial cancer: added benefits of MR imaging. Radiographics 2012;32:241–54.

138. Shin KE, Park BK, Kim CK et al. MR staging accuracy for endometrial cancer based on the new FIGO stage. Acta Radiol 2011;52:818–24.

139. Santoro A, Piermattei A, Inzani F, et al. Frozen section accurately allows pathological characterization of endometrial cancer in patients with a preoperative ambiguous or inconclusive diagnoses: our experience. BMC Cancer 2019;19:1096.

140. Traen K, Hølund B and Mogensen O. Accuracy of preoperative tumor grade and intraoperative gross examination of myometrial invasion in patients with endometrial cancer. Acta Obstet Gyn Scan 2007;86:739-41.

141. Şenol T, Polat M, Özkaya E et al. Misinterpretation of frozen section in endometrial Cancer cases: does it have any effect on disease-free and overall survival? Int J Gynecol Pathol 2017;36:550–4.

142. Papadia A, Azioni G, Brusacà B, et al. Frozen section underestimates the need for surgical staging in endometrial cancer patients. Int J Gynecol Cancer 2009;19:1570–3.

143. Case AS, Rocconi RP, Straughn JM Jr et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. Obstet Gynecol 2006;108:1375–9.