Lymphadenectomy in elderly patients with high-intermediate-risk, high-risk or advanced endometrial cancer Time to move from personalized cancer medicine to personalized patient medicine!

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Lymphadenectomy in elderly patients with high-intermediate-risk, high-risk or advanced endometrial cancer: time to move from personalized cancer medicine to personalized patient medicine!

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ABSTRACT:

BACKGROUND: Pelvic and paraaortic lymphadenectomy are recommended for women with high-intermediate, high-risk and advanced endometrial cancer (EC). Lymphadenectomy is less frequently performed in elderly patients than in younger patients. We examined the survival of elderly women diagnosed with high-risk EC according to whether lymphadenectomy was performed or not.

METHODS: We selected women over 70 years with high-intermediate risk, high-risk or advanced EC from a multicenter retrospective cohort of women diagnosed between 2001 and 2013. Multivariate logistic regression models and Cox proportional hazards survival methods for overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS) were used for analyses.

RESULTS: 71 women had lymphadenectomy and were compared with the 213 who did not. Recurrence was similar in both groups (42% vs 33%, respectively, p=0.17) but more deaths were reported in the group without lymphadenectomy (38% vs 23%, respectively, p<0.001). There was no difference in adjuvant treatment in the two groups (17% vs 27%, respectively, p=0.27). Elderly patients without lymphadenectomy had lower 3-year DFS (56% vs 71%, p=0.076), CSS (67% vs 85%, p<0.001) and OS (50% vs 71% p<0.001). The Cox proportional hazard models showed independently poorer prognosis in women without lymphadenectomy (3.027, 95% CI 1.58-5.81, p<0.001), histology type 2 (3.46, 95% CI 1.51-7.97, p=0.003) and lymphovascular space involvement (3.47, 95% CI 1.35-8.98, p=0.01) on 3-year CSS.

CONCLUSION: No lymphadenectomy in elderly patients with high-risk or advanced EC is independently associated with poorer prognosis. Elderly patients with EC should benefit from lymphadenectomy when indicated.

Key-words: high-risk endometrial cancer; elderly; surgery; lymphadenectomy; cancer-specific survival

INTRODUCTION

With the increase in life expectancy, older cancer patients are becoming more numerous (1). However, older patients are underrepresented in clinical trials (2,3), and there is consequently somewhat of a gap in the current treatment guidelines for this subgroup of cancer patients (4). Elderly patients with cancer are often undertreated both in terms of surgery (5) and adjuvant therapy (6). This undertreatment of the elderly is usually because of comorbidities, for fear of complications related to surgical or chemotherapy stress (7,8). In the United States, the number of new cases of EC per year was 61 380 with 10 920 deaths in 2017 (7th leading cause of cancer related-death in women) (9). According to studies, older patients with EC have a poorer prognosis which is due not only to more aggressive disease but also undertreatment (10-13).

According to the European Society for Medical Oncology (ESMO), European Society of Gynaecological Oncology (ESGO), and European Society for Radiotherapy and Oncology (ESTRO) guidelines, treatments of high-intermediate risk (HIR), high risk (HR) and / or advanced EC (14), include surgery (15) with hysterectomy, bilateral salpingo-oophorectomy and pelvic plus paraaortic lymphadenectomy (16,17). According to Mariani et al., 22% of patients with HR EC have metastatic lymph nodes (51% pelvic and paraaortic, 33% pelvic and 16% paraaortic) (18). Although the SEPAL study demonstrated a significant benefit of pelvic plus paraaortic lymphadenectomy on survival (19,20), lymphadenectomy was less performed in elderly patients with EC, even if lymphadenectomy was recommended by ESMO/ESGO/ESTRO guidelines (7,10,12), for fear of complications. Similarly, the older patient is less likely to receive pelvic external radiotherapy or chemotherapy which are recommended for patients with HR EC (14) (2,21). Overall then it can be said that elderly patients with EC are undertreated as a result incomplete surgical staging and less use of adjuvant therapy, which may explain why they have poorer survival rates (7,22). No studies have evaluated the impact of lymphadenectomy in this subgroup of elderly patients with HIR, HR or advanced EC.

The objective of this study is to compare disease-free survival (DFS), overall survival (OS), and

cancer-specific survival (CSS) in patients aged 70 and over with HIR, HR, or advanced EC according to whether they underwent lymphadenectomy or not.

MATERIALS AND METHODS:

Patients:

We retrospectively analyzed data collected from a database of patients with EC who received primary surgical treatment between January 2001 and December 2013. The data were obtained from nine institutions in France who maintain EC databases (Tours, Tenon, Dijon, Rennes, Lille, Reims, Creteil, Poissy, Jean Verdier Tertiary Hospitals) and from the SENTIENDO trial (23). These institutions had high gynecologic oncologic case load, with more than 70 gynecologic oncologic surgeries per year for each center. The research protocol was approved by the Institutional Review Board of the College National des Gynécologues et Obstétriciens Français (CNGOF) in 2014.

Patients 70 years of age and older with HIR, HR, or advanced EC, according to the ESMO / ESTRO / ESGO (14) criteria were selected.

The patients were divided into two groups: patients who underwent paraaortic and/or pelvic lymphadenectomy versus patients who did not undergo lymphadenectomy.

Data collection

All the patients had undergone a preoperative endometrial biopsy and abdominopelvic magnetic resonance imaging (MRI) unless contraindicated.

The demographic and clinical data collected included: age, body mass index (BMI), and comorbidities (arterial hypertension, diabetes, menopausal hormone therapy). Surgical data (surgical approach, nodal staging), histologic data (subtype, grade and stage based on the International Federation of Gynaecology and Obstetrics (FIGO 2009) (24) and adjuvant therapy were also collected.

Histology

Type 1 tumors consisted of endometrioid adenocarcinomas, villoglandular, tubular, or mucinous tumors, with or without an endometrioid component. For these tumors, histologic grade was defined by the percentage of undifferentiated component: grade 1 (<5%), grade 2 (6%-50%), and grade 3 (>50%). The grade was increased by 1 point if nuclear atypia was present. (25). Type 2 tumors were

those with at least one serous, clear cell, or carcinosarcoma component.

Lymph nodes were considered positive when macro- or micrometastases were present. A tumor was considered to have lympho-vascular space invasion (LVSI) when tumor emboli were found within a space clearly lined by endothelial cells on a hematoxylin and eosin (H&E)-stained section.

All the women were classified according to the 2009 FIGO classification after the final pathologic analysis (24). The tumors were classified into recurrence risk groups as defined by the ESMO, ESGO, and ESTRO guidelines. High-risk cancers include high-intermediate-risk (HIR) (endometrioid type 1, grade 1 or 2 tumors with deep $\geq 50\%$ myometrial invasion and unequivocally positive LVSI, and grade 3 tumors with <50% myometrial invasion regardless of LVSI status), high-risk (stage IB and grade 3, stage ≥2, type I and type II tumors) and advanced EC. (14)

Treatment and follow-up

The women underwent primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy, with or without nodal staging (pelvic and paraaortic lymphadenectomy) according to the current guidelines and at the surgeon's discretion based on their own patient evaluation (25). According to the French guidelines, pelvic and paraaortic lymph node surgical staging is required for HR groups. Adjuvant therapy included vaginal brachytherapy (VBT), and/or external beam radiotherapy (EBRT), and/or chemotherapy (CT), and clinical follow-up. Adjuvant therapy was administered on an individual basis at the discretion of a multidisciplinary committee based on the French guidelines (26).

Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings.

Outcome measures

The main outcome measures were the date of recurrence, date of death, and date of cancer-related death. Disease recurrence was diagnosed by biopsy or imaging studies and defined as a relapse without differentiating between their local or distant nature.

The secondary outcome measures were adjuvant therapy (VBT, EBRT, CT), surgical route

(minimally invasive surgery, laparotomy and vaginal surgery) and tumor characteristics (ESMO / ESGO / ESTRO group, FIGO stage, histological type, tumor size, LVSI).

Statistical analysis

Descriptive parameters are expressed as the mean (± Standard Deviation [SD]) and median [range] when indicated. Frequencies are presented as percentages. We compared the demographics and medical characteristics of the patients in the two cohorts using Chi-square for categorical variables. For continuous variables, we used t-tests. Overall survival time was calculated from the date of surgery to death (related or unrelated to cancer) or date of last follow-up for surviving patients, CSS as time from the date of surgery to cancer-related death, and DFS as time from the date of surgery to cancer recurrence. Women who were alive and without recurrence were censored at the date of last follow-up. The Kaplan-Meier method was used to estimate the survival distribution and compared with the log-rank test. Effects were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Cox proportional hazard models included established prognostic factors: pathologic type, adjuvant therapies, and nodal status. A p-value of <0.05 was considered statistically significant. Data were managed in an Excel database (Microsoft, Redmond, WA, USA) and analysed using R 3.0.2 software, which is available online.

RESULTS

Characteristics of study population

During the study period, 1227 women with EC were documented as having received primary surgical treatment. 480 women (39%) were ≥70 years old, and 284 (59%) of these women were in the high-risk group (HIR, HR or with advanced EC). Of these 284 patients, 213 (75%) underwent pelvic ± paraaortic lymphadenectomy and 71 (25%) did not undergo lymphadenectomy.

The mean age of the entire population was 76.9 years (±5.3). The mean age of the patients without lymphadenectomy was 79.6 years (±6) versus 76 years (±4.8) for patients with lymphadenectomy ($p<0.001$).

The demographic and clinicopathologic characteristics of the entire cohort are reported in Table 1. There were no significant differences in comorbidities between the two groups.

Tumor characteristics

The tumor characteristics are reported in Table 2. There were no significant differences between the two groups concerning histologic type, myometrial invasion, grade or FIGO stage.

Surgical characteristics and adjuvant treatment

Surgical procedures are reported in Table 3. In the lymphadenectomy group, 212/213 patients (99%) underwent pelvic lymphadenectomy, with an average of 11.9 (±6.19) lymph nodes removed and 25/213 patients (12%) had paraaortic lymphadenectomy, with an average of 3.85 (±6.79) lymph nodes removed. 44/212 patients (21%) had pelvic lymph node metastasis and 7/25 patients (28%) had paraaortic lymph node metastasis. Patients without lymphadenectomy had significantly fewer mini-invasive procedures (21% vs 49%, $p<0.001$).

Adjuvant treatments are reported in Table 3.

Survival results

The mean follow-up of the population was 28.52 months (+/-24.74). The mean follow-up of patients with lymphadenectomy and without were 30.29 months (+/-25.64) and 23.21 months (+/-21.12), respectively ($p=0.02$).

In the whole study population, the 3-year OS, DFS and CSS were 66.8% (95% CI, 60-74.4), 67.4% (95% CI, 60.8-74.6) and 81.3% (95% CI, 75.5-87.6), respectively. The univariate analysis of survival (DFS, OS and CSS) is reported in Table S1 and Figure 1. The 3-year CSS was significantly lower in patients in the without lymphadenectomy group (85.2% (95% CI, 78.9-92.1) vs 67.5% (95% CI, 54.8-83.1) ($p<0.001$)).The multivariate analysis of survival is shown in Table 4. No lymphadenectomy was independently associated with a lower 3-year CSS (3.027 (1.58-5.81), $p<0.001$) and 3-year OS (2.374 (1.48-3.81) $p<0.001$).

DISCUSSION

The present study showed that 25% of patients over 70 years of age with HIR, HR, or advanced EC in our cohort did not undergo lymph node assessment. In our study, no lymphadenectomy, type 2 histology and LVSI correlated in multivariate analysis with poorer CSS and poorer OS. Patients without lymphadenectomy also had significantly less adjuvant radiotherapy, contributing to the undertreatment of elderly patients who are already under-evaluated surgically (27). Finally, we found that patients without lymphadenectomy had less minimally invasive surgery in univariate analysis. A lack of knowledge of histologic lymph node status was correlated with poorer survival (CSS and OS) in multivariate analysis.

Few data dealing with HIR, HR or advanced EC and age can be found in literature (7,22), and no data focus on the validity of lymphadenectomy in elderly patients with EC. While the role of lymphadenectomy remains a subject of passionate debate (29–31), elderly patients have lower rates of lymphadenectomy (10,13,28). Todo Y et al. demonstrated that the combination of pelvic and paraaortic lymphadenectomy can significantly improve survival in patients with HR EC (19,20). Although only patients with HR, HIR or advanced EC were included in our study, the rate of paraaortic lymphadenectomy performed was low at around 12%. This low rate could be due to changes in the French recommendations (published in 2009 during the data collection period) for nodal staging which introduced paraaortic lymphadenectomy for HR, HIR and advanced EC, with increased rate of paraaortic lymphadenectomy after 2009. Secondly, in the Todo patient population, the patients were younger with a mean age of 56.2 (+/-9.2) years compared to our elderly cohort with a mean age of 76.9 (+/-5.3) years, indicating that elderly patients were not included in the Todo Y et al. study (20).

Minimally invasive surgery tends to be underused in older patients, probably due to possible contraindications to laparoscopy (32). However, recent data have demonstrated that minimally invasive surgical treatment of EC, robotically assisted or not, is feasible and safe in the elderly patient and is superior to open surgery in terms of perioperative procedure results (33), independent

of age (34,35). A minimally invasive approach could lead to a higher rate of pelvic or paraaortic lymphadenectomy in this age group, as one of the reasons for the reluctance to perform lymphadenectomy is the risks associated with xipho-pubic laparotomy. The laparoscopic procedure lasts no longer than laparotomy, involves less blood loss and a shorter hospital stay, causes fewer postoperative complications, and results in similar survival (36,37). The development of robotic surgery is going to increase the use of minimally invasive approaches for lymphadenectomy (38,39), even in older patients (40).

In the present study, only 62% of patients with lymphadenectomy and 45% of patients without lymphadenectomy had radiotherapy. It is somewhat disappointing to observe that the patients without lymphadenectomy had less radiotherapy which is widely recognized to increase survival and is generally well tolerated in elderly patients (21,41). Furthermore, we know that radiotherapy can be tailored if lymph node staging is performed (42,43). Additionally, only 21% of our population had chemotherapy (with no difference between the groups).

Some limitations to the present analysis should be taken into account when interpreting the data. As for all observational data, there is a potential selection bias: unobserved dimensions of health status, such as performance status, may determine treatment and independently affect survival without involving the choice of the patient (44). Driver JA et al., for example, showed that frailty was a more robust predictor of DFS and OS than patient age and tumor characteristics in a cohort of older women with EC (45). Nevertheless, in present study, except for a higher mean age in the group of patients without lymphadenectomy, the number of comorbidities was similar in both groups as were all the tumor characteristics. Furthermore, the rate of chemotherapy was similar in both groups (at around 21%), indicating that the perception of frailty was probably similar. Nevertheless, similarly to other studies, no objective evaluation was used to tailor surgical staging or adjuvant treatment according to frailty. Additionally, no attempt was made to replace numerical age by criteria evaluating life expectancy: we applied the cutoff of 70 years to define “the elderly patient” as in most other studies (46–51). Finally, the primary strength of this study is the use of CSS mortality as

opposed to all-cause mortality.

The sentinel lymph node technique is rarely used in the elderly: in the SENTIENDO study (23), few patients included were over 70 years old. Studies have shown good sensitivity for this technique and good NPVs by double detection (radioactive tracer and blue dye) or indocyanine green (Se 97.2%, 99.6% VPN) (52). It is less morbid than complete lymphadenectomy in cases of negative sentinel lymph node and allows lymph node staging if there is a discrepancy between the preoperative assessment and final histology (53). Finally, the technique can be performed for HR ECs (Se 95.8%, VPN 98.2) (54,55). The generalization of its use coupled with minimally invasive surgery techniques, could promote the practice of complete surgical staging in elderly patients with HR EC with minimal morbidity. Knowledge of the lymph node status by the sentinel lymph node technique would enable tailoring of the adjuvant treatment for elderly patients and could become the standard of treatment for EC in the coming years in elderly patients with EC.

CONCLUSION

This French multicenter study shows that a quarter of patients over 70 years with HIR, HR or advanced EC have no lymph node assessment. The lack of surgical nodal evaluation in these patients is correlated with poorer CSS and OS. Open surgery was also correlated with less frequent lymphadenectomy. Gynecologic oncologists should adopt a reproducible attitude in the management of EC in the elderly, based not only on preoperative evaluation of the patient's frailty status but also on minimally invasive surgical management. The sentinel lymph node technique could be a good option for elderly patients with HIR, HR or advanced EC for whom surgeons are reluctant to perform lymphadenectomy because of frailty.

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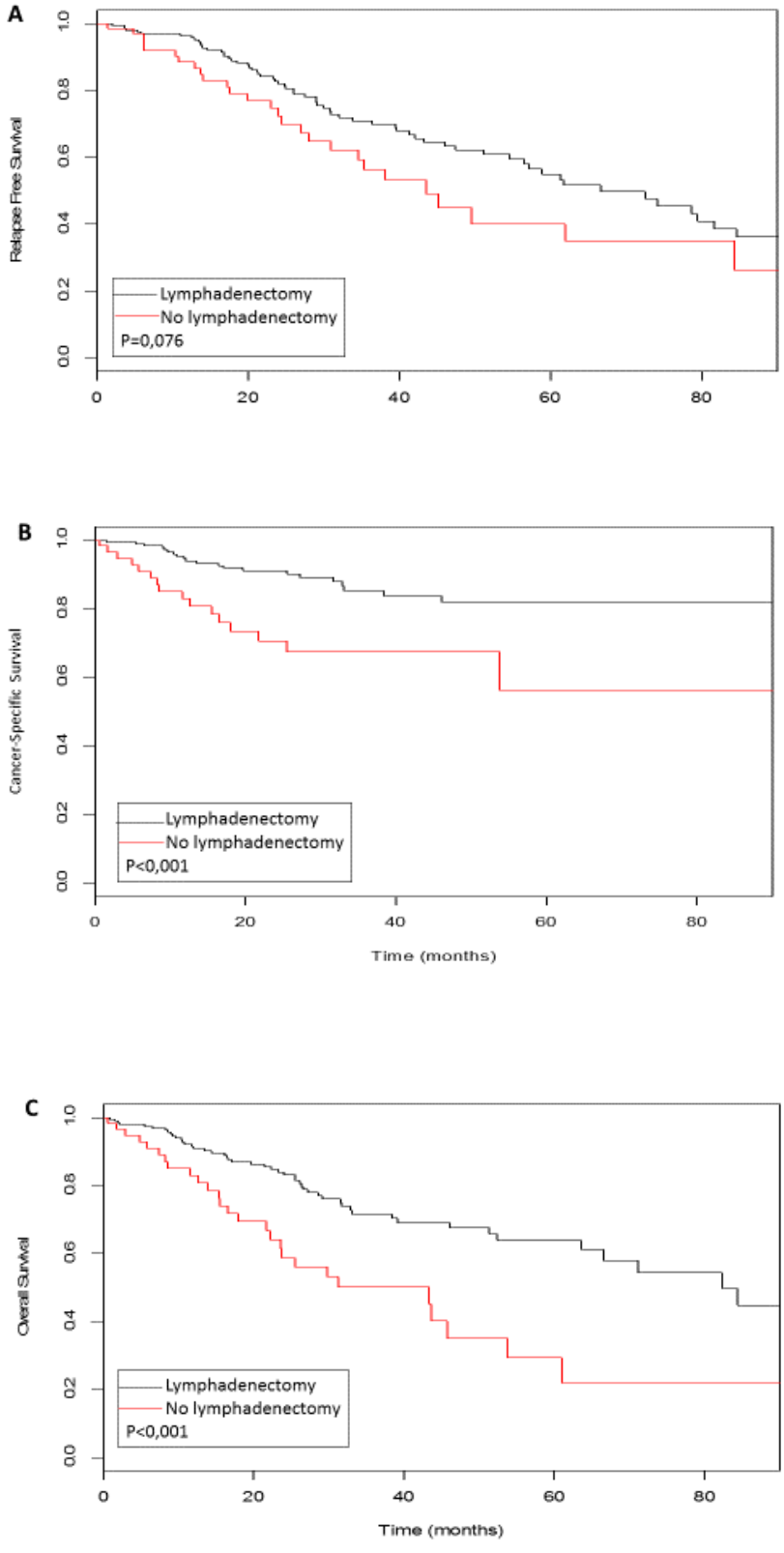

Figure 1 : Survival curves : A Relapse-free Survival, B Cancer-specific Survival, C Overall Survival.

Table 1: Patient characteristics, age ≥ 70ans

Characteristics	Population n (%) N=284	No lymphadenectomy n (%) N = 71	Lymphadenectomy n (%) N = 213	*P* value
Age (years), mean (±SD)	76.91 (±5.34)	79.63 (±6.01)	76 (±4.78)	<0.001
-70-75	128 (45%)	20 (28%)	109 (51%)	<0.001
-76-80	91 (32%)	17 (24%)	74 (35%)	
-81-85	44 (16%)	22 (31%)	21 (10%)	
->86	21 (7%)	12 (17%)	9 (4%)	
BMI (kg/m2), mean (±SD)	27.41 (±5.82)	28.44 (±7.30)	27.32 (±5.47)	0.12
Parity, mean (±SD)	2.33 (±1.90)	2.40 (±1.98)	2.31 (±1.88)	0.84
- 0	22 (8%)	7(10%)	15 (7%)	0.82
- 1	47 (17%)	10 (14%)	37 (17%)	
- ≥ 2	137 (48%)	35 (50%)	102 (48%)	
- NC	78 (27%)	19 (26%)	59 (28%)	
Arterial hypertension				
- Yes	93 (33%)	39 (55%)	94 (44%)	0.28
- No	133 (47%)	19 (27%)	74 (35%)	
- NC	58 (20%)	13 (18%)	45 (21%)	
Diabetes				
- Yes	47 (17%)	15 (21%)	32 (15%)	0.17
- No	208 (73%)	46 (65%)	162 (76%)	
- NC	29 (10%)	10 (14%)	19 (9%)	
Menopausal hormone therapy				
- Yes	38 (13%)	5 (7%)	33 (16%)	0.19
- No	133 (47%)	35 (49%)	98 (46%)	
- NC	113 (40%)	31 (44%)	82 (38%)	

NC: not communicated

Table 2: Tumour characteristics

Characteristics	Population n (%) N=284	No lymphadenectomy n (%) N = 71	Lymphadenectomy n (%) N = 213	*P* value
Tumour size				
- < 3,5 cm	60 (21%)	14 (20%)	46 (22%)	<0.001
- ≥ 3,5 cm	116 (41%)	17 (24%)	99 (46%)	
- NC	108 (38%)	40 (56%)	68 (32%)	
Tumour size				
-<1.5 cm	13 (5%)	3 (4%)	10 (5%)	<0.001
- ≥ 1.5cm	163 (57%)	28 (40%)	135 (63%)	
-NC	108 (38%)	40 (56%)	68 (32%)	
Myometrial invasion				
- < 50%	84 (30%)	27 (38%)	57 (27%)	0.10
- ≥ 50%	182 (64%)	38 (54%)	144 (68%)	
- NC	18 (6%)	6 (8%)	12 (5%)	
Histology				
- Endometrioid	161 (57%)	35 (49%)	126 (59%)	0.31
- Serous	43 (15%)	11 (16%)	32 (15%)	
- Clear cells	28 (10%)	8 (11%)	20 (10%)	
- Other *	49 (17%)	17 (24%)	32 (15%)	
- NC	3 (1%)	0	3 (1%)	
Histological type				
- Type 1	161 (57%)	35 (49%)	126 (59%)	0.24
- Type 2	109 (38%)	31 (44%)	78 (37%)	
- Other**	13 (4%)	5 (7%)	8 (3%)	
- NC	1 (1%)	0	1 (1%)	
Histological grade				
- 1	54 (19%)	12 (17%)	42 (20%)	0.77
- 2	72 (25%)	17 (24%)	55 (26%)	
- 3	153 (54%)	40 (56%)	113 (53%)	
- NC	5 (2%)	2 (3%)	3 (1%)	
Lymphovascular space involvement				
- Yes	167 (59%)	39 (55%)	128 (60%)	0.59
- No	91 (32%)	25 (35%)	66 (31%)	
- NC	26 (9%)	7 (10%)	19 (9%)	
Pelvic lymph node metastasis (N =212)				
- Yes	44 (21%)	-	45 (21%)	NA
- No	138 (65%)	-	137 (64%)	
- NC	30 (14%)	-	31 (15%)	
Para-aortic lymph node metastasis (N =25)				
- Yes	7 (28%)	-	7 (28%)	NA
- No	18 (72%)	-	18 (72%)	
- NC	0	-	0	
FIGO stage				
- I	124 (43%)	31 (44%)	93 (44%)	0.35
- II	51 (18%)	14 (20%)	37 (17%)	
- III	98 (35%)	21 (29%)	77 (36%)	
- IV	11 (4%)	5 (7%)	6 (3%)	
ESMO/ESGO/ESTRO risk groups				
- High-intermediate risk	52 (18%)	13 (18%)	39 (18%)	0.12
- High risk	220 (77%)	52 (73%)	168 (79%)	
- Advanced	12 (4%)	6 (9%)	6 (3%)	

NC: not communicated ; * mucineux, tubuleux, carcinosarcome, indifférentié ; **mucineux, tubuleux

Table 3: Surgical characteristics and adjuvant treatment

Characteristics	Population n (%) N=284	No lymphadenectomy n (%) N=71	Lymphadenectomy n (%) N=213	*P* value
Surgical approach:				
- Laparoscopy	112 (39%)	14 (21%)	98 (46%)	<0.001
- Laparotomy	128 (45%)	35 (49%)	93 (44%)	
- Vaginal approach	16 (6%)	11 (15%)	5 (2%)	
- NA	28 (10%)	11 (15%)	17 (8%)	
Sentinel lymph node (N=213)				
- Yes	77 (36%)	-	77 (36%)	NA
- No	82 (39%)	-	82 (39%)	
- NA	54 (25%)	-	54 (25%)	
Sentinel lymph node metastasis (N=77)				
-Yes			35 (46%)	
-No			24 (31%)	
-NA			18 (23%)	
Pelvic lymphadenectomy	212 (75%)		212 (99%)	
Paraaortic lymphadenectomy	25 (9%)		25 (12%)	
No. pelvic node removed, mean (±SD)	11.90 (±6.19)		11.90 (±6.19)	
No. paraaortic node removed, mean (±SD)	3.85 (±6.79)		3.85 (±6.79)	
Adjuvant treatment				
No adjuvant therapy	56 (20%)	19 (27%)	37 (17%)	0.27
VBT alone	41 (14%)	9 (13%)	32 (15%)	
EBRT +/- VBT	128 (45%)	28 (39%)	100 (47%)	
Chemotherapy +/- EBRT	59 (21%)	15 (21%)	44 (21%)	
EBRT	164 (58%)	32 (45%)	132 (62%)	

* According to 2010 French guidelines NC: not communicated; NS: not significant; EBRT: External beam radiotherapy.

Table 4: **Three-year** disease-free survival, cancer-specific survival and overall survival rates (multivariate analysis)

Characteristics	**Disease-free survival rate, % (95% CI)**	*P*	**Cancer-specific survival rate, % (95%CI)**	*P*	**Overall survival rate, % (95% CI)**	*P*
Lymphadenectomy						
-Yes	1		1		1	
-No	0.939 (0.36-2.46)	0.897	3.027 (1.58-5.81)	<0.001	2.374 (1.48-3.81)	<0.001
Age:						
-<75 years	1		1		1	
-76-80 years	1.072 (0.64-1.81)	0.792	1.196 (0.52-2.75)	0.673	1.013 (0.54-1.91)	0.967
-81-85 years	0.733 (0.34-1.59)	0.434	0.592 (0.19-1.85)	0.368	0.556 (0.23-1.33)	0.185
-≥86 years	1.059 (0.30-3.69)	0.929	1.57 (0.4-4.19)	0.519	1.193 (0.38-3.75)	0.763
Histology						
-type1	1		1		1	
-type 2	1.409 (0.85-2.34)	0.185	3.466 (1.51-7.97)	0.003	2.256 (1.23-4.13)	0.008
Lymphovascular space involvement						
-No	1		1		1	
-Yes	2.216 (1.22-4.03)	0.009	3.477 (1.35-8.98)	0.01	3.165 (1.56-6.43)	0.001
ESMO/ESGO/ESTRO risk groups						
-HR	1		1		1	
-HIR	0.808 (0.39-1.69)	0.569	0.713 (0.21-2.43)	0.588	0.839 (0.36-1.96)	0.685
Lymph node metastasis						
-No	1		1		1	
-Yes	0.848 (0.45-1.59)	0.609	1.103 (0.41-2.95)	0.846	1.629 (0.84-3.15)	0.147
- Node status unknown (Lymphadenectomy not performed)	1.713 (0.68-4.31)	0.253	2.269 (1.02-5.03)	0.044	2.389 (1.32-4.34)	0.004
Adjuvant treatment:						
- Chemotherapy +/- EBRT	1		1		1	
-No adjuvant therapy	0.84 (0.38-1.85)	0.666	2.023 (0.63-6.51)	0.238	1.26 (0.54-2.95)	0.593
-VBT alone	0.227 (0.08-0.66)	0.006	0.417 (0.08-2.23)	0.307	0.309 (0.09-1.01)	0.053
-EBRT +/- VBT	0.646 (0.36-1.15)	0.139	1.321 (0.52-3.33)	0.555	0.854 (0.43-1.68)	0.648

Table S1: **Three-year** disease-free survival, cancer-specific survival and overall survival rates (univariate analysis)

Characteristics	Disease-free survival rate, % (95% CI)	*P*	Cancer-specific survival rate, % (95%CI)	*P*	Overall survival rate, % (95% CI)	*P*
Population	67.4% (60.8-74.6)		81.3% (75.5-87.6)		66.8% (60-74.4)	
Lymphadenectomy:						
-Yes	70.94% (63.7-79)	0.076	85.2% (78.9-92.1)	<0.001	71.6% (64.07-80)	<0.001
-No	56.35% (43.4-73.3)		67.5% (54.8-83.1)		50.2% (36.9-68.2)	
Age:						
-76-80 years	68.7% (58-81.5)	0.96	81.1% (70.9-92.8)	0.51	63.7% (52.2-77.9)	0.56
-81-85 years	66.3% (49.8-88.2)		75% (58.6-96.1)		63% (46.4-85.5)	
-≥86 years	78.3% (59.2-100)		54% (27-100)		60% (35.1-100)	
Histology:						
-type1	70.8% (62.7-79.9)	0.26	84.8% (77.3-92.9)	0.009	71.3% (62.9-80.9)	0.03
-type 2	61.53% (51.1-74.1)		72.2% (62-84.2)		59.4% (48.7-72.4)	
Lymphovascular space involvement:						
-Yes	61.49% (52.9-71.5)	0.02	75.7% (67.5-84.9)	0.03	62.4% (53.6-72.7)	0.1
-No	78.7% (68.7-90.1)		86.8% (76.7-98.2)		71% (58.9-85.6)	
ESMO/ESGO/ESTRO risk groups:						
-HIR	74.2% (60.6-90.9)	0.31	86.6% (74.7-100)	0.1	77.6% (63.7-94.4)	0.12
-HR	65.68% (58.4-73.9)		78.8% (72-86.3)		64.4% (56.8-72.9)	
Lymph node metastasis N=213						
-Yes	69.69% (56.7-85.7)	0.082	74.8% (60.2-92.8)	0.121	61.7% (46.9-81)	0.015
-No	73.8% (63.7-85.5)		83.1% (73.7-93.6)		76.2% (66.1-87.9)	
- Node status unknown (Lymphadenectomy not performed)	53.12% (40.9-68.9)		74.8% (64.2-87.1)		59.7% (47.2-75.4)	
Adjuvant treatment:						
-No adjuvant therapy	67.7% (52.6-87.1)	0.003	69.9% (52.2-93.5)	0.112	54.6% (38.1-78.3)	0.002
-VBT alone	86.8% (75.3-100)		86.5% (68.3-100)		89% (77.8-100)	
-EBRT +/- VBT	68.13% (59-78.7)		79.3% (70.9-88.7)		69.1% (59.5-80.3)	
-Chemotherapy +/- EBRT	54.8% (41.2-72.8)		82.9% (71.9-95.5)		50.5% (36.2-70.3)	

CI: confidence interval