Surgical restaging of patients with early-stage endometrial cancer with lymphovascular invasion does not significantly impact their survival outcomes

BEATRIZ NAVARRO, CHRYSOULA MARGIOULA-SIARKOU, STAMATIOS PETOUSIS, ANNE FLOQUET, GUILLAME BABIN and FREDERIC GUYON

Gynaecologic Oncology Unit, Institute Bergonie, Bordeaux 33076, France

Received September 24, 2022; Accepted November 2, 2022

DOI: 10.3892/ol.2023.13708

Abstract. Lymphovascular space invasion (LVSI) is considered to be a poor prognostic factor in endometrial cancer. However, management of patients with early-stage endometrial cancer with positive LVSI remains controversial. The main objective of the present study was to investigate whether surgical restaging of such patients has a significant effect on survival outcomes or may be otherwise omitted. A retrospective cohort study was conducted at the Gynaecologic Oncology Unit, Insitut Bergonie, Bordeaux, France for the period January 2003-December 2019. The present study included patients with definitive histopathological diagnosis of early-stage, grade 1-2 endometrial cancer with positive LVSI. Patients were divided into two groups: Those being restaged with pelvic and para-aortic lymphadenectomy (group 1) and those not restaged and receiving complementary therapy (group 2). The primary outcomes of the study were overall survival and progression-free survival. Epidemiological data, clinical and histopathological characteristics as well as complementary treatment received were also studied. Kaplan-Meier and Cox regression analyses were performed. Data from 30 patients were retrieved, of which restaging with lymphadenectomy was performed in 21 patients (group 1), while another 9 patients (group 2) were not restaged and received complementary therapy. Lymph node metastasis was observed in 23.8% of patients in group 1 (n=5). No significant difference was observed between groups 1 and 2 in terms of survival outcomes. The median overall survival was 91.31 months in group 1 and 90.61 months in group 2 [hazard ratio (HR), 0.71; 95% CI, 0.03-16.58; P=0.829]. The median disease-free survival was 87.95 months in group 1 and 81.52 months in group 2 (HR, 0.85; 95% CI, 0.12-5.91; P=0.869). In conclusion, restaging with lymphadenectomy did not alter prognosis of early-stage, LVSI-positive patients. As there was no clinical and therapeutic benefit, restaging with lymphadenectomy could be omitted in such patients.

Correspondence to: Dr Stamatios Petousis, Gynaecologic Oncology Unit, Institute Bergonie, Cours de l'Argonne 229, Bordeaux 33076, France
E-mail: petousisstamatios@gmail.com

Key words: endometrial cancer, restaging, lymphovascular space invasion, early-stage, lymphadenectomy

Introduction

Management of endometrial cancer according to ESGO-ESMO-ESTRO guidelines is based on the assessment of risk for loco-regional or distant recurrence (1). Classification of a patient as low-risk necessitates only total hysterectomy with bilateral salpingo-oophorectomy, while high-intermediate or higher risk may necessitate staging with pelvic and para-aortic lymphadenectomy. In this context, histological subtype, grade, clinical stage and depth of myometrial invasion, which are the main parameters affecting assessment of risk, should and actually can be assessed preoperatively, permitting the adequate establishment of surgical plan.

Lymphovascular space invasion (LVSI), defined as the presence of tumoral cells in the lymphatic and blood vessels, has been recently considered as another decisive prognostic factor for endometrial cancer (2). This may be attributed to studies correlating LVSI with increased risk for disseminated disease (3), lymph node metastasis (4,5) and impaired overall survival (6-9) As a result, ESGO guidelines have also enrolled LVSI status in the decisional algorithm of risk assessment. Specifically, even patients with endometrioid, grade 1-2 endometrial cancer are considered of high-intermediate risk for recurrence, therefore necessitating pelvic and para-aortic lymphadenectomy, apart from standard surgical treatment.

In contrary with other prognostic factors affecting risk for recurrence according to decisional algorithm (histological subtype, grade and depth of myometrial invasion), LVSI may not be assessed easily on preoperative level. This is due to the reasonable absence of myometrium from preoperative biopsy specimen, which is actually the most frequent scenario (10). The issue acquires higher clinical significance since new origins of endometrial cancer, as those derived from adenomyosis in which involvement of LVSI is rather possible, are increasingly reported. (11,12) Therefore, an early-stage, endometrioid, grade 1-2 endometrial cancer, necessitating only a

total hysterectomy with bilateral salpingo-oophorectomy, may be upgraded to high-intermediate risk for recurrence in case of positive LVSI in final specimen. This should actually necessitate a restaging with pelvic and para-aortic lymphadenectomy based strictly on ESGO-ESMO-ESTRO guidelines with the alternative of sentinel node being also acceptable in these cases based on newly launched ESGO guidelines (1,13).

However, management of under-staged patients with these characteristics is still not well-established in the literature. There are no studies assessing the added value of such restaging in the overall prognosis of patients, taking into consideration both the increased operative risk as well as the effectiveness of complementary therapies. Therefore, the dilemma of restaging or not early-stage, initially low-risk patients that have been upgraded to high-intermediate risk only based on positive LVSI, has not yet been adequately assessed.

Main objective of the present study is to assess whether restaging with lymphadenectomy of such patients significantly affects prognosis and therefore should be always performed.

Materials and methods

Study character. A retrospective cohort study based on prospectively collected data was performed in Gynaeocologic Oncology Unit of Institut Bergonie, Bordeaux, France. Study concerned the period January 2006-May 2019. A hand-made search was performed in the electronical records of oncological patients treated in our Institution. All elements of patients are recorded prospectively on our computerized database, including all epidemiological, clinical, histopathological characteristics as well as survival and oncological outcomes from the moment of patient's admission onwards. All patients included in the present study have provided written approval for the inclusion of their elements in this retrospective cohort. As this is a retrospective study, Institutional Review Board approval was not necessitated based on the academic policy and requirements of Institution.

Inclusion and exclusion criteria. Included patients were all women with preoperative diagnosis of endometrioid, grade 1-2, clinically early-stage endometrial cancer patients that were initially treated with total hysterectomy and bilateral salpingo-oophorectomy and were postoperatively diagnosed as LVSI positive according to final histopathological specimen. Preoperative radiotherapy or chemotherapy, imaging diagnosis of nodal metastases as well as past history of any other malignancy were considered as exclusion criteria. Type of surgical approach (laparotomy or laparoscopy) was not considered as selection criterion.

Included patients were divided into two groups, the first group enrolling patients that were re-operated in order to perform pelvic and para-aortic lymphadenectomy for staging (group 1) and another group including patients with identical characteristics that were given postoperative radiotherapy without performing restaging (group 2).

Epidemiological data, primary and secondary outcomes. Age, BMI, cardiovascular risks factors, tamoxifen usage, cardiovascular risk factors were the main epidemiological aspects retrieved. Depth of myometrial invasion, grade, number of resected lymph nodes, number of invaded nodes as well as adjuvant radiation or chemotherapy treatment was recorded for all patients.

Primary study outcomes were defined to be overall survival and progression-free survival. Overall survival was defined as the time from admission to death from any cause. Progression-free survival was defined as the time from end of therapy until recurrence or death from any cause. Secondary outcome was defined as the absolute number of recurrence and death.

Statistical analysis. Frequency distributions between categorical variables were assessed by using Fisher's exact test. Survival curves between the group with lymphadenectomy and without lymphadenectomy were estimated by Kaplan-Meier curves. The log-rank test was utilized to compare the curves, while survival analysis was performed with the Cox proportional hazards model. Level of significance was defined at $P<.05$. All statistical tests were two-sided. Analysis was conducted using STATA 14.2 version.

Results

Patients and characteristics. There were overall 30 patients retrieved that fulfilled inclusion criteria and were therefore included in the present analysis, of which 21 for group 1 and 9 for group 2. The two study groups of patients were comparable in terms of age, BMI, tamoxifen use, cardiovascular risk factors, depth of invasion and grade. All patients of group 1 had more than 10 lymph nodes resected, while rate of lymph node metastasis was 23.81% (n=5).

CT after hysterectomy was performed in 9.5% of women of group 1 (n=2) and in 77.7% of patients in group 2 (n=7). Decision for further diagnostic/therapeutic approach was obtained in a Multidisciplinary Tumour Board, taking into account various epidemiological and histopathological criteria of cases on an individualized basis. Notably, all imaging results of CT were negative for the presence of nodal metastases. Furthermore, all patients enrolled in this study had preoperatively performed a CT, which was negative for suspicious nodes.

No significant difference was also observed between study groups regarding adjuvant radiation and chemotherapy administered. Indeed, 90.5% of patients of group 1 received external beam radiotherapy and brachytherapy and 9.5% only brachytherapy vs. 77.8 and 11.1% respectively of group 2 patients, which did not indicate significant difference (P=.291). Furthermore, adjuvant chemotherapy was given to 14.3% of group 1 patients, while all group 2 patients did not receive adjuvant chemotherapy.

Table I presents the epidemiological, clinical and histopathological characteristics of the two study groups.

Primary and secondary outcomes. No significant difference was observed in terms of overall survival and progression-free survival between two groups of patients based on log-rank test and Cox proportional hazards model.

Median follow-up was 49.86 months in the group 1 and 43.21 months in group 2 (P=.49). Median OS in group 1 was 91.31 and 90.61 in group 2 (HR:0.71, 95% CI: 0.03-16.58, P=0.829). Median PFS was 87.95 and 81.52 respectively for two groups (HR:0.85, 95% CI: 0.12-5.91, P=0.869).

Table I. Epidemiological, clinical and histopathological characteristics of the two study groups.

Variables	Restaging group, n (%) (N=21)	No restaging group, n (%) (N=9)	P-value
Age, years			
<55	4 (19.05)	0 (0.00)	0.15
55-70	12 (57.14)	4 (44.44)	
>70	5 (23.81)	5 (55.56)	
BMI			
Normal weight	8 (42.11)	2 (28.57)	0.33
Overweight	6 (31.58)	1 (14.29)	
Obesity	5 (26.32)	4 (57.14)	
Tamoxifen use			
Yes	1 (4.76)	2 (22.22)	0.14
No	20 (95.24)	7 (77.78)	
Cardiovascular risk factors			
Yes	7 (33.33)	6 (66.67)	0.09
No	14 (66.67)	3 (33.33)	
Depth of invasion			
IA	12 (57.14)	4 (44.44)	0.52
IB	9 (42.86)	5 (55.56)	
Grade			
1	10 (47.62)	2 (22.22)	0.19
2	11 (52.38)	2 (52.38)	
Lymph nodes removed			
<10	0 (0.00)	-	-
≥10	21 (100.00)	-	
Lymph node metastases			
Yes	5 (23.81)	-	-
No	16 (79.19)	-	
CT performed after hysterectomy			
Yes	2 (9.52)	7 (77.78)	<0.001
No	19 (90.48)	2 (22.22)	
Adjuvant radiation			
None	0 (0.00)	1 (11.11)	0.29
External beam	0 (0.00)	0 (0.00)	
Brachytherapy	2 (9.52)	1 (11.11)	
External beam+ brachytherapy	19 (90.48)	7 (77.78)	
Adjuvant chemotherapy			
Yes	3 (14.29)	0 (0.00)	0.23
No	18 (85.71)	9 (100.00)	

Table II. Primary and secondary outcomes within study groups.

Variables	Restaging group (N=21)	No restaging group (N=9)	P-value
Follow up in months, mean (range)	49.86 (7.49-95.08)	43.21 (0.68-110)	0.49
Primary outcomes[a]			
5-year OS (proportion surviving)	0.9375	1	0.83
5-year PFS (proportion alive without progression)	0.8594	0.8571	0.87
Secondary outcomes, n (%)			
Vital status, n (%)[b]			
Death	1 (4.76)	1 (11.11)	0.52
Alive	20 (95.24)	8 (88.89)	
Recurrence, n (%)[b]			
Yes	3 (14.29)	2 (22.22)	0.59
No	18 (85.71)	7 (77.78)	
Site of recurrence, n (%)[b]			
Distance	1 (33.33)	2 (100.00)	0.14
Local (pelvis)	2 (66.67)	0 (0.00)	

OS, overall survival; PFS, progression-free survival. [a]Log-rank test used, [b]Fisher's exact test used.

Furthermore, no significant difference was observed between two study groups regarding percentages of recurrence and death. Specifically, survival rate was 95.2% for patients of group 1 (n=20) vs. 88.9% of patients for group 2 (n=8), (P=.523). Recurrence rate was 14.3% for group 1 (n=3) vs. 22.2% for group 2 (n=22), (P=.593).

Finally, regarding site and kind of recurrence, there was one cerebral and two pelvic recurrences in group 1 vs. one cerebral and one pulmonary recurrence in group 2.

Table II presents the primary and secondary outcomes within study groups. Figs. 1 and 2 present the Kaplan-Meir overall survival and progression-free survival curves for study groups.

Discussion

The present study demonstrated that restaging with pelvic and para-aortic lymphadenectomy has no additional benefit on the prognosis of early-stage, endometrioid-type, grade 1-2 patients with positive LVSI in the final histopathological specimen. All examined survival parameters were comparable between these patients and patients not restaged and given directly postoperative radiotherapy. Therefore, it is assumed that the performance of lymphadenectomy based on a solely indication of positive LVSI in such patients did not improve overall survival and progression-free survival compared to no lymphadenectomy.

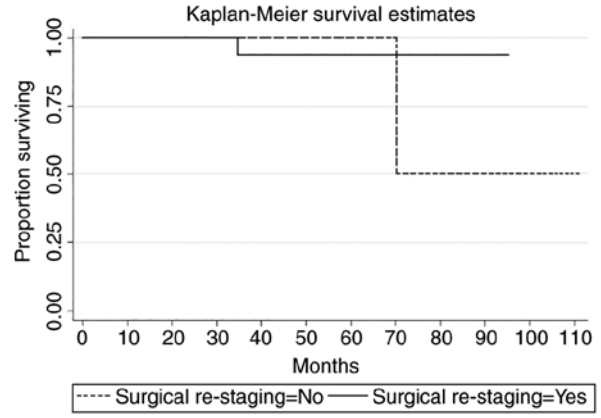

Figure 1. Kaplan-Meier overall survival curve for the study groups.

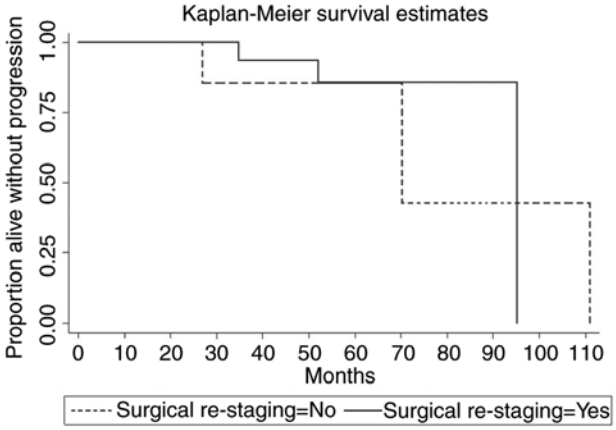

Figure 2. Kaplan-Meier progression-free survival curve for study groups.

This is potentially one amongst very few publications examining the necessity of additional restaging with lymphadenectomy in patients otherwise classified as low-risk but finally characterised as high-intermediate risk because of only positive LVSI. There has only been a relative review publication by Harris *et al* (14), in which authors discuss the additional management required in such patients. Authors underline the lack of relative studies, therefore recommending usage of an LVSI quantification system that could actually alter decision in order to distinguish between substantial or focal LVSI. Specifically, they recommend only adjuvant radiotherapy and not lymphadenectomy in case of substantial LVSI, but in cases with focal LVSI they recommend lymphadenectomy. Even if these recommendations have not yet been applicable to clinical practice, it is a parameter of importance actually to consider and evaluate not the presence of LVSI itself, but mainly the degree and kind of expression this may have to tumoral cells.

Our results may pose a new suggestion to consider for guidelines of treatment for endometrial cancer. Indeed, ESGO guidelines either in the old or in the new version do not give any treatment options in early, LVSI unstaged patients (1,13). In contrary, NCCN guidelines provide multiple options for such patients, as they give the option of imaging and thereafter lymphadenectomy in patients with suspicion of nodal metastases in imaging (15). Such a strategy could actually have two main advantages. The first one would be the avoidance of unnecessary pelvic and para-aortic lymphadenectomy, which on their own pose severe operative danger and increased risk for lymphedema, lymphocele and neuralgia (16,17). The second would be the avoidance of unnecessary complementary treatments that otherwise should be kept as additional future therapy in case of recurrence. Such a strategy is rather enhanced by our observation that lymphadenectomy for restaging does not alter prognosis of such patients and thereafter should be performed only in patients with imaging suspicion of bulky nodes. In the other hand, there should be always considered that LVSI poses a negative prognostic factor and its presence should not be underestimated in an effort to minimize complementary therapy (18-20).

An additional remark could also be that enrolment of both sentinel node and molecular profiling for endometrial cancer patients, based on revised ESGO guidelines, could further help our therapeutic strategy. First of all, as indicated by new ESGO guidelines, sentinel node should rather be performed in all intermediate risk cases, while it is highly recommended, even if not mandatory, in low-risk patients. Performance of sentinel node could rather help us in such cases as those discussed in the present study, since the staging information would be available and further treatment could be tailored based on sentinel node result (13,21).

Furthermore, evaluation of molecular profiling of endometrial cancer in the context of risk-of-disease stratification could rather undermine the added value of postoperative LVSI. However, our results have not taken into account this parameter for two major reasons. First of all, implementation of new molecular staging has not yet been globally achieved in current practice. Secondly, our remarks refer to patients of a previous era in which no molecular profiling for endometrial cancer patients was performed as standard of care. Furthermore, even with the new revised guidelines, the case might be a POLE case with positive LVSI (+) where therapeutic questions may be raised. The current study rather firmly indicated that no therapeutic and prognostic value is associated with restaging based solely on LVSI positivity, therefore, even in the era of molecular profiling, our results may actually have a significant clinical impact.

Limitations of the present study mainly concern its retrospective nature and the small number of patients. However, this is potentially the first publication to provide a direct comparison of survival parameters between two categories of such patients, those restaged and not restaged. Accordingly, our initial remark that restaging with lymphadenectomy has no beneficial impact could actually trigger the development of a relatively large multicentre RCT, enrolling sufficient sample size and with severe, prospective enrolment of patients.

In conclusion, our study indicated no survival benefit of restaging lymphadenectomy for patients with early-stage, low-grade, endometrioid-type, LVSI-positive endometrial cancer. Imaging could be an alternative to identify cases with suspicious nodes and limit the performance of lymphadenectomies only to such cases, in which full staging and resection of suspicious nodes consists of the optimal diagnostic and therapeutic option. The results of the present study rather pose a remarkable observation to be actively enrolled in daily clinical practice. Further prospective, multicentre RCTs are rather demanded in order to assess definitively the beneficial impact of restaging lymphadenectomy in such patients.

Acknowledgements

This abstract was presented at the ESGO 2022 Congress, 27-30 October, Berlin, Germany and was published as Abstract no. 1047 (https://ijgc.bmj.com/content/32/Suppl_2/A132.1).

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BN, AF, GB and FG have made substantial contributions to the conception and design of the study, and the acquisition of data. BN, CMS, GB and SP wrote the initial draft. BN, CMS, SP, AF and FG confirm the authenticity of all the raw data. BN, GB, CMS and SP performed the statistical analysis, and AF and FG have significantly contributed to the interpretation of results. GB, AF and FG have substantially reviewed the initial draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Based on Institution's policy, no ethical approval is needed in order to perform retrospective studies and therefore this criterion is not applicable for the present manuscript. Patients provided written informed consent for the inclusion of their elements anonymously for potential analysis and inclusion in future studies.

Patient consent for publication

Patients provided written informed consent for the inclusion of their elements anonymously and for publication.

Competing interests

The authors declare that they have no competing interests

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