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Original Article

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Survival implication of lymphadenectomy in patients surgically treated for apparent early-stage uterine serous carcinoma

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ABSTRACT

Objective: Uterine serous carcinoma (USC) is a rare highly aggressive disease. In the present study, we aimed to investigate the survival implication of the systematic lymphadenectomy in patients who underwent surgery for apparent early-stage USC.
Methods: Consecutive patients with apparent early-stage USC surgically treated at six Italian referral cancer centers were analyzed. A comparison was made between patients who underwent retroperitoneal staging including at least pelvic lymphadenectomy "LND" vs. those who underwent hysterectomy alone "NO-LND". Baseline, surgical and oncological outcomes were analyzed. Kaplan- Meier curves were calculated for disease-free survival (DFS) and disease-specific survival (DSS). Associations were evaluated with Cox proportional hazard regression and summarized using hazard ratio (HR).
Results: One hundred forty patients were analyzed, 106 LND and 34 NO-LND. NO-LND group (compared to LND group) included older patients (median age, 73 vs.67 years) and with higher comorbidities (median Charlson Comorbidity Index, 6 vs. 5) (p<0.001). No differences in terms of recurrence rate (LND vs. NO-LND, 33.1% vs. 41.4%; p=0.240) were observed. At Cox regression analysis lymphadenectomy did not significantly influence DFS (HR=0.59; 95% confidence interval [CI]=0.32–1.08; p=0.09), and DSS (HR=0.14; 95% CI=0.02–1.21; multivariable analysis p=0.07). Positive node was independently associated with worse DFS (HR=6.22; 95% CI=3.08–12.60; p<0.001) and DSS (HR=5.51; 95% CI=2.31–13.10; p<0.001), while adjuvant chemotherapy was associated with improved DFS (HR=0.38; 95% CI=0.17–0.86; p=0.02) and age was independently associated with worse DSS (HR=1.07; 95% CI=1.02–1.13; p<0.001).
Conclusions: Although lymphadenectomy did not show survival benefits in patients who underwent surgery for apparent early-stage USC, the presence of lymph node metastasis was

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No potential conflict of interest relevant to this article was reported.

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the main adverse prognostic factors, supporting the prognostic role of the retroperitoneal staging also in this histological subtype.

Keywords: Gynecology; Lymphadenectomy; Survival; Endometrial Neoplasms; Therapeutics

INTRODUCTION

Uterine serous carcinoma (USC) is a rare highly aggressive malignancy accounting for approximately 10% of all endometrial cancers [1,2]. Patients affected by USC are usually older and with possibly greater comorbidities than type I endometrial cancer patients. Although often diagnosed as apparent early-stage disease, women with USC have a higher recurrence rate and poorer prognosis than those with endometrioid adenocarcinoma [3]. Recent studies suggested USC to share aggressive behavior with high-grade serous ovarian carcinoma, with an extremely high 5-year recurrence rate, ranging from 31% to 80%, even if diagnosed in early stage of disease [4,5].

Standard staging surgery in case of apparent early stage USC includes hysterectomy with bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymphadenectomy, and omentectomy. Both open and minimally invasive approaches are considered safe options when performed in referral centers, and adjuvant treatment (mainly chemotherapy) is recommended following surgery [6,7].

Although the current recommendations consider lymphadenectomy as the standard-of-care treatment in patients at risk for lymphatic dissemination, the role of lymph nodes removal in apparent early-stage disease is still debated. Although accumulating evidence underline that lymphadenectomy has not a therapeutic role in endometrial cancer [8,9], the detection of nodal disease is pivotal to identify patients at risk of recurrence, and impacts postoperative treatment decisions [10]. However, lymphadenectomy has been associated with a non-negligible morbidity, including lymphorrhea, lymphocele and lymphedema, highly influencing patients' quality of life [11,12]. Additionally, patients with USC have *per se* a high risk of relapse, and adjuvant treatment (specifically chemotherapy) is often indicated independently on lymph node status [13-15].

Our study objective was to evaluate the survival implication of lymphadenectomy for USC staging by comparing the progression and survival outcomes in patients who underwent lymphadenectomy with those who underwent hysterectomy alone.

MATERIALS AND METHODS

Data of consecutive patients with histologically proven pure USC who underwent surgical treatment at six Italian tertiary referral centers (Women's and Children Hospital, University of Insubria - Varese; IRCCS National Cancer Institute - Milan; Regina Montis Regalis Hospital - Mondovì; National Cancer Institute - Naples; Spedali Civili - Brescia; Endoscopica Malzoni-Center for Advanced Endoscopic Gynecological Surgery - Avellino) between 01/01/2000 and 31/12/2015 were reviewed. For the purpose of this investigation, only patients with apparent early-stage disease at both preoperative clinical examination and intraoperative evaluation (i.e. tumor clinically confined to the uterus, absence of bulky nodes and/or extrauterine

macroscopic gross disease) have been analyzed. Retrospective observational studies involving the collection of existing data have been considered exempt from the requirement of Institutional Review Board (IRB) approval in all the participating centers. Patients with unexpected intra-operative evidence of gross extrauterine disease (FIGO stage IIIC with bulky nodes, and stage IV), preoperative neoadjuvant chemotherapy, synchronous cancer(s) and/or personal history of gynecologic malignancy were excluded. Conversely, patients with FIGO stage IIIC disease detected at final histology, with no preoperative suspicious of lymph node involvement, or intraoperative evidence of enlarged node(s) were included in our analysis. Patients with mixed cell carcinoma at final histology were not included [16]. All patients underwent surgery either via open or laparoscopic approach. As part of the treatment, all patients had total extrafascial hysterectomy; bilateral salpingo-oophorectomy was always performed as part of the staging. Patients were then stratified into two groups based on the performance of retroperitoneal staging: pelvic lymphadenectomy, with or without para-aortic lymphadenectomy and omentectomy: (LND) vs. patients who underwent hysterectomy alone (NO-LND). Baseline patients' characteristics, such as age at surgery (years), body mass index, American Society of Anesthesiologists (ASA) Classification [17], and comorbidities, defined according to with the Charlson Comorbidity Index (CCI) score [18] (1 point: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, uncomplicated diabetes; 2 points: hemiplegia, moderate to severe chronic kidney disease, diabetes with end-organ damage, localized solid tumor, leukemia, lymphoma; 3 points: moderate to severe liver disease; 6 points: metastatic solid tumor, AIDS; 1 point for every decade age 50 years and over, maximum 4 points) were collected. A stratification based on the number of lymph nodes removed was made to better assess the accuracy of the lymphadenectomy, when performed; we considered patients as “adequate staged” when >10 lymph nodes were removed, while in case of <10 lymph nodes were removed, we classified them as “inadequate staged”. As perioperative outcomes we included operative time (minutes), estimated blood loss (mL), need for blood transfusion, intraoperative and postoperative complications. Data on blood loss were extracted from the operative records. Any unintentional damage (or opening) to any organ or structure was considered as intraoperative complication; contrariwise, conversion from minimally invasive to open approach was not considered per se as a complication. The length of stay was calculated from the day of surgery to discharge. Postoperative complications within 30 days from surgery were registered and graded using the Clavien-Dindo classification system, however, only grade 2 or higher complications have been considered in the present study. Tumor stage was reported based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification.

Statistical analyses were performed using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). Baseline data were reported using standard descriptive statistics. Comparisons were made between the 2 groups (LND vs. NO-LND) using the chi-squared test or Fisher exact test for categorical variables and t tests and Wilcoxon rank-sum tests were for continuous variables. Disease-free survival (DFS) and disease specific survival (DSS) after surgery were estimated using the Kaplan-Meier method; the duration of follow-up for patients without a documented recurrence was censored at the date of their last relevant clinical follow-up. Comparisons of DFS and DSS between groups were evaluated using the log-rank test. Multivariable Cox proportional hazards regression models were fit in accordance with the significant predictors at univariate analysis ($p \leq 0.05$) and the administration of adjuvant chemotherapy in order to identify factors independently

associated with survivals. Multiple imputation with logistic regression and predictive mean matching has been used to statistically impute missing values. All estimates were presented with 2-sided 95% confidence intervals (CIs) and survival curves plotted using the "survminer" R package.

RESULTS

Over the study period, data of 140 consecutive patients meeting the inclusion/exclusion criteria have been analyzed: 106 (76%) and 34 (24%) in LND and NO-LND groups, respectively. Patients in the LND group (compared to those in NO-LND group) were significantly younger, with a median age at surgery of 67 years (43–84) vs. 73 years (54–90) (p=0.01) and with significantly lower CCI score (CCI 5±1 vs. 6±1) (p=0.01). However, no significant differences were found in the rate of patients with CCI >3 (62% vs. 74%; p=0.23). Patients in both groups had similar median ASA score (p=0.65), surgical history of open abdominal surgery (p=0.08) and personal history of non-gynecological cancer (p=0.08).

Among 106 patients in the LND group, the median number of lymph nodes removed was 24 (4–74). Twenty-five patients (24%) had retroperitoneal staging including the removal of both pelvic and para-aortic lymph nodes, while 76% underwent only systematic pelvic lymphadenectomy. Ninety-nine patients (93%) had at least 10 lymph nodes removed, and arbitrarily considered adequately staged. Upstaging for positive nodes occurred in 28/106 (26%) cases. Overall, patients in LND group were more likely to receive adjuvant treatment (LND vs. NO-LND, 84% vs. 62%; p=0.01); specifically chemotherapy was administered in 83 (78%) and 17 (50%) patients in LND and NO-LND groups, respectively (p=0.01); details of baseline patients' and tumor characteristics are shown in **Table 1**, while details of adjuvant treatment have been reported in **Supplementary Table 1**. Patients in LND group were less

Table 1. Baseline details and tumour characteristics: LND vs. NO-LND

Characteristics	LND (n=106)	NO-LND (n=34)	p-value
Age (yr)	67 (43–84)	73 (54–90)	0.01
Elderly (≥65 yr)	78 (73.6)	25 (73.5)	0.99
BMI	26.2 (17.7–46.0)	27.0 (19.0–52.0)	0.24
Charlson Comorbidity Index	5±1	6±1.5	0.01
CCI >3	66 (62.3)	25 (73.5)	0.23
AS	2 (1–4)	2 (1–4)	0.65
ASA >2	14 (13.3)	8 (23.5)	0.16
Previous open abdominal surgery	22 (20.8)	12 (35.3)	0.08
History of non-gynaecological cancer	10 (9.4)	7 (20.6)	0.08
FIGO Stage			0.69
Stage I–II	71 (67.0)	24 (70.6)	
Stage III	35 (33.0)	10 (29.4)	
Positive lymph node(s)	28 (26.8)	0*	<0.001
Positive cytology	10 (9.4)	6 (17.6)	0.22
Adjuvant Treatment	89 (84.0)	21 (61.8)	0.01
Chemotherapy alone	71 (67.0)	13 (38.2)	
EBRT alone	6 (5.7)	4 (11.8)	
Chemo-radiation therapy	12 (11.3)	4 (11.8)	
Chemotherapy ± EBRT	83 (78.3)	17 (50.0)	

Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables.
ASA, American Society of Anaesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; LND, lymph nodes removed; NO-LND, lymph nodes not removed.
*Positive lymph nodes are unknown.

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Table 2. Surgical outcomes and perioperative complications: comparison between the 2 cohorts

Variables	LND (n=106)	NO-LND (n=34)	p-value
Surgical approach			0.05
Laparoscopic	42 (39.6)	20 (58.8)	
Open	64 (60.4)	14 (41.2)	
Estimated blood loss (mL)	210 (10–1,000)	230 (10–1,200)	0.24
Operative time (min)	184 (60–540)	112 (40–330)	0.05
Intraoperative blood transfusion	6 (5.7)	3 (8.8)	0.51
Postoperative complication (Grade ≥2)	10 (9.4)	5 (14.7)	0.39
Postoperative blood transfusion	2 (1.9)	0 (-)	0.42
Complications			
Pneumonia	0 (0.0)	1 (2.9)	0.07
Surgical site infection	1 (0.9)	0 (0.0)	0.57
Pelvic abscess	3 (2.8)	0 (0.0)	0.32
Intensive care unit admission	1 (0.9)	1 (2.9)	0.39
Hospital stay (days)	5 (1–15)	5 (1–44)	0.94
Return to the operative room	0 (0.0)	0 (0.0)	0.99

Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables. Postoperative complication graded according to the Accordion Severity Grade of Complication score.

likely to undergo laparoscopic surgery (40% vs. 59%; p=0.05), and, as expected, they had significantly shorter median operative time (112 vs. 184 minutes; p=0.05). Thirty-day surgical-related outcomes were well comparable between the groups and similar complication rates, hospital stay and return to the operative room were registered (**Table 2**).

Details of the oncological outcomes and site of recurrence are reported in **Table 3**. Within a median follow-up of 33.1 months, 50 patients (36%) recurred, 35 (33%) in LND group vs. 15 (42%) in NO-LND group (p=0.24); 42 patients (30.0%) died (LND vs. NO-LND, 26 [25%] vs. 16 [47%]; p=0.01), and 37 (26%) died of disease (LND vs. NO-LND, 22 [21%] vs. 15 [44%]; p=0.01). Kaplan-Meier curves for DFS did not show significant differences in DFS between both LND vs. NO-LND (log-rank, p=0.08) and "adequate" staged vs. "inadequate" staged (log-rank, p=0.14), but significant worse prognosis for NO-LND (log-rank, p<0.001) and "inadequate" staged (p=0.01) in terms of DSS (**Fig. 1**). Though, when focusing on the potential factors associated with progression and survival (**Table 4**), the Cox proportional hazards regression analysis showed lymphadenectomy not significantly influencing DFS (hazard ratio [HR]=0.59; 95% CI=0.32–1.08; univariate analysis p=0.09), while a borderline significance was shown for DSS (HR=0.14; 95% CI=0.02–1.21; multivariable analysis p=0.07). The presence of positive node(s) was found independently associated with worse DFS (HR=6.22; 95% CI=3.08–12.60; p<0.001) and DSS (HR=5.51; 95% CI=2.31–13.10; p<0.001).

Table 3. Oncological outcomes: details on recurrence and mortality

Variables	All population (n=140)	LND (n=106)	NO-LND (n=34)	p-value
Median follow-up (mon)	33 (1–164)	37 (1–164)	25 (4–129)	0.02
Recurrence rates (%)	50 (35.7)	35 (33.1)	15 (41.7)	0.24
Single site recurrence	23/50 (46.0)	17/35 (48.6)	6/15 (40.0)	0.31
Vaginal Recurrence	10 (7.1)	7 (6.6)	3 (8.8)	0.66
Nodal recurrence	23 (16.4)	14 (13.2)	9 (26.5)	0.07
Distant recurrence	25 (17.9)	16 (15.1)	9 (26.5)	0.13
Death (overall)	42 (30.0)	26 (24.5)	16 (47.1)	0.01
Death of disease	37 (26.4)	22 (20.7)	15 (44.1)	0.01

Data is expressed as median and range for continuous variables and absolute number and percentage for categorical variables.
LND, lymph nodes removed; NO-LND, lymph nodes not removed.
*Distant recurrence: any non-vaginal other than nodal recurrence.

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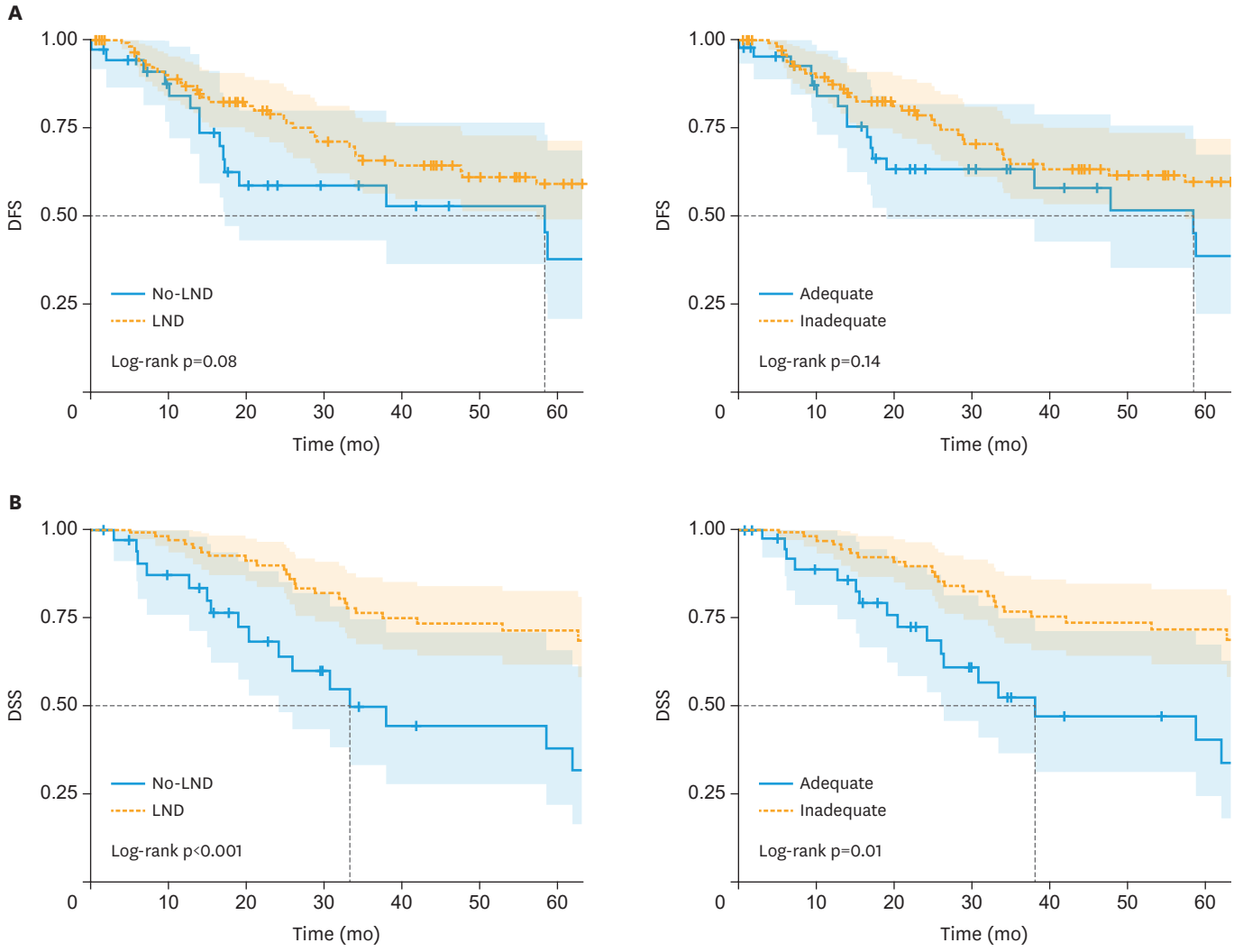

Fig. 1. DFS (A) and DSS (B) were estimated according to the Kaplan-Meier methods. LND vs. NO-LND (left side) and "Adequate" staging vs. "Non-adequate" staging (right side). Significance between the curves was calculated by the log-rank test.
DFS, disease-free survival; DSS, disease specific survival; LND, lymph nodes removed; NO-LND, lymph nodes not removed.

At multivariable analysis the administration of adjuvant chemotherapy was associated with improved DFS (HR=0.38; 95% CI=0.17–0.86; p=0.02) (Kaplan-Meyer curves stratified by adjuvant chemotherapy are shown in **Supplementary Fig. 1**), while age was independently associated with worse DSS (HR=1.07; 95% CI=1.02–1.13; p<0.001).

DISCUSSION

The results of the present multicentric study showed lymph node status, adjuvant chemotherapy and age as the most important factors influencing progression and survival outcomes in patients who underwent surgery for apparent early stage USC. Although we failed to show a survival benefit from the performance of lymphadenectomy, the relative small number of events did not allow drawing firm conclusions. On the other hand, our findings corroborate the fundamental diagnostic and prognostic role of the lymph node status evaluation, especially in patients at high risk of recurrence.

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Table 4. Cox proportional hazards regression analysis for oncological outcomes: DFS and DSS

Characteristics	DFS						DSS					
	Univariate			Multivariable			Univariate			Multivariable		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Age	1.05	(1.01–1.09)	0.02	1.03	(0.99–1.08)	0.10	1.10	(1.05–1.15)	<0.001	1.07	(1.02–1.13)	0.01
BMI	1.05	(0.99–1.10)	0.07				1.05	(0.99–1.11)	0.11			
CCI			0.05			0.28			0.06			
CCI ≤3	Referent						Referent					
CCI >3	1.88	(1.01–3.49)		1.45	(0.73–2.88)		2.01	(0.98–4.13)				
ASA score			0.01			0.10			0.01			0.19
ASA ≤2	Referent						Referent					
ASA >2	2.38	(1.25–4.54)		1.91	(0.94–3.86)		3.04	(1.49–6.20)		1.66	(0.79–3.57)	
Surgical approach			0.38						0.26			
Open surgery	Referent						Referent					
Laparoscopy	1.29	(0.73–2.30)					1.47	(0.75–2.86)				
Lymphadenectomy			0.09						0.01			0.07
LND not performed	Referent						Referent					
LND performed	0.59	(0.32–1.08)					0.34	(0.18–0.65)		0.14	(0.02–1.21)	
Adequately staged			0.14						0.01			0.51
Less than 10 nodes	Referent						Referent					
At least 10 nodes	0.64	(0.36–1.16)					0.37	(0.19–0.70)		0.67	(0.26–1.48)	
Extra-uterine disease			0.34						0.34			
Yes	Referent						Referent					
No	0.67	(0.30–1.50)					0.66	(0.27–1.57)				
Lymph node status			<0.001			<0.001			0.01			<0.001
Negative node(s)	Referent						Referent					
Positive node(s)	3.55	(2.00–6.47)		6.22	(3.08–12.60)		2.53	(1.29–4.96)		5.51	(2.31–13.10)	
Adjuvant chemotherapy			0.06			0.02			0.12			0.29
Not administered	Referent						Referent					
Administered	0.48	(0.22–1.03)		0.38	(0.17–0.86)		0.49	(0.21–1.19)		0.60	(0.23–1.56)	

Each factor was evaluated in a separate univariate Cox proportional hazards regression model, stratified by cohort (LND vs. NO-LND).
ASA, American Society of Anaesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; LND, lymph nodes removed; NO-LND, lymph nodes not removed.
*Hazard ratio per 1-year increase in age and per 1-unit increase in BMI. Multiple imputation with logistic regression and predictive mean matching has been used to statistically impute missing values.

At present, the evidence-based management of apparent early stage endometrial cancer suggests performing lymphadenectomy only in patients considered at risk of lymph node dissemination [7] to identify those with metastatic disease and help defining the most appropriate adjuvant treatment, when necessary. It may be argued whether or not lymphadenectomy has any therapeutic role; however, the results of two randomized trials failed to demonstrate a survival benefit from lymphadenectomy in early stage endometrial cancer [7]. Conversely, the value of nodal assessment to predict patterns of failure and prognosis has never been questioned.

Although women with USC have a high risk of lymph node metastasis [5], approximately one patient out of four did not receive a comprehensive staging in the present series. We could hypothesize two main reasons potentially related to the decision of not performing lymphadenectomy in in real-life settings: i) the systematic removal of regional lymph nodes in endometrial cancer is associated with a non-negligible risk of lymphatic complications (particularly lower extremity lymphedema) causing severe morbidity, especially in elderly patients [11]. In support of this hypothesis, patients in NO-LND group were significantly elderly compared to those in LND group; ii) the higher number of patients with severe comorbidities in NO-LND group might have reduced the rate of eligibility for adjuvant treatment [19], thus potentially invalidating the diagnostic role of lymphadenectomy.

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Considering the evaluation of the lymph node status pivotal to predict the risk of recurrence, and assuming the non-therapeutic value of the lymphadenectomy, we believe that our findings might bear the use of the sentinel lymph node technique also in patients with apparent early-stage USC. Although the prospective study by Soliman et al. proved the accuracy of the sentinel lymph node biopsy also in high-risk endometrial cancer [20], the results of a recent survey showed the lack of evidence as the main detractor of the adoption of sentinel lymph node technique, especially in case of G3 endometrioid or non-endometrioid histotypes [21]. Our results might further support the value of the sentinel lymph node biospy as a valid alternative to the systematic lymphadenectomy also for high-risk endometrial cancer staging, potentially reducing the well-known complications associated with the comprehensive pelvic and para-aortic staging [22,23].

Overall, the 35% recurrence-rate we found in our cohort is well-comparable to what reported in previous studies [24,25]. In accordance with the most recent published literature, we found the presence of positive lymph node(s) at final histology the main adverse factor influencing both DFS and DSS [25], while the administration of chemotherapy and age were associated with poorer progression and survival outcomes, respectively. Moreover, the updated analysis of the PORTEC 3 [26], showed a significantly improved overall survival and failure-free survival with the use of chemotherapy in addition to radiotherapy especially in patients with USC. However, it is essential to mention that USC represented only a limited percentage (about 15%) of the study-population and the study was not powered to test the effect of chemotherapy in this subset of patients. Accordingly, the role of chemotherapy in USC is still debated.

Additionally, although it was not the aim of our study, we did not find the type of surgical approach (laparoscopic or open surgery) influencing the survival outcomes. Of note, the majority of the patients in the LND group had the procedure performed via open surgery, thus not allowing drawing definitive conclusions. As recently reported, there has been a significant implementation of the minimally invasive approach for the treatment of patients with apparent early-stage endometrial cancer in the USA over the last decade [27], also for women with non-endometrioid uterine cancers [28]; however, the safety of the laparoscopic and robotic approaches for USC is still under investigation [29,30].

The present study suffers from few limitations. First, baseline characteristics and the absolute number of evaluated cases are unbalanced between the groups. These aspects fully reflect the retrospective nature of the study design with the well-known biases, including the arbitrary patients' selection. Second, we did not consider, the removal of the omentum as mandatory inclusion criteria for the LND group. Although based on the most recent international guidelines [7] staging omentectomy should be considered (level of evidence IV), this procedure is not always performed in the every-day practice. However, based on the strict inclusion criteria, we excluded from our analysis patients with macroscopic omental disease either preoperative or intraoperative detected. Third, the relatively low number of recurrences in our cohort and the high rate of overlapping between positive node and extrauterine disease might not reflect extensive generalizability of our results. Similarly, the small number of events could have been responsible for the non-significant impact of adjuvant chemotherapy on DSS in the Cox proportional hazards regression model. Fourth, both chemotherapy and radiation therapy were not administered based on defined criteria within the institutions included in this study, thus potentially representing a bias of our analysis. However, at present, it is still unclear the efficacy of adjuvant chemotherapy in patients with USC, while the role of external beam radiation therapy seems limited.

In conclusion, although we found the performance of a systematic lymph node dissection not significantly impacting on progression and survival outcomes, the role of lymphadenectomy in this subset of patients still remains under investigation. This retrospective multicenter analysis showed the presence of positive lymph node(s) at final histology as the main significant adverse prognostic factor worsening both DFS and DSS in patients who underwent hysterectomy and retroperitoneal staging for apparent early stage USC. Aiming at a reduction of surgical-related and lymphatic morbidity, our results might further support the use of sentinel lymph node biopsy also for high-risk endometrial cancer staging, such as USC. Further studies are warranted to confirm our results.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Details on adjuvant treatment following surgical therapy for apparent early stage USC

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Supplementary Fig. 1

Survival curves stratified by adjuvant chemotherapy performed vs. not performed.

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