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Lymphadenectomy and Adjuvant Therapy Improve Survival with Uterine Carcinosarcoma: A Large Retrospective Cohort Study

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Keywords
Carcinosarcoma · Endometrial cancer · Lymph node excision · Health care evaluation · Adjuvant chemotherapy · Radiotherapy · Radiochemotherapy

Abstract
Objective: Uterine carcinosarcoma is a rare, aggressive subtype of endometrial cancer. Treatment consists of hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy (LND). The survival benefit of LND in relation to adjuvant radio- and/or chemotherapy is unclear. We evaluated the impact of LND on survival in relation to adjuvant therapy in uterine carcinosarcoma. ***Methods:*** Retrospective data on 1,140 cases were combined from the Netherlands Cancer Registry (NCR) and the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). LND was defined as the removal of any nodes. Additionally, cases where 10 nodes or less (LND ≤10) or more than 10 nodes (LND >10) were removed were analyzed separately. Adjuvant therapy was evaluated as radiotherapy, chemotherapy, or radiochemotherapy. Associations were analyzed by χ^2 test, log-rank test, and Cox regression analysis. ***Results:*** Overall survival (OS) had improved after total abdominal hysterectomy with bilateral salpingo-oophorectomy with LND >10 (HR 0.62, 95% CI 0.47–0.83). Adjuvant therapy was related to OS with an HR of 0.64 (95% CI 0.54–0.75) for radiotherapy, an HR of 0.65 (95% CI 0.48–0.88) for chemotherapy, and an HR of 0.25 (95% CI 0.13–0.46) for radiochemotherapy. Additionally, adjuvant treatment was related to OS when lymph nodes were positive (HR 0.22, 95% CI 0.11–0.42), but not when they were negative. ***Conclusion:*** LND is related to improved survival when more than 10 nodes are removed. Adjuvant therapy improves survival when LND is omitted, or when nodes are positive.

Introduction

Uterine carcinosarcoma (UCS) is a rare and aggressive histological subtype of endometrial cancer. The incidence is approximately 5 cases per 1,000,000 person-years, and 5-year survival is between 32 and 39% [1–4]. Primary treatment consists of a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) and lymphadenectomy (LND).

LND as a treatment tool is still under debate [4–6]. Some relatively small studies describe no benefit of LND [7, 8]. Several larger retrospective cohort studies describe

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an improved survival of patients on whom LND was performed [2, 9, 10]. This is in accordance with studies on other aggressive subtypes of endometrial cancer like high-grade endometrial and serous endometrial cancer. Two of these studies evaluated the number of nodes that were removed in relation to survival, as it seems plausible that there may not be an optimal treatment effect when only a few nodes are removed. Nemani et al. [2] found no significant difference between removal of more than 12 and less than 12 nodes. Conversely, Temkin et al. [9] found survival to be improved when more than 11 nodes are removed.

A limitation of the studies mentioned above is that their findings were not corrected for adjuvant radio- and/or chemotherapy (CT) [2, 9, 10]. This may have influenced the findings, as adjuvant radiotherapy (RT), CT, and combined radiochemotherapy (RCT) may improve the survival of UCS patients [11–14]. It is therefore unknown how LND, RT, and CT together are related to survival with UCS.

The aim of this study was to evaluate the role of LND with or without RT and/or CT in a large retrospective cohort of 1,140 patients diagnosed with UCS undergoing primary surgery with a curative intent.

Subjects and Methods

Data Collection and Study Population

Retrospective data were obtained from the Netherlands Cancer Registry (NCR) and the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) [15]. The NCR contains data on all newly diagnosed cancers, including patient, tumor, and treatment characteristics. Data from the NCR were combined with data from PALGA by a coding system connecting the two databases. The data were delivered in password-protected sets not traceable to individual persons. According to Dutch law, no further ethical approval is required. Patients with UCS were included between January 1, 1993, and December 31, 2012. Follow-up was completed on December 31, 2013. Included were patients diagnosed with uterine carcinoma as identified by corresponding ICD-O-3 codes (C54; C55 combined with morphological code 8950, 8951, or 8980). In total, 1,310 patients were identified to be diagnosed with UCS according to the NCR. However, 170 patients did not undergo primary surgery defined as TAH-BSO with or without LND, leaving 1,140 patients available for further analysis.

Data Processing

Both sources, the NCR and PALGA, were combined into one database. Inconsistencies between PALGA and the NCR were resolved using PALGA as the reference, since this data set most accurately reflects the pathology report. An exception was made for disease stage, as the pathology review lacked information on lymph node status when LND was omitted. Therefore, disease stage was classified according to the FIGO 2009 classification and based on the NCR. Distant metastasis was defined as distant metastasis including intra-abdominal metastasis, to be described at the time of UCS-related surgery. Recurrence of disease after surgery needed to be confirmed by histology. LND was defined as the removal of any number of nodes. To further evaluate the relevance of the number of nodes removed, a distinction was made between removal of 10 lymph nodes or less (LND ≤10) and removal of 11 nodes or more (LND >10). Adjuvant treatment was documented as RT, CT, or RCT. There was no information as to the timing of adjuvant treatment with respect to other treatment. Age at diagnosis was divided into 70 years and below and 71 years and above, in line with previous publications [1–4].

Table 1. Clinicopathological characteristics of the 1,140 patients with uterine carcinosarcoma stratified by type of surgery

	TAH-BSO (n = 893)	TAH-BSO and LND (n = 247)	p value
Age			<0.001
≤70 years	418 (46.8)	148 (59.9)	
>70 years	475 (53.2)	99 (40.1)	
FIGO stage			<0.001
I	539 (63.5)	131 (54.1)	
II	47 (5.5)	7 (2.9)	
III	138 (16.3)	82 (33.9)	
IV	125 (14.7)	22 (9.1)	
Unknown	44	5	
Myometrial invasion			0.355
Less than half	417 (53.1)	111 (49.6)	
More than half	369 (46.9)	113 (50.4)	
Unknown	107	23	
Lymph nodes			–
Negative	–	172 (69.2)	
Positive	–	75 (30.4)	
Distant metastasis			0.070
No	748 (88.1)	225 (92.2)	
Yes	101 (11.9)	19 (7.8)	
Unknown	44	3	
LVSI			0.064
No	92 (26.4)	50 (34.7)	
Yes	257 (73.6)	94 (65.3)	
Unknown	544	57	
Adjuvant therapy			<0.001
None	443 (49.6)	75 (30.4)	
Radiotherapy	358 (40.1)	126 (51.0)	
Chemotherapy	73 (8.2)	31 (12.6)	
Chemoradiation	19 (2.1)	15 (6.1)	

Values are presented as n (%). Percentages were calculated without missing values. TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy; LND, lymphadenectomy with removal of any number of nodes; LVSI, lymphovascular space involvement.

Table 2. Clinicopathological characteristics of the 1,140 patients with uterine carcinosarcoma stratified by adjuvant treatment

	No adjuvant treatment (n = 518)	Adjuvant RT (n = 484)	Adjuvant CT (n = 104)	Adjuvant RCT (n = 34)	p value
Age					<0.001
≤70 years	205 (39.6)	291 (60.1)	74 (71.2)	28 (82.4)	
>70 years	313 (60.4)	193 (35.9)	30 (28.8)	6 (17.6)	
FIGO stage					<0.001
I	317 (64.7)	334 (71.5)	8 (8.0)	11 (33.3)	
II	20 (4.1)	31 (6.6)	2 (2.0)	1 (3.0)	
III	81 (16.7)	84 (18.0)	37 (37.0)	17 (51.5)	
IV	72 (14.7)	18 (3.9)	53 (53.0)	4 (12.1)	
Unknown	28	17	4	1	
Myometrial invasion					0.034
Less than half	256 (56.8)	223 (50.2)	36 (42.9)	13 (41.9)	
More than half	195 (43.2)	221 (49.8)	48 (57.1)	18 (58.1)	
Unknown	67	40	20	3	
Lymph nodes					<0.001
Negative	53 (70.7)	103 (81.7)	9 (29.0)	7 (46.7)	
Positive	22 (29.3)	23 (18.3)	22 (71.0)	8 (53.3)	
Not sampled	443	358	73	19	
Distant metastasis					<0.001
No	421 (81.3)	424 (87.6)	26 (25.0)	22 (64.7)	
Yes	97 (18.3)	60 (12.4)	78 (75.0)	12 (35.3)	
Unknown	0	0	0	0	
LVSI					<0.001
No	70 (35.9)	62 (27.3)	5 (9.4)	5 (27.8)	
Yes	125 (64.1)	165 (72.7)	48 (90.6)	13 (72.2)	
Unknown	323	257	51	16	

Values are presented as n (%). Percentages were calculated without missing values. RT, radiotherapy; CT, chemotherapy; RCT, radiochemotherapy; LVSI, lymphovascular space involvement.

Statistical Analysis

For descriptive statistics, the median and interquartile range (IQR) are given where appropriate. Overall survival (OS) was defined as the time until death, with a maximum of 5 years. Disease-free survival (DFS) was defined as the time until recurrence or death, with a maximum of 5 years. The chronological order of events for the patients started with surgery, followed by a pathology review and possibly adjuvant treatment. Therefore, we first analyzed the value of LND, followed by an analysis of all three types of adjuvant treatment (RT, CT, and RCT). Finally, we evaluated the value of adjuvant treatment in relation to lymph node status for cases where LND was performed. FIGO stage, presence of metastasis, myometrial invasion, and age were included in a multivariable analysis. To minimize the chance of bias, clinicopathological variables with more than 10% missing values, such as lymphovascular space invasion, were excluded from the survival analysis. The statistical analysis was performed with SPSS 22 (IBM, Chicago, IL, USA). Relations between variables were tested by χ^2 testing; the log-rank test and Cox regression analysis were used for survival analysis and the calculation of HRs. p values of 0.05 or less were considered significant.

Results

Patient Characteristics

The median age at diagnosis was 70 years (IQR 62–77). The clinicopathological characteristics are shown in Table 1. The majority (64%) of the patients was diagnosed with early-stage disease (FIGO stage 1–2). In 247 patients (21.7%), lymph nodes were removed in addition to a TAH-BSO. The median number of nodes removed was 12 (IQR 3–18; data not shown). LND was related to higher FIGO stage and age below 70 years ($p < 0.001$). In 75 of the 247 cases, the nodes were positive. When comparing LND ≤10 with LND >10, the percentage of positive nodes was not significantly higher when fewer nodes were removed (35 vs. 25%, $p = 0.106$). Patients from whom lymph nodes were removed more often received adjuvant treatment ($p < 0.001$).

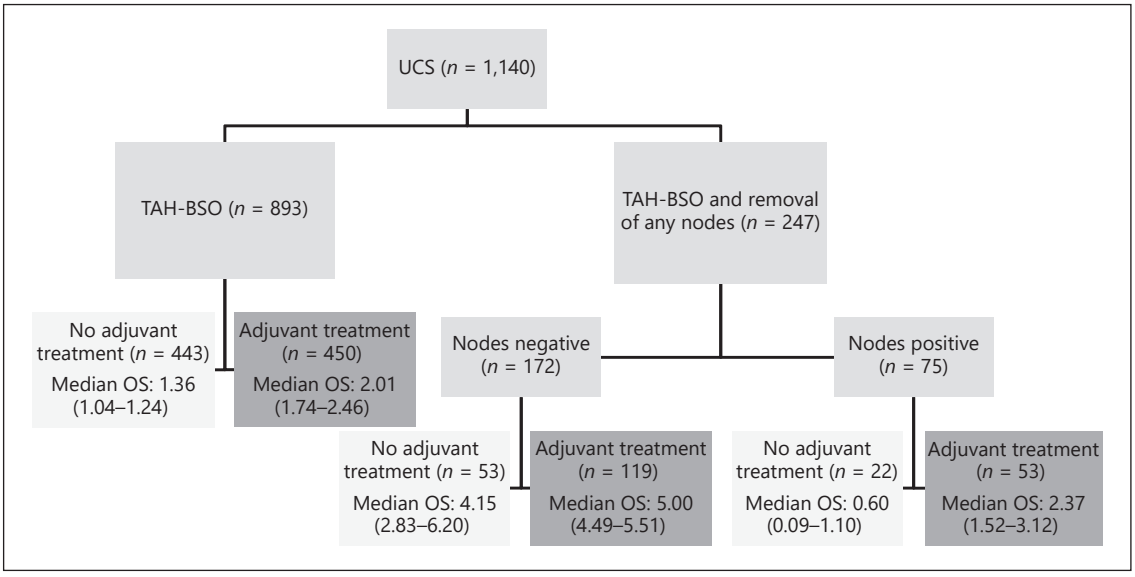


Fig. 1. Median overall survival (OS) (95% CI) in years for the 1,140 patients with uterine carcinosarcoma (UCS) according to treatment. TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Table 2 shows the clinicopathological characteristics stratified by adjuvant treatment. Of 622 patients that received adjuvant treatment, 77.8% received RT, 16.7% received CT, and 5.5% received RCT. RT consisted of external beam RT in 90.1% of the cases. Adjuvant treatment was related to age above 70 years, increased FIGO stage, myometrial invasion, lymph node status, metastasis, and lymphovascular space involvement.

Survival Analysis

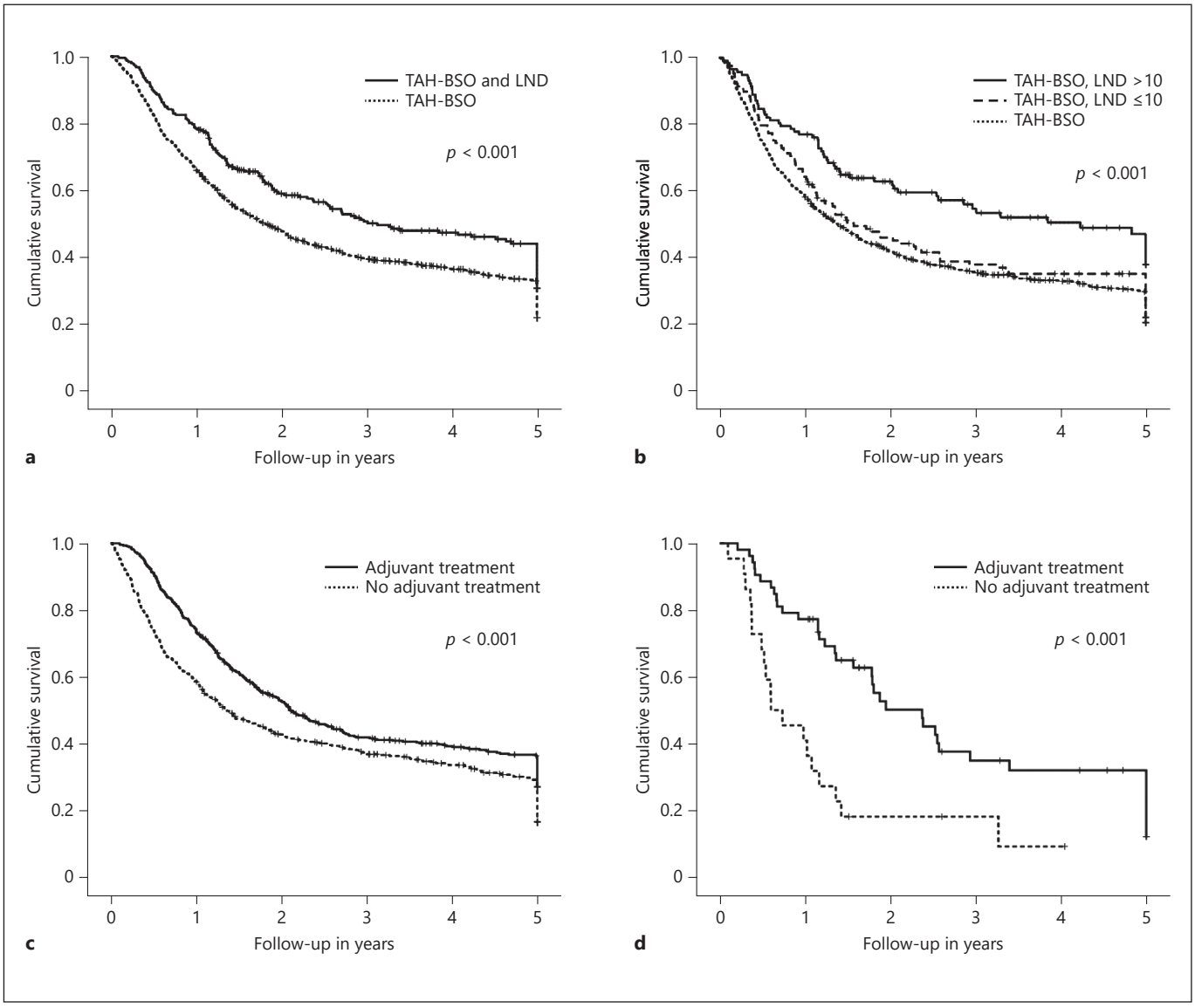
In the complete cohort of 1,140 patients, median OS was 2.03 years (95% CI 1.76–2.30) and median DFS was 1.53 years (95% CI 1.32–1.76). Histologically proven recurrence was present in 302 cases (26.5%). Distant recurrence was more common than pelvic or local recurrence (55.6 vs. 10.9 and 32.1%, respectively, $p < 0.01$; data not shown). Frequency and location of recurrence were not related to FIGO stage or age ($p > 0.05$).

Figure 1 provides a general overview of the distribution of the various treatment modalities next to median OS per subgroup. As expected, median OS was better in cases where lymph nodes were removed and turned out negative. In this group, there was no difference in median OS between patients who did and those who did not receive adjuvant treatment (4.15 years [95% CI 2.83–6.20] and 5.00 years [95% CI 4.49–5.51], respectively). When nodes were positive, median OS was much shorter, with 0.60 years (95% CI 0.09–1.10) for patients who did not receive adjuvant treatment and 2.37 years (95% CI 1.52–3.12) for patients who did receive adjuvant treatment. Median OS for patients with surgery limited to TAH-BSO was also shorter, with 1.36 years (95% CI 1.04–1.68) for patients without adjuvant treatment and 2.01 years (95% CI 1.74–2.46) for patients with adjuvant treatment. Online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000488531) shows similar results for median DFS, with a significant effect of adjuvant treatment in cases where no nodes were removed or the nodes turned out to be positive.

Univariate Survival Analysis

Figure 2 shows Kaplan-Meier curves for OS according to the extent of surgery and adjuvant treatment. LND was related to improved OS (log-rank $p < 0.001$; Fig. 2a). Figure 2b shows survival according to the extent of surgery with a distinction between LND ≤10 and LND >10. Survival with TAH-BSO and LND ≤10 was similar to survival with TAH-BSO without LND. LND >10 was related to improved survival. Since a cutoff of 10 nodes is arbitrary, we also analyzed OS for different cutoff values (removal of 8 or 12 nodes) and found similar results (data not shown).

Figure 2c zooms in on 893 cases where surgery was limited to TAH-BSO and illustrates an advantage of adjuvant treatment in this subgroup ($p < 0.001$). In univariate Cox regression analysis, RT and RCT but not CT were



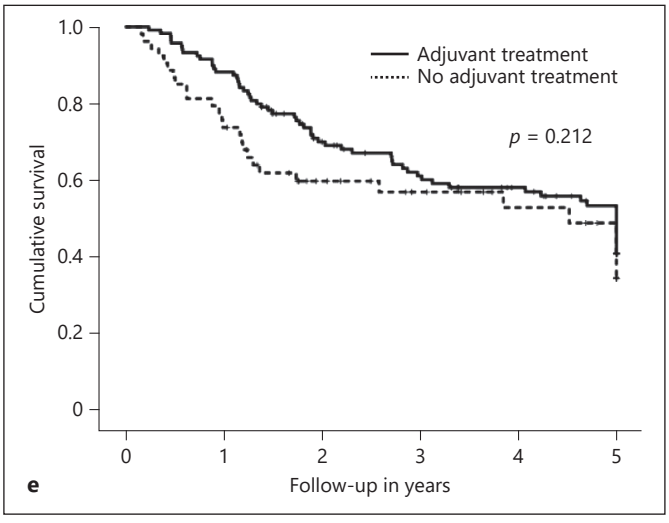


Fig. 2. Kaplan-Meier curves for overall survival (OS) according to treatment. **a** OS and extent of surgery (total abdominal hysterectomy with bilateral salpingo-oophorectomy [TAH-BSO] vs. TAH-BSO with lymph node dissection [LND]) (n = 1,140). **b** OS and extent of surgery (TAH-BSO vs. TAH-BSO and removal of 10 nodes or less [LND ≤10] or removal of more than 10 nodes [LND >10]) (n = 1,140). **c** OS and adjuvant treatment for surgery limited to TAH-BSO (n = 893). **d** OS and adjuvant therapy for patients with LND, nodes positive (n = 75). **e** OS and adjuvant treatment for patients with LND, nodes negative (n = 172).

Table 3. Multivariable Cox regression analysis of overall survival according to extent of surgery, adjuvant therapy, and clinicopathological variables (n = 1,140)

	HR (95% CI)	p value
Extent of surgery		
TAH-BSO	reference	
TAH-BSO and LND ≤10	0.83 (0.65–1.05)	0.124
TAH-BSO and LND >10	0.67 (0.50–0.89)	0.006
Adjuvant therapy		
None	reference	
Radiotherapy	0.65 (0.55–0.77)	<0.001
Chemotherapy	0.66 (0.49–0.89)	0.006
Chemoradiation	0.25 (0.14–0.47)	<0.001
Age		
<70 years	reference	
≥70 years	1.58 (1.35–1.84)	<0.001
FIGO stage		
I	reference	
II	1.60 (1.13–2.29)	0.009
III	2.17 (1.76–2.68)	<0.001
IV	2.48 (1.69–3.65)	<0.001
Myometrial invasion		
Less than half	reference	
More than half	1.61 (1.36–1.90)	<0.001
Distant metastasis		
No	reference	
Yes	1.47 (0.99–2.18)	0.054

TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy; LND ≤10, lymph node dissection of 10 nodes or less; LND >10, lymph node dissection of more than 10 nodes.

related to improved OS (HR 0.64 [95% CI 0.55–0.75], HR 0.32 [95% CI 0.18–0.57], and HR 1.20 [95% CI 0.95–1.52], respectively, $p < 0.001$). On the other hand, when LND was performed and the nodes were positive, adjuvant treatment was also related to improved survival (log-rank $p < 0.001$; Fig. 2d). In the cases where the nodes were negative, there was no relation between adjuvant treatment and survival.

Of the clinicopathological variables with less than 10% missing values, lower FIGO stage (HR 1.47, 95% CI 1.39–1.57), less myometrial invasion (HR 1.86, 95% CI 1.69–2.16), no distant metastasis (HR 2.69, 95% CI 2.19–3.31), and age below 70 years (HR 2.16, 95% CI 1.59–2.11) were related to improved OS.

Multivariable Analysis

Table 3 shows the results of the multivariable analysis of OS for the 1,140 patients who received TAH-BSO with or without LND. Corrected for adjuvant therapy, FIGO stage, age below/above 70 years, myometrial invasion, and distant metastasis, LND >10 was an independent predictor of OS (HR 0.65, 95% CI 0.48–0.87). LND ≤10 was not related to OS (HR 0.83, 95% CI 0.65–1.05). Adjuvant therapy was also related to improved OS. RT and CT had similar HRs of 0.64 (95% CI 0.54–0.75) and 0.65 (95% CI 0.48–0.88), respectively. RCT had an HR of 0.25 (95% CI 0.13–0.46). The results were similar for DFS, with LND > 10 and adjuvant treatment related to improved DFS (data not shown).

Table 4 shows the subgroup analyses stratified by lymph node status. In accordance with the findings from the univariate analysis, adjuvant treatment was not related to OS when the nodes were negative. However, when the nodes were positive, adjuvant treatment was related to improved OS, with an HR of 0.17 (95% CI 0.07–0.39) for RT, an HR of 0.40 (95% CI 0.19–0.84) for CT, and an HR of 0.04 (95% CI 0.03–0.18) for RCT.

Discussion

In this large cohort study, LND was related to improved survival specifically in those cases where more than 10 nodes were removed. Adjuvant therapy improves survival when LND is omitted, with a similar effect for RT and CT. Possibly, the combination of RCT had a cumulative effect. When LND was performed, adjuvant treatment was related to improved survival when the nodes were positive but not when they were negative.

The finding that removal of lymph nodes improves survival is in accordance with previous publications [2, 5, 6, 10]. In the largest study, Nemani et al. [2] evaluated the role of lymph node dissection in 1,855 patients with stage I–III UCS using data from the Surveillance, Epidemiology, and End Results (SEER) program in the USA. In the 57% of cases where lymph nodes were removed, OS was improved. However, there was no relation between the number of nodes removed and survival when a cutoff of 12 nodes was used. This is different from our findings, since we describe different outcomes for LND ≤10 and LND >10. This may be due to case selection, as lymph nodes were removed in fewer cases (22%) in our cohort. In our cohort, the nodes were positive in 30% of the cases, whereas they were positive in only 14% in the SEER cohort. Temkin et al. [9] described 47 cases of UCS where at least 1 node was removed, and they also found improved survival in cases where more than 11 nodes were

Table 4. Multivariable Cox regression analysis of overall survival after TAH-BSO plus LND stratified by lymph node status (n = 273)

	TAH-BSO + LND, nodes negative (n = 129)		TAH-BSO + LND, nodes positive (n = 75)	
	HR (95% CI)	p value	HR (95% CI)	p value
Adjuvant therapy				
None	reference		reference	
Radiotherapy	0.65 (0.39–1.09)	0.100	0.17 (0.07–0.39)	<0.001
Chemotherapy	1.47 (0.42–5.10)	0.544	0.40 (0.19–0.84)	0.015
Radiochemotherapy	0.68 (0.20–2.34)	0.545	0.04 (0.03–0.18)	<0.001
Age				
<70 years	reference		reference	
≥70 years	1.72 (1.09–2.72)	0.021	2.02 (1.06–3.85)	0.032
FIGO stage				
I	reference		–	
II	1.59 (0.56–4.48)	0.383	–	
III	1.70 (0.83–3.46)	0.145	reference	
IV	1.30 (0.17–10.02)	0.798	1.22 (0.41–3.64)	0.722
Myometrial invasion				
Less than half	reference		reference	
More than half	0.99 (0.61–1.59)	0.955	1.37 (0.64–2.95)	0.417
Metastasis				
No	reference		reference	
Yes	1.18 (0.06–21.94)	0.914	1.55 (0.50–4.80)	0.446

TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy; LND, lymphadenectomy with removal of any number of nodes.

removed. The improved survival in the LND >10 subgroup could be explained by a higher probability of removal of all metastatic nodes when more than 10 nodes are removed. Another explanation could be that these patients are cared for by more specialized surgeons or cancer centers.

When LND is performed, adjuvant treatment may improve survival when the nodes are positive but not when the nodes are negative. Apparently, cases with positive nodes are at an increased risk of recurrence despite LND. This finding corresponds to the recent findings of the PORTEC-3 trial, which investigated the benefit of adjuvant treatment for other histologic types of high-risk endometrial cancer [16]. A clinical consequence could be to omit adjuvant treatment when nodes are negative. Preferably, these findings should be confirmed in a randomized trial of adjuvant treatment for UCS. Nonetheless, it is an argument in favor of LND for staging purposes at this point. As to the type of adjuvant treatment, Wright et al. [12] evaluated adjuvant RT in 1,819 patients with early-stage UCS also from the SEER database. In accordance with our findings, adjuvant RT improved OS, but only in cases where LND had been omitted. In another study including 2,461 cases from the SEER database, adjuvant treatment was related to improved survival for patients with advanced disease [11]. This may be because of lymph node metastasis in advanced disease, since we found improved survival among patients with positive nodes. The relation remained significant in a multivariate analysis including FIGO stage.

A few small studies have described a possible survival advantage with adjuvant CT similar to that with RT. In a small retrospective study on 111 patients with early-stage UCS, CT was related to improved survival [13]. Survival was similar with CT and RT and further improved with RCT. In an even smaller sample of 49 cases, RCT had a positive effect on survival, similar to that of RT alone [17]. In our large retrospective cohort, we also found a survival advantage for CT when LND was omitted or the nodes were positive. The HRs for CT and RT are within a similar range, in accordance with a randomized study comparing adjuvant RT with CT [18]. That study randomized

232 patients with stage I–IV UCS and found no significant difference in survival.

As with other retrospective studies, our study has limitations related to the study design. For example, 25.1% of the patients who received LND had FIGO stage IIIc cancer compared to 1.1% of the patients without LND ($p < 0.001$). Likely, this is because of upstaging of patients who received LND, which complicates the comparison of these two groups. Additionally, the relationship between adjuvant treatment and survival in this cohort is similar for RT and CT. However, the patient characteristics of these two groups are different. For example, the type of adjuvant therapy was related to FIGO stage (Table 2). Patients presenting with early-stage disease more often received RT, whereas CT was more common for patients presenting with advanced-stage disease. Another issue is the cutoff value of 10 nodes to differentiate between lymph node sampling and debulking. Assuming that LND improves outcome, it is likely that this effect is related to the number of nodes removed. We set the cutoff at 10 nodes, but we are aware that this is arbitrary. As mentioned above, we found a similar relation to survival when using a cutoff of 8 or 12 nodes.

A strength of this study is the use of a large cohort of patients, including information on both RT and CT. In addition, the use of two national registries as a source of our data improves the reliability of these data.

In conclusion, we describe a survival advantage for LND in patients with UCS. In our cohort, the survival benefit was limited to cases where more than 10 nodes were removed (LND >10). Adjuvant therapy improved survival when surgery was limited to TAH-BSO. When LND was performed, the effect of adjuvant treatment was limited, although adjuvant treatment was related to improved survival when the nodes were positive. Considering the type of adjuvant therapy, survival with RT and CT was similar, whereas RCT may have further improved survival. Our findings can be used in counseling of patients with newly diagnosed UCS, for whom LND can improve survival, especially when more than 10 nodes are removed. It remains unclear whether adjuvant treatment improves survival when the lymph nodes are negative. When the nodes are positive, adjuvant treatment is likely to further improve survival.

Disclosure Statement

The authors declare that they have no conflict of interest.

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