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Original Research

Bilateral salpingo-oophorectomy in patients with uterine sarcoma: a multi-centre retrospective analysis

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Objective: The aim of this study is to assess the effect of bilateral salpingo-oophorectomy (BSO) in patients with uterine sarcoma on recurrence rate and overall survival. *Methods*: Medical records of patients diagnosed with uterine sarcoma were reviewed. Survival rates and recurrence rates of patients with BSO and with ovarian preservation (OP) were calculated. *Results*: Fifty-one patients were included. Hysterectomy with BSO was performed in 21 patients (41%). Hysterectomy only, with OP was performed in 18 cases (35%). In 8 cases (17%) in addition to hysterectomy with BSO, a lymphadenectomy or debulking surgery was performed. The five-year overall survival rate (OS) for patients with OP was 78% and for patients with BSO only it was 52%. A Kaplan-Meier analysis showed a survival difference between patients with OP and patients with BSO, in favour of patients who had OP (log-rank $P = 0.014$). In the group of patients with FIGO stage 1&2, again a survival benefit was seen for patients who had OP (log-rank $P = 0.020$). The recurrence rate for patients with OP was 33% and 48% for patients with BSO ($P = 0.366$). The five-year OS for all patients with uterine sarcoma was 57% with a five-year recurrence of 33%. *Conclusion*: There is no significant decreased survival of patients who had OP surgery compared to patients who had BSO in case of uterine sarcoma. Primary ovarian sparing surgery can be considered for specific patients with uterine sarcoma.

Keywords

Uterine sarcoma; Treatment; Bilateral salpingo-oophorectomy; Survival; Recurrence

1. Introduction

Uterine sarcomas account for 4% of all the uterine malignancies in the Netherlands [1]. They can be subdivided into leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), undifferentiated endometrial sarcoma (UES) and adenosarcoma (AS). Mainly retrospective studies have been conducted due to the low incidence and histological diversity of sarcomas. Therefore, there is no evidence for the optimal treatment of patients with uterine sarcoma. Currently the mainstay of treatment for uterine sarcomas is surgical resection. The most commonly performed surgery includes hysterectomy, bilateral salpingo-oophorectomy (BSO), and debulking surgery if the tumor is present outside the uterus [2, 3]. Ovaries are frequently removed because of the perceived risk of metastases and to reduce the presumed risk of tumor progression or recurrence due to stimulation by endogeneous steroid hormones [2, 3]. The expression of hormone receptors differs between the subtypes of uterine sarcoma, in which endometrial stromal sarcoma have the highest level of hormone receptor expression (70–80%) [4]. The added value of BSO remains controversial in all subtypes of uterine sarcoma since there are studies that show no difference in survival between patients with and without BSO [2, 5]. Chemotherapy (CT), hormone therapy (HT) and radiotherapy (RT) have all been used as adjuvant therapy and as primary treatment for inoperable patients although evidence of efficacy is lacking [2, 3]. The overall survival for patients with uterine sarcoma is poor, with a five-year survival between 36% and 51% [6–8]. This study is a retrospective study describing the survival and recurrence of patients diagnosed with uterine sarcoma, with special focus on BSO, in the Netherlands Comprehensive Cancer Centre South Region.

2. Materials and methods

2.1 Study design and population

This study is designed as a multicentre, retrospective single-cohort study. Medical ethical approval was granted for this study. A computerised database was used to identify patients diagnosed with uterine sarcoma from the Netherlands Comprehensive Cancer Centre South Region. This region includes eight district hospitals. All patients with a histologically verified uterine sarcoma, treated between January 2004 and December 2011, were included. Patients diagnosed with a carcinosarcoma (CS) were excluded from the study since CS has been reclassified as a dedifferentiated or metaplastic

form of endometrial carcinoma [3]. Medical records were reviewed for patient characteristics, clinical and pathological data, treatment data and recurrence and survival data. A random sample of patients was chosen for pathologic review of their slides. Tumor stage was corrected according to the 2009 FIGO criteria for uterine sarcoma [9], based on surgical and pathological findings. The differentiation between ESS and UES and between AS with and without sarcomatous overgrowth (SO), was retrospectively assigned. UES was defined according to the WHO classification 2003 [10]. AS with SO was defined as the presence of pure sarcoma occupying at least 25% of the tumor [11]. LMS was also defined according the WHO classification 2003.

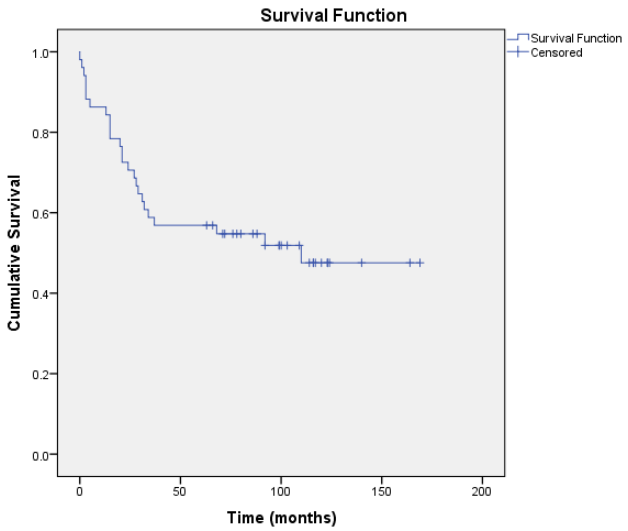

Fig. 1. Kaplan-Meier curves of overall survival of all patients.

2.2 Statistical analysis

The primary outcome is overall survival (OS). Secondary outcome is recurrence rate. Data was censored at January 2017. Due to the small groups of histological subtypes, medians with interquartile range (IQR) are presented. Five-year overall survival rates were calculated following generation of Kaplan-Meier curves. For the smaller groups, survival rates were calculated by cross-tabulation. Five-year recurrence rates were also calculated by cross-tabulation. Comparison of survival curves were made with the Log Rank test. Since we have a minimal of 5 year follow up of every living patient, univariate comparisons of percentages between groups were calculated using the χ^2 test or the Fisher exact test in cases of small numbers. A P value less than 0.05 was considered statistically significant. The data was analysed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics, version 24.0).

3. Results

3.1 Patient demographics

Over the study period, 114 patients were identified with uterine sarcoma. Sixty-three patients with CS were excluded and described elsewhere [12]. Fifty-one patients were included of which 21 patients were diagnosed with LMS (41%), 16 patients with ESS (31%), nine patients with UES (18%) and five patients with AS (10%) (Table 1). Of the five patients with AS, in only two cases either the presence or the absence of SO was mentioned in the pathology report. One patient was diagnosed with AS and SO, she had FIGO stage I disease and was alive at the end of the study. The other patient had AS without SO, FIGO stage I disease. She was also alive at the end of the study. Since the presence or absence of SO was unknown in the other 3 patients, from now all patients with AS are described as one group. Due to the small groups of histological subtype, results will be described for all histological subtypes combined as one group. Results from the histological subtypes separately, are described in Supplemental Digital Content Table 1 and 2 and depicted in Supplemental Digital Content Fig. 1.

Patients characteristics are described in Table 1. The median age at time of treatment was 54 years. The median follow-up period of the surviving patients was 102 months. Abnormal vaginal bleeding was the most frequent presenting symptom. Other reported symptoms were abdominal pain and abdominal mass. Most of the patients were postmenopausal. For 24 patients the initial tumor size was known with a median size of 6.9 cm. According to the FIGO staging 34 patients were stage I (67%), two patients stage II (4%), six patients stage III (12%), and seven patients stage IV (13%). For two patients, reclassification of FIGO stage was not possible because of incomplete data. Pathological slides from ten patients (20%) were randomly reassessed by the pathologist. All these reviews were corresponding with the primary pathological diagnosis.

3.2 Treatment modalities

Total hysterectomy with only BSO was performed in 41% of the patients (Table 1). In one case both ovaries were already removed during previous surgery. Hysterectomy with ovarian preservation (OP) was conducted in 35% of the cases. Of the patients with OP, in one case unilateral BSO was conducted. Other types of surgery were hysterectomy with BSO and lymphadenectomy (8%) and debulking surgery (8%). Four percent of the patients underwent CT and RT as primary therapy. Four percent of the patients were not treated at all because of their general condition and stage of disease, both were diagnosed with UES, FIGO stage IV. When removed, lymph nodes turned out to be tumor free (Table 1). Fifty-five percent of the patients were treated with surgery only and 37% of the patients also received postoperative adjuvant therapy. RT was the most frequently used adjuvant treatment (24%) (Table 1). Of the patients who had OP 17% received postoperative RT, of the patients that had BSO only 38% received postoperative RT.

3.3 Survival

Survival rates are described in Table 2. The five-year OS was 57% (95% confidence interval (CI) 43–71%) (See Fig. 1).

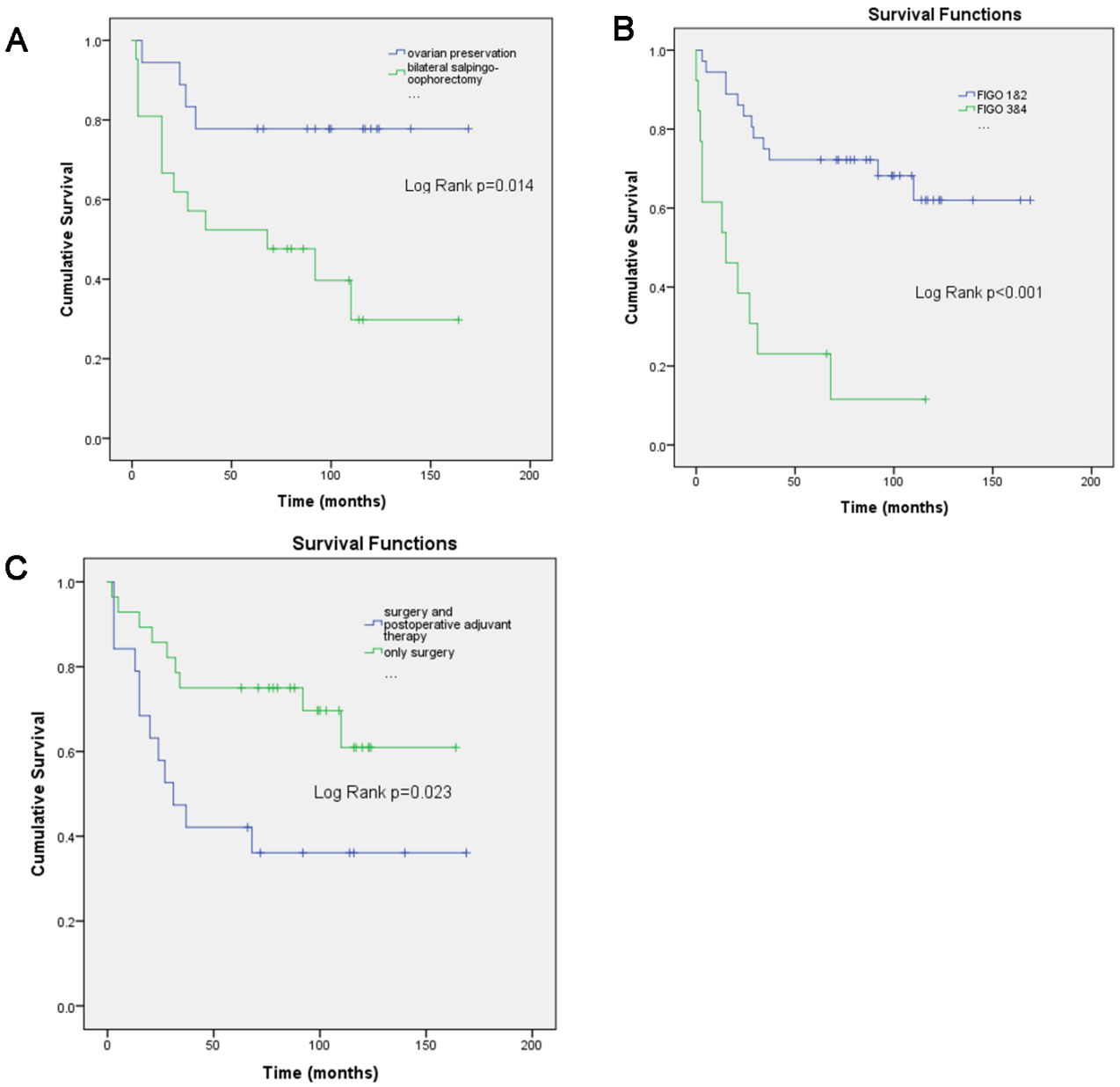

Fig. 2. Kaplan-Meier curves of overall survival. (A) Ovarian preservation vs. bilateral salpingo-oophorectomy (Log Rank $P = 0.014$). (B) FIGO stage 1&2 vs. FIGO stage 3&4 disease (Log Rank $P < 0.001$). (C) Surgery and postoperative adjuvant therapy vs. only surgery (Log Rank $P = 0.023$).

The median survival was 71 months. Five-year OS for patients who had OP and patients who had BSO were 78% (95% CI 58–97%) vs. 52% (95% CI 31–74%). A Kaplan-Meier analysis showed a long-term survival difference between patients who had OP and patients who had BSO, in favour of patients who had OP (log-rank $P = 0.014$) (See Fig. 2A). If patients who had OP and RT are considered as if they had BSO due to the loss of endogenous function, survival rates are similar (five-year OS of 80% (95% CI 54–94%) vs. 54% (95% CI 34–75%); Kaplan-Meier log-rank $P = 0.027$). In the group of patients with ESS, which in general has the highest expression of hormone receptors, no significant survival difference was seen between patients who had OP and who had BSO (100% (95% CI 55–100%) vs. 50% (95% CI 18–81%); Fisher exact $P = 0.182$) (See Supplemental Digital Content Table 2). In the group of patients with FIGO stage 1&2 disease, improved survival was seen for patients who had OP compared to patients who had BSO (log-rank $P = 0.020$) (See Fig. 3A). Patients with FIGO stage 1&2 had a better survival compared to patients with FIGO stage 3&4 (log-rank $P < 0.001$) (See Fig. 2B). Patients who were treated only surgically had an improved survival compared to patients who also received postoperative adjuvant therapy (log-rank $P = 0.023$) (See Fig. 2C). In the group of patients with FIGO stage 1&2 disease, no difference in survival was seen between patients who had only surgery and patients who had postoperative adjuvant ther-

Table 1. Characteristics and symptoms of patients with uterine sarcoma.

	All Uterine sarcoma (N = 51)	OP (N = 18)	BSO (N = 21)	Other (N = 12)
Median age (years) (IQR)	54 (46–65)	49 (45–53)	62 (54–72)	55 (48–72)
Histological subtype				
LMS	21 (41%)	11 (61%)	8 (38%)	2 (17%)
ESS	16 (31%)	6 (33%)	6 (29%)	4 (33%)
UES	9 (18%)	1 (5%)	4 (19%)	4 (33%)
AS[a]	5 (10%)	0	3 (14%)	2 (17%)
Symptoms				
Vaginal bleeding	31 (61%)	9 (50%)	15 (71%)	7 (58%)
Mass	4 (8%)	1 (5%)	1 (5%)	2 (17%)
Pain	7 (13%)	3 (17%)	3 (14%)	1 (8%)
No symptoms	3 (6%)	3 (17%)	0	0
Unknown	6 (12%)	2 (11%)	2 (10%)	2 (17%)
Parity				
Nulli	5 (10%)	1 (5%)	2 (10%)	2 (17%)
Multi	30 (59%)	10 (56%)	15 (71%)	5 (42%)
Unknown	16 (31%)	7 (38%)	4 (19%)	5 (42%)
Postmenopausal				
Yes	28 (55%)	4 (22%)	17 (81%)	7 (58%)
No	23 (45%)	14 (78%)	4 (19%)	5 (42%)
Type of recurrence				
No recurrence	30 (58%)	11 (61%)	11 (52%)	8 (67%)
Lung	6 (12%)	2 (11%)	4 (19%)	0
Abdominal	4 (8%)	1 (5%)	2 (10%)	1 (8%)
Local	5 (10%)	3 (17%)	2 (10%)	0
Lymph node	2 (4%)	1 (5%)	1 (5%)	0
Other	4 (8%)	0	1 (5%)	3 (25%)
Median tumor size (IQR)[b]	6.9 cm (4.1–10.6 cm)	8 cm (5.4–10.3 cm)	4.7 cm (3.1–8.8 cm)	13 (4.5–13)
FIGO stage				
I	34 (67%)	15 (83%)	13 (62%)	6 (50%)
II	2 (4%)	0	2 (10%)	0
III	6 (12%)	2 (11%)	3 (14%)	1 (8%)
IV	7 (13%)	0	3 (14%)	4 (33%)
Unknown	2 (4%)	1 (5%)	0	1 (8%)
Positive lymph nodes	-	-	-	0/4
Adjuvant Therapy				
No adjuvant	30 (59%)	12 (67%)	12 (57%)	6 (50%)
RT	11 (22%)	3 (17%)	7 (33%)	1 (8%)
CT	4 (9%)	1 (5%)	1 (5%)	2 (17%)
CT/RT	1 (2%)	0	1 (5%)	0
HT	3 (6%)	2 (11%)	0	1 (8%)
Primary Therapy				
RT	1 (2%)	0	0	1 (8%)
CT	1 (2%)	0	0	1 (8%)

LMS, leiomyosarcoma; ESS, endometrial stromal sarcoma; UES, undifferentiated endometrial sarcoma; AS, adenosarcoma; OP, ovarian preservation; BSO, bilateral salpingo-oophorectomy; IQR, interquartile range; CT, chemotherapy; HT, hormone therapy; RT, radiotherapy.
[a]One patient with sarcomatous overgrowth (SO) one patient without SO. 3 patients SO status unknown. [b]Tumor size know of 24 patients.

apy (log-rank 0.308) (See Fig. 3B). Due to small numbers, different survival rates of patients with FIGO stage 3&4 disease were not calculated.

3.4 Recurrence

Recurrence rates are described in Table 2. The five-year recurrence rate was 33% (95% CI 22–47%). The median time to recurrence was 13 months. The most frequently affected metastatic site was the lungs (Table 1). For patients who had OP and those who had BSO, no difference was seen in the five-year recurrence rate (χ^2 $P = 0.366$). When patients who had OP and RT are considered as if they had BSO, still no difference was seen in the five-year recurrence rate (χ^2 $P = 0.440$). Similarly, in the group of patients with ESS no dif-

Table 2. Overall 5-year survival rates and overall 5-year recurrence rate for all patients.

Histology	Alive at 5 years FU (%) (95% CI)	Median survival in months (IQR)	Recurrence rate at 5 years FU (%) (95% CI)	Median time to recurrence in months (IQR)
All	29/51 (57%) (43–71%)	71 (21–109)	17/51 (33%) (22–47%)	13 (4–37)
Figo stage I&II	26/36 (72%) (57–87%)	90 (35–116)	12/36 (33%) (20–50%)	20 (6–63)
Figo stage III&IV	3/13 (23%) (8–51%)	15 (3–49)	5/13 (38%) (18–65%)	4 (3–10)
Surgery without adjuvant	21/28 (75%) (59–91%)	90 (41–115)	8/28 (29%) (15–47%)	16 (4–54)
Surgery with adjuvant	8/19 (42%) (20–65%)	31 (15–92)	8/19 (42%) (23–64%)	10 (3–34)
No surgery	0/4 (0%)	11 (0–27)	1/4 (25%) (3–71%)	22
Hysterectomy	14/18 (78%) (58–97%)	99 (55–121)	6/18 (33%) (19–59%)	8 (2–63)
Hysterectomy + BSO	11/21 (52%) (31–74%)	68 (15–101)	10/21 (48%) (28–68%)	13 (4–22)
Hysterectomy without RT	12/15 (80%) (54–94%)	99 (63–117)	5/15 (33%) (15–59%)	4 (2–30)
Hysterectomy + BSO and hysterectomy + RT	13/24 (54%) (34–75%)	70 (15–110)	11/24 (46%) (28–65%)	14 (4–36)
Hysterectomy + BSO + lymphadenectomy	3/4 (75%) (31–118%)	90 (45–118)	0/4 (0%)	
Debulking	1/4 (25%) (18–68%)	26 (15–62)	0/4 (0%)	

BSO, bilateral salpingo-oophorectomy; RT, radiotherapy; IQR, interquartile range; CI, confidence interval; FU, follow up.

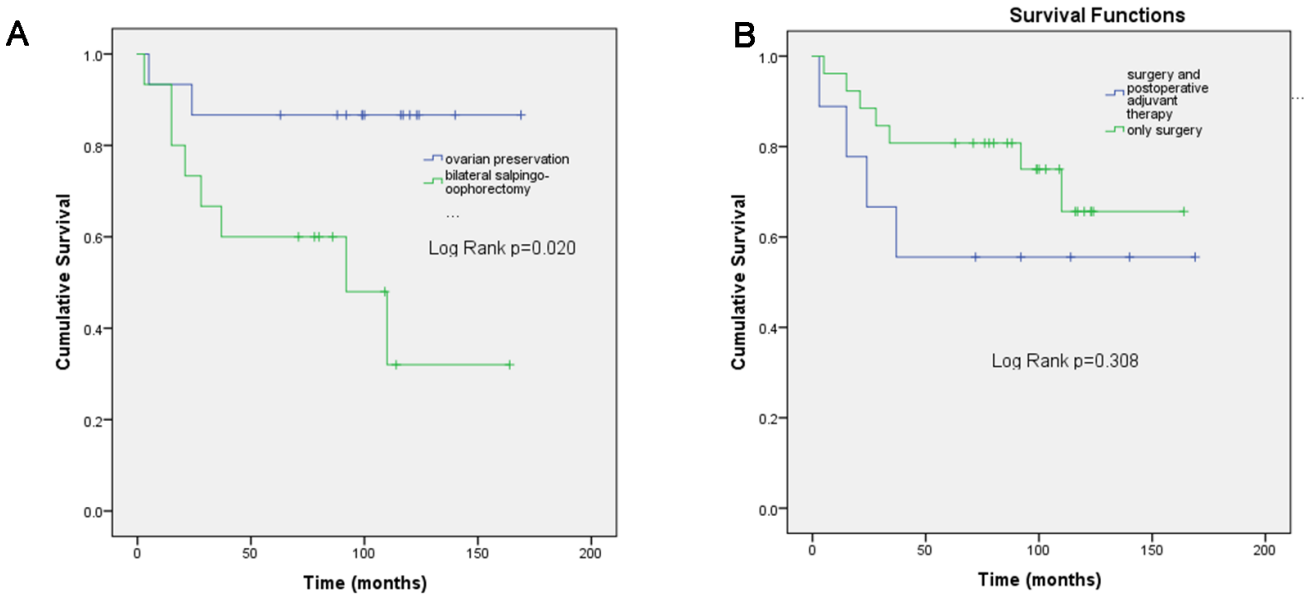

Fig. 3. Kaplan-Meier curves overall survival in patients with FIGO stage 1&2 disease. (A) Ovarian preservation vs. bilateral salpingo-oophorectomy (Log Rank $P = 0.020$). (B) Surgery and postoperative adjuvant therapy vs. only surgery (Log Rank $P = 0.308$).

ference was seen in the five-year recurrence rate between OP and BSO (Fisher exact $P = 0.567$) (See Supplemental Digital Content Table 2).

No difference was seen in the five-year recurrence rate for patients diagnosed with FIGO 1&2 disease and those diagnosed with FIGO 3&4 disease (χ^2 $P = 0.746$). There was no difference between the five-year recurrence rate for patients who were treated only surgically and those who also received postoperative adjuvant therapy (χ^2 $P = 0.337$).

4. Discussion

In this study 51 patients with uterine sarcoma were included. Our analysis shows that in univariate analysis OP was associated with better survival compared to patients who had BSO, but not with a lower recurrence rate.

Current evidence about the effect of BSO in patients with uterine sarcoma is inconclusive. Our analysis suggest that OP may be associated with better survival. Since multivariable analysis was not possible because of the small number of patients, no recommendation can be made based on this analysis. No hypothesis has thus far been proposed to explain that OP results in a better survival in comparison to BSO. The most logical explanation is selection bias for the indication to perform an ovarian sparing surgery or to perform hysterectomy with BSO. As shown in Table 1, in the group of patients who had BSO, more patients with UES and more patients with advanced disease are included, which have a poor survival.

Studies that have investigated survival differences between OP and BSO for patients with LMS, ESS and AS are summarized in Supplemental Digital Content Table 3 [5, 13–23]. No significant improved survival is found for either op-

tion, but it seems that there is an association of improved survival after OP. BSO is almost always performed in patients with UES due to its aggressive behaviour [24, 25]. Only one study described survival of patients with UES who had OP in which no difference was seen in survival compared to patients with BSO [22]. Important to note is that not all studies corrected for confounding factors like RT or postmenopausal status since in both cases the ovarian function is lost. As far as we know, there are no studies which investigated the effect of BSO and OP in relation to hormone receptor expression in patients with uterine sarcoma. Consequently, it remains to be seen if BSO will have a beneficial effect on the survival of patients with uterine sarcoma with an active hormone receptor signalling transduction pathway.

Overall, the observation that there is no difference in survival can help to decide whether or not to perform a second surgery to remove the ovaries in patients who underwent a hysterectomy because of initial suspicion of benign disease which later turned out to be an uterine sarcoma. Especially in cases of LMS and ESS, but also for specific patients, like young women with low stage uterine sarcoma, primary and intentional OP surgery can be considered.

Our study also suggests that postoperative adjuvant treatment is not associated with improved survival. Again, since multivariate analysis was not possible, no clear conclusions can be drawn. Previous reports show that there may be some benefit of postoperative adjuvant treatment depending on the histological subtype and type of adjuvant treatment. Improved survival after postoperative RT is reported in cases of LMS and UES [25–28]. CT is not commonly used as postoperative adjuvant treatment for a primary tumor. Increased survival after CT has only been reported in cases of UES [28]. Reports on HT in patients with ESS and LMS describe no significant improved survival [18, 28–30]. Conversely, a meta-analysis of *Cui et al.* shows that RT reduces the risk of recurrence [31]. Based on our results and results from previous studies, there is limited place for postoperative adjuvant therapy in patients with uterine sarcoma.

The five-year overall survival in our study was 57%, with a five-year recurrence rate of 33%. Remarkable is the low recurrence rate. A possible explanation is that patients died of progression of the primary tumor rather than recurrent disease. This also explains the low incidence of recurrence in patients with FIGO stage 3&4 disease. Only a few other studies described survival and recurrence rates of patients with uterine sarcoma excluding patients with CS. In the study of *Boll et al.* and *Pietzner et al.* a five-year relative survival of 49% and 53% respectively, were seen [1, 32]. Two studies described a recurrence rate of 29% and 43% during the whole study period [33, 34]. The most frequent recurrence-site is the lungs, which is comparable with our study.

A strong point of our study is that we reviewed the clinical practice and outcomes of uterine sarcoma, excluding patients with CS, with an extended follow-up period. Also the latest FIGO staging and definitions were used. There are limitations as well. Only a random sample of pathology slides are reassessed. Since we could only perform the statistical analysis on the entire population due to the small sample seize, this had no consequences. The expression of hormone receptors is not known for all patients, so subanalysis based on hormone receptor status was not possible. The retrospective methodology produces incomplete and not standardized data. Due to the small sample size, multivariate analysis was not possible. Also due to the small sample size, analysis could only be made for the whole study population and not for the histological subgroups. A well powered randomized controlled trial would give definite answers on the best treatment options for patients with uterine sarcoma. Due to the low incidence of the tumor, effective accrual for such a trial seems to be unlikely.

In conclusion, there is no significant decreased survival of patients who had ovarian sparing surgery compared to patients who had bilateral salpingo-oophorectomy in case of uterine sarcoma. Primary ovarian sparing surgery can be considered for specific patients with uterine sarcoma.

Author contributions

GWJvR, CSB and JMJP contributed to the design, planning and implementation of the study. Data was collected by GWJvR, CSB, JMJP and EAB. AAMvdW reassessed the pathological slides. GWJvR, CSB, RLMB and SH contributed to analysis of the results. GWJvR took the lead in writing the manuscript. All authors provided critical feedback and helped shape the manuscript. JMJP supervised the study.

Ethics approval and consent to participate

The study protocol was revised and approved by the ethics committee of Brabant (Nw 2015-36). Since the study is a retrospective records study, no informed consent of the subjects was deemed necessary by this ethics committee of Brabant.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo.2021.02.2259.

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