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Uterine serous carcinoma: a historic evaluation of therapy

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Summary

Objective: Uterine serous carcinoma (USC) is an aggressive, histological subtype of endometrial cancer with a poor prognosis. This study evaluates the additional effect of staging surgery above total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) on the use of adjuvant therapy and subsequent survival outcomes in clinical early-stage USC patients. *Materials and Methods:* This retrospective cohort study includes 75 women treated for clinical early-stage USC. *Results:* In 33 (44%) clinical early-stage patients surgical staging was performed and 15 patients (45%) proved to have lymphatic or abdominal metastasis. Use of adjuvant therapy was similar in patients, both staged with no metastasis (n=18) and patients who underwent TAH and BSO only (n=42, $p = 0.17$). No significant survival difference was found between surgically staged and TAH+BSO patients. *Conclusions:* Surgical staging proved to be important to determine stage of disease and hence prognosis. Surgical staging did not lead to selective avoidance of adjuvant therapy in patients with no metastasis.

Key words: Uterine serous carcinoma; Surgical staging; TAH; BSO.

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the Western world [1-3]. In the Netherlands 1,900 women are diagnosed with endometrial cancer annually, while 380 women die as a result of this disease [4]. Uterine serous carcinoma (USC) is a histopathological subtype of endometrial cancer found in 10% of the women with endometrial cancer. USC is considered a high-grade carcinoma by definition and is responsible for 40% of the deaths, due to its aggressive behavior with early spread to the peritoneal cavity and lymph nodes [5]. Women with endometrial cancer are primarily treated with surgery, i.e. total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO). Given the aggressive nature of USC, surgical staging has become standard in clinical early-stage USC patients over the last decade [6]. This is similar to the surgery performed in clinical early stage ovarian serous carcinoma (OSC) as these two tumor types share histological features and the same aggressive mode of spread beyond the uterus [1, 2, 7]. Surgical staging includes TAH, BSO, washings and biopsies from the peritoneum, omentectomy, pelvic lymphadenectomy, and para-aortic lymphadenectomy or sampling [2, 8, 9]. A limited number of retrospective studies found that USC patients have a survival benefit of paclitaxel-platinum chemotherapy [10-13]. Studies investigating the effects of pelvic radiation in patients with all types of endometrial cancer found an improvement of relapse-free survival, but no significant effect of radiotherapy on overall survival [14-16]. Some retrospective studies show beneficial prognostic effects of radiotherapy in USC patients as well [17, 18].

Due to the relatively small incidence of USC, research regarding this histopathological subtype is scarce. Most guidelines for the treatment of USC are based on research findings in patients with OSC [19-21]. The present authors' aim was to evaluate the consequences of staging surgery in clinical early-stage USC patients on the use of adjuvant therapy and subsequent survival outcomes in a population-based retrospective study.

Materials and Methods

Patient cohort

The population of this retrospective cohort study included all clinical early-stage women diagnosed and treated for USC between 1995 and 2012 in one of the three hospitals connected to the Centre of Gynaecologic Oncology in Amsterdam: the Academic Medical Centre (AMC), the VU University Medical Centre (VUmc), and the Antoni van Leeuwenhoek hospital (AvL). USC patients were identified according to pathology reports from the national database system (PALGA). Data were collected using the electronic patient registry databases and medical files. In case of missing survival data, general practitioners were contacted.

Characteristics

Patients were defined as clinical early stage if there were no signs of peritoneal or lymphatic metastasis during physical examination and/or on imaging modalities. Clinical early-stage patients were subdivided in those receiving a TAH+BSO only and

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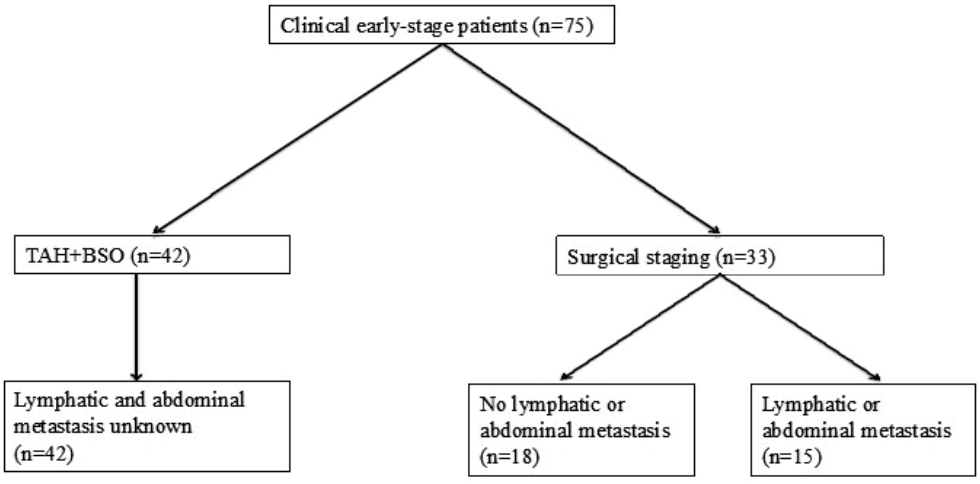

Figure 1. — Distribution of surgical therapy in the study group.

those receiving surgical staging. Patients receiving a TAH+BSO were treated before the implementation of the new Dutch protocol in October 2011 that recommends surgical staging for all USC patients. Staging surgery included TAH, BSO, washings and biopsies from the peritoneum, partial omentectomy, and pelvic/para-aortic lymphadenectomy. Tumor stage, according to FIGO 2009, was identified from pathology reports or medical reports from gynecologic oncologists. In the present study patients were divided in three groups: 1) surgically staged patients who proved to have no lymphatic or abdominal metastasis (FIGO Stage ≤3B); 2) surgically staged patients with abdominal or lymphatic metastasis (FIGO Stage ≥$IIIC_1$); 3) patients who received a TAH+BSO only, in these patients lymphatic or abdominal spread of disease is unknown (Figure 1). Use of adjuvant therapy was scored, consisting of chemotherapy (carboplatin/taxol regimens) and radiotherapy (pelvic radiation and vaginal cuff brachytherapy).

Statistics

Adjuvant therapy in different patient groups was compared using Fisher exact tests. All differences were assumed to be statistically significant if $p < 0.05$. Progression free survival (PFS) was calculated as the time from the day of primary surgery until first relapse or death. Overall survival (OS) was defined as the time from the day of primary surgery until death. In the absence of progression or death patients were censored at July 1st 2012. Both PFS and OS were estimated by the Kaplan-Meier method. Survival curves were compared with the log-rank test as well as with Cox proportional Hazard models, with and without age as a covariate. SPSS statistical software (version 20.0) and R, a language and environment for statistical computing (version 2.15.1), were used for all statistical analyses [22].

Results

Patient, stage and treatment characteristics

The distribution of surgical therapy of the 75 clinical early-stage patients included in this study is shown in figure 1. Ages ranged from 47 to 85 years with a median age of 66 years. The median follow up time was 2.5 years (range: 0.8 – 16.08). The surgical staging procedures included pelvic lymphadenectomy and in 30% of the surgically staged patients para-aortic lymphadenectomy. In two (6%) surgically staged patients, no lymphadenectomy was performed because abdominal metastasis were found during the operation, hence were staged as FIGO IV, and lymphadenectomy would not change stage or adjuvant treatment for these patients.

Table 1. — *Stages of clinical early-stage patients (n= 75).*

	Number of patients (%)		
Stages	LN negative[1]	LN positive [2]	LN unknown[3]
IA	7 (39)	0 (0)	14 (33)
IB	11 (61)	0 (0)	9 (21)
II	0 (0)	0 (0)	5 (12)
IIIA	0 (0)	0 (0)	13 (31)
IIIB	0 (0)	0 (0)	1 (2)
IIIC1	0 (0)	7 (47)	0 (0)
IIIC2	0 (0)	1 (7)	0 (0)
IVA	0 (0)	1 (7)	0 (0)
IVB	0 (0)	6 (40)	0 (0)

[1] No lymphatic or abdominal metastasis/surgical staging.
[2] Lymphatic or abdominal metastasis/surgical staging.
[3] Unknown lymphatic or abdominal metastasis/TAH+BSO.

Staging

Of the 75 clinical early-stage USC patients, 33 (44%) underwent surgical staging and 42 (56 %) a TAH+BSO. The stages of disease of all 75 clinical early-stage USC patients are listed in Table 1. Fifteen (45%) of the surgically staged patients had abdominal or lymphatic metastasis found during staging surgery.

Adjuvant therapy

Use of adjuvant therapy in surgically staged patients without metastasis did not differ significantly from patients with unknown metastasis who received a TAH+BSO only ($p = 0.17$). Surgically staged patients more often received chemotherapy and less radiotherapy, in comparison to TAH+BSO patients (Table 2, $p = 0.008$). Surgically staged

Table 2. — *Received forms of adjuvant therapy after surgical staging or a TAH+BSO.*

Adjuvant therapy	Number of patients (%)		
	Staging surgery 33 (44)	TAH+BSO 42 (56)	Total 75 (100)
No adjuvant therapy	9 (27)	13 (31)	22 (29)
Only chemotherapy	13 (39)	8 (19)	21 (28)
Only radiotherapy	4 (12)	18 (43)	22 (29)
Radio- and chemotherapy	7 (21)	3 (7)	10 (13)

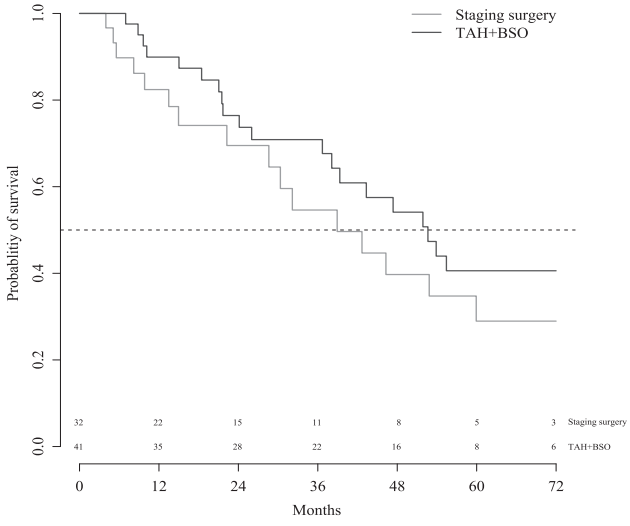

Figure 2. — Kaplan-Meier curves of overall survival by surgical therapy.

patients without metastasis did not receive significantly different adjuvant therapy compared to surgically staged patients with metastasis ($p = 0.65$).

Overall survival and progression-free survival

In the group of surgically staged patients (n = 33), there were 16 deaths and 21 deaths in the TAH+BSO group (n = 42). The median OS was 38.9 months in surgically staged group and 52.6 months in the TAH+BSO only group (HR 1.36 (95% CI: 0.71–2.6), $p = 0.36$, Figure 2). When correcting for age, the hazard ratio (HR) of OS was 1.56 (95% CI: 0.8–3.0) for surgical staging compared to TAH+BSO.

Kaplan-Meier curves for PFS are shown in Figure 3. In the surgically staged group there were 17 events (i.e. death or relapse), in the TAH + BSO group there were 27 events. The median PFS was 27.7 months in the surgically staged group and 21.7 months in the TAH+BSO group (HR 0.86, (95% CI: 0.47–1.6), $p = 0.62$). When correcting for age, the HR for PFS was 0.95 (95% CI: 0.51–1.8) for surgical staging compared to TAH+BSO. Follow-up data of two patients was incomplete, one patient in the surgically staged group, and one in the TAH+BSO group.

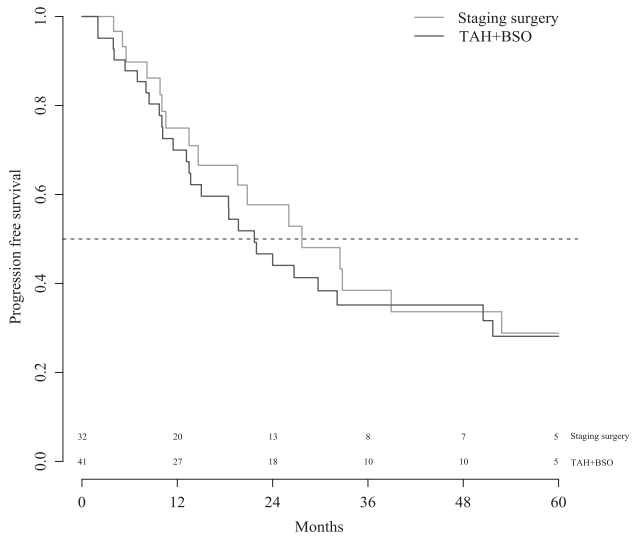

Figure 3. — Kaplan-Meier curves of progression-free survival by surgical therapy.

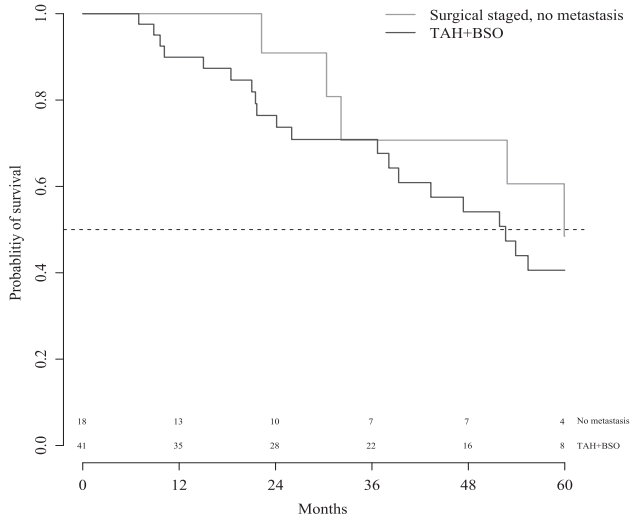

Figure 4. — Kaplan-Meier curves of overall survival of patients with no lymphatic and abdominal metastasis and patients with unknown lymphatic or abdominal metastasis who underwent a TAH+BSO only.

Overall survival of patients by stage

Among the patients with no metastasis, there were five deaths and 11 deaths among the patients with metastasis. The OS of surgically staged patients with no metastasis was significantly longer in comparison to patients with proven metastasis (HR 0.20 (95% CI: 0.07–0.59) p=0.003). Follow-up data of one patient was incomplete in the group with proven metastasis.

In Figure 4 the outcome of patients with no metastasis was compared to patients with unknown spread of disease.

No significant survival difference was found between the two groups (HR 0.62 (CI 0.23–1.6) $p = 0.33$).

Discussion

USC is an aggressive type of endometrial cancer with early metastasis beyond the uterus [23-25]. This study compared the effects of TAH+BSO and staging surgery on the use of adjuvant therapy and subsequent PFS and OS in USC patients. Many (45%) clinical early stage patients proved to have abdominal or lymphatic metastasis. These data are similar to the results of staging surgery found in other studies [26, 27].

Surgically staged patients received significantly more often chemotherapy and less radiotherapy in comparison to TAH+BSO patients. This difference in use of adjuvant therapy was not attributable to the metastasis obtained during staging surgery. New treatment guidelines for uterine carcinoma were implemented during the inclusion period of this study and recommended surgical staging in all clinical early-stage patients and the more frequent use of chemotherapy. This might explain the joint rise of use of chemotherapy and surgical staging in this study.

Studies investigating optimal adjuvant therapy in USC patients are scarce. The prospective NSGO-EC-9501/EORTC-55991 study investigated the additional effect of chemotherapy to radiotherapy in 378 patients. These patients, with all types of endometrium carcinoma had a high risk for micrometastatic disease according to departmental guidelines. They found a significant difference in PFS favoring the group treated with both chemotherapy and radiotherapy compared with the group treated with radiotherapy alone (HR 0.64 $p = 0.04$). No significant difference in OS was found [28, 29].

To further investigate the effect of chemoradiation in high-risk and advanced-stage endometrial cancer the PORTEC-3 study [30] compares concurrent chemoradiation and adjuvant chemotherapy with pelvic radiation alone. The results of this study are not yet available but might give a more conclusive answer to the optimal adjuvant treatment of USC and provide possibilities to improve the treatment protocol for USC patients.

The present results show that clinical early-stage patients who proved to have metastasis during surgery had significant worse survival rate in comparison to patients without metastasis ($p = 0.003$). Turner *et al.* studied 38 FIGO Stage I USC patients and found a significant five-year OS benefit for completely staged patients (n=21) compared to patients who underwent a TAH+BSO (n=17, two of whom received limited surgical staging) [31]. In the present study survival of patients with no metastasis and patients with unknown metastasis who received a TAH+BSO and adjuvant chemo- and/or radiotherapy did not differ significantly. The results of Turner *et al.* and the present results of a high rate (45%) of patients with advanced stage of disease found during staging show that clinical staging is not reliable in USC patients. Surgical staging is needed to predict prognosis.

No survival benefit was seen in the surgically staged patients with no metastasis as compared to the group of patients who underwent TAH+BSO only. Adjuvant therapy in these groups did not differ. It may be hypothesized that the staged patients with no metastasis were overtreated. The STATEC trial will answer this question by studying the effects of selective avoidance of adjuvant therapy in high-risk endometrial cancer with no lymphatic metastasis proven during surgical staging [32].

As a retrospective historic cohort study the present data has its limitations. The cases were collected over more than a decade and in three hospitals. In the more recent years of the study period treatment guidelines were implemented. Before implementation of these guidelines, it was standard practice to receive either surgical staging or TAH+BSO based on the physician's preference. This could have created a biased distribution of patients in each group. However correction for age did not lead to significant differences. The pathologic definition of USC changed during the inclusion period of this study. In contrary to earlier definitions, there is now a trend to define all tumors with any component of serous uterine carcinoma as USC.

In conclusion surgery proved to be important to determine true stage of disease and prognosis. Adjuvant therapy and outcomes of surgically staged patients with no metastasis did not differ significantly from TAH+BSO patients. A prospective randomized controlled trial is needed to determine whether and which adjuvant therapy will improve prognosis of women diagnosed with USC.

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