Prognostic Factors and Treatment-related Outcome in Patients with Uterine Papillary Serous Carcinoma

EMAD R. SAGR[1*], DOMINIK DENSCHLAG[1,2*], ABBAS KERIM-DIKENI[1], GERALD STANIMIR[1], GERALD GITSCH[2] and LUCY GILBERT[1]

[1]*Division of Gynecological Oncology, Department of Obstetrics and Gynecology, McGill University, Montreal, Canada;* [2]*Department of Obstetrics and Gynecology, University of Freiburg School of Medicine, Freiburg, Germany*

Abstract. *A retrospective analysis was performed in order to evaluate prognostic factors and treatment-related outcome in patients with uterine papillary serous carcinoma (UPSC). Patients and Methods: Between 1989 and 2003 forty-five patients with UPSC were treated at the McGill University Health Centre (MUHC), and therefore were included in the analysis. Age, race, history, tumor stage and grade, invasion and metastasis, treatment and outcome for each patient were evaluated. Results: According to FIGO classification, Stage I, II, III, and IV tumors were identified in 36%, 9%, 44%, and 11% of the patients, respectively. At the time of analysis, 37.8% of patients (17/45) were dead due to disease, with a mean survival of 22 months (SD±7.5 months). Cause-specific survival for the entire group was 69%, 66%, and 58% at 2, 3, and 5 years, respectively. With respect to disease stage, 5-year cause-specific survival for stage I, II, III, and IV was 100%, 75%, 43%, and 0%, respectively. Univariate analysis comparing cause-specific survival curves demonstrated a statistically significant difference for disease stage ($p<0.0001$) and depth of myometrial invasion ($p=0.008$). However, in multivariate analysis, only disease stage had a significant impact on cause-specific survival ($p<0.01$). Conclusion: Disease stage is the only independent significant prognostic factor regarding cause-specific survival in patients with UPSC.*

Differences in epidemiology and presentation suggest that there are two biologically distinct forms of uterine cancer: In the more common, hormone-dependent cancer type, Type I (well-differentiated endometrioid adenocarcinoma) accounting for 75 to 80 percent of endometrial cancer, the proliferating effects of an estrogen excess on the endometrium appear to induce a precursor lesion, which ultimately might result in an invasive growth pattern. In contrast to this, the less frequent, endometrial carcinomas (Type II) seem to be unrelated to estrogenic effects. These types of tumors tend to be more aggressive, are often poorly differentiated and commonly present at a more advanced stage. Thus these subtypes may confer a poorer prognosis in general.

First described by Hendrickson *et al.* in 1982 (1), uterine papillary serous carcinoma (UPSC) is an aggressive histological subtype, which accounts for only approximately 5% of all endometrial cancers (2). These tumors have distinct clinical and pathological characteristics and account for a disproportionately high number of recurrences and deaths compared to the more common types of endometrial cancer. In fact, women with UPSC have a poorer prognosis with an overall survival of less than 50% at 5 years (3). Even when myometrial invasion is minimal, UPSC is often associated with distant metastasis at the time of initial presentation (4).

However, due to the low incidence of this malignancy, there is a lack of evidence regarding the identification of risk factors for poor outcome, as well as the implementation of tailored therapeutic strategies. Thus, there is considerable variation in the management of patients with these tumors. As a result of the lack of prospective data for patients with UPSC, disease-tailored management remains a challenge.

This study reviews the experience of the McGill University Health Center (MUHC) in the management of patients with UPSC to assess prognostic factors, clinical outcome and the role of adjuvant treatment in the management of these patients.

Patients and Methods

Between 1989 and 2003, 1,194 patients with a histologically verified endometrial cancer were identified from the tumor registry

*Both authors contributed equally to this paper.

Correspondence to: Dominik Denschlag, MD, Division of Gynecological Oncology, Royal Victoria Hospital, 687 Pine Avenue West, Women's Pavilion, F9.29, McGill University Health Center, Montreal H3A 1A1, Montreal, QC, Canada. Tel: +1 514 843 2833, Fax: +1 514 843 2830, e-mail: Dominik.Denschlag@muhc.mcgill.ca or Dominik.Denschlag@uniklinik-freiburg.de

Key Words: UPSC, prognostic factors, staging, adjuvant therapy, outcome.

Table I. *Patient characteristics.*

	n (%)
Overall cases	45
Median age (range)	67 years (32-89)
Median weight (range)	69 kg (45-114)
Caucasian race	41 (91.1%)
History of previous cancer	13 (28.9%)
History of diabetes mellitus	19 (42.2%)
History of hypertension	7 (15.6%)
Stage at time of diagnosis	
I	16 (35.6%) (IA: 6; IB: 5; IC: 5)
II	4 (8.9%) (IIA: 3; IIB: 1)
III	20 (44.4%) (IIIA 13; IIIB: 1; IIIC 6)
IV	5 (11.1%)

Table II. *Histological characteristics according to stage.*

Characteristics	Stage I	II	III	IV	Total
Myometrial invasion					
Non-invasive	6	0	0	0	6 (15.4%)
<50%	5	2	3	0	10 (25.6%)
>50%	5	2	13	3	23 (59.0%)
LVSI					
Pos.	7	3	12	3	25 (64.1%)
Neg.	9	1	4	0	14 (35.9%)
Peritoneal washing					
Pos.	0	0	10	3	13 (33.3%)
Neg.	16	4	6	0	26 (66.7%)
Lymph node metastasis*					
Pos.	0	0	4	1	5 (31.3%)
Neg.	6	3	2	0	11 (68.7%)

*Only 16 patients had a lymph node dissection. n=39.

pathology database at the McGill University Health Centre (MUHC). Forty-five of them (3.8%) presented with papillary-serous carcinoma at final pathology and were therefore included in the final analysis. The clinical records and surgical pathology reports of the patients were reviewed for data on demographics, management and outcome. Institutional review board approval was obtained for this study.

It is the customary practice at the MUHC, as elsewhere in the province of Quebec, that early stage, low risk endometrial cancer (on the basis of endometrial biopsy/curettage) is operated on by general gynecologists. An experienced Gynecological Pathologist reviews all of the final histopathology. All patients were staged using the FIGO classification for endometrial adenocarcinoma (http://www.figo.org/Staging%20Booklet.pdf). The data obtained from the records were used to form a database that was transferred into the Statistical Package for the Social Sciences (SPSS) software program (SPSS Inc., Chicago, Illinois), version 13.

The following variables were included in the study: age at the time of diagnosis, race, history of previous cancer, family history, disease stage, tumor grade, presence of lymph vascular space invasion, operative procedure, adjuvant radiotherapy, adjuvant chemotherapy, as well as overall survival and disease status.

Surgery. Sixteen patients only had a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), 7 had a TAH-BSO and omentectomy, 6 had a TAH-BSO and lymph node dissection, and 7 had a TAH-BSO, omentectomy and lymph node dissection. A radical hysterectomy including lymph node dissection due to extensive disease was performed in 3 patients. Six patients did not undergo primary surgery and only had a biopsy because of metastatic disease or medical conditions.

Adjuvant treatment. Adjuvant treatments were performed in selected patients at the discretion of the tumor board, with respect to the risk of recurrent disease.

No additional treatment was recommended for 10 patients (22.2%). Fifteen patients received radiotherapy alone, fifteen patients received chemotherapy alone, and the remaining 5 patients received combined radio- and chemotherapy.

If indicated, external beam radiation therapy (EBRT) was delivered with a dose of 40-50 Gy in 20-28 fractions using a standard pelvic four-field box technique. When used, brachytherapy was delivered by high dose rate equipment and typically a dose of 6 Gy was prescribed to the vaginal vault in a single session. Brachytherapy was given in conjunction with EBRT. All of the 15 patients who underwent chemotherapy only, as well as all of the 5 patients who underwent chemo- and radiotherapy, were treated with a combination of paclitaxel and carboplatinum using a standard dose regimen of 175 mg/m^2 paclitaxel *i.v.* over 3 h and carboplatinum at a calculated area under the curve (AUC) of 5.

Statistical analysis. The objectives were to evaluate prognostic factors and to assess treatment related outcome. The endpoint was cause-specific survival.

Initial univariate analysis associated with cause-specific survival was performed using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Multivariate analysis was performed using Cox regression analysis to assess the significance of prognostic factors; p-values <0.05 were considered statistically significant.

Results

Patient characteristics. Demographic information is presented in Table I.

The most common symptom at presentation for patients with any stage disease was abnormal uterine bleeding (88.9%). More than half the patients (25/45) had advanced disease at surgery, although the majority (59%) were thought to have early stage endometrioid adenocarcinoma preoperatively on the basis of initial pathology and clinical assessment.

Histological characteristics according to the final pathology report are presented in Table II.

Survival. The mean follow-up of patients alive at the time of analysis was 55 months (range 4-161 months).

At the time of analysis, 37.8% of patients (17/45) were

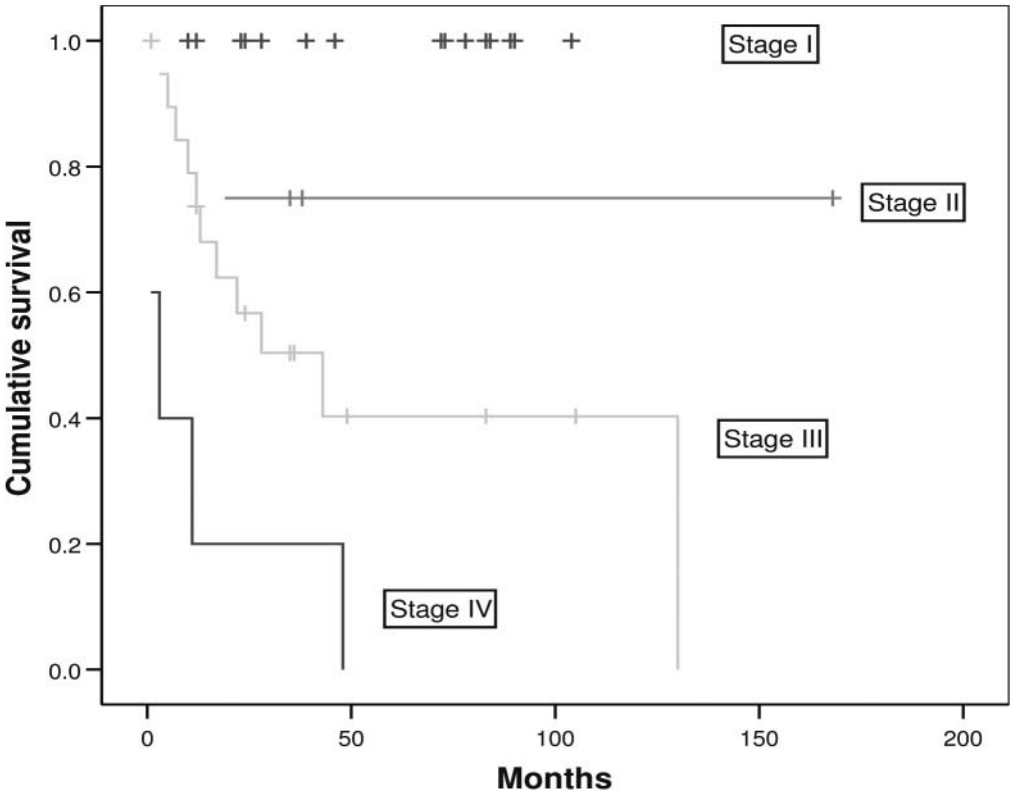

Figure 1. *Cause-specific survival according to stage.*

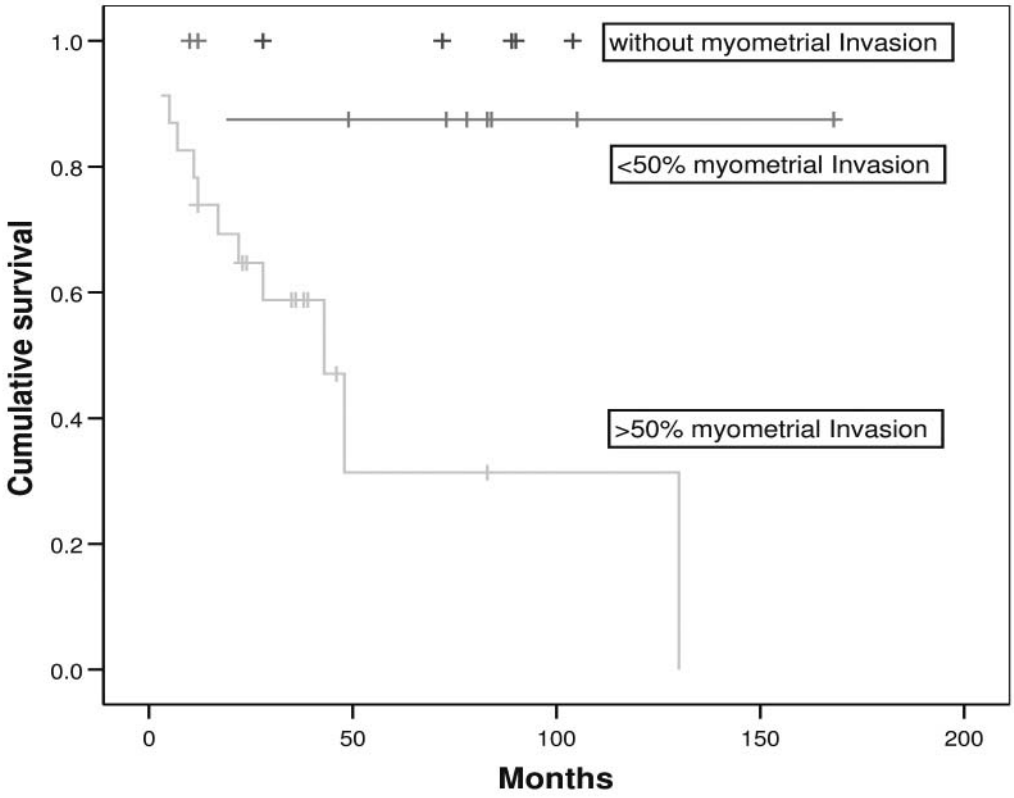

Figure 2. *Cause-specific survival according to myometrial invasion.*

dead due to disease, with a mean survival of 22 months (SD±7.5 months); 13.3% of patients (6/45) died due to other reasons not related to UPSC or its specific treatment; 13.3% of the patients (6/45) were alive with recurrent disease, and 35.6% (16/45) were alive without evidence of recurrent disease. Cause-specific survival for the entire group was 69%, 66%, and 58% at 2, 3, and 5 years, respectively. According to disease stage, 5-year cause-specific survival for stage I, II, III, and IV was 100%, 75%, 43%, and 0%, respectively.

Prognostic factors. The cause-specific survival curves according to disease stage and depth of myometrial invasion are shown in Figures 1 and 2, with a significant difference between the stages and depth of myometrial invasion, respectively ($p<0.0001$ and $p=0.008$, respectively). In contrast to this, there were only borderline significant survival differences between patients with or without the histological appearance of lymph vascular space invasion ($p=0.075$).

Treatment-related outcome. The use of radiotherapy did not have a statistically significant impact on cause-specific survival in univariate analysis ($p=0.503$), while adjuvant chemotherapy was associated with a worse prognosis by univariate analysis (5-year cause-specific survival 30% *vs.* 76%; $p=0.043$).

In multivariate analysis, only advanced disease stage remained a significant predictor for cause-specific survival ($p=0.01$).

Discussion

UPSC is an aggressive malignancy with distinct pathological and clinical characteristics, and the management of this histological variant is controversial.

In our study, 29% (13/45) of the patients had a history of previous cancer, with the majority of them previously having breast cancer (22%). Other studies have revealed similar associations of UPSC with breast cancer (12-25%) (3, 5-7). Some case reports have demonstrated a relationship between BRCA1 germline mutations and UPSC (8, 9). Furthermore, there may be unidentified genes that predispose women to both UPSC and breast cancer. However, so far definite link between genetic predispositions for developing both tumors has not been shown.

UPSC tends to simulate the behavior of epithelian ovarian cancer in terms of extra-uterine spread. Several studies have demonstrated extra-uterine spread of disease in UPSC, even in the absence of myometrial invasion. The significance of comprehensive surgical staging was reported in a study published by Chan *et al.* who reviewed complete staging procedures in patients with non-invasive UPSC (4). In this study, omental assessment revealed that 25% of the patients had stage IV disease due to omental involvement. Therefore, some authors propose that these patients should undergo a staging laparotomy similar to the procedure undertaken for patients with ovarian cancer (5, 10). Thus the surgery should include at least TAH-BSO, partial omentectomy, peritoneal washings as well as peritoneal biopsies, and pelvic and paraaortic lymph node dissection similar to an ovarian cancer staging procedure (3).

In light of these data, one feels compelled to offer UPSC patients who were primarily treated only with TAH-BSO alone, a second laparotomy to complete the surgical staging, including an omentectomy as well as a complete lymph node dissection.

Our data on cause-specific survival for the entire group (69%, 66%, and 58% at 2, 3, and 5 years, respectively) is in agreement with recently published series which demonstrated a 5-year survival between 57% and 66% (11, 12).

In our series, in multivariate analysis including disease stage, myometrial invasion, lymph vascular space invasion and adjuvant treatment modalities, only disease stage remained a significant predictor of cause-specific survival. These data are in accordance with Craighead *et al.*, who was able to demonstrate that disease stage is the most important independent prognostic factor affecting recurrence and survival (13).

Because of the poor results with surgery alone, both radiation and chemotherapy have been added postoperatively in order to improve the outcome. However, the benefit of adjuvant therapy is still controversial.

Postoperative radiotherapy (RT) is commonly recommended for women with stage IB, IC, and II UPSC, and following adequate cytoreductive surgery for stage III or IV disease, mainly in order to improve local control (13). In this retrospective review including 103 patients, the authors were able to demonstrate a significantly lower incidence of pelvic recurrence in patients who were treated with pelvic RT compared to patients who did not receive RT ($p<0.005$); however these patients still had a high distant failure rate. Furthermore, the authors reported a significantly longer survival in patients with stage IV disease who were treated with chemotherapy compared to patients who did not receive chemotherapy (8.0 *vs.* 2.5 months).

These data were confirmed by another retrospective analysis including 129 patients (3). In this series the authors reported a 3-year progression free- and overall survival in patients with stage I disease of 68.6% and 84.9%, in patients with stage III disease of 41.1% and 49.7%, and in patients with stage IV of 26.4% and 35.8%, respectively. Comparing the patients with stage III disease who received chemotherapy to those who did not, the authors reported a significantly longer overall survival in the former group (69.7 *vs.* 29.4 months). This beneficial effect of adjuvant

chemotherapy in combination with RT in terms of disease-free and overall survival could even be confirmed in patients with early stage UPSC (14, 15).

According to these data combination of chemo- and radiotherapy may be more effective than either radiotherapy or chemotherapy alone in the adjuvant setting. A pilot study including 23 women with uterine papillary serous carcinoma noted a higher overall survival in patients treated with RT and additional paclitaxel/carboplatin chemotherapy compared to those treated with RT alone (80% *vs.* 30%) (16).

In our study, we were not able to demonstrate a significantly prolonged survival in patients who received radiotherapy.

The fact, that chemotherapy was associated with a worse outcome in univariate analysis is likely related to the common practice of recommending adjuvant chemotherapy for patients who present with advanced disease and therefore carry a worse prognosis.

Due to limited numbers of patients included in this series, no definitive conclusions, especially about the combination of radio- and chemotherapy, regarding a potential benefit can be made.

Conclusion

In our series disease stage was the only independent significant prognostic factor regarding cause-specific survival in patients with UPSC, supporting the role of full surgical staging whenever feasible.

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