Long-term Survival in Uterine Clear Cell Carcinoma and Uterine Papillary Serous Carcinoma

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Abstract. *Uterine clear cell carcinoma (UCC) and uterine papillary serous carcinoma (UPSC) are rare entities that differ in clinical behavior from endometrial adenocarcinoma. Compared with endometrioid adenocarcinoma, they more often metastasize early and more commonly in the upper abdomen including the omentum. Treatment programs of UCC and UPSC at different stages vary and range from no adjuvant therapy in stage Ia to a wide variety of chemotherapies and radiotherapies in more advanced stages. This study presents the outcome of 109 patients with UCC or UPSC treated according to essentially the same treatment program from May 1993 to December 2004. Most patients were treated with a simple hysterectomy with no further adjuvant treatment. In stage Ia, 2/46 patients died of their disease and amongst all the stages, 30/109 patients died of their disease. These survival outcomes are comparable to or better than those presented previously.*

Uterine clear cell carcinoma (UCC) and uterine papillary serous carcinoma (UPSC) are rare entities that differ from endometrial adenocarcinoma in their clinical behaviour. Compared with endometrioid adenocarcinoma, they more often metastasize early and more commonly in the upper abdomen including the omentum. Treatment programs of UCC and UPSC at different stages vary and range from no adjuvant therapy in stage Ia to a wide variety of chemotherapies and radiotherapies in more advanced stages. UCC was described as early as 1967 by Scully and Barlow (1) using a description by Schiller (2) regarding the same entity in ovarian carcinoma. The poor prognosis regarding UCC was first reported by Kurman and Scully in 1976 (3) and confirmed by Christophersson *et al*. in 1982 (4). The poor outcome of UPSC was first shown by Hendrickson *et al*. (5) and Christophersson *et al*. in 1982 (6). The treatment results in Scandinavia were shown by Abeler *et al*. in 1996 (7).

Since then, numerous studies on UCC and UPSC have been published but the outcome of treatment has not improved. In 1993, Rosenberg *et al*. (8) published results indicating a better survival among UPSC patients if they were more intensively treated. They proposed a treatment schedule which was also adopted in the Southern Health region of Sweden as described below.

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Materials and Methods

The treatment program for evaluation ran from May 1993 to December 2004. During that time 55 patients with UCC and 56 patients with UPSC were identified and treated in the Southern Healthcare Region in Sweden. All patients were treated with a simple hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymph nodes were removed only if enlarged or otherwise suspected to be metastatic. According to treatment program all patients with UCC and UPSC were planned to receive external pelvic radiotherapy and chemotherapy, although this was actually achieved in only 48 patients. Thirteen patients received cytostatics only as postoperative/adjuvant treatment. Another 29 patients had a simple hysterectomy or a hysterectomy according to Wertheim-Meighs but received no further adjuvant treatment. The remaining patients (n=21) had radiotherapy as the only adjuvant therapy. After completion of therapy, the patients were followed up at least once every 6 months for two years, thereafter once a year until 5 years after treatment. The histopathology of the tumours was classified according to WHO classification of female genital tumours (9).

The Southern Health Region of Sweden has a population of approximately 1.7 million. During the study period, surgery for endometrial cancer was performed at 11 different hospitals in the region, all aiming to follow a standardised treatment protocol. All patient files were sent to the Department of Gynecological Oncology, University Hospital of Lund, where the decision was taken regarding postoperative treatment and where all adjuvant radiotherapy was performed. Over the years, in order to achieve a uniform histological evaluation, all specimens were re-examined at the Department of Pathology, University Hospital of Lund. All cancer diagnoses were reported to the local Regional Cancer

Table 1. *Number of patients in relation to stage and deaths in disease.*

Stage	1a	1b	2	3	4
Patients	46	24	4	24	12
Deaths due to disease	2	4	3	14	9

One stage Ia and one stage 3 patients were lost to follow-up.

Registry. With the use of this Registry and the unique personal identification number assigned to each person living in Sweden, all patients with the diagnosis of clear cell or papillary serous carcinoma of the corpus uteri were identified. They were followed up for 5 years or until death. Two patients were lost to follow-up and three patients were followed up for only 4 years. The FIGO staging was revised according to the FIGO Committee on Gynecologic Oncology 2009 (10).

Results

Of 109 patients with follow-up data (one lost to follow-up for unknown reasons, one had moved abroad), 32 died from their their disease within the follow-up period. More details are given in Table I. When comparing the death rate in UCC and UPSC there was no difference between the two histological subtypes (Figures 1-3). Therefore the results of both subtypes of cancer were merged to enhance the power of the analysis of the results (Figure 4). It was found that the dead of disease (DOD) rate was low (6/70, 9%) in stage 1. In stage 2, there were only 4 patients but in stages 3 and 4, 23 out of 36 patients (64%) died of their disease. Although the treatment program recommended operation, adjuvant radiotherapy and chemotherapy, only 48/109 (44%) followed the complete treatment program. Of the remaining patients, 29/109 were treated with operation without any adjuvant therapy, 13 with adjuvant cytostatics only and 19 with adjuvant radiotherapy only. Some patients were given additional progesterone therapy. Although patients with only an operation had a higher frequency of DOD, the difference in DOD between the treatment modalities used was not statistically significant (Figure 5). One reason for the high frequency of patients only treated by an operation may be that three patients died due to adjuvant treatment, which reduced the compliance for the planned treatment schedule.

Discussion

The results regarding DOD in UCC and UPSC are almost identical in this study. Similar results were presented at the 2005 ASCO Annual meeting by Slomovitz *et al*. (11). This study also showed that the results are very good for patients in stage 1a (2/46 DOD), but when the disease is spread outside uterus the DOD rate is high (23/36, 64%, see Table I). The current treatment results are comparable to earlier published

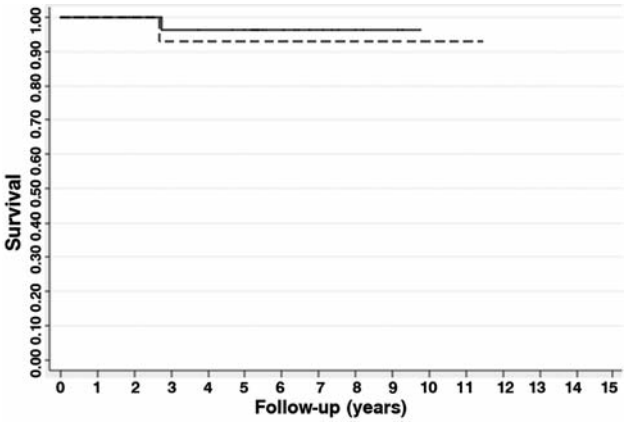

Figure 1. *Stage Ia uterine clear cell cancer and uterine serous papillary cancer indicating that the frequency of death disease was the same.*

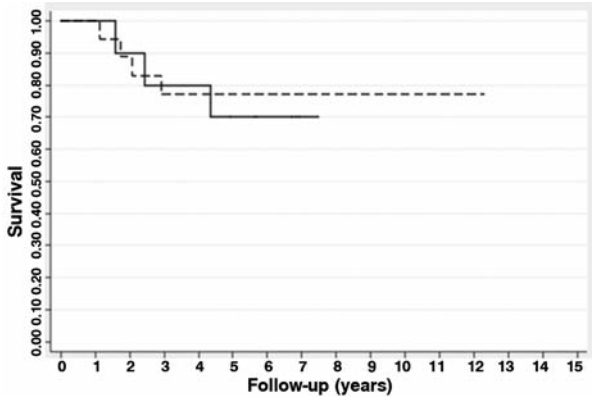

Figure 2. *Stage Ib and stage II uterine clear cell cancer and uterine serous papillary cancer indicating that the frequency of death due to disease was the same.*

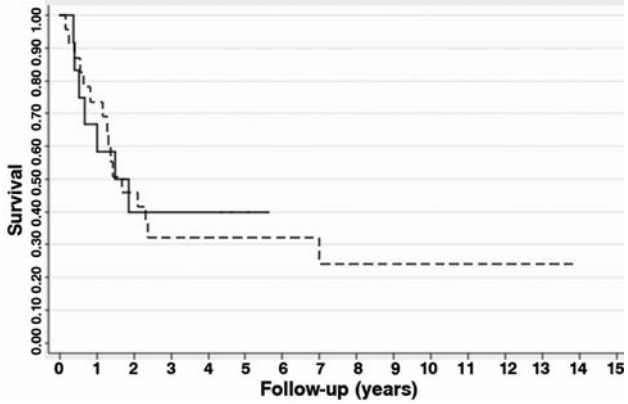

Figure 3. *Stage III uterine clear cell cancer and uterine serous papillary cancer indicating that the frequency of death due to disease was the same.*

results. In 2006, Sutton *et al*. (12) published their results of the same type of cancer patients (n=34) treated with whole abdominal radiation with/without cytostatics. In stage I-II, the DOD rate was 11/24 compared to 9/74 in the current study, although some patients in the Sutton study possibly had been upstaged by a generally applied aortic lymph glandular sampling. Tay and Ward (13) showed that careful staging increased the frequency of stage IV in their study from 2% to 73%. Chan *et al*. (14) found that omental sampling was very important as 25% of their patients (n=16) had omental involvement although they had non-invasive disease (stage 1A according to previous classification). Without this careful staging, the frequency of DOD in stage I is only 9% in the current study. Huh *et al*. (15) published the results of 60 patients with UPSC stage I. Among those, 40 patients did not receive any adjuvant therapy at all, 12 received radiation therapy and 7 received chemotherapy, without finding any statistical differences between outcomes. In the current study, the corresponding figures were 25/109, 25/109 and 13/109 respectively; 2 patients were not followed up properly. In the study of Huh *et al*. (15), 8/60 (13%) patients died of disease even though they were completely staged compared to 10/109 (9%) in the current study. Sagr *et al*. (16) published better survival in stage I (0% DOD) but equal results regarding stages III-IV (43% and 0%). In a review from 2001, Tropé *et al*. (17) strongly recommend a complete staging and no adjuvant therapy in stage Ia. In the current study, without this complete staging, a better survival is reported than in studies that report the results of staged patients. This difference is difficult to explain, but as seen in Figures 5 and 6, the frequency of death in intercurrent disease is twice as high as DOD in the current patients. An alternative explanation may be that cytostatics given in this group of patients have a better effect than earlier used cytostatics, which was also described by Rosenberg *et al*. (8). Moreover, one might speculate whether a full staging may add morbidity or negatively affect the immune system of an elderly cancer patient.

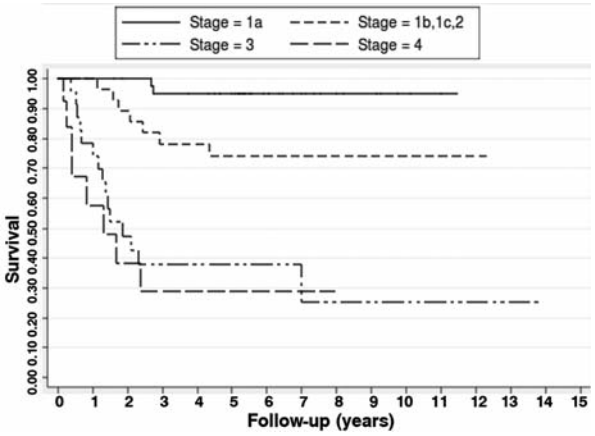

Figure 4. *Survival in clear cell and papillary carcinoma according to cancer stage.*

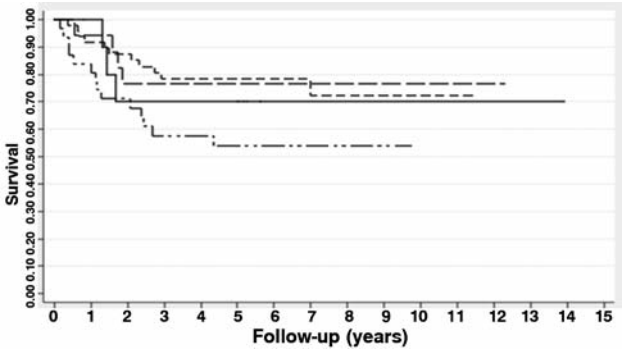

Figure 5. *Survival according to therapy.*

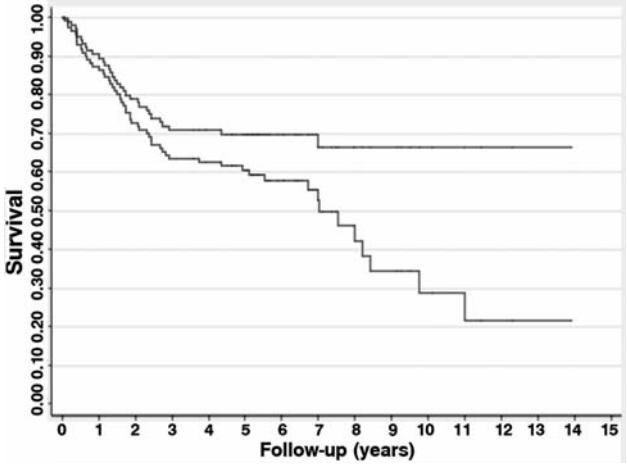

Figure 6. *The frequency of DOD (upper curve) and frequency of survival (lower curve).*

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