# Relapse of Endometrial Carcinoma: Follow-up of 272 Patients with Relapse

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**Abstract.** *A total of 2090 patients with endometrial carcinoma were followed-up for at least five years. The treatment modalities, as well as the results of treatment, regarding 272 patients with disease relapse are presented. The results are not encouraging. We found no statistically significant difference regarding overall survival, when the patients were divided according to initial stage or ploidy status. There was also no significant difference between overall survival and the mode of treatment. 108 out of 272 patients with relapse died of their disease. Regarding patients in stage I-II we present the survival for every studied year, where we compared those with more than one site of metastasis (n=108), more than one metastasis (n=59), or no relapse at all (n=1289) with an age-corrected Swedish female population. We found that the vast majority of patients did not die from their cancer-related illnesses, and also found an increased death-rate among those with cancer without relapse, compared to those without cancer (20% compared to 14%, 5 year follow-up). We conclude that the majority of patients would benefit from an increased effort to cure other illnesses rather than concentrating on cancer treatment alone.*

The treatment results of patients with relapsing endometrial carcinoma are disappointing. As there are no agreements in regard to treatment, the treatment of choice depends on the localization of the disease, previous treatment, the performance status of the patients and the doctors involved. Thus a wide variety of treatment modalities are available, used alone and in combination.

When the patient presents a single relapse, the preferred therapy is surgery, radiotherapy or their combination. When multiple or distant relapses are present, cytostatics or hormone therapy is used, although chemotherapy has been more common and with better results in the last decades (1). The results of radiotherapy are better if not given earlier as adjuvant therapy. The chosen treatment is also dependent on the speciality of the doctor finding the relapse.

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*Key Words:* Endometrial carcinoma, follow-up study, patient

## Patients and Methods

A total of 2090 patients were followed-up for at least five years. The treatment modalities and results regarding the 272 patients with relapsing endometrial adenocarcinoma are presented. The treatment program for evaluation ran from May 1993 to December 2004. The results of that treatment program have been published (2). During that time, 2090 patients with uterine endometrial carcinoma were identified and treated in the Southern Healthcare Region in Sweden. All patients with adenocarcinoma stage I-II were treated with a simple hysterectomy and bilateral salphingo-oophorectomy. Pelvic lymph nodes were removed only if enlarged or otherwise suspected to have metastatic disease. According to the treatment program, in patients with non-diploid tumors, adeno-squamous or undifferentiated carcinoma, vaginal vault, brachytherapy was given. In cases of stage III or IV diseases, individual therapy was given. The treatment of serous and papillary carcinoma has also been reported (3). After completion of therapy, the patients were followed-up at least once every six months for two years, thereafter once a year for three more years. The histopathology of the tumors was classified according to the WHO classification of tumors (4).

The Southern Health Region of Sweden has a population of approximately 1.7 million inhabitants. During the study period, surgery for endometrial cancer was performed at 11 different hospitals in the region, all following the stated 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 all adjuvant radiotherapy was performed. Over the years, in order to achieve a uniform histological evaluation, almost all specimens were re-examined at the Department of Pathology, University Hospital of Lund. All cancer diagnoses were reported to a Regional Cancer Registry.

Moreover with the use of the Registry, and the unique personal identification number assigned to each person living in Sweden, all patients with the diagnosis of carcinoma of the corpus uteri were identified. They were followed-up for five years or until death, and one person of our group visited regularly each hospital and read the files of every patient. The frequency of relapse and survival have been published earlier (2). Here we present the results of treatment of relapse.

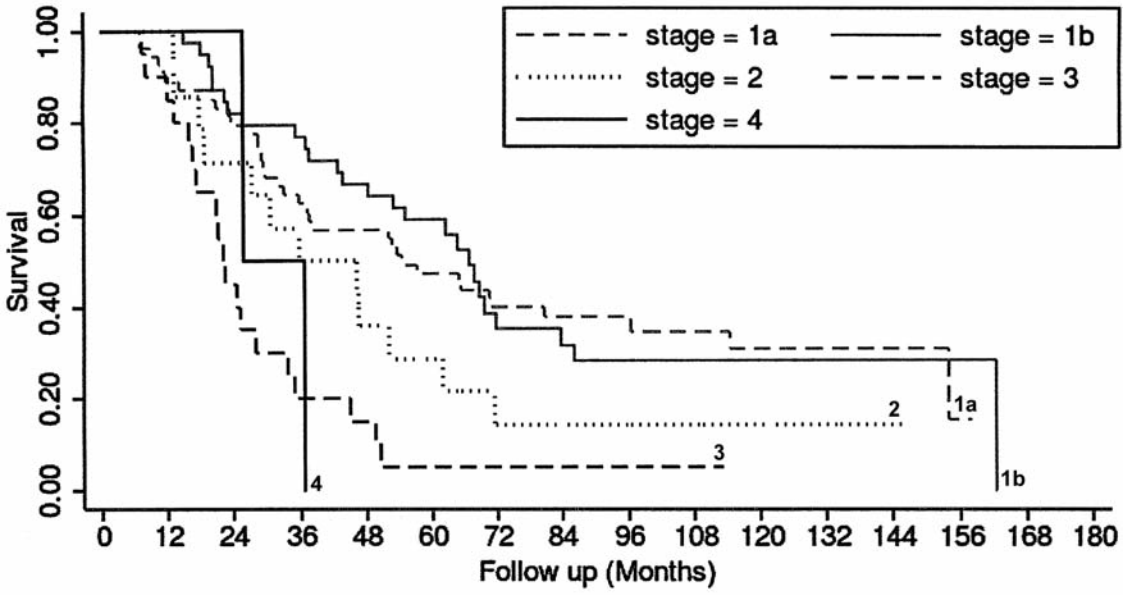


Figure 1. *Overall survival after relapse related to initial stage. Number of patients stage 1a 106, Stage Ib n=69, stage II n=23, stage III n=29 and stage IV n=36. No significant difference. p<0.0001.*

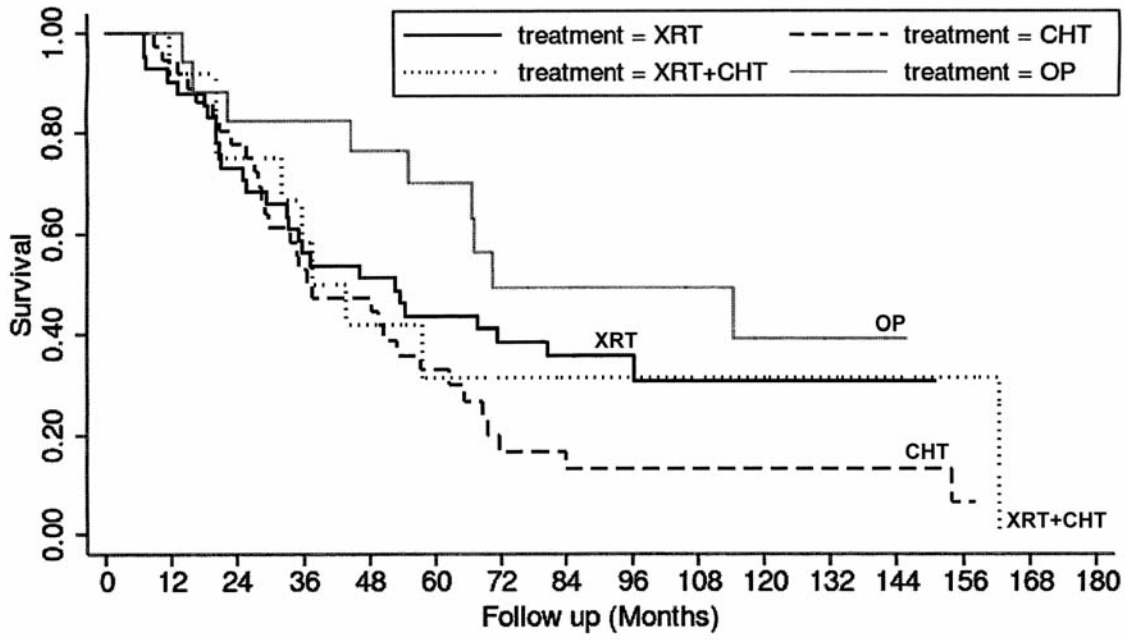


Figure 2. *Overall survival comparing treatment of relapse in stage 1A-1B (n=55). Number of patients treated with XRT 3, CHT 2, XRT and CHT 7, and operation 11. No statistical difference.*

*Statistical methods*. Survival was calculated using the Kaplan-Meier method and hypothesis tests were performed using the log-rank test. Covariates were included using Cox-regression. Comparisons with the background population was performed using relative survival and the program STATA package strs (5). Population data was obtained from Statistics Sweden. The significance level was set at 0.05. STATA v12 was used for all calculations. General mortality was calculated from the mortality of the total population considering the age and the sex of the studied population.

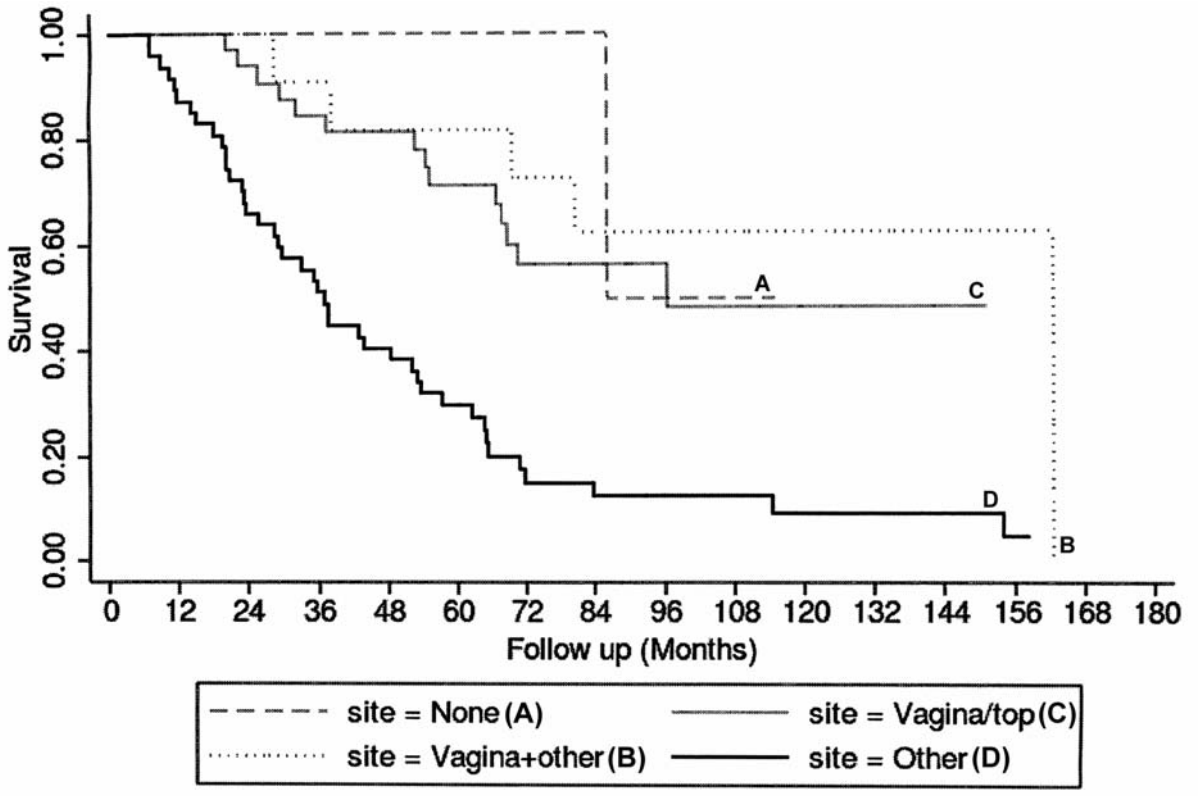


Figure 3. *Overall survival related to site of relapse. Relapse-site vaginal top n=59. Relapse-other sites n=108. p<0.0001.*

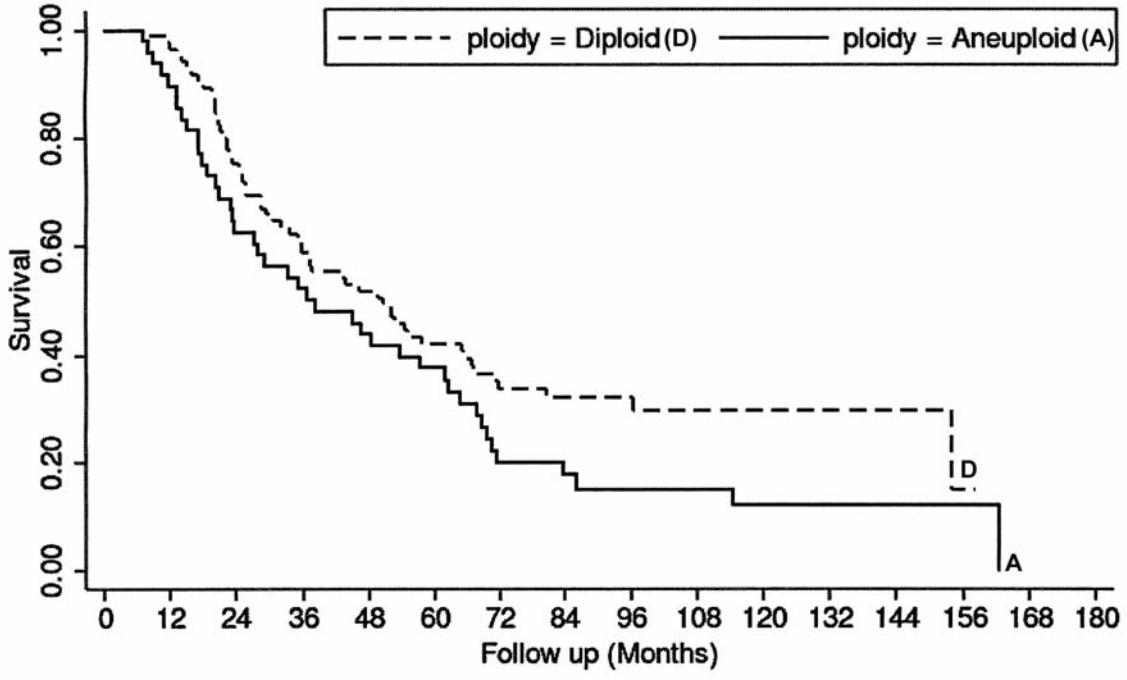


Figure 4. *Overall survival of patients with vaginal relapse divided according to ploidy at initial diagnoses. Patients with diploidy n=45 and non-diploidy n=10. No statistical difference. p<0.07.*

Table I. *Comparing overall survival in patients with endometrial carcinoma with or without metastasis and the general mortality of age adjusted population without endometrial carcinoma.(n) number of patients*

| Years | (n) | Vag metastasis | Same age no cancer | (n) | Metast other loc | Same age general mortality | (n) | No metastasis | Same age general mortality |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 59 | 0.9487 | 0.9432 | 108 | 0.8889 | 0.9779 | 1284 | 0.9435 | 0.9766 |
| 1 | 55 | 0.8269 | 0.8883 | 96 | 0.6667 | 0.9528 | 1192 | 0.9091 | 0.9538 |
| 2 | 47 | 0.5982 | 0.8378 | 72 | 0.5093 | 0.9289 | 1128 | 0.8827 | 0.9300 |
| 3 | 34 | 0.5624 | 0.7837 | 55 | 0.3889 | 0.9040 | 1041 | 0.8624 | 0.9056 |
| 4 | 31 | 0.4655 | 0.7339 | 42 | 0.2917 | 0.8764 | 935 | 0.8363 | 0.8813 |
| 5 | 22 | 0.4165 | 0.6828 | 28 | 0.2083 | 0.8449 | 627 | 0.7969 | 0.8550 |
| 6 | 14 | 0.4165 | 0.6359 | 14 | 0.1540 | 0.8194 | 161 | 0.6982 | 0.8197 |
| 7 | 10 | 0.4165 | 0.5828 | 6 | 0.1540 | 0.7995 | 51 | 0.5585 | 0.7764 |
| 8 | 3 | 0.4165 | 0.5733 | 2 | 0.1540 | 0.7749 | 21 | 0.4998 | 0.7248 |
| 9 | 3 | 0.4165 | 0.5641 | 2 | 0.1540 | 0.7502 | 15 | 0.2999 | 0.6667 |

In each column we can follow the frequency of survival and compare to the column to the right indicating the survival frequency of age-corrected Swedish females. Due to the small number of relapse in the columns the figures are not changing after some years.

## Results

The survival rate after recurrence regardless of therapy but according to initial stage is shown in Figure 1. There is a significant difference between the initial stage and outcome of therapy after recurrence. The survival rate, separated according to therapy is shown in Figure 2. We were unable to identify any significant difference in survival rate due to therapy. When comparing the survival rate of those patients with one location of recurrence compared to those with more than one, there was a significantly better survival of patients with just one location of recurrence (Figure 3). We also investigated the results of therapy in those with vaginal relapse divided into those with diploid and those with non-diploid primary tumours; we found no difference in survival (Figure 4). However, when comparing survival rates for those dead due to their disease to that of overall survival by all causes, we noticed a high death rate in the studied group. In Table I we can see the overall survival in patients with vaginal metastases, with metastases in other locations and in those without metastases. The difference in survival between those with and without metastases shows the frequency of patients who died from their disease. This might be why it is so difficult to arrive at a conclusion as how to treat recurrences in this group of patients. We also compared the survival rate in those with endometrial carcinoma without relapse to that of an age-corrected Swedish female population. If we first compare overall survival of patients with vaginal relapse with that of an age-corrected population without cancer and then that of patients with endometrial carcinoma but without relapse to an age-corrected Swedish population (Table I), we find the difference after two years to be 24%, decreasing to only 14% after nine years. Regarding patients with the worst prognosis, the highest difference is 67% after six years.

## Discussion

The prognosis for patients with relapsing endometrial carcinoma is not encouraging. The Portec Trial (6) reported vaginal relapse in 35 patients while in 31 patients complete remission was obtained, and after 44 months, 24 patients were still disease-free. There was no statistical difference in survival when comparing patients with or without adjuvant therapy. No patient with multiple metastases survived for a longer period of time. In a larger series published by Jhingran *et al*. (7), 91 patients with vaginal relapse were treated with radiotherapy, with a 5-year local control rate of 69%, and an overall survival of 43%. Kuten *et al*. (8) studying a small series of 17 patients with vaginal-only relapse reported a 5-year survival of six patients. Jereczek-Fossa *et al*. (9) reported a 5 year-survival of 25% in 73 patients, and Lin *et al*. reported a 5-year overall survival of 40% in 50 patients (10). In a review article, Rauh-Hain and del Carmen (11) reported a 5-year survival rate of 25-50%. In more advanced cases of recurrence, chemotherapy has been preferred; the results are not encouraging with a survival rate of about 20% (11, 12).

When looking at overall survival we see that these figures are very poor, much worse than the figures describing patients who died from ther disease. These figures gave us the idea of comparing overall survival with the survival of an age-adjusted population in Sweden and also of comparing the overall survival in those with endometrial carcinoma without relapse. Then suddenly the results were not as poor (Table I). Thus we could be rather satisfied regarding the group with vaginal metastasis but among that small group with distant or multiple metastasis the results could be improved. When comparing the frequency of deaths in patients with endometrial carcinoma without relapse to that

of a normal female population we see that the frequency of deaths is already from the beginning higher in the cancer group, the difference being accelerated after 5 years. We also know that the frequency of adipositas, diabetes and hypertension is higher in patients with endometrial carcinoma, which might explain the lower overall survival in that group compared to non-cancer patients.

The number of patients dead from their recurrent disease compared to the total number of patients, is however very small (108/2090=5%), meaning that a higher frequency of deaths is roughly 3% after 5 years, comparing to the overall survival in those with endometrial carcinoma without relapse (20%).

Thus by using this information we could determine that our efforts should focus in identifying and treating those non-tumour illnesses causing the majority of deaths.

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*Received March 5, 2012*
*Revised May 11, 2012*
*Accepted May 14, 2012*