

## Case Series

## Vaginal vault recurrences of endometrial cancer in non-irradiated patients – Radiotherapy or surgery



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## ARTICLE INFO

## Article history:

Received 25 October 2014

Accepted 8 January 2015

Available online 17 January 2015

## Keywords:

Endometrial

Cancer

Vault

Recurrence

Radiotherapy

Surgery

## ABSTRACT

**Background:** The treatment of locally recurrent endometrial cancer is based on limited evidence. The standard treatment is radiotherapy (RT) which is effective for local control and the effect has been documented in prospective studies. Investigations of surgical treatment (ST) of recurrences are few and limited to previously irradiated patients or patients with advanced disease. Investigation of surgical treatment for isolated vaginal vault recurrence is practically nonexistent. The aim of this study is to evaluate the efficacy of RT and ST in a non-irradiated group with recurrent endometrial cancer limited to the vaginal vault.

**Methods:** Patients treated for recurrent endometrial cancer at Odense University Hospital, Denmark between 2003 and 2012 were identified,  $n = 118$ . Thirty-three patients had an isolated vaginal vault recurrence and were treated with either RT, ST or both.

Re-recurrence rates and survival rates were calculated at 2 year follow-up using Fishers exact test.

**Results:** Twenty-six patients were treated with RT, 5 with ST, 2 with both. The mean (SD) follow-up-time was 4.4 years (2.99) (RT) and 3.9 years (0.90) (ST). Two year re-recurrence rates were 40% (RT) (95 CI 9.2–48%) and 0% (ST) (95 CI 0–60%). Two-year survival rates were 83% (RT) (95 CI 71–100%) and 100% (ST) (95 CI 40–100%) ST had one re-recurrence at 2.3 years.

**Conclusion:** This study indicates that ST is an appropriate treatment for locally recurrent endometrial cancer. Our study involves a limited number of patients and is made retrospectively, therefore prospective and ideally randomized trials evaluating both survival and complications are warranted.

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## Introduction

Worldwide endometrial cancer is the fifth most common cancer in women. Furthermore, it is the most common gynecologic cancer in developed countries (Cancer W.I.A.F.R.O., 2012). The continuing rise in incidence is most likely explained by increased fat consumption and obesity in developed countries and previous use of unopposed estrogens. Both are well recognized risk factors for endometrial cancer (Amant et al., 2005).

Endometrial cancer is often detected in early stage because of abnormal uterine bleeding which is the most frequent symptom. Around 5–10% of women with this symptom are diagnosed with endometrial cancer and the risk increases with age and other additional risk factors (Gredmark et al., 1995).

Women diagnosed with endometrial cancer generally have a favorable prognosis. Seventy-five percent are diagnosed in FIGO stage I and have a 5-year survival of 85%. Women diagnosed in FIGO stage II have a 5-year survival of 75%, 40% for FIGO stage III and 20% for FIGO stage IV (Amant et al., 2005; Danish Gynecological Cancer Group D, 2010). Approximately 6–13% of all patients with endometrial cancer will develop recurrent disease. The majority of the recurrences occur during the first 3 years after a primary disease and most of these are located in the vaginal vault (Creutzberg et al., 2011; Huh et al., 2007).

In Denmark primary disease is surgically treated according to national guidelines with total hysterectomy with bilateral salpingo-oophorectomy including cytological examination of the peritoneal fluid. In grades 1 and 2 endometrioid adenocarcinomas (EAC) peroperative evaluation of myometrial invasion determines if lymph node excision is performed (performed if invasion exceeds 50%). In grade 3 EAC and type 2 histology (serous, clear cell, undifferentiated carcinomas and carcinosarcomas) it is performed without evaluation of myometrial invasion. In stage II radical hysterectomy is performed. Patients with type 2 histology furthermore have the omentum removed. FIGO stages

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III–IV are generally treated with adjuvant chemotherapy (Danish Gynecological Cancer Group D, 2010). The patients in our department are offered follow-up three times/year during the first two years, then twice a year on the third year after treatment for low risk primary cancer and for further 3 years in other groups (Danish Gynecological Cancer Group D, 2010).

Recurrent disease is most often treated by radiotherapy which is in accordance with recommendations in the international literature (van Wijk et al., 2009). Surgical extirpation is in addition a valid and well recognized treatment albeit not as common (van Wijk et al., 2009). To the best of our knowledge publications describing the evidence for surgical treatment of isolated vaginal vault recurrences of endometrial cancer in non-irradiated patients do not exist.

At our department, the Department of Gynecology and Obstetrics at Odense University Hospital (OUH), the treatment of recurrent disease has been either surgery or radiotherapy at the discretion of the treating gynaec-oncologist.

In order to investigate potential differences in the outcome of radiotherapy versus surgical treatment, we conducted a retrospective cohort study based on patients treated for recurrent disease in the vaginal vault.

## Materials and method

All the patients treated for endometrial cancer at Odense University Hospital, Odense, Denmark between January 1st 2003 and December 31st 2012 were identified in the electronic patient data system FPAS, by searching for the diagnosis code DC549 cancer corporis uteri (n = 896).

Patient records and pathology reports were examined to identify those with recurrence of endometrial cancer.

Records from patients found to have recurrent disease were examined further and the following data recorded; date of birth, date of death (or alive at follow up), date of primary cancer diagnosis, histological type and grade of primary cancer, primary and adjuvant treatment of primary cancer, FIGO stage (2009 revision), degree of myometrial invasion, number and location of malignant and non-malignant lymph nodes, and other metastases at the time of diagnosis. The date which the recurrence was diagnosed, location of recurrence, treatment plus neo-adjuvant and adjuvant treatments were recorded as were dates of re-recurrences along with their size and location. Furthermore, data regarding tumor size for the recurrences were collected.

For all included patients' dates of primary cancer diagnosis, recurrence and re-recurrence were verified by histological samples and pathology reports. Follow up was conducted on April 1st, 2014.

The patients included were selected by these criteria 1) recurrence of endometrial cancer in the period from January 1st 2003 to December 31st 2012 2) recurrence was local (vaginal vault or directly connected) and 3) treatment was started with curative intent, either surgically or with radiotherapy. Patients with distant metastases or recurrence on the pelvic sidewall were excluded.

The radiotherapy treatment consisted primarily of external beam radiation with a dosage of 50 Gy in 27 fractions and pulse dose rate brachytherapy with a dosage of 15 Gy in 3 treatments. Surgical treatment consisted of excision of tumor along with a border of tumor free tissue. There were no cases in which bladder or bowel resection was performed.

The palliative treatment chosen for the re-recurrences (n = 7) and not cured first recurrence (n = 2) in the radiotherapy group (all re-recurrences including re-recurrences at 2 year follow-up) consisted in three cases of endocrine treatment (aromatase inhibitors), one patient was in a too poor condition to receive any treatment, one patient declined any treatment, three patients received chemotherapy with Taxol and carboplatin, and in one case a patient received additional radiotherapy against lung metastasis. The single re-recurrence in the

surgical treatment group was treated with Caelyx, a cytostatica of the topoisomerase inhibitor group.

For comparison of our results regarding re-recurrence rate and survival after surgical treatment of locally recurrent endometrial cancer, we conducted a PubMed search in September 2014 using these terms: endometrial cancer, endometrial carcinoma, uterine cancer, recurrence, vaginal vault, vaginal recurrence, pelvic exenteration, surgical treatment, and surgical resection.

The study was approved by the Danish Data Protection Agency.

## Statistical analysis

As the number of included patients is only 33 with 5 in one group (surgery), 26 in the other group (radiotherapy) and 2 patients receiving combined treatment in a third group, we decided against elaborate survival analysis such as cox proportional hazards regression. The limited number of data would not be able to give statistically meaningful and valid results.

We conducted univariate analysis of risk factors using logrank test and Cox regression for continuous variables.

We decided on a descriptive approach presenting the data using Fisher's exact test to calculate re-recurrence and survival rates.

Re-recurrence rate and survival rates were calculated at 2 years of follow-up.

## Results

Fig. 1 presents the process of identifying the 33 patients included in the analysis. All the patients were treated with curative intent; 26 received radiotherapy, 5 received surgical treatment and 2 received a combination of treatment modalities.

Table 1 shows the number of all recurrences per year in the collected material, and in which year the included patients had a recurrence.

Table 2 presents descriptive data on all 33 patients included in our study. Two year follow-up data was available for all but five patients in the radiotherapy group. These 5 patients are not included in the two year rates. At the two year follow-up the 21 patients in the radiotherapy group presented with the following outcomes; 15 patients had no re-recurrence and 4 patients had re-recurrence of which 2 died within the 2 year follow-up. Two patients never became free of

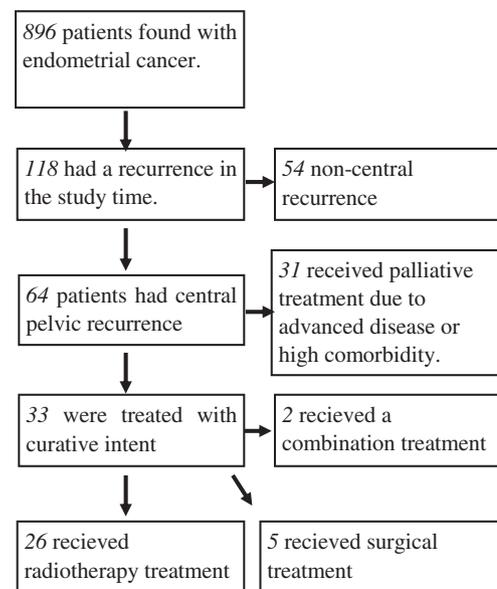


Fig. 1. Flow chart describing inclusion process.

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