



## Prognostic value of local relapse for patients with endometrial cancer

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### Abstract

**Background:** The objective of our study was to determine survival and prognostic factors associated with isolated local recurrence of endometrial cancer.

**Methods:** Data of 1229 patients with endometrial carcinoma treated between 2000 and 2012 were extracted from maintained databases of nine French University Hospitals as well as from the Senti-Endo trial. Patients with isolated central pelvic and vaginal recurrence were selected for further analysis.

**Results:** Two hundreds and twenty five patients recurred during the inclusion period, 20 with isolated central pelvic recurrence and 23 with vaginal recurrence. Patients without recurrence had initially significantly less lymphovascular space invasion ( $p = 0.01$ ), less advanced diseases ( $>$ stage II) ( $p < 0.001$ ) and more often low or intermediate risk tumours than patients with local recurrence. Local recurrence was statistically associated with better overall survival than non-local recurrence ( $p = 0.028$ ) but dramatically decreased overall survival when compared to patients without any recurrence ( $p < 0.001$ ). The site of recurrence, *i.e.* vaginal or central pelvic, was significantly associated with overall survival ( $p = 0.015$ ). Patients without brachytherapy at initial management were more likely to have local recurrence of their disease when compared to those without recurrence ( $p = 0.03$ ). None of the prognostics factors for survival in patients with local recurrence was statistically significant in multivariate analysis.

**Conclusions:** Local recurrence is a key event in endometrial cancer evolution severely impacting overall survival. Better understanding of the factors associated with prolonged survival is mandatory to improve our management of these patients.

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**Keywords:** Endometrial cancer; Recurrence; Local; Central pelvic; Vaginal

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## Introduction

Endometrial cancer remains the most common gynaecology malignancy in France and in Western countries [1,2]. However, even if early diagnosis is carried out in most cases [International Federation of Obstetrics and Gynaecology (FIGO I–II), 10–15% of patients will eventually recur, mostly within 3 years after initial diagnosis [3,4]. These patients have poor outcome with a mortality rate of around 25% at five years [3,5].

Predictive factors for survival after recurrence in endometrial carcinoma are unclear. Some of them have been described such as time to recurrence from initial therapy [6], initial FIGO stage and histological grade of the lesion [7,8]. The treatment of local recurrences remains a challenge and guidelines for treating those patients are not yet bringing all the answers [9]. This emphasises the lack of data regarding the prognosis factor and response to treatment in endometrial cancer recurrence. The site of recurrence has been investigated as an independent prognostic factor for survival after recurrence. Indeed, some studies reported that patients with isolated vaginal recurrence have significantly better prognosis than patients with extravaginal recurrence [10,6,11]. However, data regarding specifically isolated local recurrence, *i.e.* vaginal or central pelvic, are rare.

Our objective was to compare characteristics and prognosis of patients with local recurrence with those of patients with non-local recurrence and those without recurrence.

## Materials and methods

### *Patients included*

Patients included were selected from maintained endometrial cancer databases in nine French institutions (Creteil University hospital, Tenon University Hospital, Reims University Hospital, Dijon cancer center, Lille University hospital and Lille cancer center, Tours University hospital, Bondy University hospital, Rennes University hospital) in France as well as from the Senti-Endo trial [12]. The research protocol was approved by the Institutional Review Board (IRB) of the French College of Obstetrics and Gynaecology (CEROG 2014-GYN-020).

These databases included all patients treated with primary surgery for an endometrial malignancy between January 2000 and December 2012. The main characteristics of the patients included were extracted from their medical charts: age, BMI, medical and surgical history, surgical procedure, 2009 International Federation of Gynecology and Obstetrics (FIGO) stage [13], final pathological analysis, treatment received.

### *Initial management*

Primary surgical treatment consisted with at least total hysterectomy with bilateral salpingo-oophorectomy. Lymphadenectomy, either pelvic or para aortic or, both, was

associated at the time of primary surgery if indicated according to French guidelines at the time the patient was treated. Patients enrolled within the Senti-Endo trial underwent Pelvic sentinel lymph node biopsy and pelvic lymphadenectomy. If the pelvic sentinel lymph node happened to be metastatic either at intraoperative or at final histology, para aortic lymphadenectomy was secondary performed.

Decision of adjuvant therapy (chemotherapy and/or brachytherapy and/or radiotherapy) was based on the French guidelines after discussion in multidisciplinary committee [14]. The follow up protocol was based on the European recommendations [15] *i.e.* clinical exam every 3 or 4 months for the first two years and then with a six months interval until 5 years.

### *Definition and classification of recurrence*

Radiological exam, Abdominal pelvic CT-scan or PET CT, were performed if clinically indicated or for the assessment of suspected recurrent endometrial cancer. Disease recurrence was diagnosed on biopsy or imaging exam. Site of recurrence was usually assessed on both clinical exam and abdominal pelvic CT scan. Date of initial surgery was used to calculate Overall Survival (OS).

Local recurrence was defined as isolated central pelvic or vaginal vault recurrence after initial therapy. Non-local recurrence was defined as a recurrence occurring after initial therapy anywhere but in the vaginal vault or the central pelvic, such as peritoneal carcinomatosis, lymph node metastasis and/or distant metastasis.

Treatment options were discussed in multidisciplinary committee that included at least a surgeon, a radiotherapist and a medical oncologist. Medical history and past adjuvant therapy were considered to elect the most appropriate treatment.

### *Statistical analysis*

Statistical analysis was based on the Student's *t* test for continuous variable and the  $\chi^2$  test or Fisher's exact test for categorical variables. The Kaplan Meier method was used to estimate the survival distribution. Comparisons of survival were made using the log rank test. A Cox proportional hazards model including all the parameters statistically significant in univariate analysis, was used to account for the influence of multiple variables. Values of  $p < 0.05$  were considered to denote significant differences.

Data were managed with an Excel database (Microsoft Corporation, Redmond, WA, USA) and analysed using R 3.0.2 software, available online.

## Results

### *Main characteristics of the patients included*

During the inclusion period, 1229 patients with endometrial carcinoma were included in all the participating

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