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Original Research

The nature of early-stage endometrial cancer recurrence—A national cohort study

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Abstract ***Background and aims:*** The aim of the study was to present a comprehensive analysis of disease recurrence in a large Danish cohort of women with early-stage endometrial cancer treated according to national guidelines.
Methods: All women diagnosed with stage I or II endometrial cancer in 2005–2009 were included in a population-based historical cohort derived from the Danish Gynaecological Cancer Database. Disease recurrence up to 3 years after the primary diagnosis was identified using national registers and hospital charts. Follow-up on survival ended on 31st December 2014. We evaluated the predictive value of clinico-pathological and sociodemographic variables using multivariate logistic regression.
Results: Recurrence within 3 years of the primary treatment was diagnosed in 183 (7%) of the included 2612 women. Site of recurrence significantly impacted on overall survival as the 5-year survival rate was 64.8% for women with vaginal recurrence and 17.5% in women with distant recurrence. Factors predictive of recurrence included the International Federation of Gynaecology and Obstetrics (FIGO) stage (OR: IB = 1.91, stage II = 3.91), Charlson comorbidity index of 3 (OR 1.86), non-endometrioid histology (OR 1.81) and being outside of the workforce (OR 1.81). Vaginal recurrence was predicted by FIGO stage only (OR: IB = 1.88, II = 2.79), while extra-vaginal recurrence was predicted by FIGO stage (OR: IB = 2.12, II = 3.31), Charlson comorbidity index of 3 (OR 1.88) and non-endometrioid histology (OR 2.51).

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Conclusions: Future research should seek to understand the underlying mechanisms of the identified predictive factors to improve recurrence prediction and to reduce morbidity and mortality.

1. Introduction

Understanding the nature of early-stage endometrial cancer recurrence is the first step in evaluating the need for follow-up after treatment. Although endometrial cancer has a good prognosis, patients undergo post-treatment surveillance of varying intensity, including vaginal ultrasound, computed tomography scans and vaginal cuff cytology. The patient group is known to be heterogeneous in terms of survival, and identification of predictive factors of recurrence may guide the follow-up strategy.

Several histological prognostic markers have been proposed in risk stratification systems and are used in planning of treatment and follow-up of endometrial cancer [1–5]. The core variables used to predict recurrence are quite similar and include age at diagnosis, histological type and grade, FIGO stage and lymphovascular space invasion. However, the significance of the different factors varies [6], and none of the systems are accurate in predicting the risk of recurrence [6] leaving future risk stratification systems to be improved by new predictors.

We identified a national cohort of stage I and II endometrial cancer patients treated according to national clinical guidelines, making our population more homogeneous than observed in previous studies [1–5]. In addition to clinico-pathological risk factors, we included sociodemographic factors, as earlier studies have demonstrated a significant impact of these on the incidence of and survival after endometrial cancer [7]. Social inequality in cancer care may partly be explained by earlier primary diagnosis in women with higher socioeconomic status leading to better treatment options and compliance [7].

The objectives of the current study were i) to assess the 3-year recurrence pattern in a large national cohort of early-stage endometrial cancer patients, ii) to analyse the impact of recurrence localisation on overall survival and iii) to identify clinico-pathological and sociodemographic predictors of disease recurrence, and specifically of vaginal and extra-vaginal recurrence.

2. Patients and methods

2.1. Population and study design

All women diagnosed with stage I or II endometrial carcinoma in Denmark between 1st January 2005 and 31st December 2009 were followed until death or to the end of the study period (31st December 2014). Within the time frame of 3 years after hysterectomy, a woman was defined as having recurrent disease if i) the primary treatment left no residual disease and ii) the relapse was radiologically or histologically verified.

2.2. Management of endometrial cancer in the study period

FIGO stage was converted to the 2009 FIGO guidelines [8]. Stage I disease was subdivided into three risk groups: low risk comprised grade 1 and 2 disease and <50% myometrial invasion; intermediate risk comprised grade 3 disease with <50% myometrial invasion, or grade 1 and 2 with >50% myometrial invasion and high risk had grade 3 disease with >50% myometrial invasion or more than 10% clear cell, serous and undifferentiated carcinoma in the tumour tissue [9]. Treatment of stage I disease consisted of total hysterectomy with bilateral salpingo-oophorectomy (BSO). Removal of pelvic lymph nodes was recommended in the intermediate and high risk groups. Furthermore, external pelvic radiation was recommended after surgery in high risk patients. Treatment of stage II disease consisted of either radical hysterectomy with BSO and lymphadenectomy or simple hysterectomy, BSO and external pelvic radiation [10]. Patients, who were up-staged to stage IIIC or IV due to histologically verified lymph node or abdominal metastases, were excluded from the sample.

2.3. Data sources

Data were extracted from seven national registers and from the patients' hospital charts.

i) The Danish Gynaecological Cancer Database, established in 2005, covers all gynaecologic cancers and includes information on diagnosis, treatment and patient characteristics [11].
ii) The Danish National Pathology Register was established in 1999 and contains results of all cytology and histopathology specimens obtained in Denmark [12].
iii) The National Patient Register, established in 1977, records all in- and out-patient discharges from public hospitals in Denmark, with information on admission and discharge dates, procedures performed, main diagnosis and up to 20 sub-diagnoses [13].