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Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO Consensus Conference risk groups: Results from the FRANCOGYN study Group☆

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HIGHLIGHTS

- Endometrial cancer is associated with a specific pattern of recurrence.
- High risk group and histological type 2 are associated with a poor prognosis.
- Patterns of recurrence provide useful information for follow-up recommendations.

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ABSTRACT

Objectives. The purpose of this study was to analyse the endometrial cancer (EC) patterns of recurrence based on a large French multicentre database according to ESMO-ESGO-ESTRO classification.

Methods. Data of women with histologically proven EC who received primary surgical treatment between January 2001 and December 2012 were retrospectively abstracted from seven institutions with prospectively maintained databases. The endpoints were recurrence, recurrence free survival (RFS) and overall survival (OS). Time to the first EC recurrence in a specific site was evaluated by using cumulative incidence analysis (Gray's test).

Results. Data from 829 women were analysed in whom recurrences were observed in 176 (21%) with a median and mean time to recurrence of 13 and 19.5 months, respectively. High (35%) and high-intermediate risk groups (16%) were associated with higher recurrence rates compared with low (9%) and intermediate (9%) risk patients ($p < 0.0001$). Women with high risk EC had a higher 5-year cumulative incidence of distant recurrence (20.7%) than women with high-intermediate, intermediate and low risk EC (5.6%, 3.5%, 3.3%), ($p < 0.001$), respectively. Women with high risk and high-intermediate risk EC had a higher 5-year cumulative incidence of loco-regional recurrence (24.3% and 16.6%, respectively) than women with intermediate and low risk EC (6.6% and 6.5%, respectively), ($p < 0.001$).

Conclusions. We report specific time and site patterns of first recurrence according to the ESMO/ESGO/ESTRO classification. Sites and hazard rates for recurrence differ widely between subgroups over time. Defining patterns

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of EC recurrence may provide useful information for developing follow-up recommendations and designing therapeutic approaches.

1. Introduction

Endometrial cancer (EC) has been reported to be one of the most common gynaecological tumours in developed countries representing the fifth most common cancer overall and the 14th cancer in terms of mortality (76,000 deaths per year worldwide) [1,2]. Most ECs (75%) are diagnosed at an early stage (International Federation of Obstetrics & Gynaecology (FIGO) stages I or II) with a 5-year overall survival (OS) ranging from 74% to 91% (ref). In comparison, for advanced stages (FIGO stages III and IV), the 5-year OS is 57–66% and 20–26%, respectively [3].

Although EC is characterized by a good prognosis, a great heterogeneity has been reported by several authors, especially for early-stage ECs, exposing women to recurrent disease [3–5]. EC site-specific recurrence patterns are influenced by classic prognostic factors such as histological type and grade, depth of myometrial invasion, lymphovascular space involvement (LVSI), and nodal status [3,6–9]. It is now well established that recurrences after primary surgical treatment are mostly located in the true pelvis with events generally occurring in the regional pelvic lymph nodes or in the vaginal vault [3,6–8]. However, other locations including distant metastases or peritoneal carcinomatosis can also be observed underlining the prognostic heterogeneity of the disease [3,6,7,10]. In addition, EC recurrences vary considerably over time and are influenced by adjuvant therapeutic modalities. Nevertheless, despite this recognized variability, more than 70% of recurrences occur within the first 2–3 years after treatment [11–13].

To take this heterogeneity into account, the European Society for Medical Oncology (ESMO) with the support of the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO) recently proposed a multidisciplinary evidence-based classification for clinical practice [3]. However, in light of the evolving classification of EC, limited information is available for each EC subgroup with regard to patterns of disease recurrence and prognosis. This is of major importance as such information may impact indications for adjuvant therapies and modalities of follow-up for each subgroup. We thus conducted an analysis of EC patterns of recurrence based on a large French multicentre database according to ESMO-ESGO-ESTRO conference consensus classification [3].

2. Materials and methods

2.1. Study population

Data of women with histologically proven EC who received primary surgical treatment between January 2001 and December 2012 were retrospectively abstracted from seven institutions with prospectively maintained EC databases in France (Tenon University Hospital, Reims University Hospital, Dijon Cancer Center, Rennes University Hospital, Lille University Hospital, Tours University Hospital, and Creteil University Hospital) and from the Senti-Endo trial. All the women had given written consent to participate in the study. The research protocol was approved by the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2014-GYN-020).

All enrolled women underwent preoperative abdomino-pelvic magnetic resonance imaging (MRI) unless contraindicated, in which case a computed tomography (CT) scan was performed. Clinical, surgical, pathological and adjuvant therapies data were collected: the woman's age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), surgical procedure, nodal staging, final pathological analysis (histological type and grade, depth of myometrial invasion, and LVSI status) and adjuvant therapies. All women were classified according to the FIGO 2009 classification [14] after final pathological analysis.

2.2. Treatment and follow-up

All women had undergone primary surgical treatment, including at least total hysterectomy with bilateral salpingo-oophorectomy. The surgery was performed according to the Institut National du Cancer (INCa) guidelines [15]. Adjuvant therapy was administered on an individual basis at the discretion of a multidisciplinary committee, based on the INCa guidelines, and included vaginal brachytherapy (VBT) and/or external beam radiotherapy (EBRT) and/or chemotherapy (CT) and clinical follow-up [16]. Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings. Follow-up sessions were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

2.3. Subgroup definitions

In line with the ESMO guidelines, histological type 1 EC includes endometrioid tumour whatever the histological grade, and histological type 2 includes clear cell adenocarcinomas, serous adenocarcinomas and carcinosarcoma [16]. According to the ESMO-ESGO-ESTRO classification, women were classified into four subgroups of risk based on the final pathological results: i) low risk group included Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative tumours; ii) intermediate risk group included Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative tumours; iii) high-intermediate risk group included Stage I endometrioid tumours, grade 3, <50% myometrial invasion, regardless of LVSI status or Stage I endometrioid tumours, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion; iv) high risk group included Stage I endometrioid tumours, grade 3, ≥50% myometrial invasion, regardless of LVSI status, Stage II tumours, Stage III endometrioid tumours with no residual disease and type 2 ECs [3].

2.4. Definition and classification of recurrence

Recurrent disease was assessed by physical examination, histological findings, clinical follow-up and imaging (i.e., CT, MRI, ultrasonography, bone scintigraphy, FDG-PET and specific X-ray exams or investigations).

According to previous reports, we applied the following definition to stratify the recurrence events [17]: i) local recurrence was defined by a vaginal vault location; ii) central pelvic recurrence was defined by a location within the pelvis but with no involvement of the vaginal vault or pelvic nodes, iii) nodal recurrence included pelvic and/or para aortic nodal locations; iv) distant recurrence included distant metastasis (bone, liver, lung and brain); v) peritoneal carcinomatosis consisted exclusively of peritoneal involvement. The first site of EC recurrence was defined as follows: loco-regional (vaginal vault, isolated pelvic, nodal, peritoneal carcinomatosis) and distant (bone, liver, lung brain metastases and supradiaphragmatic nodes).

2.5. Recurrence free and overall survival and sites of recurrence

Recurrence free survival (RFS) was defined as the length of time from the date of primary surgery to any EC recurrence and was censored

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