Gynecologic Oncology 142 (2016) 50–53

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Relapse and disease specific survival in 1143 Danish women diagnosed with borderline ovarian tumours (BOT)

Nikoline Marie Schou Karlsen [a,*], Mona Aarenstrup Karlsen [a,b], Estrid Høgdall [a], Lotte Nedergaard [c], Ib Jarle Christensen [a], Claus Høgdall [b]

[a] Molecular Unit, Department of Pathology, Herlev University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark
[b] Department of Gynecology, University Hospital of Copenhagen, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
[c] Department of Pathology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

HIGHLIGHTS

- Optimal management of women with borderline ovarian tumour (BOT) is controversial
- Relapse and survival was evaluated combining data from national registries
- A total of 3.7% and 0.6% of 1143 women experienced relapse or died from their BOT.
- Long-term follow-up is not necessary in stage IA BOT and no residual disease or microinvasion

ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form 5 May 2016
Accepted 6 May 2016
Available online 20 May 2016

Keywords:
Borderline ovarian tumour
Gynaecologic tumours
Prognosis
Relapse
Survival
Posttreatment follow-up

ABSTRACT

Objective. The aim of the study was to evaluate the rate of relapse as well as disease-free, overall, and disease-specific survival in women with borderline ovarian tumour (BOT). Furthermore, the study aims to identify the clinical parameters correlated to relapse.

Methods. National clinical data of women diagnosed with BOT from January 2005 to January 2013 constituted the basis for our study population. The prognostic influence of clinical variables was evaluated using univariate and multivariate analyses.

Results. A total of 1143 women were eligible for analysis, with 87.9% in FIGO stage I and 12.1% in FIGO stages II–IV. Relapse of BOT was detected in 3.7%, hereof 40.5% with malignant transformation. The five-year disease-free survival was 97.6% in FIGO stage I and 87.3% in FIGO stages II–IV. Younger age, laparoscopic surgical approach, fertility sparing surgery, FIGO stages II–IV, bilateral tumour presence, serous histology, implants and microinvasion of the tumour were significantly associated with relapse in univariate analyses. The overall five-year survival rate was 92.2% in FIGO stage I and 89.0% in FIGO stages II–IV. Out of 77 deaths in total, only seven women died from BOT.

Conclusions. A general favourable prognosis in women with BOT was confirmed in our study. Our findings indicate that systematic, long-term follow-up does not seem necessary in women treated for FIGO stage IA BOT with no residual disease or microinvasion.

1. Introduction

Borderline ovarian tumours (BOTs) represent a heterogeneous group of ovarian tumours, accounting for up to 20% of all epithelial ovarian tumours. BOTs are considered a separate entity from benign ovarian cyst adenomas and epithelial ovarian carcinomas (EOC) [1,2]. They are histologically classified as serous, mucinous, endometrioid, seromucinous, or the rare clear cell and Brenner subtypes according to the predominating cell type in which the serous and mucinous types represent the majority [3].

BOTs differ from EOC. Firstly, they do not exhibit a destructive invasion of the underlying stromal tissue [1]. Some microinvasion, however, defined as one or several foci $<10\ mm^2$, is accepted [4]. Secondly, majority of women with BOT are diagnosed in an early stage. Depending on the tumour distribution in the pelvis and the spread to the peritoneum and lymph nodes (called implants), BOTs are postoperatively staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification [5]. Up to 90% of patients with BOT are diagnosed in FIGO stage I compared with 20–30% in EOC [6–8]. In stage I BOT, five-year survival is reported above 95% [6,9–12], whereas five-year

* Corresponding author.
E-mail addresses: nikoline.s.karlsen@gmail.com, nikoline.marie.schou.karlsen.02@regionh.dk (N.M.S. Karlsen).

http://dx.doi.org/10.1016/j.ygyno.2016.05.005
0090-8258/

survival in FIGO stages II–IV BOT is 65–92% [6,11]. Accordingly, the prognosis for women with BOT is in general favourable.

A subgroup of patients with BOT, however, will experience relapse of the disease [3], and malignant transformation is seen in 20–60% of relapses, with a poor prognosis to follow [2,3,13]. Presently, no clinical tools or biological markers are optimal to stratify between women with BOT into high-risk and low-risk categories. Clinical risk parameters for selecting high-risk patients that will benefit from more extensive surgery and close follow-up to increase survival are needed. Hereby, morbidity for low-risk patients, where extensive surgery and close follow-up could be avoided, may also be minimized.

The aim of the study was to evaluate the rate of relapse as well as disease-free, overall and disease-specific survival in one of the largest cohorts of women with BOT reported to date. Furthermore, the study aims to identify the clinical parameters correlated to relapse.

2. Method

Clinical and pathological data from women diagnosed with BOT are continuously registered in the national Danish Gynecological Cancer Database (DGCD) [16]. The DGCD is a multicentre database that contains information from gynaecologists, pathologists, and oncologists on all women in Denmark who are diagnosed with either ovarian, corpus, or cervical cancer. Danish women diagnosed with BOT from January 2005 to January 2013 constituted the basis for our study population. All women were surgically treated and postoperatively followed according to national guidelines [3]. Exclusion criteria were active cancer or former BOT before January 2005.

By means of the person-specific social security number, data from the DGCD were combined with information from patient files and three other Danish registries to validate the occurrence of relapses and cause-specific death. The three other registries used were the Danish National Patient Registry (NPR), the Danish Pathological Data Bank (Patobank), and the Cause of Death Registry. The NPR is a comprehensive health registry containing information on all patient contacts in Danish hospitals, including diagnoses and treatment [14,15]. The Patobank contains information on the histological examinations of all resected tissue or biological material carried out by pathologists in the Danish pathology departments [16]. The Cause of Death Registry provides information on all death causes among Danish citizens [17].

The incidence of relapses was estimated from January 2005 to January 2015. We defined *relapse* as a histologically verified recurrence of disease six months or later (≥6 months) after primary surgery. Information on deaths was evaluated from January 2005 to April 2013. Death causes were validated with information from the Cause of Death Registry, patient files, and data from all of the abovementioned registries. Data from the Cause of Death Registry was available from January 2005 to December 2012 (year of the latest inventory). The study was approved by the Danish Data Protection Agency (Jr.nr. 30-1153).

3. Statistical analysis

Comparison of general characteristics between groups were done using χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney's *U* test for continuous variables. Disease-free and overall survival probabilities were estimated by the Kaplan-Meier method. Relapse probability between groups was estimated using univariate and multivariate Cox regression analyses. The starting point was the date of primary operation. Women alive or emigrated at the end of follow-up or dead from other causes than BOT were censored. Due to a small number of deaths caused by BOT ($n = 7$), univariate and multivariate analyses were not performed with this outcome. It was assumed that missing values occurred at random, and therefore no imputations were done. A p-value ≤ 0.05 was considered statistically significant. All data analyses were conducted using IBM SPSS Statistics 19.0.

4. Results

4.1. General characteristics of the study population

A total of 1177 women diagnosed with BOT were registered in the DGCD. In total, 34 (2.9%) women were excluded either due to revised diagnosis ($n = 27$), primary diagnosis before January 2005 ($n = 4$), or cancer at time of diagnosis ($n = 3$), leaving 1143 women for evaluation in this current study. Clinical characteristics of the 1143 women are listed in Tables 1 and 2. Median age at diagnosis was 55 years (range 13–94 years), and 17.3% ($n = 198$) were below the age of 40 years at diagnosis (all stages). A total of 87.9% ($n = 1005$) were diagnosed in FIGO stage I. The vast majority were of serous (48.2%) or mucinous (46.8%) histology (Table 1). Serous histology was significantly more common in advanced FIGO stage (stages II − IV) ($p < 0.001$) (Tables 1 and 2). Laparotomy was used as the initial surgical approach in 90.1% ($n = 1030$). A total of 16.0% ($n = 183$) underwent fertility sparing surgery, and fertility sparing surgery was significantly more common in FIGO stage I ($p = 0.045$) (Table 1).

4.2. Relapse rate and disease-free survival

We found a total of 42 women (3.7%) with relapse during follow-up. The median time to first relapse was 56 months (range 6–97 months). Malignant transformation was observed in 17 cases of the 42 relapses (40.5%), of which nine were of serous histology, six of mucinous histology, one Brenner tumour, and one seromucinous. A total of 662 women (57.9%) were followed in ≥5 years, and in that group, the five-year disease-free survival was 96.4% in all FIGO stages (95% confidence interval (CI); 95.0–97.8), 97.6% in FIGO stage I (95% CI; 96.4–98.8), and 87.3% in FIGO stages II − IV (95% CI; 80.0–94.6).

4.3. Clinical risk factors for relapse

We found a significant and negative influence of younger age ($p = 0.001$), laparoscopic surgical approach ($p = 0.022$), fertility sparing surgery ($p < 0.001$), higher FIGO stages ($p < 0.001$), bilateral tumour presence ($p < 0.001$), serous histology ($p = 0.037$), implants ($p < 0.001$), and microinvasion of the tumour ($p = 0.026$) on the risk of relapse (Table 3). Residual disease (visible residual disease left after primary surgery) ($p = 0.249$), invasive or noninvasive character of the implant ($p = 0.515$), and evidence of disease at the second operation within six months (<6 months) after primary surgery ($p = 0.885$) showed no significant impact on the risk of relapse. We found that residual disease ($p = 0.036$), FIGO stages II –IV ($p < 0.001$), implants ($p < 0.001$), and microinvasion ($p = 0.034$) were significantly associated with malignant relapse (Table 3). Furthermore, we found fertility sparing surgery ($p < 0.001$) and advanced FIGO stages ($p = 0.017$) to be significant predictive factors for relapse in a multivariate analysis. A total of 718 women were diagnosed in FIGO stage IA with no residual disease or microinvasion. Hereof, a total of 13 (1.8%) had relapse, and malignant transformation was observed in four women (0.6%). Looking upon those who underwent in the same group of women, a total of five out of 562 suffered relapse (0.9%).

4.4. Overall and disease-specific survival

A total of 77 women (6.7%) died during a median time of follow-up of 49.9 months (range 3.5–99 months). The one-year overall survival was 98.3% (95% CI; 97.5–99.1) in all FIGO stages. The five-year overall survival rate was 91.8% (95% CI; 82.6–93.8) in all stages, 92.2% (95% CI; 90.2–94.2) in stage I, and 89.0% in stages II–IV (95% CI; 81.9–96.1).

Fig. 1 illustrates the validation of death causes of the 77 deaths during follow-up. Disease specific death causes from the Cause of Death Registry were available in 70 cases. All 77 deaths underwent a retrospective investigation of data from other registries and patient files in