Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2007;63:132–136
DOI: 10.1159/000096435

Received: January 9, 2006
Accepted after revision: May 3, 2006
Published online: October 19, 2006

Long-Term Survival of Patients with Apparent Early-Stage (FIGO I–II) Epithelial Ovarian Cancer: A Population-Based Study

Patrick Petignat[a] Daniel de Weck[b] Frederic Goffin[d] Georges Vlastos[a]
Reto Obrist[c] Jean-Christophe Luthi[b]

[a]Gynecologic Oncology and Senology Service, University Hospitals of Geneva, Geneva, and [b]Cancer Registry, Health Observatory, Canton of Valais, and [c]Departement Valaisan d'Oncologie, Central Institute of Valais Hospitals, Sion, Switzerland; [d]Division of Gynecological Oncology, University of Liège, Liège, Belgium

Key Words
Early-stage ovarian cancer · Laparotomy · Cancer staging · Survival

Abstract
Background: Women with presumed early-stage epithelial ovarian cancer (EOC) who have not received comprehensive surgical staging are at risk for recurrence. The aim of our study was to analyze the overall long term survival of EOC patients with a presumed early stage EOC. ***Methods:*** A population-based cancer registry was used to identify patients with an early-stage EOC cancer diagnosed between 1989 and 1997. The area under study has no surgical gynecologic oncologist and no tertiary referral center. We categorized patients into two subgroups: low-risk (Ia-Ib well and moderately differentiated) and high-risk (Ia-Ib poorly differentiated or IC-II). Survival curves were calculated from the time of surgery using Kaplan-Meier methods and statistical comparisons were performed using the log-rank test and the Cox proportional hazards regression model. ***Results:*** Fifty patients having an apparent early-stage disease (FIGO I–II) were evaluated. Forty-one patients have been operated by obstetrician-gynecologists and 9 by general surgeons. Twenty-one (42%) have been categorized as low-risk and 29 (58%) as high-risk. An optimal, modified, minimal and inadequate surgical staging was performed in 6, 10, 26 and 58, respectively. The median follow-up time was 147 months (range: 2.5–165). The 5- and 10-year overall survival was 95 and 89% for low-risk and 72 and 33% for high-risk subgroups, respectively. ***Conclusions:*** The surgical staging is frequently incomplete when performed in small hospitals with few patients by nonspecialists. Women in the high-risk group and incompletely staged have a less favorable prognosis than those reported in the literature.

Introduction

Epithelial ovarian cancer (EOC) is the fifth most common cancer among women in Western countries and is the leading cause of death due to gynecologic malignancy [1, 2]. The region under study is a geographically and politically well-defined area, located in the Swiss Alps, without a tertiary referral center and no surgical gynecologic oncologist. Patients with gynecologic cancer are operated either by generalist obstetrician-gynecologists (OG) or general surgeons.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0378–7346/07/0633–0132$23.50/0

Accessible online at:
www.karger.com/goi

Patrick Petignat, MD
CHUM – Hôpital Notre-Dame
1560 Sherbrooke Est
Montréal, Québec, H2L 4M1 (Canada)
Tel. +41 22 382 6818, Fax +41 22 382 4186, E-Mail patrick.petignat@hcuge.ch

Stage of EOC is defined as the extension of disease at the time of an exploratory surgery with an incision that permits evaluation and surgical management of the primary tumor and possible sites of metastasis. If an apparent early-stage disease is present, there is now extensive supporting literature and widespread agreement that a comprehensive surgical staging including peritoneal cytology, blind peritoneal biopsies, total abdominal hysterectomy (TAH), bilateral salpingo-ophorectomy (BSO), omentectomy, pelvic and para-aortic lymphadenectomy should be performed [3–7].

Without rigorous staging procedures, a significant number of patients who were initially believed to have localized disease, have after a comprehensive re-staging procedure, a more advanced stage [8–12]. Most of the patients with stage Ia-Ib GI-II, who have received a complete surgical staging may be safely managed by surgery alone without chemotherapy. Trimbos et al. [13] reported a 5-year disease-free survival of 100% for patients who underwent a complete surgical staging and had a well-differentiated Ia, Ib, Ic and IIa (FIGO 1976).

The aim of our report is to address this problem by analyzing outcomes of unstaged or partially staged patients with apparent early-stage disease.

Materials and Methods

Data Collection

The Valais cancer registry is a population-based registry which records all incident cancers occurring in the resident population (approximately 280,000 inhabitants) of the Canton. A total of 186 women with an EOC were registered between January 1989 and December 1997; 123 (65%) women with a stage III–IV and 63 (35%) with a stage I–II. We excluded patients who have been operated outside the area under study (n = 9) and without complete data (n = 4). Finally, a total of 50 patients having an apparent early-stage EOC (FIGO I–II) were analyzed. These patients were all hospitalized in 1 of the 6 public hospitals or 2 private clinics in the area under study.

Surgical Staging

The details of the surgical procedures attempted were collected by reviewing the operative and cytopathological reports with specific attention to the presence of peritoneal washing, random peritoneal biopsies, TAH, BSO, omentectomy and retroperitoneal lymphadenectomy. Missing or insufficient detailed information was allocated to a not-known category. Surgical staging following TAH and BSO was classified into four different categories (optimal, modified, minimal and inadequate) as previously defined in the Adjuvant Chemotherapy in Ovarian Neoplasm Trial [6]. Briefly, the classification system for determining the quality of surgical staging is as follow: (1) Optimal = biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy; (blind) biopsies of right hemi diaphragm, right and left paracolic gutter, of the pelvic sidewalls, ovarian fossa, bladder peritoneum, and cul-de-sac; sampling of iliac and para-aortic lymph nodes. (2) Modified = everything between optimal and minimal staging. (3) Minimal = biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy. (4) Inadequate = less than minimal staging but at least careful inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases.

Follow-Up

Follow-up information was obtained by review of tumor registry information which assesses the survival. Mortality causes were derived from death certificates supplied by the Swiss Federal Office of Statistics, Neuchâtel, Switzerland.

Statistical Analysis

Comparisons between groups of patients were accomplished by two-tailed, χ^2 or Fisher's exact test when appropriate for categorical data, and t test for continuous numerical data. The Kaplan-Meier method was used to estimate the survival distribution for subgroups of patients with the log-rank test. We also implemented multivariate analyses using Cox proportional hazards regression models. Statistical significance was determined if $p < 0.05$. All analyses were conducted with the SAS software version 8.02 (SAS Institute Inc., Cary, N.C., USA).

Results

Patients' Characteristics

A total of 50 patients with early-stage disease (FIGO I–II) were evaluated, 21 (42%) had FIGO stage Ia-Ib GI-II (low-risk subgroup) and 29 (58%) had stage Ia-Ib poorly differentiated (GIII) or IC-IIC (high-risk subgroup). The median age at presentation was 56.5 years (range: 26–84). The distribution of histology and grade are outlined in table 1.

Surgical Staging

An optimal, modified, minimal and inadequate surgical staging was performed in 6, 10, 26 and 58%, respectively (table 1). Among biopsies performed, the omentum was the site most frequently biopsied, followed by the pelvic peritoneum and finally the pelvic and para-aortic lymph nodes.

Physician Specialty

A total of 22 surgeons, including 6 GS and 16 OG, managed these cases. The median number of cases managed per surgeon over the 9-year study period was less than 3 cases (range: 1–5) and the number of cases per year is one or less per surgeon. Patients operated by OG were more likely to attain an optimal staging when compared

Table 1. Patient's characteristics in early-stage (FIGO I–II) epithelial ovarian cancer (n = 50)

Characteristics	Total (%)	Stage Ia-Ib GI-II (%)	≥ Stage Ia-Ib GIII* (%)	p value
Number of patients	50	21	29	
Age (mean ± SD)	57.0 ± 15.0	55.1 ± 15.6	58.3 ± 14.7	0.472
Histologic cell type				0.212
Serous	20 (40.0)	7 (33.3)	13 (44.8)	
Mucinous	20 (40.0)	11 (52.4)	9 (31.0)	
Endometroid	6 (12.0)	3 (14.3)	3 (10.3)	
Others	4 (8.0)	0 (0.0)	4 (13.8)	
Cell differentiation				0.0001
Grade 1	29 (58.0)	19 (90.5)	10 (34.5)	
Grade 2	12 (24.0)	2 (9.5)	10 (34.5)	
Grade 3	9 (18.0)	0 (0.0)	9 (31.0)	
Quality of staging**				0.862
Optimal	3 (6.0)	1 (4.8)	2 (6.9)	
Modified	5 (10.0)	2 (9.5)	3 (10.3)	
Minimal	13 (26.0)	7 (33.3)	6 (20.7)	
Inadequate	29 (58.0)	11 (52.4)	18 (62.1)	

* ≥ Stage Ia-Ib GIII include Stage Ia GIII, Ib GIII, Ic GI-III, IIa GI-III, IIB GI-III and IIC GI-III. ** Surgical staging categories are defined in 'Materials and Methods'.

Table 2. Surgical staging according to the physician specialty (n = 50)

Surgical staging category*	Physician specialty						p value
	OG (n = 41)		GS (n = 9)		total		0.316
	n	%	n	%	n	%	
Optimal	3	100.0	0	0.0	3	6.0	
Modified	5	100.0	0	0.0	5	10.0	
Minimal	12	92.3	1	7.7	13	26.0	
Inadequate	21	72.4	8	27.6	29	58.0	

* Surgical staging categories are defined in 'Materials and Methods'. OG = Obstetrician-gynecologist; GS = general surgeon.

to GS, although this difference was not statistically significant (p = 0.316). Quality of surgical staging attempted according to the physician specialty (OG vs. GS) is depicted in table 2. The 50 surgical procedures have been managed in 6 public hospitals and 2 private clinics. Fewer than 3 patients have been treated per year in each of the hospitals. None of the 'unstaged' patients with apparent early disease have been re-operated to complete the staging procedures, but 4 of them received an adjuvant platinum-based chemotherapy because of incomplete staging. Adjuvant platinum-based chemotherapy was offered to 24 of 29 patients in the high-risk group.

Survival

The median follow-up was of 147 months (range: 2.5–165). Kaplan-Meier survival curves are presented in figure 1, showing a better survival for low-risk compared to high-risk subgroup (log-rank test: p = 0.001). During the follow-up period, 2 low-risk patients died of tumor-independent reasons without evidence of recurrence. A total of 15 of 26 (58%) high-risk women died of their cancer (two of them had Ia GIII disease). Histologic differentiation was one of the most sensitive indications of prognosis. The Cox proportion hazards models showed that high-risk patients (HR = 5.96, p = 0.03) had a significant-

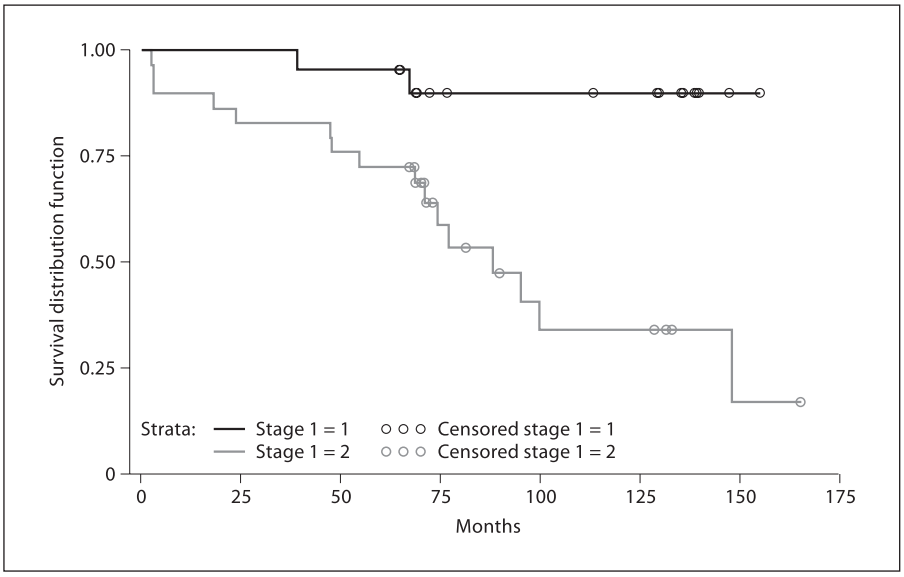

Fig. 1. Kaplan-Meier survival curves in early-stage (FIGO I–II) ovarian cancer. 1 = Stage Ia-Ib GI-II; 2 = stage Ia-Ib GIII or higher. Log-rank test: p = 0.001.

Table 3. Multivariate analysis (Cox proportional hazards model) of factors influencing survival in early-stage (FIGO I–II) ovarian cancer (n = 50)

Stage	Hazard ratio	95% CI	p value
Age (continuous)	1.02	0.98–1.06	0.277
Stage Ia-Ib GI-II	1.00		
Stage Ia-Ib GIII or higher	5.96	1.19–29.85	0.030
Cell differentiation			
Grade 1	1.00		
Grade 2	1.43	0.40–5.11	0.586
Grade 3	3.61	0.98–13.28	0.054
Physician specialty			
GS	1.00		
OG	0.74	0.24–2.38	0.623

OG = Obstetrician-gynecologist; GS = general surgeon; grade 1.

ly worse survival, while controlling for age and physician specialty (table 3). For cell differentiation, patients with high grade (GIII) have a higher risk of dying of ovarian cancer (HR = 3.61, p = 0.054), the difference between grades being statistically borderline. The 5-year disease-specific survival for the low-risk subgroup was 100%. The 5- and 10-year overall survival was 95 and 89% for the low-risk and 72 and 33% for the high-risk subgroups, respectively.

Discussion

The population-based methodology employed here provides a useful tool for addressing current questions surrounding the outcome of patients with an apparent early-stage disease EOC, because it avoids potential selection and follow-up bias.

The area under study is sparsely populated located in the Swiss Alps, and is served by 6 community and 2 private hospitals for a small population size. As a consequence, there is no sufficient surgical experience and not enough hospitalized patients to achieve expertise in the field; the majority of surgeons managed fewer than 2 cases per year and less than 3 patients per year are operated in each of the 8 hospitals. Women with early stage EOC were operated on primarily by general surgeons and general gynecologists and, clearly, they do not adhere to standards of clinical practice. We believe that the absence of surgeon expertise and case volume may explain the very low rate of optimal staging and failure to follow surgical guidelines [14, 15]. It should be a major objective in the next few years to identify information and training that could improve the likelihood for patients to receive the recommended surgical treatment based upon contemporary evidence from the medical literature.

Most patients with stage Ia-Ib GI-II can be safely managed by surgery alone without chemotherapy, if they have been optimally staged [13]. But, how to manage 'incompletely' or 'partially' staged patients with apparent stage Ia-Ib GI-II? Should these patients have additional surgery

to more definitively stage the disease? Should adjuvant therapy be given without further staging or should only a 'wait and see' policy be applied? The current trend is that patients with presumed early-stage disease should undergo either a restaging procedure or receive chemotherapy for the possibility of an occult advanced disease [9, 16, 17]. The management of unstaged patients, especially if they can be cured with surgery only, is problematic and the lack of proper staging is associated with both undertreatment and overtreatment [18]. Because the aim of surgical treatment in early stage EOC is to offer a curative therapy while minimizing treatment-related morbidity, all clinically early-stage EOC patients should receive a complete surgical staging surgery.

In our series, patients in the high-risk group had a poor overall survival rate, comparing unfavorably with survival rate reported in the ACTION and ICON-1 trials [6]. In our series, one reason is probably that a significant number of these women with presumed early-stage disease were in fact not 'true' early-stage, but stage III disease. In other series where complete surgical staging have been performed, approximately one-third of patients with apparent early-stage ovarian cancer were found to have a more advanced stage when complete surgical staging was performed [8]. Therefore, it is likely that some patients thought to have an early-stage disease had a more advanced disease and poorer prognosis than expected. Another potential concern could be that chemotherapy treatment was not optimal; however, details on specific regimen were not available.

The strength of our study is that it is a population-based study reflecting a report of the daily life situation in an area deprived of adequate surgical oncology care. Limitation is that this is a small series and as other population-based series, our report was limited by a lack of central pathology review.

In conclusion, surgical staging is frequently incomplete when performed in small hospitals with few patients by nonspecialists. Women in the high-risk group and who are incompletely staged have a poor prognosis.

References

1 http://www.obs-vs-sante.ch.

2 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ: Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.

3 Trimbos JB: Staging of early ovarian cancer and the impact of lymph node sampling. Int J Gynecol Cancer 2000;10:351–355.

4 Benedet JL: Progress in gynecologic cancer detection and treatment. Int J Gynaecol Obstet 2000;70:135–147.

5 ACOG Committee Opinion: Number 280, December 2002. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. Obstet Gynecol 2002; 100:1413–1416.

6 Trimbos JB, Parmar M, Vergote I, Guthrie D, Bolis G, Colombo N, Vermorken JB, Torri V, Mangioni C, Pecorelli S, Lissoni A, Swart AM: International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst 2003;95: 105–112.

7 Moore DH, Rubin SC: Primary surgical management of early epithelial ovarian carcinoma; in Rubin SC (ed): Ovarian Cancer. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 201–218.

8 Young RC, Decker DG, Wharton JT, Piver MS, Sindelar WF, Edwards BK, Smith JP: Staging laparotomy in early ovarian cancer. JAMA 1983;250:3072–3076.

9 Soper JT: Management of early-stage epithelial ovarian cancer. Clin Obstet Gynecol 1994;37:423–438.

10 Stier EA, Barakat RR, Curtin JP, Brown CL, Jones WB, Hoskins WJ: Laparotomy to complete staging of presumed early ovarian cancer. Obstet Gynecol 1996;87:737–740.

11 Leblanc E, Querleu D, Narducci F, Chauvet MP, Chevalier A, Lesoin A, Vennin P, Taieb S: Surgical staging of early invasive epithelial ovarian tumors. Semin Surg Oncol 2000; 19:36–41.

12 Munstedt K, Franke FE: Role of primary surgery in advanced ovarian cancer. World J Surg Oncol 2004;2:32.

13 Trimbos JB, Schueler JA, van der Burg M, Hermans J, van Lent M, Heintz AP, Fleuren GJ: Watch and wait after careful surgical treatment and staging in well-differentiated early ovarian cancer. Cancer 1991;67:597–602.

14 Petignat P, Vlastos G: Why do ovarian cancer patients not consult a gynecologic oncologist? Gynecol Oncol 2002;87:157.

15 Petignat P, Vajda D, Joris F, Obrist R: Surgical management of epithelial ovarian cancer at community hospitals: a population-based study. J Surg Oncol 2000;75:19–23.

16 Trimbos JB, Vergote I, Bolis G, Vermorken JB, Mangioni C, Madronal C, Franchi M, Tateo S, Zanetta G, Scarfone G, Giurgea L, Timmers P, Coens C, Pecorelli S: Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J Natl Cancer Inst 2003; 95:113–125.

17 Trimbos JB, Timmers P: Chemotherapy for early ovarian cancer. Curr Opin Obstet Gynecol 2004;16:43–48.

18 Le T, Adolph A, Krepart GV, Lotocki R, Heywood MS: The benefits of comprehensive surgical staging in the management of early-stage epithelial ovarian carcinoma. Gynecol Oncol 2002;85:351–355.