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Chapter 7

Prognostic value of Ic substages in invasive epithelial ovarian carcinoma

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Submitted
ABSTRACT

Objectives: Since the incorporation of capsule rupturing and other prognostic variables in the FIGO staging system for epithelial ovarian cancer, stage I is an admixture of different substages. The current study describes FIGO stage Ic ovarian cancer patients with a heterogeneity of different clinical presentations like capsule rupturing, ascites containing malignant cells, surface tumor and positive peritoneal fluid in relation to disease-free and overall survival.

Methods: Of the 448 patients randomized in the ACTION trial, 417 FIGO stage I ovarian cancer patients and 31 stage IIa patients were used for the recurrence-free and overall survival analysis.

Results: From the 417 FIGO stage I patients 155 (36%) were stage Ia, 37 stage Ib (9%) and 223 stage Ic (53%) patients. The 5-year overall survival was 82% for stage Ia, 86% for stage Ib and 81% for stage Ic, no statistical difference was found between these substages. Both disease-free and overall 5-year survival was not significant different for the Ic subcategories capsule rupture (71/80%), external surface tumor (76/88%) and positive ascites or malignant washings (67/78%). The time of capsule rupturing, before or during surgery, was not a prognostic factor.

Conclusions: This large series of early ovarian cancer patients shows no difference in prognosis between stage Ic patients compared to the other stages Ia and Ib patients. This study challenged the clinical significance of definition of stage Ic. Further clinical trials maybe define better prognostic factors in these ovarian cancer patients which could be incorporated in the FIGO staging system.
INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for approximately 25% of patients with disease confined to the ovaries (FIGO stage I). These patients are further subdivided according the last International Federation of Gynecology and Obstetrics FIGO classification in 1985 depending whether one ovary (Ia) or both ovaries (Ib) are involved or if there was capsular rupture, surface tumor, ascites present that contains malignant cells or positive peritoneal washings (Ic) [1]. The importance of capsule rupturing was already incorporated in the FIGO staging system in 1971 [2]. The implications of substage in stage I are that it is generally supposed that the factors which assign patients to Ib or Ic carry a worse prognosis [3,4]. In several studies the 5-year survival for stage Ia patients is around 90-95% which decreases to 80-85% and 75-80% for stage Ib and Ic respectively [5-10]. However, many controversies still exist with regard to the relative importance of prognostic variables within stage I and in particular the independent significance of capsule rupture before or during surgery, surface tumor and positive peritoneal cytology. Some authors suggest that rupture of the tumor capsule [11,12] have a relevant impact on survival of early ovarian cancer patients and Ahmed et al. [10] identified the presence of ascites and surface tumor as independent prognostic factors. On the other hand, other studies did not confirm these findings [13,14].

The vast majority of the patients randomized in the EORTC ACTION trial 55904 were FIGO stage Ic patients. To clarify the relevance of the different Ic substages we performed the current study. This analysis of patients randomized in the EORTC ACTION trial shows the results of the subgroups of FIGO stage Ic patients which consist of a heterogeneity of clinical presentations which may do have different impact in relation to recurrence rate and overall survival.

PATIENTS AND METHODS

All 448 patients were randomized in the European Organisation for Research and Treatment of Cancer (EORTC) Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION, 55904) trial which run between November 1990 and March 2000. Patients with FIGO stages Ia-Ib, grade 2 and 3, FIGO stages Ic-IIa, grade 1-3 and all grade stages Ic-IIa clear cell carcinoma were eligible for the study. Patients were randomized after surgical treatment between cisplatinum-based chemotherapy or no adjuvant chemotherapy (observation arm). Patients in the chemotherapy arm received at least four courses of platin-based chemotherapy. Patients in the observation arm were followed and treated according the institution policy by a clinically or histologically proven recurrence.
For this analysis 417 patients FIGO stage I epithelial ovarian cancer patients (93%) and 31 stage IIa patients (7%) were used. From the 417 FIGO stage I patients 155 (36%) were Ia, 37 stage Ib (9%) and 223 stage Ic (53%) patients. Information about clinical and histopathological features as well as for surgical staging were available for all patients. The mean follow-up at the time of the analysis was 5.6 years. For a detailed description and results of this trial we refer to a previous publication of Trimbos et al. [15]. Subgroup analysis was performed on the different FIGO stage Ic groups (n=223). Patients were classified according the International Federation of Gynecology and Obstetrics FIGO stage of 1985 [1].

Statistical analysis was performed using SPSS version 15.0 (SPSS inc., Chicago, IL). The Kaplan-Meier method was used for generating the disease-free and overall survival curves [16]. Comparison of survival distributions were made with the log-rank test with a significance defined as the \( P \) value < 0.05.

RESULTS

Table 1 shows the different FIGO stages of the 448 patients randomized in the EORTC ACION trial for both treatment arms. The FIGO stages were well balanced between the observation and the chemotherapy arm. The distribution of the FIGO stages was as follows: one-third of the patients (36%) were FIGO stage Ia (n=155), 9% stage Ib (n=37), 53% stage Ic (n=223) and 2% IIa (n=31). Further substages of the 223 Ic patients were 50 carcinomas on the ovarian surface (22%), 116 patients with Ic capsule rupture (52%) and 57 patients Ic with malignant washing or ascites (26%). From the

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Observation Arm N=224(%)</th>
<th>Chemotherapy arm N=224(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>76 (34%)</td>
<td>79 (35%)</td>
</tr>
<tr>
<td>Ib</td>
<td>18 (8%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Ic ovarian surface</td>
<td>28 (12%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Ic capsule rupture</td>
<td>52 (23%)</td>
<td>64 (29%)</td>
</tr>
<tr>
<td>Ic malignant washing/ascites</td>
<td>33 (15%)</td>
<td>24 (11%)</td>
</tr>
<tr>
<td>IIa</td>
<td>15 (7%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>
116 patients with Ic capsule rupture, 84% of the rupturing occurred during operation, while 16% took place before surgery. The FIGO stage was missing in two patients. No significant difference was shown in the Ic stage for treatment arm, surgical staging category and differentiation grade as represented in Table 2.

![Table 2. Patients Characteristics of FIGO stage Ic substages](image)

Figure 1 shows the 5-year disease-free survival (DFS) of all 448 patients randomized in the ACTION trial with no significant difference for the different stages ($P = 0.06$). Figure 2 represents the overall survival curves of the three FIGO Ic substages. The 5-year overall survival for Ic substages, tumor on the surface, capsule rupturing and ascites or malignant cells containing peritoneal fluid were 76%, 71% and 67% respectively ($P = 0.47$). In the group of 223 FIGO stage Ic patients 53 recurrences occurred, 11/50 ovarian surface (22%), 26/116 capsule rupture (22%) and 16/57 malignant washing or ascites (28%). The 5-year disease-free survival ranged between 78 and 88% ($P = 0.71$) for the different Ic stages as shown in Figure 3. From the 223 patients in the FIGO stage Ic group, 40 (18%) died of the disease.

No significant difference was found in both disease-free and overall survival between the Ic capsule rupturing group before and during surgery. Although the 5-year disease-free survival was better in the group with rupturing during operation (74%) compared to the group of rupturing before operation (64%), the overall 5-year survival showed an advantage in the group rupturing before surgery in comparison to rupturing during surgery, 85 versus 78% respectively. These differences were not statistically significant.
Figure 1. Kaplan - Meier curves for disease-free survival in patients with early ovarian cancer in both treatment arms of the trial by FIGO stage; Ia (n = 155), Ib (n = 37), Ic ovarian surface (n = 50), Ic capsule rupture (n = 116), Ic ascites/malignant washing (n = 57) and Ila (n = 31). P = 0.06 using the log-rank test.

Figure 2. Kaplan - Meier curves for overall survival in patients with early ovarian cancer in both treatment arms of the trial by FIGO Ic substages; Ic ovarian surface (n = 50), Ic capsule rupture (n = 116), Ic ascites/malignant washing (n = 57). P = 0.47 using the log-rank test.
In the ACTION trial and the combined ACTION/ICON 1 analysis [11], FIGO stage was not a prognostic factor. FIGO stage Ic disease was not associated with a higher risk of recurrence or death compared to moderately and poorly differentiated FIGO stage Ia and Ib. In a recent meta-analysis of more than 1500 cases of early ovarian cancer patients, Vergote et al. found that stage Ic had a similar prognosis as stage Ib [17]. On the other hand, some other investigators showed a worse outcome in relation to tumor rupture [4] and capsule penetration [11,12], while Dembo et al. [14] found cyst rupture and capsular penetration not prognostic. This last study did not perform lymph node sampling and peritoneal biopsies in the absence of a palpable abnormality. Furthermore, most of these studies are retrospective analyses of small numbers of patients with sometimes unknown surgical staging procedure. Another reason for the inconsistency of the results may be the diverse treatment modalities. No difference in survival was observed between stage I subgroups ovarian carcinomas and stage Ila in a study of Sigurdsson et al. [6]. Our data confirm these findings, the 223 patients with

![Figure 3. Kaplan-Meier curves for disease-free survival in patients with early ovarian cancer in both treatment arms of the trial by FIGO Ic substages; Ic ovarian surface (n = 50), Ic capsule rupture (n = 116), Ic ascites/malignant washing (n= 57). P = 0.71 using the log-rank test.](image-url)
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Ic ovarian cancer showed a 5-year disease-free survival of 70% and a 5-year overall survival of 82% which was not worse than those patients with stage Ia and Ib. Although the statistical power of the current analysis was 0.63, the results of the ACTION trial describe the largest series of early ovarian cancer patients in a randomized trial until now. In our study also no survival difference was found between the different stage I patients, giving a 5-year overall survival of 83% for stage Ia (n=155), 88% for stage Ib (n=37), 82% for stage Ic (n=223) and 78% for stage Ila (n=31) patients. In a study done by Piver [18], the 5-year progression-free survival of 32 stage Ic grade 3 patients with invasive epithelial ovarian cancer was 90.5% and the 5-year survival was 93.3%, treated with cisplatin-based chemotherapy. In contrast to our findings, Brugghe et al. found FIGO substage the strongest prognosticator in 102 adequately staged Ia-Ic ovarian cancer patients who received no postoperative treatment [19].

In studies concerning stage Ic ovarian cancer patients a different prognostic value of capsule rupturing has been found. In a study of Krafft et al. [20] rupture and ascites drastically reduced the changes of survival in 60 patients with early ovarian cancer. Sainz de la Cuesta et al. [21] found a significant difference (P = 0.03) in the recurrence-free survival of stage Ia (97 months) compared to stage Ic capsule rupture (78 months). The disease-free survival of the other Ic group (capsular invasion, positive ascites or washings) did not differ significantly from the Ic rupture group. The hazard ratios for overall survival associated with stage Ic-rupture and each potential confounder, except for bloating, exceeded 6.5. They concluded that intra-operative rupture of malignant epithelial ovarian neoplasms may worsen the prognosis of patients with stage I ovarian cancer. Prognostic factor analysis in 162 stage I high risk ovarian cancer patients performed by Tropé et al. showed that extracapsular growth and tumor rupture were significant independent factors with \( P \) values of 0.0005 and 0.04 respectively [22]. A multivariate analysis by Kodama et al. showed that capsular rupture caused by the surgeon did not affect the prognosis in stage I and II ovarian cancer [23]. Looking at our data the subcategories of Ic patients including capsule rupture (n=116), surface invasion (n=50) and ascites or malignant cells containing washings (n=57) showing 5-year disease-free survival of 71%, 75% and 68% respectively (\( P = 0.71 \)). The survival prognosis was not influenced by the different categories, giving 5-year overall survival percentages of 80% for Ic capsule rupturing, Ic surface of 89% and Ic positive ascites or washings of 79%. Villa et al. [9] reported a significant difference of 5-year survival between patients with tumor presence on the surface (88%) compared to intra-operative tumor rupture (72%).

The specific importance of rupture before or during operation is still unclear. Sevalda et al. reported no influence on survival rates for stage Ic capsule rupture during surgery
and therefore they considered that these patients do not belong to the subgroup Ic as suggested by the FIGO committee [5]. In a multivariate analysis of Vergote et al. both rupturing before as during surgery were independent predictors of disease-free survival, with rupturing before operation giving a higher change of recurrent disease [17]. The results of a study done by Mizuno et al. showed better survival curves for patients with rupturing during operation compared to the other Ic patients [24]. In contrast to these findings, Sjövall et al. found no difference in survival between those patients whose tumors had intact capsules and patients in whom rupture occurred during surgery, 78% versus 85% respectively. The conclusion was drawn that manipulation during surgery which results in puncture or rupture does not have a negative influence on the outcome for the patients. On the other hand, a significant difference in survival was found between patients in whom rupture occurred before surgery and those with intra-operative rupture, 59% and 85%, respectively [25]. The results of our analysis with further subdivision of the Ic capsule rupture group into 19 patients where rupture occurred before surgery and 97 patients with rupturing during surgery shows a difference in both 5-year recurrence-free survival (65% versus 74%) and overall survival (80% versus 89%) in favor of capsule rupturing during surgery but this difference reached no significance.

In conclusion, in this large randomized trial in early ovarian cancer patients with a subset of more than 200 stage Ic patients no significant difference was found in recurrence rate and survival in the subsets of Ic patients, also no clear negative impact on survival and recurrence rate could be found for capsule rupturing before or during surgery. The current used FIGO staging system does not differentiate between low and high risk early ovarian cancer patients. Maybe other prognostic factors, like DNA ploidy and degree of differentiation should be incorporated in a new staging system to divide patients with different prognosis.
## Appendix 1
Capsule rupturing in the International Federation of Gynecology and Obstetrics (FIGO) staging system

<table>
<thead>
<tr>
<th>Year</th>
<th>Stage Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>Capsule rupture not incorporated in staging system</td>
</tr>
<tr>
<td>1964</td>
<td>Stage Ic growth limited to one or both ovaries, ascites containing malignant cells</td>
</tr>
<tr>
<td>1971</td>
<td>Stage Ia1/Ib1 growth limited to one ovary/both ovaries, capsule ruptured, no ascites</td>
</tr>
<tr>
<td>1971</td>
<td>Stage Ia2/Ib2 growth limited to one ovary/both ovaries, capsule not ruptured, no ascites</td>
</tr>
<tr>
<td>1971</td>
<td>Stage lc1 growth limited to one or both ovaries, capsule ruptured, ascites containing malignant cells</td>
</tr>
<tr>
<td>1971</td>
<td>Stage lc2 growth limited to one or both ovaries, capsule not ruptured, ascites containing malignant cells</td>
</tr>
<tr>
<td>1975</td>
<td>Stage Ia1/Ib1 growth limited to one ovary/both ovaries, no tumor external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>1975</td>
<td>Stage Ia2/Ib2 growth limited to one ovary/both ovaries, tumor external surface and/or capsule ruptured, no ascites</td>
</tr>
<tr>
<td>1975</td>
<td>Stage lc tumor either stage Ia or Ib and ascites present or positive peritoneal washings</td>
</tr>
<tr>
<td>1985</td>
<td>Stage Ia growth limited to one ovary, no tumor external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>1985</td>
<td>Stage Ib growth limited to both ovaries, no tumor external surface, capsule intact, no ascites</td>
</tr>
<tr>
<td>1985</td>
<td>Stage lc tumor either stage Ia or Ib, tumor on the external surface or capsule ruptured or ascites containing malignant cells or positive peritoneal washings</td>
</tr>
</tbody>
</table>
REFERENCES
