Adjuvant radiotherapy in stage I-II epithelial ovarian cancer

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Summary

Objective: The purpose of this study was to assess the efficacy and side-effects of abdominopelvic irradiation applied as adjuvant postoperative therapy in early stage ovarian carcinomas.

Methods: From 1 January 1988 to 31 December 1993, 113 patients with FIGO stage IA-IIC epithelial ovarian carcinoma were treated with postoperative radiotherapy. Whole abdominal irradiation or lower abdominopelvic irradiation was used. The dose of specification was 20 Gy to the upper part of the abdominal cavity and 40 Gy to the lower part of the abdomen and the pelvic region.

Results: Primary cure was achieved in 110 patients (97%). During the period of follow-up, 33 cases of tumor recurrences (30%) were recorded. Abdominopelvic metastases were most frequent (18%). The overall 5-year survival rate for the complete series was 69% and the cancer-specific survival rate was 72%. Tumor grade was an independent and significant prognostic factor (Cox multivariate analysis; $p = 0.007$). Early radiation reactions of any type were noted in 93% of the cases and, in 11%, discontinuation of radiotherapy was necessary. Late radiation reactions were noted in 58% of the cases and the most common side-effect was diarrhea, but in most cases these reactions were of limited clinical significance. The incidence of severe bowel toxicity was 10% and, in two patients (1.8%), surgery was necessary due to late radiation reactions.

Conclusions: Adjuvant abdominopelvic radiotherapy is one option among others (e.g. various types of chemotherapy ôr no further treatment) in primary treatment of early stage ovarian carcinoma. The optimal adjuvant therapy for this group of patients is not known today and further prospective and randomized studies are needed.

Key words: Ovarian cancer; Early stages; Adjuvant therapy; Radiotherapy; Prognosis.

Introduction

Epithelial ovarian cancer, which is the most common histologic type of ovarian malignancy (85-90%), is mainly diagnosed in advanced stages (III-IV). Two-thirds of the patients present with tumors outside the pelvis at the time of the diagnosis [1]. The less common histologic subtypes, such as germ cell tumors and sex cord-stromal tumors will not be dicussed in this article.

Early stage cancers (FIGO stages I-II) are important with regard to optimal therapy because the majority of these tumors are potentially curable [2]. There is a distinct association between tumor stage, degree of differentiation, and the age of the patient. Early stage tumors are often better differentiated and the patients are significantly younger than those with advanced stage disease (FIGO stages III-IV) [3, 4].

Among the histologic subgroups, mucinous and endometrioid cancers have been diagnosed relatively more often in stage I and serous and undifferentiated tumors more often in stages II-III [5]. The cornerstone of primary treatment of ovarian cancer is surgery. In early stage disease, the surgical procedure comprises total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing for cytology, infracolic omentectomy, blind biopsies of the pelvic peritoneum, right and left paracolic gutters, and the peritoneal surface of the diaphragm. Adhesions close to the primary tumor in the pelvis should also be biopsied and the pelvic and para-aortic lymph nodes should be sampled. Metastatic involvement of the para-aortic lymph nodes may be found even if there are no metastases to the pelvic nodes. The lymphatic drainage of the ovaries via the infundibulopelvic ligament is regarded as the main pathway. About 30% of patients with inadequate primary surgical staging are found to have more advanced disease when restaged properly [6-8, 11, 12]. Schueler *et al.* found that, in 13 out of 45 patients (29%), the restaging laparotomy resulted in upstaging, with 54% of the tumors being finally allotted to FIGO stage III. The complication rate in secondary staging procedures appeared to be significantly higher than in primary procedures, 77% versus 23% ($p < 0.05$). Upstaging was significantly correlated with the serous histologic type ($p < 0.005$), but not with age or histologic grade [7].

In one study of early ovarian cancer, lymph node metastases were found in 32 out of 242 patients (13.2%). The incidence of positive nodes was nearly the same among the patients with tumor stage IA, IB, or IC. The significantly highest incidence of metastases (25%) was found in the group of serous adenocarcinomas when compared with other histologic subtypes ($p < 0.001$) [9].

Complete surgical removal of all macroscopic disease in early ovarian cancer is not synonymous with a cure, as a significant proportion of the patients will eventually die of their disease despite appropiate surgery [10].

There is a lack of consensus regarding the postoperative management of early stage, optimally debulked ovarian cancer, around the world [12]. Patients who are thought to have early stage disease on the basis of inadequate staging procedures should either undergo a restaging laparotomy or receive postoperative adjuvant therapy due to the possibility of occult residual disease [1, 13].

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There appears to be a subgroup of patients suffering from epithelial ovarian cancer who have a favorable prognosis and do not require any further treatment after primary surgery. An adequate identification of this subgroup would be beneficial in the planning of further treatment and follow-up after primary laparotomy [14]. Based on data from the GOG trials, most authors would agree that tumors in stage IC, grade 3, and all stage II tumors require additional postoperative therapy [1, 12].

Abdominopelvic external beam radiotherapy as an adjuvant postoperative treatment after comprehensive surgical staging in completely resected stages of ovarian carcinoma has been employed worldwide for many decades. During the last ten years, the use of radiotherapy in this setting has decreased and has often been replaced by adjuvant chemotherapy. This change in treatment policy is not based on firm data from clinical trials, but more on extrapolation of data from the treatment of ovarian carcinoma in advanced stages.

In early stage high-risk ovarian cancer patients, abdominopelvic radiation therapy was the only treatment found to yield a survival benefit in a randomized trial. Randomized trials indicate that chemotherapy and intraperitoneal radiophosphorus therapy may reduce the frequency of relapses, but they do not increase the overall survival. There is now increasing pressure to adopt paclitaxel and cisplatin as standard chemotherapy also for early stage disease, based on the apparent improvement in outcome for patients with suboptimally debulked advanced disease, as reported in the GOG #111 study [12].

The aim of our study was to evaluate postoperative whole abdominal and lower abdominal irradiation as adjuvant treatment in a series of early stage (FIGO IA-IIC) ovarian carcinomas. Long-term survival data are presented for various stages and risk groups as well as the rates of early and late radiation reactions. The results are also compared with other data reported in the literature.

Materials and Methods

During the period 1 January 1988 to 31 December 1993, 171 women with early stage invasive epithelial ovarian carcinoma were referred to the Department of Gynecologic Oncology, Örebro Medical Center Hospital. Five of these patients with stage IA tumors received no postoperative treatment at all, but they were followed-up with clinical control visits, as were the treated patients. Four of these patients had tumor recurrences during the follow-up period. One patient with a stage IC tumor and only 26 years of age at the time of the diagnosis underwent unilateral salpingo-oophorectomy and is still alive with no evidence of disease after 97 months. Two patients were treated with both radiotherapy and chemotherapy and another three had radiotherapy but were excluded from the analysis because of deviations from the standard treatment protocol. Another 48 cases were treated with adjuvant chemotherapy, usually four to six courses of cisplatin and doxorubicin in combination. In 24 of these patients, the tumor stage was IC and, in 13 cases, it was IIC. In the remaining 11 patients, there were one or more contraindications to radiotherapy, e.g. known abdominal adhesions, a history of ileus or subileus, diverticulitis of the sigmoid colon, or repeated abdominal surgery.

Table 1. — *FIGO stages versus histopathology and grade distributions in the complete series (n = 113).*

FIGO stages	IA	IB	IC	IIA	IIB	IIC
	No (%) 55 (49)	No (%) 4 (4)	No (%) 34 (30)	No (%) 3 (3)	No (%) 8 (7)	No (%) 9 (8)
Histopathology	IA	IB	IC	IIA	IIB	IIC
Serous	20 (36)	3 (75)	13 (38)	1 (33)	6 (75)	3 (33)
Mucinous	18 (33)	0	5 (15)	0	1 (13)	0
Endometrioid	12 (22)	1 (25)	7 (21)	1 (33)	1 (13)	4 (44)
Clear cell	5 (9)	0	9 (26)	1 (33)	0	1 (11)
Anaplastic	0	0	0	0	0	1 (11)
$p = 0.034$ (χ^2)						
Tumor grade	IA	IB	IC	IIA	IIB	IIC
G1	24 (44)	3 (75)	8 (24)	1 (33)	3 (38)	1 (11)
G2	20 (36)	1 (25)	15 (44)	2 (67)	4 (50)	4 (44)
G3	8 (15)	0	8 (24)	0	1 (13)	3 (33)
Not graded	3 (5)	0	3 (9)	0	0	1 (11)
$p = 0.407$ (χ^2)						

Seven tumors were not graded (all clear cell carcinomas).

From 1 January 1994, the standard treatment at the department was changed from radiotherapy to chemotherapy for all patients, using a combination of cisplatin and cyclophosphamide (4 courses given on a 4-weekly schedule).

The remaining 113 patients, all in FIGO stages IA-IIC, were treated using a standardized adjuvant radiotherapy protocol and were included in the analyses of this study. The FIGO stage distribution, histopathology, and tumor grades are presented in Table 1. The median age of the patients was 62 years (range 26-82 years). Sixty patients (53%) had a history of previous abdominal surgery, and 86 patients (76%) had a history of one or more concurrent diseases (Table 2). The standard primary surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, appendectomy, multiple peritoneal biopsies, and cytology of ascitic fluid or peritoneal washings. Surgery was performed at five different gynecology and obstetrics departments in the Örebro Medical Region (in central Sweden). The total population of this region is 820,000 inhabitants. All the patients were referred to the Department of Gynecologic Oncology in Örebro four to six weeks after the primary surgery for final staging and classification of the tumor and to draw up a treatment plan. All patients underwent a gyne-

Table 2. — *History of previous abdominal surgery and concurrent diseases.*

Abdominal surgery	Patients	Percentage
None	53	47.0
Appendectomy	27	23.9
Cholecystectomy	12	10.6
Gastrointestinal	3	2.6
Urogenital	1	0.9
Gynecological	17	15.0
Concurrent diseases	**Patients**	**Percentage**
None	27	23.9
Cardiovascular	41	36.3
Diabetes mellitus	1	0.9
Rheumatic disease	8	7.0
Gastrointestinal	6	5.3
Urogenital	6	5.3
Other malignancy	4	3.5
Other	20	17.8

cologic examination under anesthesia. The histopathologic specimens were reviewed and, if necessary, reclassified at the Department of Pathology, Örebro Medical Center Hospital. The primary evaluations of the histopathologic specimens were done at three different departments of pathology in the region serving the five referring gynecologic departments.

The routine postoperative adjuvant therapy for early stage ovarian carcinoma confined to the pelvis during this period was irradiation of the lower abdomen and the pelvis. A-P fields were used and treatment was given daily, 5 days a week, comprising 23 fractions. The dose per fraction was 1.7 Gy and it was defined as a midplane dose. The total dose was 39.1 Gy. In cases with potential tumor spread outside the pelvis, mostly in stages IC or IIC (ascitic fluid, rupture of the tumor capsule) or with a residual tumor (stage II), the whole abdominal cavity was irradiated. A-P fields were used and the upper border was set 1 cm above the domes of the diaphragm on expiration. The lower border was set just below the obturator foramina and the lateral borders well beyond the anterior iliacal spinae. Both fields were treated each day. The midplane dose was 1.0 Gy per fraction, and 20 fractions were given over four weeks. No shielding was employed. As a boost, the lower part of the abdominal cavity (upper border at the disc between L3 and L4) and the pelvis were given another 20.4 Gy in 12 fractions (1.7 Gy per fraction). The external beam irradiation was given with 18-MV linear accelerators. Parallel with, and in addition to, the external beam therapy, intracavitary vaginal irradiation was given using a high-dose rate (HDR) afterloading technique (^{60}Co or ^{192}Ir). The total dose was 12.0 Gy, given in 2 fractions of 6.0 Gy each and specified at a depth of 5 mm below the surface of the vaginal mucosa with an interval of one week. The upper two-thirds of the vagina was treated using a perspex vaginal obturator (diameter 20-30 mm). The intracavitary vaginal irradiation in adjuvant radiotherapy for ovarian cancer was given as a boost to the vaginal walls to prevent local recurrences. The concept was the same as for adjuvant vaginal treatment of endometrial carcinoma.

The median follow-up time of the complete series was 74 months and the range was 3-125 months. The patients were followed-up every 3-4 months during the first three years, and then every six months up to five years at the Department of Gynecologic Oncology. Between five and ten years, the patients were followed-up once a year at the referring department. One patient emigrated to Italy and was lost to follow-up. In most cases of recurrence, the patients were treated with platinum-containing chemotherapy.

Pearson's chi-square, Yates' chi-square, the Student's t-test, the log-rank test, and the Cox multivariate analysis were used in the statistical analysis. The Statistica (StatSoft™) package for personal computers was used for the analyses.

Results

Primary cure was achieved in 110 patients (97%). In three cases the tumor progressed and the patients died of their disease within a few months. Residual carcinoma was noted in eight of the 23 stage II patients at the postoperative evaluation performed under anesthesia at the Department of Gynecologic Oncology. Residual carcinoma was not a significant prognostic factor in the multivariate analysis with regard to long-term survival in our series.

During the follow-up period, 33 cases (30%) with tumor recurrences were recorded in this series of 110 patients.

Table 3. — *Clinicopathologic characteristics as prognostic factors in the complete series (n=113).*

Features	Patients with recurrent disease (n=33)		Patients with non-recurrent disease (n=80)		p value
Age (mean) years	62.5		59.6		0.263 (t-test)
FIGO stage	N	%	N	%	
IA-IB	16	48.5	43	53.8	
IC	10	30.3	24	30.0	
IIA-IIB	2	6.1	9	11.3	
IIC	5	15.2	4	5.0	0.309 (χ^2)
Histopathologic subtype					
Serous	14	42.4	32	40.0	
Mucinous	8	24.2	16	20.0	
Endometrioid	7	21.2	19	23.8	
Clear cell	3	9.1	13	16.3	
Anaplastic	1	3.0	0	0.0	0.784 (χ^2)
Tumor grade					
G1	7	21.2	32	40.0	
G2	11	33.3	36	45.0	
G3	12	36.4	8	10.0	
Not graded	3	9.1	4	5.0	0.002 (χ^2)

There were 24 recurrences (26%) in FIGO stage I and nine recurrences (45%) in FIGO stage II. This difference was not statistically significant (p = 0.309) (Table 3).

On the other hand, the grade of the tumor was statistically significantly (p = 0.002) associated with tumor reccurence. The histopathologic subtype showed no statistically significant (p = 0.784) association with tumor reccurence. The histopathologic subtype distribution was statistically significantly (p = 0.034) associated with the FIGO substages (Table 1). The most notable observation was that mucinous carcinomas (2c) mostly belonged to FIGO stage IA (75%).

The overall relapse rate in patients with FIGO stages IA-IB disease was 24% (14 of 59 cases) and in those with FIGO stages IC-II disease, 35% (19 of 54 cases). In Table 4, the frequency and sites of recurrences are presented for the different types of postoperative radiotherapy. Abdominopelvic metastases (18%) were most frequent, while abdominopelvic and distant metastases (5%) and distant metastases alone (4%) were less common. Isolated pelvic recurrences were detected in only two cases (2%). One case occurred after lower abdominopelvic irradiation and another case after whole abdominal irradiation. Combined pelvic and abdominal recurrences were more frequent in the group treated with whole abdominal irradiation (25%) than in the one treated with lower abdominopelvic irradiation (14%). Distant metastases occurred with the same frequency in the group treated with whole abdominal irradiation (11%) and the one treated with lower abdominopelvic irradiation (9%). The mean time from treatment to recurrence was 26 months (range 6-92 months) in the complete series.

The overall 5-year survival rate in this series of 113 cases was 69% and the cancer-specific survival rate was 72%. The 5-year relapse-free survival rate was 70% in the complete series.

The cancer-specific survival in FIGO stage I was 74% and in FIGO stage II it was 63%.

Table 4. — *Frequency and sites of recurrences versus type of postoperative radiotherapy.*

Type of field	Pelvic n (%)	Pelvic-abdominal n (%)	Pelvic-abdominal-distant n (%)	Distant metastases n (%)	Total rate of recurrences n (%)
Complete series (n = 113)	2 (1.7)	20 (17.7)	6 (5.3)	5 (4.3)	33 (29.2)
Whole abdominal (n = 36)	1 (2.7)	9 (25.0)	1 (2.8)	3 (8.3)	14 (38.9)
Lower abdominal (n = 77)	1 (1.3)	11 (14.3)	5 (6.5)	2 (2.6)	19 (24.7)

Table 5. — *Cox's multivariate analysis of prognostic factors in early stage ovarian carcinoma.*

Factor	Beta	SE	Exp Beta	95% C.I.	Wald statistics	p value
FIGO stage	0.006	0.016	1.006	0.974-1.038	0.125	0.724
Grade	0.951	0.280	2.587	1.495-4.477	11.540	0.001
Histology	-0.128	0.162	0.880	0.640-1.210	0.619	0.431
Residual tumor	-0.034	0.592	0.966	0.303-3.081	0.003	0.954
Tumor rupture	-0.554	0.439	0.574	0.243-1.358	1.596	0.954
Age	0.006	0.016	1.006	0.974-1.038	0.125	0.724

The cancer-specific survival rate was used as the end-point in the Cox proportional hazard regression analysis.

The corresponding figure in FIGO stage II with residual carcinoma was 62% and, in stage II without any macroscopic residual tumor, it was 66%. In this study, the type of histology was not significantly (p = 0.916) associated with survival rates in univariate analyses (Figure 1), but FIGO substage was of borderline significance (p = 0.073). On the other hand, tumor grade was highly significantly (p = 0.002) associated with survival in univariate analyses (Figure 2), and it was also an independent and significant prognostic factor in Cox's multivariate analysis (p = 0.007) (Table 5). Thus, the grade of the tumor was a highly significant prognostic factor for the complete series of 113 patients. In FIGO stage I (n = 90), the grade of the tumor continued to be the only significant (p = 0.002) prognostic factor. In FIGO stage II (n = 23), tumor substage was not significant (p = 0.296), and rupture of the tumor capsule was of borderline prognostic significance (p = 0.070). Age, type of histology, grade, or

Table 6. — *Five-year survival data.*

FIGO stage	5-year (%) overall survival data
Complete series (n = 113)	68.8
Stage I (n = 93)	70.6
Stage IA (n = 55)	76.2
Stages IA and IB (n = 59)	75.9
Stage IC (n = 34)	61.5
Stage II (n = 20)	60.0
Stages IIA and IIB (n = 11)	81.8
Stage IIC (n = 9)	33.0
	5-year (%) cancer-specific survival data
Complete series (n = 113)	72.4
Stage I (n = 93)	74.2
Stage IA (n = 55)	77.9
Stages IA and IB (n = 59)	77.4
Stage IC (n = 34)	68.5
Stage II (n = 20)	63.3
Stages IIA and IIB (n = 11)	81.8
Stage IIC (n = 9)	38.2

Table 7. — *Tumor stage distribution versus type of abdominal radiation.*

FIGO stage	Whole abdominal fields n (%)	Lower abdominal fields n (%)
IA	5 (14) *	50 (65)
IB	0	4 (5)
IC	25 (69)	9 (12) #
IIA	0	3 (4)
IIB	0	8 (10)
IIC	6 (17)	3 (4) #

Pearson's chi-square = 52.365; p < 0.0001. *Intraoperative rupture of the tumor capsule; #One or more contraindications to whole abdominal irradiation.

Table 8. — *Early radiation reactions.*

	Complete series (n = 113) n (%)	Whole abdominal fields (n = 36) n (%)	Lower abdominal fields (n = 77) n (%)	p value
Diarrhea	90 (79.7)	24 (66.7)	66 (85.7)	0.0191
Diarrhea with blood	7 (6.2)	3 (8.3)	4 (5.2)	0.5190
Dysuria	21 (18.6)	4 (11.1)	17 (22.1)	0.1626
Abdominal pain	9 (7.9)	2 (5.6)	7 (9.1)	0.5178
Nausea and vomiting	33 (29.2)	15 (41.7)	18 (23.4)	0.0463
Other	13 (11.5)	6 (16.7)	7 (9.1)	0.2396

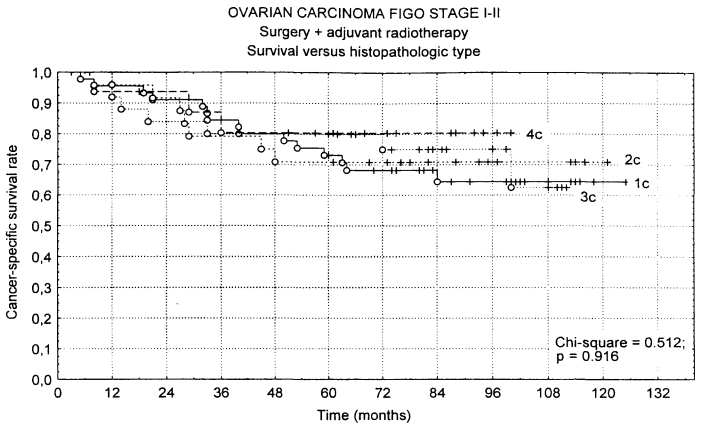

Figure 1. — Cancer-specific survival versus type of tumor histology calculated for the complete series (n = 113). Survival rate was not associated with type av histology (p = 0.916).

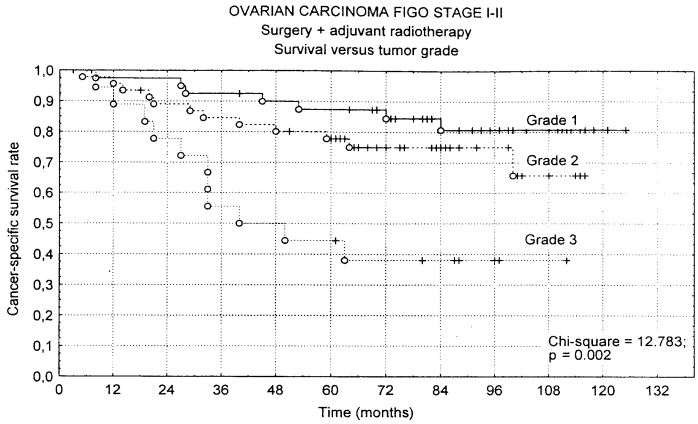

Figure 2. — Cancer-specific survival versus tumor grade in the complete series (n = 113). There was a highly significant association between survival and tumor grade (p = 0.002).

residual tumor had no further prognostic significance in stage II tumors. Presence of ascitic fluid (p = 0.368), residual tumor (p = 0.540), and rupture of the capsule of the tumor (p = 0.510) were not associated with a poorer survival rate in univariate or multivariate statistical analyses.

In this series, clear cell carcinomas had a suprisingly good prognosis, with a cancer-specific 5-year survival rate of 80% in FIGO stages I-II. The elapsed time from surgery to the start of radiotherapy (median 42 days, range 24-208 days) did not have any influence on the recurrence or cancer-specific survival rates.

Survival data (overall and cancer-specific) for all FIGO substages (IA-IIC) are presented in Table 6. Ovarian carcinoma in FIGO stage IA, grade 1, had total 5-year and 10-year survival rates of 92%. The cancer-specific 5-year survival rate was 78% in FIGO stage IA, all grades, and the relapse-free survival rate was 73%. Ovarian carcinoma in FIGO stage IA, grade 1, in this series did indeed have a good prognosis, but these results were achieved with the treatment protocol presented here. FIGO substage distribution versus type of radiotherapy is presented in Table 7.

Early radiation reactions of any type or grade were noted in 93% of the cases. In 12 cases (11%), interruption of the radiotherapy was necessary due to acute radiation reactions. Neither hematuria nor peritonitis was recorded as early reactions (Table 8). Late reactions of any type or grade were noted in 58% of the cases, but in most cases they were mild and not of great clinical significance. The most common side-effect (early and late) was grade 1 diarrhea of limited duration. In the group with other late complications, there were often hidden problems associated with sexual intercourse (dyspareunia) (Table 9). All adverse events were recorded even if the relationship to the radiotherapy was not confirmed. Intestinal obstruction was recorded in two cases (1.8%) and, in both of them, surgery was necessary. No cases of intestinal fistula were recorded. Permanent dysuria was recorded in four cases (3.5%), but no cases of hematuria or urogenital fistula were seen.

Nausea and vomiting during treatment were significantly (p = 0.046) more frequent during whole abdominal irradiation (42%) than during lower abdominopelvic irradiation (23%). Other types of acute and delayed radiation reactions were not significantly different for whole abdominal and lower abdominopelvic radiotherapy.

Table 9. — *Late radiation reactions.*

	Complete series (n = 113) n (%)	Whole abdominal fields (n = 36) n (%)	Lower abdominal fields (n = 77) n (%)	p value
Diarrhea	38 (33.6)	16 (44.4)	22 (28.6)	0.0961
Diarrhea with blood	10 (8.9)	2 (5.6)	8 (10.4)	0.3992
Intestinal obstruction	2 (1.8)	1 (2.8)	1 (1.3)	0.5785
Abdominal pain*	47 (41.6)	19 (52.8)	28 (36.4)	0.0990
Dysuria	4 (3.5)	1 (2.8)	3 (3.9)	0.7644
Other	15 (13.3)	3 (8.3)	12 (15.6)	0.2898

*All types of abdominal pain recorded in the patient records, not necessarily related to the abdominal irradiation per se.

Discussion

The overall rate of recurrence in the complete series of FIGO stage I-II epithelial ovarian tumors was 33 cases out of 110 or 30%. In FIGO stage IA, there were 12 recorded recurrences out of 55 treated patients (22%). In a series of 115 patients with FIGO stage I tumors, in which surgery was complete both macroscopically and microscopically and in which postoperative external beam radiotherapy was given as adjuvant therapy, Reinfuss *et al.* found that 28 patients (24%) died of their ovarian cancer within five years [15]. In our series of stage I tumors, 26% of the patients died of their disease within five years. The overall 5-year survival rate of our complete series was 69% and the 5-year relapse-free survival rate was 70%.

According to the latest Annual Report, the overall 5-year survival in FIGO stage I was 82% and, in FIGO stage II, 59% [16]. Several series reported in the literature confirm survival rates of approximately 70% in selected patients following whole abdominal radiothe-

rapy [17]. Dembo *et al.* reported survival rates of 75% and 68% at five and ten years, respectively, in 224 intermediate-risk patients (stage I, grades 2-3, and stages II and III, grade 1, with residual tumors of less than 2 cm) [18]. In another study from the the Princess Margaret Hospital in Toronto, ovarian cancer stages I-II and asymptomatic stage III were divided into three groups with regard to the method of treatment after primary surgery comprising total abdominal hysterectomy and bilateral salpingo-oophorectomy. For patients receiving abdominopelvic irradiation (43 out of 115), the relapse-free survival was 82%, for those receiving pelvic irradiation plus chlorambucil (42 out of 115), 52%, and for those (30 out of 115) receiving pelvic irradiation alone, it was 50%. The conclusion drawn from this study was that pelvic irradiation alone was not an adequate postoperative treatment for stage IB-II ovarian carcinoma [19].

Radiation reactions in our series were recorded as early in 93% of the cases and in 58% as late reactions. The incidence of severe bowel toxicity in our series was 9.8% and, in two out of 113 irradiated cases (1.8 %), surgery was required due to late radiation complications.

The radiation therapy was tolerated quite well by the majority of our patients. Only 12 patients (11%) had to discontinue their radiotherapy due to acute reactions. We were not able to find more relapses in this group of patients.

In a study by Leer *et al.* of 127 patients with ovarian cancer in stages I, II, and III with no or only minimal residual disease postoperatively, who were treated with radiotherapy using the moving strip technique, there were eight patients who had to discontinue the treatment. More relapses were found in this group of patients with poor tolerance of irradiation [20].

In our series we observed treatment-related nausea in 29% and diarrhea in 86% of the cases but, in a review of 1,098 patients by Dembo, transient treatment-related nausea and vomiting was found in up to 95% and diarrhea in 60% of the cases [21].

Long-term complications in our series mostly involved intestinal dysfunction and the rate of moderate to severe bowel toxicity (11%) was somewhat higher than that reported by many other authors, but, on the other hand, the percentage of patients requiring surgery (1.8%) was somewhat lower. Sell *et al.* observed intestinal symptoms requiring surgery in eight patients in a series of 118 patients (7%) [22]. In the review by Dembo of 1,098 patients from ten different reports, 6% of the patients required surgery for bowel obstruction. The complication rates were related to the total dose, the dose per fraction, and prior surgery (especially para-aortic lymph node dissection). With a total dose of 22.5 Gy in 22 fractions to the upper part of the abdomen, the risk of serious late toxicity was less than 5% [17, 21].

Intracavitary irradiation of the proximal two-thirds of the vaginal wall was added to the external beam therapy in our series and we did not see any local recurrences of the vaginal vault or the vaginal wall. In 67% of the cases the site of the first relapse was confined to the pelvic-abdominal cavity. Some other studies report that the first relapse of the tumor is confined to the abdominal cavity in about 85% of the patients [23]. Residual carcinoma was not a significant prognostic factor in the multivariate analysis in our series. On the other hand, residual carcinoma was noted in only eight cases among the 23 stage II patients. Our series is therefore quite small for analyses and conclusions regarding the importance of residual carcinoma.

Tumor grade was a strong and independent prognostic factor in our series, and other studies confirm our results. In a very interesting study from England, 194 patients with FIGO stage I tumors were followed-up without any adjuvant therapy (median follow-up 54 months with a range of 7-157 months), and a multivariate analysis identfied tumor grade as a significant ($p < 0.001$) and independent prognostic factor. Other independent prognostic factors in that study were presence of ascitic fluid ($p < 0.05$) and tumor growth on the surface of the tumor capsule ($p < 0.01$) [24]. In another study from two centers, prognostic factors for patients with epithelial ovarian carcinoma, FIGO stage I, were analyzed and data on 252 patients from Canada and 267 patients from Norway were reviewed. This study also confirmed that tumor grade (differentiation) was the most powerful predictor of relapse ($p < 0.001$), followed by dense adherence ($p < 0.05$) and a large volume of ascitic fluid (> 250 ml) ($p < 0.05$) [25].

In the present study, tumor grade was also statistically significantly associated with tumor recurrence. Levesque *et al.* [26] have demonstrated, in a study on early stage ovarian carcinoma, that p53-positivity of the tumors, in combination with a high tumor grade, were associated with an increased tumor recurrence rate.

The FIGO substage was not a significant prognostic factor in the complete series of 113 patients as determined by Cox´s multivariate analysis, but it reached borderline significance ($p < 0.10$) in the 23 stage II patients. Risk factors for recurrences were evaluated in 224 surgical stage I ovarian cancer patients in an Italian multicenter study. In this study, the risk of recurrence was significantly related to the FIGO substage ($p < 0.0001$) and to the tumor grade ($p < 0.0001$), but not to the histopathologic subtype. However, in Cox´s proportional hazard model, the tumor grade was the only independent prognostic factor for disease-free survival [6]. Several prognostic factors in a series of 351 patients with stage I ovarian cancer were analyzed in another study from Italy. Optimal staging was performed in 100 patients, peritoneal staging in 107 patients, and incomplete staging in 144 patients. With a median follow-up of 108 months, 64 patients (18%) had tumor recurrences. In a multivariate analysis, only the tumor grade and the type of staging were significant and independent prognostic factors for both disease-free and overall survival. FIGO substage, histopathologic type, rupture of the tumor capsule, and the age of the patient were not independent prognostic factors [27]. The histopathologic subgroup was not a significant prognostic factor in our series but, on the

other hand, a statistically significant association was found with the FIGO substages, where most of the mucinous tumors belonged to substage IA. According to Diebold *et al.* [28], there are two major prognostic groups with regard to the histopathologic subtypes and p53 status: (1) a less malignant group of mucinous and endometrioid carcinomas with rare p53 alterations and mainly diploid DNA content and (2) a more malignant group of serous and anaplastic carcinomas with frequent p53 alterations and a mostly non-diploid DNA pattern.

Clear cell carcinomas had a good prognosis with a cancer-specific 5-year survival of 80% in our series. Many other studies have reported clear cell type to be a bad prognostic factor when analyzed stage by stage because of its relative insensitivity to chemotherapy [8]. It is possible that this subgroup of patients is benefited most by radiotherapy.

Age and menopausal status were not significant prognostic factors in our patients. The high-risk patients in our series were found in FIGO stage IIC, where six of the nine patients lost their lives due to disease during the follow-up period. The 5-year overall survival rate in this substage was only 38.5%. On the other hand, relatively few patients were included in this substage, which makes statistical analyses and conclusions uncertain regarding this subgroup.

A linear curve, with no threshold, reflects the elimination of subclinical disease from a small percentage of patients by means of low radiation doses or chemotherapy. From a theoretical point of view, it should therefore be important to institute the adjuvant therapy as early as possible after surgery to minimize the probability of release of new metastatic clonogens. Micrometastases grow faster than macroscopic tumors and a delay in postoperative treatment would allow the metastatic cell burden to exceed the limit of curability by radiation doses within the tolerance of normal tissues [29]. These theoretical considerations were not supported in our study as the time elapsed from surgery to the start of radiotherapy did not influence the probability of overall or cancer-specific survival.

Several other prognostic factors have been identified for patients with early stage ovarian cancer, some of them being incorporated in the FIGO staging system, but one of the most important prognostic factors, tumor grade, is not considered in the staging system. The excellent prognosis for patients with stage IA, grade 1 tumors treated with surgery alone is widely recognized [30], but there is a lack of consensus on the best type of postoperative therapy for patients with tumors in all other substages and grades. As a result, a wide variety of postsurgical therapeutic modalities have been used [8]. Earlier studies have evaluated postoperative adjuvant treatment with alkylating agents or irradiation, either as a peritoneal isotope (radioactive gold ^{198}Au or phophorus ^{32}P colloid) instillation or as total abdominal irradiation [30]. Intraperitoneal ^{32}P instillation seven days after laparotomy in 28 patients with FIGO stage I-II carcinomas was not an effective adjuvant therapy; disease-free survival at five years was only 65% [34]. In a randomized study from Norway, Vergote *et al.* compared cisplatin (n = 171) with radioactive phosphorus (n = 141) or whole abdominal irradiation (n = 28) as adjuvant treatment of ovarian cancer in FIGO stages I-III without residual disease after primary laparotomy. The crude and disease-free survival rates were similar for all groups. Patients with stage I disease and grade 2 or 3 tumors had a 5-year crude survival rate of 75%. Because of the high frequency of late bowel complications after ^{32}P treatment, cisplatin was recommended as the standard adjuvant treatment in subsequent controlled studies [32]. Peters *et al.* did not find ^{32}P to be an effective consolidation therapy after at least four courses of cisplatin or carboplatin and a negative second-look laparotomy. The relapse rate was 40% in stage IC, 33% in stage II, 52% in stage III with optimal surgery, and 100% in stage III with suboptimal surgery [33]. Intraperitoneal carboplatin given as adjuvant chemotherapy for early stage ovarian cancer had only a moderate effect. Forty-seven patients with epithelial ovarian cancer in FIGO stages IB-IIC were eligible and 43 patients were evaluable for recurrence. Among these patients, recurrences were documented in ten (23%) after a median disease-free period of 11.5 months [34]. In a Gynecologic Oncology Group (GOG) study, no difference in survival was reported for patients with poorly differentiated stage IA-B, IC, or stage II ovarian cancer randomized to receive either melphalan or intraperitoneal ^{32}P. The same study demonstrated no advantage of adjuvant treatment with melphalan compared with no treatment for patients with stage IA or IB well or moderately well differentiated tumors [35, 36].

In our series of 113 patients, the 36 patients treated with whole abdominal irradiation had a significantly higher rate of recurrence (39%) than patients (n = 77) treated with lower abdominopelvic irradiation (25%). Since patients were selected to whole abdominal irradiation if the tumor stage was IC or IIC and in cases of residual carcinoma, presence of ascitic fluid or rupture of the tumor capsule, the efficacy of the two irradiation techniques cannot be compared [13]. In a study by Dembo *et al.*, the relapse-free survival rate of patients with stage II tumors was compared after pelvic irradiation (46%) and pelvic plus abdominal irradiation (79%). The reported 5-year survival difference was significant ($p = 0.02$). This study indicated that pelvic irradiation alone was not adequate postoperative therapy in ovarian cancer in stage II [37]. In our series of early stage ovarian cancer, only stage IA and grade 1 tumors could be classified as low-risk cancers. This group of patients had a 10-year survival of 92% after primary surgery and lower abdominopelvic irradiation. Many authors recommend only surgery for this subgroup of patients with a 96% survival probability with or without treatment [16, 37].

Further prospective and randomized studies are needed to determine the optimal adjuvant therapy in early stage ovarian carcinoma. Abdominal irradiation is one of the modalities that should be further evaluated in this group of patients.

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