

Whole abdomen irradiation in epithelial ovarian cancer – a single institution study

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SUMMARY

Background: The examination of the use of whole abdomen irradiation open field technique in optimally debulked patients with no residual disease with epithelial ovarian cancer (OC).

Methods: Between 1993 and 2007, 20 patients with optimally cytoreduced epithelial OC were treated with WAI. The stage distribution was stage I in 15 patients, stage II in 1, and stage III in 4. The grade distribution was grade 1 in 10 patients, grade 2 in 4, and grade 3 in 6. WAI consisted of 30 Gy, delivered in daily fractions, mainly of 1.5 Gy (95%), 5 days/weekly, in 14 patients. After abdominal irradiation, in 75% of the patients a pelvic boost, and in 7 a boost to other risk sites was given to reach 45 - 50 Gy. Nine patients received platinum based chemotherapy (CT). Median follow-up was 7.96 years.

Results: The overall survival (OS) rate was 82% and 70% at 5 and 10 years. A tendency to better survival was found in patients with age ≤ 40 than in those with > 40 years (100%:100% vs. 68%:51%; $p=0.03$). Patients with grade 1-2 tumors had significantly better 5- and 10-year survival rate than those with grade 3 tumors (100%:100% vs. 40%:20%; $p<0.00$). The 5- and 10-year OS for the patients "with" and "without" a pelvic boost turned to be in favor of the patients "with" the boost (91%:91% vs. 60%:40%; $p=0.02$). In 15 patients (75%) RT was transiently interrupted because of acute gastrointestinal and hematological toxicity. Neither grade 4 acute complications nor was mortality observed. Late gastrointestinal effect developed in 1 patient, presented with grade 4 complications. The development of second primary malignancy was not observed during the follow-up period.

Conclusion: WAI achieves a quite favorable 5- and 10-year survival rate with an acceptable risk of acute and late side effects in properly selected patients with epithelial OC.

Key words: Ovarian Neoplasms; Radiotherapy; Whole-Body Irradiation

INTRODUCTION

Ovarian cancer (OC) is a highly lethal disease and is the fifth cause of cancer death among Bulgarian women (1). It has the highest mortality of all gynecologic cancers with an annual mortality rate of 10.8/100,000 women (1).

Worldwide the death rate has been fairly constant during the greater part of the 20th century, despite the advances in combined treatment of OC. Unfortunately, regardless the introduction of platinum- and taxane-based chemotherapy (CT) regimens, many patients with OC have recurrence in the abdomen or pelvis (2-5).

Whole abdomen irradiation (WAI) as radiotherapy (RT) technique that specifically targets the anatomic sites at highest risk for dissemination of epithelial OC has long been recognized as an effective adjuvant treatment for women with early-stage optimally debulked disease (6). In the late 80's of the last century, Dembo reported the possibility of WAI to reduce the rate of abdominal failure (7) by 40%. Multiple single-institution studies and randomized trials exploring WAI, reported 5- and even 10-year survival rates reaching up to 70% (8-10). Despite these publications the controversy on the role of WAI remains. Over a period of more than three decades, the use of RT in OC has profoundly decreased. However, the achieved treatment results, during the last decade, were not noteworthy. The contemporary chemotherapeutic schemes require further research and development of new therapeutic approaches, with radiotherapy as a part of the combined modality approach and as a salvage therapy for patients with small volume persistent disease after primary cytoreductive surgery and chemotherapy (7-10).

The objective of this single institution study was to examine the use of WAI open field technique in optimally debulked patients with no residual disease with epithelial OC.

METHODS

From January 1993 to December 2007, 20 patients with epithelial OC were treated with WAI open field technique. Characteristics of 20 patients based on the surgicopathologic findings and the distribution of potential prognostic factors are shown in Table 1. The age distribution ranged from 18 to 65 years, with a median of 48 years. According to tumor histology, serous tumors were prevalent – 6, followed by mucinous tumors – 4. Ten patients had grade 1 tumors, 4 had grade 2 tumors, and 6 had grade 3 tumors. There were 15 patients with FIGO stage I disease, 1 with stage II, and 4 with stage III. In 4 patients, a second-look procedure was carried out before the RT referral to. In all cases, no macroscopic residual disease was left after surgery. Ascites was present in 3 patients. In all patients, peritoneal washing was investigated, establishing positive cytology in 4 patients. Chest X ray, computed tomography scan of the abdomen and pelvis and CA-125 values were obtained pre- and postoperatively as a baseline for future comparison.

Surgery in most cases consisted of thorough inspection of the abdomen and pelvis, cytologic examination of ascites or peritoneal washing and total abdominal hysterectomy, bilateral salpingo-oophorectomy, targeted biopsies of suspected metastases, and omentectomy. Additional surgical procedures were also applied in some of the patients, including selective pelvis and para-aortic lymphadenectomy.

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Table 1. Patient characteristics (n=20)

	Number of patients	%
Stage of disease		
I	15	75
II	1	5
III	4	20
Grade of disease		
1	10	50
2	4	22
3	6	28
Histopathology		
serous	6	30
mucinous	4	20
other	10	50
Second-look laparotomy		
+ second-look laparotomy	4	20
- second-look laparotomy	16	80
Ascites		
+ ascites	3	15
- ascites	17	85
Peritoneal cytology		
+ peritoneal cytology	4	20
- peritoneal cytology	16	80
Chemotherapy		
+ chemotherapy	9	45
- chemotherapy	11	55

After surgery, the patients were discussed at multidisciplinary gynecologic oncology tumor rounds. Nine patients received platinum-based CT (range 3 - 6 cycles). Because of the nature of the study, CT was not given according to the program or protocol but according to the physician's preferences. The RT technique, with clinical target volume (CTV) encompassing the entire peritoneal cavity, was as follows: parallel opposed anterior-posterior, extended SSD, whole abdominal Co 60 photon fields, delivered in daily fractions of 1.0 -1.5 Gy (with mainly application of 1.5 Gy (95%)), 5days/weekly. The field borders extended from 1.5 cm above the diaphragms in quiet expiration, to 1 cm below the inferior aspect of the obturator foramen. Laterally the fields extended beyond the peritoneal reflection. Anterior/posterior kidney and hepatic shields were introduced at 16-20 Gy to maintain the total kidney and hepatic dose at less than 20 Gy. In 70% of the patients, the dose delivered was 30 Gy to the whole abdomen, and for the remaining patients the dose was 25 Gy (20%) and 20 Gy (10%), respectively. In 15 patients, subjected to WAI open field technique, the pelvis was given an additional dose, using mainly 1.8 Gy/fraction to reach a total pelvic dose of 45-50 Gy. In 7 patients, a boost was applied in other risk sites and varied between 45 and 50 Gy. Most often, these were the primarily engaged or the persisting after CT formations, situated outside the pelvis. In most of the cases, these were para-aortic lymphatic chains. All patients were analyzed with regard to acute and late toxicity. Acute toxicity was recorded according to the common toxicity criteria (CTC) (11) and late toxicity was classified pursuant to the Radiation Therapy Oncology Group Eastern Cooperative Oncology guidelines (12). Patients were evaluated for general tolerance and side effects weekly during RT. Antiemetic, antidiarrheal or other symptomatic medications were prescribed as required. Complete blood counts were obtained at least 2 times per week, and daily if necessary.

RT was temporarily withheld if the absolute neutrophile count was $<1 \times 10^9/L$ or the platelet count was $<50 \times 10^9/L$.

Patients were followed after the treatment at regular intervals. Median follow-up of surviving patients was 7.96 years (range 1.0 -16.68) from the date of initial surgery for OC.

Survival was analyzed in an actuarial fashion, using the Kaplan-Meier method (13). An appropriate prognostic factor analysis used the long-rank test. Associations between variables were tested by χ^2 and Wilcoxon rank sums.

RESULTS

The treatment time ranged from 30-91, median 45 days. With a median follow-up of 7.96 years, the 5- and 10- years OS rate was 82% and 70%, respectively (Figure 1).

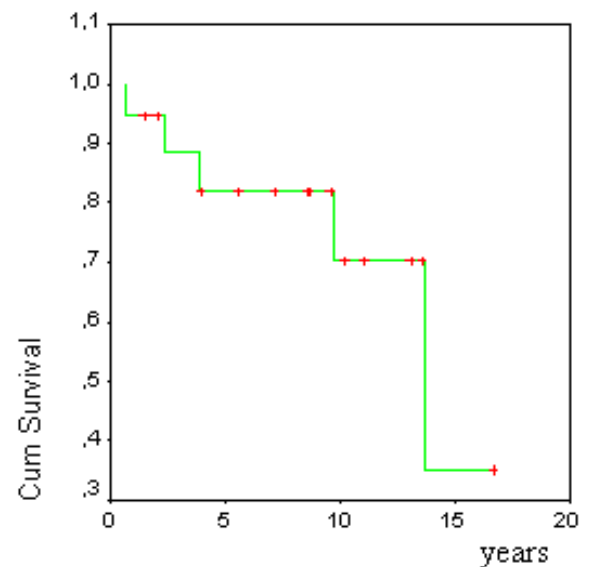


Figure 1. Overall actuarial survival of patients with whole abdomen irradiation

From the statistically significant patient-related characteristics, better OS was observed in patients with age ≤ 40 compared with age >40 ($p=0.03$) – the ratio of 5- and 10-year OS was 100%:100% vs. 68%:51%, respectively.

From the tumor-related characteristics, we studied the impact of the grade on OS. The 5- and 10-year OS was better among the patients with well- or moderately differentiated tumors compared to those with grade 3: 100%:100% vs. 40%:20%, $p<0.00$ (Figure 2). We had not studied the effect of the stage and histology of the OC, as well as the existence of ascites and positive peritoneal cytology due to the small number of cases in the single subgroups of the patients with OC.

From the treatment-related characteristics, we studied the impact of pelvic boost and the effect of necessarily applied split in RT. The 5- and 10-year OS in the groups with (14) and without (5) a pelvic boost were related as 91%:91% vs. 60%:40%, $p=0.02$, with no survived "without"-boost patients in the 13th year, while the survived ones from the "with"-boost group continued to be 91% in the 15th year (Figure 3). No statistically significant difference in OS was established depending on the inclusion of split in the WAI application ($p=0.12$).

Univariate survival analysis of three potential clinical and surgicopathological prognostic factors was performed according to the Kaplan-Meier method. From the studied factors, grade and pelvic boost exerted a significant impact on the OS (Table 2).

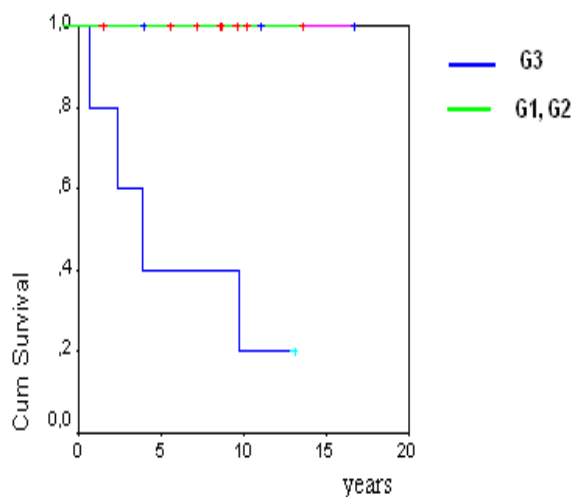


Figure 2. Actuarial survival according to grade of the tumor

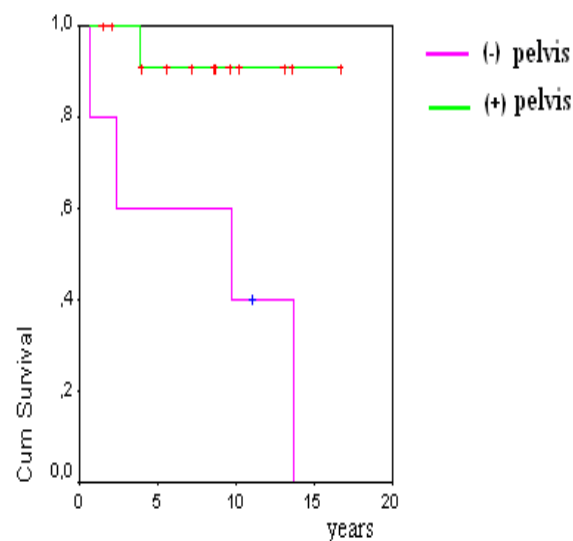


Figure 3. Actuarial survival according to pelvic boost

Table 2. Predictive variables of outcome

Prognostic factor	Mean OS (years)	SE	95% CI	p-value
Grade				
G1	13.59			<0.001
G2	13.59			
G3	5.93	2.10	1.82-10.05	
Pelvic boost				
(+) Pb	15.51	1.11	13.33-17.69	0.02
(-) Pb	8.04	2.85	2.42-13.58	
Split in RT				
(+) split	7.71	2.20	3.39-12.02	0.12
(-) split	13.37	1.50	10.43-16.30	

All patients were analyzed with regard to the most frequently observed acute and late gastrointestinal and hematological toxicity. Five patients received their treatment with no interruption, and in 15 patients RT was transiently interrupted because of acute toxicity. Treatment interruptions were for 10 days (median) (range 4 - 82 days). The reason was gastrointestinal toxicity in 4

patients, hematological toxicity in 10 and only in 1 patient there was another reason. Most grade 1 or 2 patients experienced nausea or diarrhea, or both, during WAI. The symptoms of nausea and vomiting were usually manifested at the beginning of the treatment with subsequent gradual attenuation. On the other hand, diarrhea was mainly observed at the end of the treatment. The management of clinical symptomatic was realized with antiemetics and adstringents. In 8 patients the reason for interruption was neutropenia (grade 1-3), and in 2 patients – thrombocytopenia (grade 3). Neither grade 4 acute complications nor mortality while receiving treatment were observed. The patients were carefully monitored during RT, and there were no serious consequences such as sepsis or hemorrhage. None of the patients required transfusion during the treatment. All of these toxicities resolved upon completion or cessation of the treatment.

Late side effects developed in 1 patient, presented with grade 4-complication (small bowel obstruction treated surgically). The patient had clear cell grade 2 epithelial OC, diagnosed in 1996. Six CT cycles were carried out post-operatively. In 1999, large formations of para-aortic lymphatic nodes were found. After the second line CT a second look laparotomy with para-aortic lymphadenectomy were performed and a metastatic process was proved. Taking under consideration the exhausted possibilities of CT, the treatment was continued with consolidative WAI with up to 30 Gy, followed by boost in the para-aortic area with up to 47.5 Gy. The patient showed good RT tolerance, without substantial gastrointestinal and hematological toxicity and no split was required during the treatment. Nine months later the patient developed small bowel obstruction, which was not successfully managed with conservative measures alone and required surgical intervention. Furthermore, the patient exhibited complete clinical remission, 10 years after the application of the treatment.

During the cited 15-year period, the second malignancy development was not observed in any of the patients.

DISCUSSION

At the present stage of oncological practice, there is no clear insight into the optimal therapeutic behavior for epithelial OC. The main challenge in future will be the early diagnostic of OC, as well as the improvement of the complex treatment of the patients.

The experience accumulated during the last decades proves that platinum-based CT, although producing good response rates and palliation, may not improve long-term survival rates over previous treatments (14). We share the opinion of Macatsoris et al. (15) that epithelial OC is successfully treated but seldom cured with standard platinum-based CT regimens. Thus, carboplatin/paclitaxel CT has become a standard treatment after surgery for patients with epithelial OC (3-5). However, the high recurrence rates of more than 60% in 10 years and the presence of residual disease at second-look laparotomy in approximately half of the patients who appear to be in complete remission post-chemotherapeutically, have prompted the researchers to consider the additional treatment (2-5).

Adjuvant WAI has proven therapeutic possibilities in optimally debulked, without residual disease patients with OC. As early as in 1979 Dembo et al. showed the preference of WAI compared to local irradiation in the pelvis (7). Their results were confirmed by many other authors and clinical studies (14, 16). The complex treatment including WAI and cisplatin took place in the last

decade of the past century (11,12). In the first years of the new century, positive results of the performed prospective studies on the therapeutic possibilities of WAI combined with carboplatin and paclitaxel in patients with advanced OC were reported (17,18). According to the number of authors, except as a consolidative treatment, WAI should be considered also as a salvage treatment in patients who fail initial CT, since its results appear to be as good as or better than the second line CT, particularly in platinum-refractory patients (19-24).

During the 15-year period, not many patients with OC were the objects of analysis of the therapeutic potential of complex treatment including WAI open field technique. The reason was the insufficient interest of the majority of Bulgarian radiotherapists in routine application of large field techniques, as well as the domination of CT in the treatment of OC.

The achieved OS, respectively 82%:70%, 5-, 10-year OS, are close to the good ones, cited in reference literature (Quentin P et al., 1998 - 60%:22% 5-, 10-year OS (25); Hepp et al., 2002 - 55% 5-year OS (26); Skirnisdottir et al., 2005 - 69% 5-year OS (27); Dinniwell et al., 2005 - 92% 4-year OS and 57% disease-free survival (DFS) (28).

The prognostic significance of age of the patients was confirmed by some authors (6, 29), as well as in our clinical study. Copeland et al analyzed the results for 246 patients with OC (29). The analysis of OS, relapse-free survival (RFS) and DFS in 50 of them exhibiting data for microscopic positive second-look laparotomy confirmed the age of patients under 40 as a significant prognostic factor.

The stage, histology of tumor, presence of ascites and positive peritoneal cytology were not subjected to investigation due to the small number of patients in the single subgroups. As confirmed by other studies, the grade was one of the most important prognostic factors (29-32). In our study, patients with grade 1 and 2 tumors had a significantly better OS than grade 3 patients (100%:100% vs. 40%:20%, respectively; $p=0.00$). After Dembo et al. (6,7), the difference in the achieved survival depending on grade was also reported by Carey et al. in 1993 (achieved OS of 96%:78%:62% in stage I patients with grade 1, 2 and 3 tumors, respectively) (32) and Copeland et al. in 1994 (100%:79%:36% 5-year OS for the grade 1-3 tumors) (29).

In the analysis of the treatment factors, we did not investigate the effect of the total dose, as well as the inclusion of CT in the complex treatment on OS, because the small number of patients precludes meaningful statistical analyses. Due to toxicity of the performed WAI, in some of the patients it was impossible to carry out the planned boost in the pelvis. We analyzed the effect of pelvic boost on the achieved OS and proved the statistical significance of this factor ($p=0.02$) with considerably better 5- and 10-year OS for the group "with" boost. We could not find similar analysis in the literature available to us, obviously due to the aspiration of the majority of authors to realize the planned dose in the pelvis. Our results showed that the achievement of a cancericidal dose in the tumor bed exerted positive impact on local tumor control and respective survival improvement.

The assessment of acute and late toxicity from WAI as a sole or as a part of a combined treatment represents a topic of a number of clinical trials. It is generally acknowledged that in this large field technique, acute toxicity is common but infrequently severe and late toxicity is acceptable and predictable (33-37). Most of the studies have also shown that the addition of WAI does not limit the ability of patients to tolerate salvage CT (19,28,38). Our study showed acceptable early and late toxicity of combined treatment including

WAI open field technique, similar to those cited in reference literature (33-37). We consider that the low rate of small bowel obstruction, regardless of the use of WAI on total dose of 30 Gy, in the majority of patients reflects mainly selection of the patients without extensive prior abdominal surgery.

The established late consequences and secondary neoplasms in the patients of our study were similar with respect to frequency and clinical manifestation to those reported in literature.

CONCLUSION

The overall outcome of the small number of patients in this study appears favorable and supports the continued evaluation of this aggressive combined modality approach. The obtained therapeutic results support the National Institutes of Health Consensus Development Conference, which recommends the reevaluation of WAI possibilities in modern oncological practice. From the present position, we would also add the discussion of new radiotherapeutic techniques (38). Obviously, the future role of WAI will be estimated with application of new complex approaches with participation of innovative radiotherapeutic techniques.

Conflict of interest

We declare no conflicts of interest.

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