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Whole abdominal radiotherapy in ovarian cancer

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ABSTRACT

Objectives: The aim of the study was to evaluate the clinical outcome and toxicity after adjuvant whole abdominal radiotherapy (WART) in patients with ovarian cancer.
Material and methods: Ten patients with optimal cytoreduced ovarian cancer, with a mean age of 58 years (40–70) and stage Ic: 4, stage II: 2, stage III: 4, were treated with WART and adjuvant chemotherapy (9/10). The total radiation dose was 22.5 Gy in the whole abdomen and 42–45 Gy in the pelvis.
Results: The mean follow-up was 8 years. The 5-year actuarial disease-free survival (DFS) was 60%, and the overall survival (OS) was 70%. Four patients had disease recurrence. The sites of recurrence were the abdomen in 2 patients and distant metastases in the other 2 patients (liver and brain metastasis). Gastrointestinal toxicity was as follows: acute 3/10 grades I and II, and late toxicity: 2/10 grades I and II, and only 1 patient developed small bowel obstruction (SBO) that required surgery.
Conclusions: Whole abdominal radiotherapy after surgery and platinum-based chemotherapy achieves high locoregional disease control with an acceptable risk of acute toxicity.

1. Introduction

Epithelial ovarian cancer represents the first cause of death from gynaecological cancer in Western countries, with approximately 26,000 new cases diagnosed in the United States each year.[1–3]

More than two-thirds of patients with epithelial ovarian cancer are diagnosed in an advanced stage of disease at presentation because of the absence of specific symptoms and signs. Tumour stage is the most important prognostic factor. According to the annual report of the International Federation of Gynecology and Obstetrics (FIGO),[4] the 5-year overall survival ranges from 89% for stage IA to 13% for stage IV disease.

Chemotherapy-based platinum and paclitaxel is currently considered the standard of treatment after surgical staging and resection of abdominal and pelvic disease. A high proportion of patients (60–80%) with advanced ovarian epithelial cancer respond to first-line chemotherapy, but most of these patients (about 70%) will later have disease progression and thus be candidates for second-line chemotherapy. The selection of salvage therapy is commonly based on whether women are sensitive or resistant to initial treatment.[5]

Unfortunately, despite the advances in surgical cytoreduction and chemotherapy, many patients develop abdominal

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or pelvic recurrence, with a low response rate to further chemotherapy and with subsequent poor prognosis. Abdominal radiotherapy offers the possibility of improved tumour control in patients classified by Dembo as intermediate risk with microscopic residuum after optimal surgical cytoreduction and chemotherapy.[6] Consequently, the potential role of radiotherapy for improving disease control in the abdomen and pelvis may increase the disease-free interval and survival.[7]

The aims of the present study were to analyse the clinical outcome and survival time and to evaluate the acute toxicity of whole abdominal radiotherapy (WART).

2. Materials and methods

From March 1993 to January 1998, 10 patients diagnosed with ovarian cancer were treated with WART. All patients underwent initial surgical staging and cytoreduction. This included total abdominal hysterectomy, bilateral salpingo-oophorectomy, cytological examination of ascites or peritoneal washings, thorough inspection of the abdomen and pelvis, infracolic omentectomy, and targeted biopsies of suspected metastases. CA-125 was determined preoperatively and postoperatively. Chest X-ray and computed tomography (CT) scan of the abdomen and pelvis were obtained postoperatively as a baseline for future comparison.

There were 4 FIGO stage Ic, 2 Stage IIc and 4 Stage IIIc tumours. The most frequent histological diagnosis ($n = 8$) was serous papillary adenocarcinoma followed by 1 case of clear cell carcinoma and 1 case of poorly differentiated ovarian carcinoma. The residual macroscopic tumour remaining after surgery was ≤ 2 cm. Thus, according to the risk classification of Dembo et al.,[8,9] all patients were classified as intermediate risk and assigned to receive additional adjuvant treatment. Table 1 describes the risk groups of the Dembo criteria.

Nine patients received 6 cycles of platinum-based chemotherapy before WART. The chemotherapy consisted of 6 cycles of carboplatin (300 mg/m^2) plus cyclophosphamide (500 mg/m^2) in 5 patients, 6 cycles of cisplatin (80 mg/m^2) plus cyclophosphamide (500 mg/m^2) in 3 patients and Adriamycin (50 mg/m^2) plus TDCI plus cisplatin (80 mg/m^2) in 1 patient. One patient did not receive further adjuvant chemotherapy due to medical contraindications for chemotherapy and remained free of disease until the onset of the second malignancy, a clear cell carcinoma of the kidney.

The radiotherapy technique was parallel opposed anterior and posterior whole abdominal fields, 6–18 MV photons. The superior margin of the field was 1.5–2 cm above the diaphragm and the inferior margin extended below the obturator foramina. The total dose delivered was 22.5 Gy to the whole abdomen at mid-plane with an additional boost to the pelvis up to a total dose of 42–45 Gy, in daily fractions of 1.25 Gy, 5 days/week. All patients were treated without shielding the liver. The kidneys were shielded from the posterior beam by 5 half-value layers of lead placed on a satellite platform. These kidney shields were introduced at 15 Gy to maintain the total kidney dose below 20 Gy. Kidney localization was performed by X-ray examination of the renal pelvis using endovenous radiopaque contrast or by demarcation of the renal silhouette on abdominal radiography. Gastrointestinal toxicity was graded according to the EORTC/RTOG score toxicity.[10]

Disease progression was defined as: new lesions, consistent with new sites of disease, on imaging—including CT, magnetic resonance imaging (MRI), ultrasound, scintigraphy and/or plain X-ray; new elevation of CA-125; biopsy/histology of new lesions and new signs on clinical exam or symptoms consistent with new sites of disease. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of recurrence of ovarian cancer at any site of the body. Actuarial survival curves were calculated by the Kaplan–Meier method.

3. Results

The mean age at diagnosis was 58 years old (range: 40–70). The mean follow-up was 8 years (range: 2–14). The mean survival time (MST) for the entire group was 104 months (95% confidence interval (CI): 71–136 months). Seven out of 10 patients (70%) died during follow-up, but 3 of them did so for reasons unrelated to ovarian cancer: the first died because of a cerebral haemorrhage, the second as a consequence of an acute myocardial infarction and the third developed a second tumour histology of clear cell carcinoma of the kidney.

Four patients (40%) relapsed between 16 and 35 months after diagnosis. The mean time to disease progression was 117 months (95% CI: 70–163 months). The 5-year actuarial DFS was 60%, and the overall survival (OS) was 70%. The sites of recurrence were the abdomen in 2 patients (20%), with nodal relapse in a poorly differentiated ovarian carcinoma stage IIIc in 1 case and peritoneal carcinomatosis in a serous papillary carcinoma stage II in the other patient. Distant metastases were seen in 2 patients (20%) as the first site of relapse. The sites involved were the liver in 1 patient, and the brain in the other. This unusual isolated location in ovarian cancer was biopsy proven and previously reported.[11] None developed pelvic recurrence. At the last follow-up, only 3 patients (30%) were alive without evidence of disease. Three of 6 patients without relapse died because of intercurrent illness (1 cerebral haemorrhage, 1 acute myocardial infarction and 1 developed a second tumour with histology of clear cell carcinoma of the kidney).

Table 1 – The Dembo criteria[8].

Stage	Residuum	Grade 1	Grade 2	Grade 3
I	0	Low Risk		
II	0		Intermediate Risk	
II	< 2 cm			
III	0			High Risk
III	< 2 cm			

All patients received the treatment without interruption. The treatment was fairly well tolerated, with 30% (3/10) of the patients presenting acute gastrointestinal side effects. Neither grade 3–4 acute complications nor mortality while receiving treatment were observed. Only 2 patients (20%) developed late side effects grade 1–2, and only 1 patient (10%) developed small bowel obstruction (SBO) that required surgery 24 months after WART, although surgery was performed 4 times before treatment with irradiation (the first surgery was an appendectomy, 10 years before the diagnosis of ovarian cancer; the second intervention was an exploratory laparotomy to determine the diagnosis; the third consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, cytology of ascites or peritoneal washing, thorough inspection of the abdomen and pelvis, and infracolic omentectomy as crunched oncology; and the last surgery was a second look after the chemotherapy treatment).

4. Discussion

Chemotherapy is the main standard adjuvant treatment for ovarian carcinoma. Until the advent of chemotherapy, postoperative irradiation was the only adjuvant treatment modality available for advanced ovarian carcinoma. A well-known randomised study by the National Cancer Institute of Canada reported by Smith and Rutledge[12] comparing WART with melphalan concluded that both modalities had similar effects in terms of OS and DFS (the 5-year OS was similar for the 2 arms, 71 and 72% respectively; in FIGO stage I the 5-year DFS was 85 and 90% and the OS 100 and 86% for WART and melphalan respectively; the differences were not statistically significant), with less toxicity and eventually lower cost for chemotherapy leading to a significant decline in the use of radiotherapy.

The role of WART was extensively studied by Dembo[13] and the definition of the intermediate-risk group of patients with epithelial ovarian cancer was widely accepted and used to define the subgroup of patient candidates for WART. A variety of WART techniques and doses have been previously described with comparable results in terms of local control and toxicity. Commonly, studies of WART utilize an open field technique with abdominal doses of 22.5–30 Gy and pelvic doses of 45–50 Gy, with acceptable morbidity and survival.[14,3]

Recently, the combination of paclitaxel and cisplatin/carboplatin became the standard treatment for ovarian cancer. Most of the studies that demonstrated a benefit of this combination focused on patients with advanced stage III or IV disease, 20–30% of whom enjoyed long-term disease-free survival.[15,16] These results have been extrapolated to more favourable patients.[17] However, the high recurrence rates of more than 60% at 10 years and the presence of residual disease at second-look laparotomy in approximately half of the patients, who appeared to be in complete remission after chemotherapy, have prompted researchers to consider additional treatments. There is a continued need to improve regional control and, therefore, new consolidation therapies are being developed and tested in the adjuvant setting. Therapies that have been previously investigated include intraperitoneal ^{32}P, radioimmunotherapy, intraperitoneal chemotherapy, and high dose chemotherapy with haematopoietic support. Most of these therapies have not undergone sufficient evaluation to conclusively determine their efficacy. In patients with microscopic residual disease or complete pathological response in the abdomen and pelvis, WART consolidation should be considered as an effective regimen. The stage, grade and amount of residual disease are widely accepted prognostic factors for ovarian carcinoma for both chemotherapy and WART. The present study includes patients at intermediate risk as defined by Dembo.[8]

Table 2 – Pooled series reporting outcomes of small bowel obstruction (SBO) for intermediate-risk ovarian cancer after whole abdominal radiation therapy.

Author	Total radiation dose (Gy)	SBO%
Fyles AJ et al.[9]	22.5–27.5	3
Dembo AJ[8]	22.5–25	1.3
Hruby G et al.[14]	22–25	6.4
Lindner H et al.[19]	22.5	1
Macbeth FR et al.[20]	22.5	3.5
Firat S et al.[21]	36	11
Schray MF et al.[22]	30	9
Whelan TJ et al.[23]	22.5	8.6
Present study	22.5–22	10

The analysis of survival showed 5-year OS rates of 70%, comparable to previous reports using WART for intermediate-risk patients (57–80%).[18–20] The 5-year DFS rate was 60%, similar to other results reported with WART or cisplatin-based chemotherapy that ranged from 45 to 68% at 5 years.[11,16]

Numerous studies have evaluated the toxicity of WART. The largest series published was an analysis of 598 patients reported by Fyles et al.[9] showing a 3% incidence of SBO requiring surgery after a total dose of radiation of 22.5–27.5 Gy. Similar rates of SBO have been reported in other studies with WART of 22.5–30 Gy.[12,18,19,21] Schray et al.[22] reported an SBO rate of 9% at 3 years with an open field technique, and increased risk was observed with high dose boosting for residual disease. Another study showed a 9% rate of SBO requiring surgery for cisplatin chemotherapy followed by WART.[23] In this study, WART > 22.5 Gy and second-look laparotomy before WART was associated with an increasing risk of SBO. In our study, only 1 patient developed SBO with 3 previous abdominal operations in addition to surgery for ovarian cancer (Table 2). To achieve a low rate of small bowel obstructions patients should be properly selected, without extensive prior abdominal surgery, avoidance of second-look laparotomy, and use of a tolerable whole abdominal radiation dose.[7,9,22] The results of our study support the view that the aggressiveness of the surgeons plays a role in developing future complications after WART. In previous reports there is no reference concerning the interval between WART and SBO events, or the relation with the number of previous abdominal surgeries. SBO events post-WART are a major concern and SBO may be considered as secondary to previous surgery itself.

5. Conclusion

Definitive control of abdominal disease in intermediate risk patients with ovarian cancer still remains a challenge. The results of the present study show good locoregional control of disease after chemotherapy and WART, with a low rate of gas-

trointestinal toxicity, and suggest the need for re-evaluation of this technique in the management of a well defined subset of ovarian cancer patients.

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