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Current Controversies in Cancer

Is Abdomino-pelvic Radiation Therapy the Optimal Treatment for Completely Resected Stage I and II High Risk Ovarian Cancer?

A. Fyles | G. Bolis, C. Ferraris & F. Parazzini | M. Bolla

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A. Fyles

Department of Radiation Oncology, Princess Margaret Hospital and University of Toronto, 610 University Avenue, Toronto, Canada M5G 2M9

THERE IS a lack of consensus regarding the postoperative management of early stage optimally debulked ovarian cancer throughout the world. Twenty years ago, it was demonstrated that radiation therapy to the whole abdomen with a pelvic boost was superior to pelvic radiation and chemotherapy. Subsequent studies have compared radiation and single agent or combination chemotherapy with and without cisplatin. These studies have included patients with varying degrees of risk depending upon histopathological and clinical features, but have not established a clearly superior treatment. Furthermore, patients within the optimally debulked group are frequently described as having an intermediate or high risk of recurrence without agreement on the characteristics that define these categories. Therefore, at present, treatment policy tends to depend on local preference and experience, particularly with the use of whole abdominal radiation therapy.

PROGNOSTIC FACTORS FOR RELAPSE

In contrast to the uncertainty regarding treatment, unequivocal prognostic features for relapse have been demonstrated in various studies in patients with early ovarian cancer. Predominant among these are the tumour grade and the presence of dense adherence to other surrounding structures or metastases to other pelvic organs [1–4]. Large volume ascites (>250 ml) has been demonstrated to worsen the prognosis in one study from the Princess Margaret Hospital (PMH) and the Norwegian Radium Hospital (NRH) [2]. Despite the inclusion of features such as cyst rupture, capsular excrescences and positive peritoneal cytology in the FIGO staging system, it is not at all clear that these features are independently predictive of relapse in addition to grade and adherence. It is evident from prospective studies and randomised trials, such as the GOG study of melphalan versus observation alone, that patients with stage I and grade 1 tumours are at very low risk of relapse and require no postoperative therapy after appropriate surgery [5]. Patients with stage I grade 2 and 3 or stage II disease are at sufficiently high risk of recurrence that postoperative adjuvant therapy is frequently recommended.

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RATIONALE FOR THE USE OF ABDOMINO-PELVIC RADIATION THERAPY

The majority of first relapses in patients with early ovarian cancer occur in the abdomen and pelvis, indicating that if radiation is used it must encompass the entire peritoneal cavity [4, 7]. However, due to the low radiation tolerance of organs such as the liver and kidneys and the large amount of bowel included in the treatment volume, it is necessary to limit the total dose and/or shield these organs during part of the radiation treatment. The maximum dose that can be used without encountering unacceptable hepatic complications is approximately 3000 cGy in 100–150 cGy fractions. In the PMH studies, total abdominal doses of 2250–2750 cGy in 100 cGy fractions have been used with acceptable rates of late complications. In a recent analysis of 598 patients treated at PMH using this technique, serious late bowel complications were observed in only 4.2% of patients [6]. This compares with a 2% risk of bowel obstruction in patients receiving cisplatin alone in the NRH randomised study (vide infra) [4]. Although the radiation doses used are lower than those generally required for control of gross tumour, it is clear from several reports in the literature that abdomino-pelvic radiotherapy (APRT) is able to cure patients with known residual disease in the pelvis and abdomen, particularly if it is less than 2 cm in size [7–9]. In 91 patients treated at the PMH with macroscopic residual stage II and III disease, the 10-year relapse-free rate was 38% [7]. Most of these patients had stage II disease with residual disease in the pelvis where higher doses of radiation were used to boost areas of gross disease. Modelling of clini-

cal dose–response data on the use of radiation for subclinical disease predicts a 40% reduction in relapse with these doses [10, 11]. These data indicate that these doses of radiation can cure patients with gross residual tumour, and that patients with only microscopic tumour are likely to benefit to an even greater degree.

STUDIES OF RADIATION THERAPY AND CHEMOTHERAPY

Results from randomised studies of APRT in patients at intermediate to high risk of relapse following surgery are summarised in Table 1. A study conducted at the PMH compared pelvic radiotherapy alone or with chlorambucil versus APRT in stages I–III [12]. The 5- and 10-year actuarial results show a significant improvement in overall survival of patients treated with APRT compared with pelvic radiation + chlorambucil (58% versus 41% and 46% versus 31%, respectively, $P = 0.05$). This benefit occurred only in a subgroup of patients with small or no macroscopic residual tumour (78% versus 51% 5-year and 64% versus 40% 10-year survivals, $P = 0.007$). Three other studies comparing single agent chemotherapy to radiation in the preplatinum era have shown no difference in survival between the two treatment arms [13–15]. However, two of these trials used pelvic radiation (which may have contributed to the outcome) in addition to chemotherapy [13, 14], and there have been criticisms of each study with regard to the technical details of adjuvant APRT, as well as the concern that the dose of chlorambucil used in the PMH study was low. The study undertaken by the National Cancer Institute of Canada [13] included a radiotherapy review, and demonstrated that adequate radiation therapy was associated with significantly improved 5-year survival compared to radiation treatment where margin violations occurred (76% 5-year survival versus 33%, $P = 0.01$). None of these studies were of sufficient size to have detected small differences in survival.

These studies do not address the fundamental question of the role of radiation therapy compared with cisplatin-containing chemotherapy in the management of early ovarian cancer. A study from the NRH compared cisplatin with intraperitoneal ^{32}P in patients with predominantly stage I and II tumours and again found no difference in outcome [4]. The GICOG study randomised two groups of patients with stage I ovarian cancer [16]. Patients with stage Ia1 and Ib1, grade 2 and 3 were randomised between six courses of cisplatin and no further treatment, and a second group of patients with stage Ia2 and Ib2 or Ic were randomised to cisplatin or intraperitoneal radiophosphorus. In 85 patients in the first study, the 5-year overall survival was 88% in the platinum arm and 82% in the no-treatment arm. In 161 patients in the second group, the 5-year survival was 81% in the platinum arm and 79% in the radiophosphorus arm. Neither difference was significant. These data indicate that patients with grade 2 and 3 tumours (and possibly with cyst rupture, excrescences or positive cytology) do not benefit from postoperative adjuvant chemotherapy or chromic phosphate, but they do not address the potential benefits of whole abdominal radiation therapy. Intraperitoneal radiophosphorus should not be considered equivalent to APRT as the doses with the former may be quite heterogeneous whereas external radiation achieves much more consistent dose delivery to the tissues at risk [17]. This includes the para-aortic nodes which, although infrequently involved in early-stage ovarian cancer, are treated during APRT but not with radiophosphorus.

Several trials comparing whole abdominal radiation and cisplatin-containing chemotherapy have been reported but failed to accrue sufficient numbers of patients and were closed prematurely. The National Institute for Cancer Research in Italy randomised 70 patients with stage I grade 3 and stage II ovarian cancer to six courses of cisplatin and cyclophosphamide versus APRT to an abdominal dose of 30 Gy [18]. Protocol violations occurred in 8 patients randomised to APRT who received chemotherapy instead. Five-year survival was 71% in the patients assigned chemotherapy versus 53% in the radiation arm ($P = 0.16$). In the West Midlands study, only 40 patients were recruited, 15 of whom had stage III disease [19]. Five courses of cisplatin as a single agent at a dose of 100 mg/m^2 were compared with abdominal moving strip radiation. Five-year survival was 62% in the chemotherapy group and 58% in the radiation group.

With the lack of adequate randomised studies comparing modern chemotherapy and APRT, consideration may be given to retrospective data to address this question. Recent results from Vancouver suggest the superiority of a combined protocol of chemotherapy with radiation to chemotherapy alone in a group of patients with stage I and II grade 3 or stage III no residual disease, any grade [20]. Two sequential protocols were evaluated. The first, between 1983 and 1989, used six courses of cyclophosphamide and cisplatin with APRT given between cycles 3 and 4. Because of concern about toxicity and the uncertainty of the contribution of the radiation therapy, a subsequent cohort of patients between 1989 and 1991 were treated with six courses of cisplatin chemotherapy alone (at the same 75 mg/m^2 dose as the first protocol). There were 84 patients entered during the earlier period and 47 during the later,

Table 1. Randomised trials of APRT and chemotherapy in early ovarian cancer

Study [Ref.]	Number of patients	Stages	Treatments	Outcome (5-year survival)
PMH [12]	147	I–III	APRT	58%
			P + chlorambucil	41%
				$P = 0.05$
NCIC [13]	257	I–III	APRT	61%
			P + melphalan	62%
DACOVA [14]	118	IB–II	APRT	55%*
			P + cyclophosphamide	63%
MDAH [15]	149	I–III	APRT	71%
			Melphalan	72%

P, pelvic radiotherapy.
* 4-year survival.

with a significant difference in 5-year overall survival (82% versus 48%, $P = 0.05$) and relapse-free survival (68% versus 48%, $P = 0.02$) in favour of the combined modality treatment. Multivariate analysis identified stage and treatment regimen as the only independent predictors of survival. Bowel obstruction occurred in 2 patients in the combined modality arm and a further 2 patients developed a malabsorption syndrome. There were no bowel complications in the patients treated with cisplatin alone. The patients appear to be reasonably well-balanced between the two groups and, although this was not a randomised study, it reflects a change in treatment policy during two sequential time periods, rather than patient selection. The significant increase in relapse-free and overall survival in these patients with the addition of radiation (and cyclophosphamide) to cisplatin has resulted in the Vancouver group resuming the use of combined modality treatment.

SELECTION OF PATIENTS FOR ABDOMINO-PELVIC RADIATION THERAPY

The selection of appropriate patients for APRT has been well documented in a series of studies undertaken by Dembo and colleagues, and confirmed in other centres around the world. Table 2 has been redrawn from a recent analysis of the PMH data, where patients have been subdivided by stage, grade and the amount of residual tumour [1]. Patients with stage I grade 1 tumours have a high rate of freedom from relapse without adjuvant treatment. An intermediate risk group of patients with an approximately 75% 5-year freedom from relapse was identified and includes patients with stage I grade 2 and 3 and stage II grades 1–3 tumour with no macroscopic residual tumour, or grade 1 and 2 with small macroscopic residual disease confined to the pelvis. In addition, stage III patients with grade 1 tumours appear to have a favourable outcome following APRT. This prognostic grouping has consistently predicted long-term outcome in the PMH population during two time periods, i.e. 1971–1978 and 1979–1985 [1, 7]. Other groups in Europe and North America have confirmed these results in similar prospective studies with 5- to 10-year survival rates of 70–77% [21–24]. The high risk group of stage II grade 3 with small residual tumour and stage III grade 2 or 3 patients were treated with six courses of cisplatin–cyclophosphamide chemotherapy followed by APRT, which has been shown to double median survival compared to APRT alone [25].

Table 2. Results in early ovarian cancer at PMH

Stage	Residual disease	Grade 1	Grade 2	Grade 3
I	0	97 ± 2 (80)		
II	0			
II	< 2 cm			21 ± 11 (14)
III	0		26 ± 14 (12)	29 ± 11 (20)
III	< 2 cm		45 ± 11 (20)	39 ± 10 (27)

1979–1985, per cent 5-year RFR (%) ± S.D. (and patient number).

Risk category:

▒, Low (LR); ■, Intermediate (IR); □, High (HR)

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Acute toxicity during APRT is usually mild and easily treated [19]. In the PMH analysis, 61% of patients complained of nausea ± vomiting, but in only 6% was it severe (requiring hospitalisation or intravenous hydration). Diarrhoea occurred in 68% of patients and again was only severe in 6% [6]. Only 10% of patients failed to complete treatment, a result confirmed in a more recent study using three courses of cisplatin followed by APRT where 89% of patients completed full dose radiation [26].

CONCLUSION

The only treatment to demonstrate a survival benefit in a randomised trial in early stage high risk ovarian cancer is abdomino-pelvic radiation therapy. Randomised trials indicate that chemotherapy and intraperitoneal radiophosphorus may reduce relapse, but they do not increase overall survival. These various modalities are associated with different toxicities, but the relative magnitudes of these effects have not been well studied nor has the quality of life of patients been compared. The EORTC Radiotherapy Group (with collaboration from our group in Toronto) is conducting a randomised study of APRT versus platinum chemotherapy in stages Ia/b grade 2/3 and stage Ic and IIa/b patients that is designed to answer these questions. However, in addition to the impediments to studies comparing chemotherapy and radiation already mentioned, there is now increasing pressure to adopt paclitaxel and cisplatin as standard chemotherapy for early ovarian cancer, on the basis of the apparent improvement in outcome from the GOG 111 study in suboptimally debulked advanced disease. The analogy could be made that this is similar to adopting adjuvant chemotherapy in node-negative breast cancer on the basis of the results from randomised trials in node-positive patients, without having performed the appropriate studies. It would be most unfortunate if the EORTC trial failed because of a lack of commitment to study all therapeutic options in these patients, and due to the premature adoption of unproven and potentially more toxic chemotherapy. Studies of combined chemotherapy and APRT versus chemotherapy alone in patients with higher risk disease, such as stage II grade 3 and optimally debulked stage III, should be considered based on the improved outcome with combined treatment in the Vancouver study.

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Contra:

G. Bolis,[1,2] C. Ferraris[1,2] and F. Parazzini[3]

[1]Istituto di Clinica Ostetrico Ginecologica Prima, Università di Milano, Milan; [2]Istituto Nazionale Tumori via Venezian, Milan; and [3]Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy

EARLY OVARIAN cancer (stage I and IIa according to the FIGO classification) is not rare amounting to approximately 30% of all ovarian cancers at initial diagnosis [1]. In the U.S., 5000–7000 new cases of early ovarian cancer are diagnosed per year [2] and in Europe, the figure is 7000–8000 cases [3]. The estimated numbers of deaths due to early ovarian cancer are, respectively, approximately 1500–2000 in the U.S. and 2000–2500 in Europe [2, 3]. Thus, the identification of effective treatments for this condition may have an impact at the public health level.

After completely resecting surgery, three kinds of therapy (chemotherapy, intraperitoneal or external radiotherapy) have been suggested as adjuvant treatment in early ovarian cancer. To define their role, and particularly for the scope of this debate, to define the utility of radiotherapy, we have to answer two questions:

- Has postoperative therapy shown any improvement in survival?
- Which therapy (chemotherapy or intraperitoneal or external radiotherapy) is the most efficacious as adjuvant treatment of ovarian cancer?

There is general agreement that sound scientific evidence comes from randomised controlled clinical trials. Thus, to

Correspondence to G. Bolis.