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ORIGINAL ARTICLE

Fractionated Palliative Pelvic Radiotherapy as an Effective Modality in the Management of Recurrent/Refractory Epithelial Ovarian Cancers: An Institutional Experience

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Abstract

Background The advent of effective chemotherapeutic agents for ovarian carcinoma has made radical abdomino-pelvic radiation redundant. Nevertheless, palliative pelvic radiotherapy still has a role in palliating local symptoms. However, its effect on progression-free survival (PFS) may be debated.

Aims To study the outcome of fractionated palliative pelvic radiotherapy in relapsed ovarian cancers in terms of symptom control and PFS.

Methods Twenty-three patients of ovarian cancers, heavily pretreated with chemotherapy and with recurrent or residual pelvic masses, were planned for palliative pelvic radiotherapy to the dose of 46–50 Gy in 23–25 fractions in 4.5–5 weeks. Symptom control and outcomes have been analyzed.

Results Post-radiotherapy, abdominal pain was controlled in 15 out of 17 patients (88.2 %), bleeding per vaginum in all 5 patients and vaginal discharge stopped in 4 out of 5 patients (80 %). On follow-up, of 23 patients, 17 (74 %) had progressive disease post-radiation, and median time to disease progression was 10 months (range 1–49). On univariate analysis, increased PFS was observed in patients who received radiation late in their course of disease, those with serous histology, and with lesser disease bulk in pelvis ($\leq$2 cm) prior to radiation initiation.
Conclusion Fractionated palliative pelvic radiotherapy is an efficient method for symptom palliation in relapsed ovarian cancers. Patients who are heavily pretreated with chemotherapy and have a small-volume pelvic disease may show a prolonged PFS with addition of pelvic radiotherapy. Indications of radiotherapy, however, need to be defined.

Keywords Ovarian cancer · Recurrent · Radiotherapy · Palliation · Progression-free survival

Introduction

Ovarian cancer is the leading cause of death from gynecological malignancies worldwide. The ideal management is aggressive surgical removal of tumor (debulking) and platinum-based chemotherapy [1]. At present, role of radiotherapy in ovarian cancers is confined to symptom palliation alone. However, these cancers are known for relapse, and the relapses are often associated with low response rates to further chemotherapy and subsequent poor prognosis [2]. In recent years, there has been resurgence of interest in the use of radiotherapy in ovarian cancers especially with localized pelvic recurrences.

The present study is the retrospective analysis of ovarian cancer patients treated with surgery and chemotherapy, and who have recurred frequently. They were treated with radiotherapy especially when the recurrences were confined to pelvis, and the outcomes were analyzed.

Materials and Methods

Patients

Between January 2008 and December 2013, patients of ovarian carcinoma who at any time during their course of treatment received pelvic radiotherapy were analyzed. Twenty-three such patients were identified. All these were managed on the lines of standard treatment of ovarian cancer, i.e., early-stage patients had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) followed by paclitaxel and platinum-based chemotherapy. Locally advanced patients underwent maximum debulking surgery followed by adjuvant chemotherapy, or neoadjuvant chemotherapy followed by maximum debulking surgery and adjuvant chemotherapy. For second-line chemotherapy, patients with platinum-sensitive disease were treated with Injection Carboplatin and Liposomal Doxorubicin, and those with platinum resistance or refractory disease received single-agent liposomal doxorubicin. In selected patients, in whom multiple recurrences were managed by two or three lines of chemotherapy, and post-chemotherapy, recurrence was localized to pelvis (confirmed by contrast enhanced computed tomography (CECT) chest abdomen pelvis, or Positron emission tomography (PET), or further chemotherapy could not be tolerated, radiation was used with palliative intent.

Radiation Technique and Dose

Patients were simulated on Simulator CT and treated with 6- or 15-MV photons, by parallel opposed anterior-posterior portals, or conformal radiation. Dose delivered to pelvic region was 46–50 Gy in 23–25 fractions in 4.5–5 weeks.

Follow-Up

Patients were monitored weekly during radiotherapy for acute radiation toxicity [gastrointestinal (GI) and genitourinary (GU) toxicities] using RTOG (Radiation Therapy Oncology Group) toxicity scoring for acute reactions. Weekly hemogram was done during the course of radiotherapy for assessing hematological toxicity. First follow-up after radiation was scheduled at 4 weeks with repeat CT scan and CA-125, and thereafter patients were followed every 3 months with clinical examination and CA-125 levels. RECIST criteria 1.0 (Response evaluation criteria in solid tumors) was used for response evaluation following radiotherapy. Partial response was documented by at least 30 % decrease in tumor size and progressive disease by more than 20 % increase in tumor size [3].

Statistical Analysis

Frequency tables were used to describe treatment characteristics of the patients. Symptom control was defined in terms of response rates. Progression-free survival (PFS) was calculated by Kaplan–Meier method. Univariate analysis was done using log-rank test.

Results

Patient Profile

Table 1 defines the characteristics of the patients, who later in their course of disease received pelvic radiotherapy.

Relapse Pattern

Median follow-up period was 50 months. At the time of first relapse, 20 patients (87 %) had relapsed loco-regionally in the pelvis and 3 (13 %) had distant metastasis.

Treatment After Relapse

All patients were planned with chemotherapy at the time of their first relapse. In 4 patients (17.4 %), radiotherapy was delivered after second line of chemotherapy, in 12 patients (52.2 %) after third line of chemotherapy, in 4 patients (17.4 %) after fourth line of chemotherapy and in 3 patients (13 %) after fifth line of chemotherapy.

Fifteen patients (65.2 %) out of these had received six cycles of three weekly chemotherapy immediately before radiotherapy, and 8 (34.8 %) were planned with radiotherapy without upfront chemotherapy.

Reasons for Treating with Pelvic Radiotherapy

All these patients were planned with pelvic radiotherapy with palliative intent, with the aim to treat local pelvic symptoms, like lower abdominal pain in 10 patients, bleeding per vaginum in 2 patients, discharge per vaginum in 3 patients, both abdominal pain and bleeding in 3 patients, abdominal pain and discharge in 2 patients. Also, all these patients at the time of radiotherapy were not suitable in terms of their general condition for any further systemic chemotherapy.

On evaluation by CT scans, at the time of radiotherapy, 11 patients (47.8 %) had local pelvic tumor size of $\leq$2 cm; rest had tumor size ranging from 3 to 8 cm in the largest dimension. CA125 levels ranged from 2 to 326 U/ml.

Table 1 Patients characteristics

Median age (years)	48	
Stage	II	8 (34.7 %)
	III	14 (60.9 %)
	IV	1 (4.3 %)
Histology	Serous	7 (30.4 %)
	Mucinous	10 (43.5 %)
	Clear cell	1 (4.3 %)
	Poorly differentiated	5 (21.8 %)
Treatment	Surgery followed by adjuvant chemotherapy	19 (82.6 %)
	Neoadjuvant chemotherapy followed by surgery	4 (17.4 %)
First-line chemotherapy regimen	Paclitaxel and carboplatin	17 (73.9 %)
	Cisplatin and cyclophosphamide	6 (26.1 %)

Acute Toxicity

During radiotherapy, hematological toxicity was seen in 3 patients (13 %). Two out of three patients had neutropenia which required gap in the radiotherapy for 2 and 3 days, respectively, and 1 developed anemia, which required blood transfusion. Acute grade 1 and 2 GU toxicity was seen in 3 (13 %) and 1 patient (4.3 %), respectively. All these 4 patients had received chemotherapy prior to radiation. Acute grade 1 and 2 GI toxicity was seen in 5 (21.73 %) and 2 (8.7 %) patients, respectively, but these were easily manageable. None experienced grade 3 or 4 toxicities.

Late Toxicity

None of the patients experienced late GI toxicity in the form of bowel obstruction, or perforation.

Response to Radiotherapy

Response to treatment was assessed clinically by analyzing symptom control and radiologically by CT scans done 4–6 weeks after radiotherapy completion.

Pain control was seen in 15 out of 17 patients (88.2 %). Bleeding per vaginum was controlled in all 5 patients (100 %). Vaginal discharge stopped after radiotherapy in 4 out of 5 patients (80 %). None of the patients had obstructive symptoms before they were started on radiotherapy.

At week 6, radiological complete response to radiation (disappearance of pelvic mass) was seen in 9 patients (39.1 %), partial response in 5 patients (21.7 %), and progressive disease was seen in 9 patients (39.1 %). None had stable disease.

Disease Progression and Survival Post-Radiation

At the time of last follow-up, out of 23 patients, 17 (74 %) had progressive disease. The median time to disease progression post-radiotherapy was 10 months (range 1–49). Out of these 17, 5 had local pelvic residual disease, 10 progressed distally, and 2 patients had rising CA 125 alone.

PFS and Univariate Analysis (Table 2)

Univariate analysis was done to find a correlation between the PFS post-radiotherapy and timing of radiation (early or late radiotherapy), histology (serous or non-serous), and initial tumor bulk on CT scans prior to radiotherapy (less than or more than 2 cm). Here early radiotherapy refers to the timing of start of radiation immediately after first line of chemotherapy, and late radiotherapy means timing of radiotherapy at least after two or more lines of chemotherapy.

As seen in Fig. 1, increased PFS was seen in patients who received radiation late in their course of disease [10-month PFS = 54.2 vs. 33.3 %, respectively ($p = 0.9$; HR 1.05, 95 % CI 0.23–4.68)]. In addition, patients who had non-serous histology had lower PFS compared to patients with serous histology [10-month PFS = 32.2 vs. 85.7 %, respectively ($p = 0.01$; HR 4.5, 95 % CI 1.18–16.68)] (Fig. 2). And finally, the patients who had bulky disease prior to radiotherapy had lower PFS compared to those patients who had less volume of disease in pelvis [10-month PFS = 40.4 % vs. 61.4 %, respectively ($p = 0.13$; HR 2.2, 95 % CI 0.77–6.3)] (Fig. 3). However, correlation between histology and PFS only could reach statistical significance.

Table 2 Progression-free survival

Variables	10-month progression-free survival
Late radiotherapy versus early radiotherapy	54.2 versus 33.3 %, $p = 0.9$
Non-serous histology versus serous histology	32.2 versus 85.7 %, $p = 0.01$
Bulky disease versus non-bulky disease	40.4 versus 61.4 %, $p = 0.13$

Discussion

Post-radical surgery, local pelvic radiotherapy was long before tried in curative management of ovarian malignancies. However, ovarian cancer disseminates dominantly throughout the peritoneal cavity. In fact, at first relapse, regardless of therapy, tumor is confined to the abdominal cavity in approximately 85 % of patients [4]. Thus, for radiation to be of curative benefit, techniques that encompass the whole peritoneal cavity, rather than just the pelvis, are likely to be most beneficial. In the past, whole abdomen radiation (WAR) has been used in ovarian cancers as part of a combined modality approach; in early-stage cancers as adjuvant therapy and in advanced stages as consolidative therapy. [5, 6]. However, its use has long been declined now in view of the radiation toxicities and emergence of newer and effective role of chemotherapeutic drugs [7, 8].

At present, radiotherapy in ovarian cancers is largely limited to palliation/consolidation alone, either for local pelvic symptoms or for metastatic disease in bone or brain. For palliation, hypofractionated schedules like 30 Gy in ten fractions, 20 Gy in five fractions, or single fractions of 5–10 Gy are used in clinical practice [9].

The standard management for ovarian cancers is platinum-based chemotherapy. Even on relapse, further several

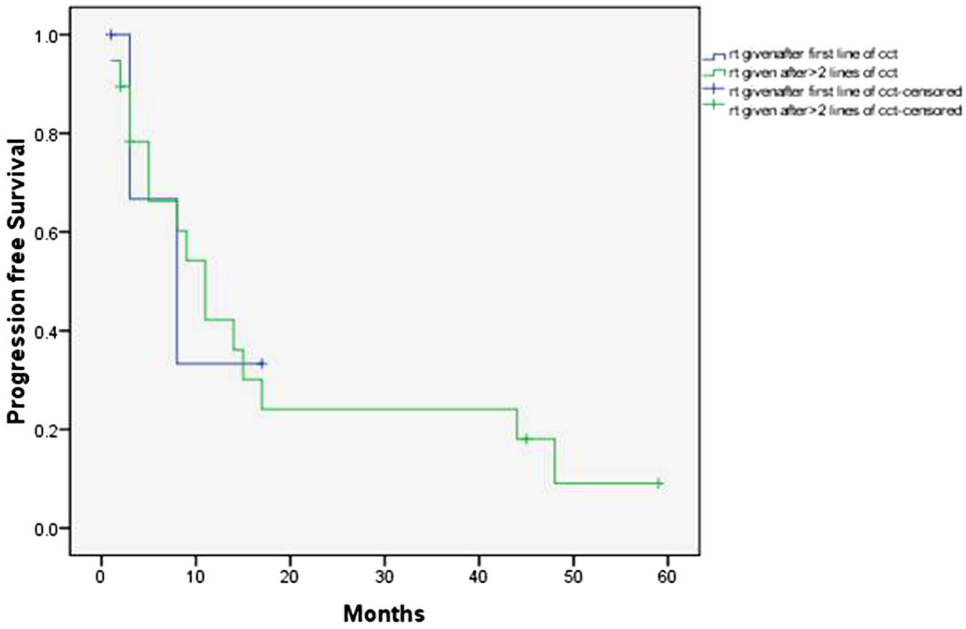

Fig. 1 10-month PFS: early versus late radiotherapy

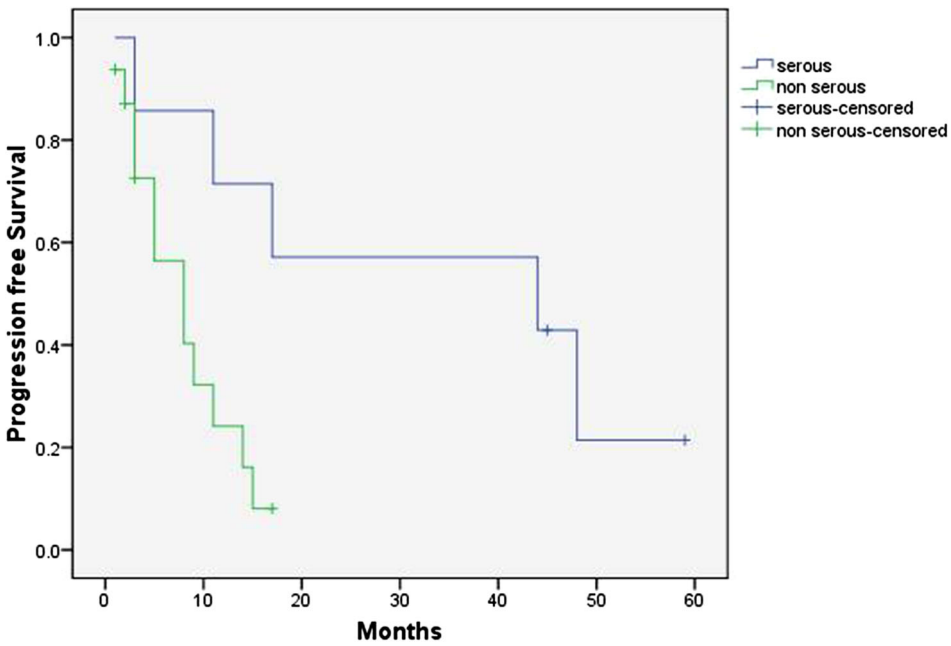

Fig. 2 10-month PFS: serous versus non-serous histologies

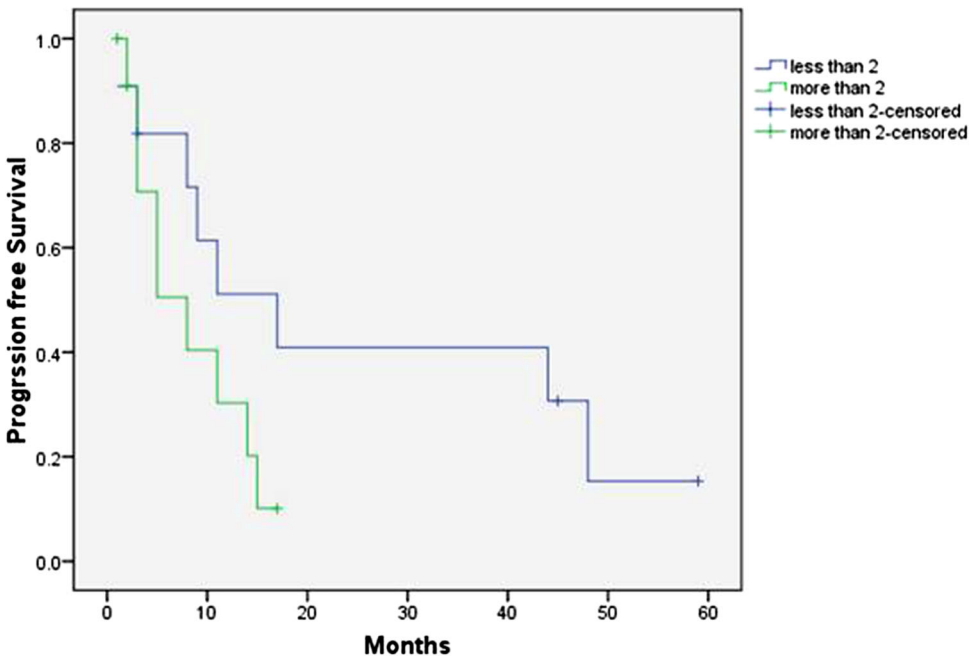

Fig. 3 10-month PFS: pre-radiotherapy tumor bulk less than 2 cm versus more than 2 cm

lines of chemotherapy are tried and have been found useful in increasing survival of the patients. However, these drugs have their own limitations. Once platinum-insensitive, the response rates to chemotherapy fall to 10–15 % [10]. In addition, at some point of time, patient fails to tolerate these drugs.

Radiotherapy as palliative modality in ovarian cancer is often neglected but may be useful if the dominant symptomatic problem for patient is localized to the site, that can be safely encompassed in a radiation field.

In our study, we have tried to find out when and how local pelvic radiotherapy can be best and judiciously utilized for ovarian cancer patients during relapse. Patients in this study were treated with fractionated radiotherapy, and symptoms in terms of local pain, bleeding or discharge per vaginum, were effectively controlled without producing significant side effects.

Reports on symptomatic response to fractionated pelvic radiotherapy treatment in ovarian cancer are lacking in the literature. Most of the results are with hypofractionated

regimens. Corn et al. [11] treated 33 patients in the pelvis with response rate of 90 % for vaginal bleeding. They reported that patients who received biologically effective dose of at least 44 Gy10, equal to 35 Gy in 14 fractions, had higher chance of achieving complete response. Choan et al. [10] reported their experience with 53 patients treated with pelvic radiotherapy, 25 were complaining of vaginal bleeding and their response rate to treatment was 100 and 88 % achieved a complete response; however, hypofractionated regimens of 30 Gy/10# and 20 Gy/5# were most commonly utilized regimens.

In present study also, effective palliation was achieved. Additionally, this study demonstrated another aspect of treating relapsed patients with local pelvic radiotherapy. In our study, median time to disease progression post-radiotherapy was 10 months, which is significant especially in patients in whom multiple lines of chemotherapy have already been utilized, and further chemotherapy is not possible. Also, our study indicates that early introduction of radiotherapy in ovarian cancers has no benefit in increasing PFS.

On analyzing these four patients who received pelvic radiotherapy early in their course, i.e., immediately after first-line chemotherapy, it was found that all these were platinum-refractory patients (who relapsed within three to 4 months of completion of chemotherapy). This could be a possible reason why early radiotherapy was introduced in these patients, with the concern that further chemotherapy may not be of additional benefit. Also, 3 out of these 4 patients had mucinous histology and 1 had clear cell histology. This also explains the lower PFS in these patients, as non-serous histologies like mucinous and clear cell histologies are usually considered to show poor response to chemotherapy. In addition, all these patients had bulky pelvic disease prior to radiotherapy.

Our study also demonstrated higher PFS rates in patients with low-volume pelvic disease prior to radiotherapy (tumor size on CT scan $\leq$2 cm). Survival data on the use of local pelvic radiotherapy in relapsed/recurrent ovarian cancers are limited. Most of the studies in past have used WAR and that too in adjuvant setting or in initially advanced ovarian cancers showing minimal residual disease after second-look laparotomy [6].

Dembo analyzed patients who had surgery followed by WAR in five published trials [5]. The studies revealed that approximately 40–50 % of the patients who had minimal residual (<2 cm) disease were cured after radiotherapy. The proportion of survivors was directly related to the amount of residual disease post-surgery.

Sorbe assigned 98 ovarian cancer patients (who had initial cytoreductive surgery followed by chemotherapy), to receive either chemotherapy, WAR, or no further treatment [12]. The patients who had WAR had significantly better PFS rate (56 %) compared to chemotherapy (36 %) and no further treatment (33 %).

Pickel et al. [13] used WAR for consolidation in stage III ovarian cancer patients and showed survival advantage in those patients who had clinical remission after chemotherapy.

Though these studies have used WAR, but these do demonstrate that bulk of the disease prior to radiotherapy has an impact on PFS, and low-volume pelvic disease at the time of relapse/recurrence can be judiciously taken up for local pelvic radiotherapy.

Our study also demonstrated decreased PFS post-radiotherapy in non-serous histologies like mucinous, clear cell and endometrioid type; however, the results are not consistent with those in the literature. Studies by Nagai et al. [14] and Hoskin et al. [15] have shown better DFS and OS in patients with clear cell and mucinous histologies, treated with WAR post-surgery and chemotherapy, but in these patients, radiotherapy was given as consolidative treatment. As these histologies are poor responders to chemotherapy compared to serous histology, therefore DFS and OS are better when radiotherapy is added immediately after chemotherapy [16]. The possible reason for this variable outcome with respect to histology in our study could be because of small number of patients and also because all these were relapsed/recurrent cases of ovarian cancer, where the disease prognosis is already dismal.

Regarding toxicities, these were initially of concern when patients were planned with WAR. However, in the present study, local pelvic radiation was well tolerated despite the fact that most patients had received chemotherapy immediately prior to radiation. This can be explained by the use of conformal techniques by which desired dosimetric parameters can be achieved with maximal sparing of organs at risk [17]. Thus, radiotherapy may have a greater role in future.

Though clinical outcomes of WAR cannot be directly extrapolated to local pelvic radiotherapy, the results of our study demonstrate that limited relapsed disease/small-volume persistent disease in pelvis can be well taken care by using fractionated pelvic radiotherapy as a salvage treatment, especially in patients in whom further chemotherapy is not feasible.

The retrospective nature of this study and small number of patients do make it difficult to provide significant impact of certain important factors (like timing of radiotherapy and tumor bulk) on PFS, yet this study provides the scope for further possible research with larger number of patients, utilizing palliative radiotherapy, in refractory ovarian cancer, in an attempt to achieve higher PFS rates.

Conclusion

Fractionated pelvic radiotherapy is an efficient method to provide complete or partial, durable response for pelvic pain, vaginal bleeding or discharge and is especially useful for patients, heavily pretreated with chemotherapy, in terms of higher PFS.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent Since this is retrospective study, formal consent was not required.

Animals Rights There are no ethical issues with animal subjects. This article does not contain any studies with animals performed by any of the authors.

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