Adjuvant Pelvic Radiotherapy in Ovarian Cancer: Outcomes By Risk Factors

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Research

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Abstract

Background: Radiotherapy (RT) is not the current standard treatment option for ovarian cancer (OC) patients. The present study aims to explore the risk factors of adjuvant pelvic RT for patients with OC and to investigate prognostic factors associated with longer progression free survival (PFS) and overall survival (OS) period.

Methods: From April 2004 to September 2020, OC patients administered with RT were collected retrospectively at our institution and those who received pelvic RT were selected for further analysis. Kaplan-Meier method was employed to estimate the PFS, OS and local control (LC) rate. Univariate and multivariate cox regression model were established to identify potential beneficiaries of pelvic RT.

Results: Overall, a total of 89 OC patients underwent RT were identified, 70 of whom were treated with adjuvant pelvic RT and were eligible for final analysis. Median follow-up was 51.0 months. The estimated 3-year OS rate was 48.1% and 3-year PFS rate was 26.8%, respectively. CACTE grade 4 to 5 toxicities were observed in 2 patients. Multivariate cox model illustrated that high-grade serous carcinoma (HGSC), advanced stage disease (FIGO stage III & IV), receiving pelvic RT during multiple relapses as well as no previous chemotherapy (CT) were independent risk factors for PFS. Additionally, patients with 0-1 risk factor had a longer PFS time than those with 2-4 risk factors.

Conclusions: Pelvic RT was well tolerated and had favorable efficacy in OC patients with low risk factor (0-1), which might confer prolonged survival. However, further investigations are needed.

Background

Ovarian cancer (OC), a common gynecological malignancy, accounts for the fifth leading cause of cancer-related mortality in women (1). The established cornerstone treatment for OC patients consists of aggressive cytoreductive surgery and platinum based chemotherapy (CT) (2). Although most patients demonstrate an optimal response to the gold treatment and enter into clinical remission, over 70% of them will experience relapse during the course of disease, leading to a 5-year survival rate of approximately 30% (3).

Historically, radiotherapy (RT) served a dominant role in the postoperative adjuvant setting for patients with early stage or minimal residual disease (4). Over years, systematic platinum-based CT, obtaining higher response rates, were introduced to clinical practice and consequently, in the 1980s, RT were used sparingly for OC patients due to the conflicting clinical findings as well as severe toxic events including myelosuppression and gastrointestinal intolerance (5).

More recently, given the improvement of RT delivery techniques such as intensity-modulated radiotherapy (IMRT) and the exhibited platinum-resistance, the role of RT in specific clinical scenarios ought to be re-defined. A prospective research figured out that whole abdomen irradiation delivered with IMRT technique could be performed with acceptable toxicity for patients receiving radical cytoreductive surgery and
platinum-based adjuvant CT (6). Along with the gratifying results in terms of overall survival (OS) and progression free survival (PFS) observed in a subsequent trial, whole abdomen irradiation might offer a potential therapeutic option for advanced stage OC patients (7). However, limited literatures shed light on the identification of patients who would in particular stand to benefit from RT.

In the present study, we retrospectively assessed the efficacy and toxicity of pelvic RT for OC patient population in the adjuvant setting, aiming to define the potential beneficiaries of pelvic RT, which would be of utmost importance to procure a longer regional control.

**Materials And Methods**

**Study population**

We conducted a retrospective study, reviewing the data of 89 OC patients that received RT from April 2004 to September 2020 in the Department of Radiation and Medical Oncology of Zhongnan hospital of Wuhan University. Clinical information was derived from the electronic medical records system of our institution. We obtained permission from the Ethics Committee of Zhongnan hospital of Wuhan University for data acquisition and analysis, and all patients enrolled gave a verbal or written informed consent. Inclusion criteria were as follows: (a) histologically diagnosed ovary malignancy; (b) received pelvic RT either at the time of initial treatment or recurrence; (c) follow up for $\geq$ 3 months. A total of 70 OC patients were finally included in the analysis.

According to the 2014 WHO guidelines, we further categorized grade II, III and IV serous carcinomas and reclassified grade III/IV endometrioid into high-grade serous carcinoma (HGSC). Tumors with other histological types were considered as non-high-grade serous carcinoma (NHGSC). Initial stage of disease was assigned using the International Federation of Gynecology and Obstetrics (FIGO) criteria. Platinum-sensitive and platinum-resistant were defined as a progression/relapse more than or within 6 months from the last dose platinum-based CT, respectively. Clinical characteristics are displayed in Table 1.
Table 1
Clinical characteristics

| Characteristics                   | No. | %  |
|-----------------------------------|-----|----|
| No. of patients                   | 70  |    |
| Age, y                            |     |    |
| ≤ 50                              | 26  | 37.1|
| >50                               | 44  | 62.9|
| Median (Range)                    | 54 (34–77) | |
| Histology                         |     |    |
| HGSC                              | 55  | 78.6|
| NHGSC                             | 15  | 21.4|
| Initial FIGO Stage                |     |    |
| I & II                            | 26  | 37.1|
| III & IV                          | 37  | 52.9|
| Unknown                           | 7   | 10.0|
| History of relapse                |     |    |
| Initial treatment                 | 9   | 12.9|
| First relapse                     | 42  | 60.0|
| Multiple relapses                 | 19  | 27.1|
| Tumor sites                       |     |    |
| Pelvic                            | 44  | 62.9|
| Pelvic and abdomen                | 19  | 27.1|
| others                            | 7   | 10.0|
| Surgery before RT                 |     |    |
| Optimal debulking                 | 32  | 45.7|
| Suboptimal debulking              | 14  | 20.0|
| No surgery                        | 24  | 34.3|
| Chemotherapy cycle before RT      |     |    |
| 0                                 | 11  | 15.7|

HGSC, high-grade serous carcinoma; NHGSC, non-high-grade serous carcinoma; RT, radiotherapy.
| Characteristics                  | No. | %  |
|---------------------------------|-----|----|
| < 3                             | 14  | 20.0 |
| 3–6                             | 36  | 51.4 |
| > 6                             | 9   | 12.9 |
| Platinum sensitivity            |     |     |
| Platinum-sensitive              | 40  | 57.1 |
| Platinum-resistant              | 30  | 42.9 |
| Family history of cancer        |     |     |
| Yes                             | 10  | 14.3 |
| No                              | 60  | 85.7 |

HGSC, high-grade serous carcinoma; NHGSC, non-high-grade serous carcinoma; RT, radiotherapy.

**RT Policy**

In cases with external beam radiotherapy (EBRT), patients were placed in a supine position with arms elevated overhead. The clinical target volume (CTV) encompassed the entire pelvic cavity and draining lymph node regions, ranging from the 5th lumbar to the bottom of symphysis pubis. The planning target volume (PTV) was defined as extending the CTV by 7–10 mm in all dimensions. Organs at risk (OARs) included small intestine, colon, bladder, femoral head and neck, and spinal cord. Dose was prescribed to cover 95% of PTV with 100% isodose line and hot spot regions were localized in CTV. OAR dose criteria were taken from the published RTOG 0418 protocol. Radiation dose planning was performed on the CMS XiO (Varian, USA) treatment planning system (TPS) utilizing a superposition/convolution algorithm. IMRT plans were performed using multiple noncoplanar photon beams. Following EBRT, 5 patients underwent additional intracavity brachytherapy by a high-dose-rate afterloading system using iridium-192 source which was performed once or twice per week, with a cumulative dose ranging from 12 Gy to 33 Gy. RT characteristics are displayed in Supplementary table 1.

**Post-treatment follow up**

Follow-up data was obtained from clinical examinations and/or telephone survey. Clinical examination items including routinely physical examination, chest computed tomography, abdominal computed tomography, pelvic magnetic resonance imaging, and serum tumor markers were performed every 3 months for the first 2 years, semiannually for the next 3 years and annually thereafter. Patients were observed until death or loss to follow-up. OS was defined as the date elapsed between RT initiation and death from any cause or the last follow-up visit. PFS was defined as time from start of RT to the first observation of progression, relapse or death, whichever occurred first. Local control (LC) was defined as no new tumors within the previous radiation field.
Treatment-related complications were also recorded during follow-up and graded on the basis of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

**Statistical analysis**

Statistical analysis was carried out using SPSS statistical software, ver. 23.0 (IBM, Inc., Armonk, NY, USA). We employed Kaplan-Meier method was employed to compute OS, PFS, LC rates with 95% confidence intervals (CIs). Univariate cox proportional hazards regression model was established to figure out the prognostic factors. Variables with statistical significance (p < 0.1) or clinical significance were selected for the multivariate model. A two-sided p-value < 0.05 was considered to reflecting statistical significance.

**Results**

**Population**

The cohort of 70 OC patients treated with pelvic RT identified in the current study had a median age of 54 years (34–77 years). The histology was predominantly HGSC, presenting in 55 (78.6%) patients. Initial diagnosis at stage III & IV was dominant, accounting for 52.9 % of the population. A total of 42 (60.0%) patients received pelvic RT during first relapse, 19 (27.1%) patients received pelvic RT when experiencing multiple relapses and others received adjuvant pelvic RT after cytoreductive surgery at the initial treatment. There exist 32 (45.7%) patients undergoing optimal debulking, 14 (20.0%) patients undergoing suboptimal debulking and 24 (34.3%) patients without surgery before pelvic RT, respectively. A majority of patients received several cycles of platinum-based CT before pelvic RT and 40 (50.7 %) patients were platinum-sensitive. Only 10 (14.3%) patients had a family history of cancer (Table 1).

**Efficacy**

The median follow-up time was 51.0 months (95% CI: 39.0–63.0 months) in the present study. The median OS was 37.0 months (95% CI: 24.3–49.7) and the estimated 1-year, 2-year, 3-year OS rate after pelvic RT were 85.4%, 69.1%, 48.1%, respectively. Localized failure occurred in 13 patients with a median time of 11.0 months (95% CI: 6.5–15.5 months). The 1-year, 2-year, 3-year LC rates after pelvic RT were 87.3%, 79.3%, 75.5%, respectively. In terms of PFS, 52 patients (52/70, 74.3%) experienced progression or relapse in the duration of follow-up. The median PFS was 14.0 months (95% CI: 8.0-19.1 months) and PFS rates were 53.1% after 1-year, 34.8% after 2-year, 26.8% after 3-year, respectively (Fig. 1). The predominant sites for progression were lymph nodes and visceral organs, presenting in 26 patients (26/52, 50.0%).

**Univariate and multivariate analysis**

Prognostic factors analysis based on univariate regression model was displayed in Table 2. The result indicated that histology, initial FIGO stage, surgery before RT, and history of relapse exerted a most pronounced influence on PFS (p < 0.01). Along similar lines, platinum-sensitivity was also strongly correlated with PFS (p < 0.05). Age, chemotherapy cycle before RT and family history of cancer were not
significant factors for PFS. Initial FIGO stage and surgery before RT were found to influence OS ($p < 0.05$),
while no effect of other factors on OS was seen. In terms of LC, none of the predictors in the model had a
significant effect on LC.
## Table 2
Univariate analyses for factors associated with PFS and OS

| Variates                          | Univariate analysis of PFS (%) | Univariate analysis of OS (%) |
|-----------------------------------|--------------------------------|-------------------------------|
|                                   | HR    | 95% CI          | P    | HR    | 95% CI          | P    |
| Age, y                            |       |                 |      |       |                 |      |
| >50 vs ≤ 50                       | 1.442 | 0.796–2.610     | 0.217| 1.244 | 0.609–2.542     | 0.550|
| Histology                         |       |                 |      |       |                 |      |
| NHGSC vs HGSC                     | 0.269 | 0.112–0.647     | **0.003**| 0.356 | 0.125–1.010     | 0.052|
| Initial FIGO Stage                |       |                 |      |       |                 |      |
| III & IV vs I & II                | 2.792 | 1.475–5.287     | **0.002**| 3.565 | 1.582–8.032     | **0.002**|
| Unknown vs I & II                 | 1.914 | 0.680–5.384     | 0.219| 2.500 | 0.751–8.330     | 0.136|
| History of relapse                |       |                 |      |       |                 |      |
| First relapse vs multiple relapses| 0.338 | 0.183–0.623     | **0.001**| 0.605 | 0.302–1.215     | 0.158|
| Initial treatment vs multiple relapses| 0.135 | 0.044–0.418 | **0.001**| 0.170 | 0.037–0.791     | **0.024**|
| Tumor sites                       |       |                 |      |       |                 |      |
| Abdomen and pelvic vs pelvic      | 1.398 | 0.756–2.584     | 0.285| 1.538 | 0.758–3.122     | 0.233|
| Other vs pelvic                   | 2.019 | 0.869–4.689     | 0.102| 1.303 | 0.438–3.877     | 0.634|
| Surgery before RT                |       |                 |      |       |                 |      |
| Suboptimal debulking vs optimal debulking | 1.103 | 0.489–2.489 | 0.813| 1.716 | 0.636–4.628     | 0.286|
| No surgery vs optimal debulking   | 2.565 | 1.402–4.694     | **0.002**| 3.726 | 1.759–7.894     | **0.001**|
| Chemotherapy cycle before RT      |       |                 |      |       |                 |      |
| < 3 vs 0                          | 0.364 | 0.146–0.909     | **0.030**| 0.499 | 0.167–1.489     | 0.213|

PFS, progression free survival; OS, overall survival; HGSC, high-grade serous carcinoma; NHGSC, non-high-grade serous carcinoma; RT, radiotherapy.
| Variates                     | Univariate analysis of PFS (%) | Univariate analysis of OS (%) |
|-----------------------------|--------------------------------|--------------------------------|
|                             | HR    | 95% CI     | P   | HR    | 95% CI     | P   |
| 3–6 vs 0                    | 0.556 | 0.267–1.159| 0.117| 0.825 | 0.350–1.945| 0.660|
| > 6 vs 0                    | 0.381 | 0.137–1.061| 0.065| 0.110 | 0.013–0.897| 0.039|
| Platinum sensitivity        |       |            |     |       |            |     |
| Platinum-resistant vs platinum-sensitive | 2.046 | 1.180–3.546| **0.011**| 1.877 | 0.965–3.651| 0.065|
| Family history of cancer    |       |            |     |       |            |     |
| No vs yes                   | 0.635 | 0.307–1.311| 0.220| 0.947 | 0.392–2.292| 0.905|

| Variates                     | Univariate analysis of PFS (%) | Univariate analysis of OS (%) |
|-----------------------------|--------------------------------|--------------------------------|
|                             | HR    | 95% CI     | P   | HR    | 95% CI     | P   |
| Platinum sensitivity        |       |            |     |       |            |     |
| Platinum-resistant vs platinum-sensitive | 2.046 | 1.180–3.546| **0.011**| 1.877 | 0.965–3.651| 0.065|

PFS, progression free survival; OS, overall survival; HGSC, high-grade serous carcinoma; NHGSC, non-high-grade serous carcinoma; RT, radiotherapy.

Given that chemotherapy cycle before RT was also associated with response to RT and survival outcome (8, 9), it was also included in the multivariate model other than variables with statistical significance (p < 0.1). As shown in Fig. 2A, it was noticeable that patients dispensed with pelvic RT during initial treatment and first relapse displayed better PFS (p < 0.05) compared with those treated with pelvic RT when experiencing multiple relapses. Meanwhile, NHGSC and more than 6 cycles of CT before RT were related with a longer PFS (p < 0.05). Furthermore, advanced FIGO stage at diagnosis led to a remarkable ominous PFS (p = 0.002, HR = 3.156, 95% CI [1.541–6.464]) and OS (p = 0.001, HR = 4.622, 95% CI [1.876–11.385]) and the survival benefit of CT > 6 cycles expanded to OS (p = 0.017, HR = 0.066, 95% CI [0.007–0.612]) (Fig. 2B).

Furthermore, in order to estimate more precisely the PFS period after RT for OC patients, we stratified patients into two subgroups according to the risk factors related with PFS in multivariate cox model: HGSC, FIGO stage III & IV, multiple relapses and no previous chemotherapy: low risk group (0–1 risk factors) (n = 30), high risk group (2–4 risk factors) (n = 39). As shown in Fig. 3, PFS time in high risk group was significantly shorter than in low risk group, indicating that more aggressive and effective treatment regimens should be taken into practice to achieve a better local control for high risk patients.

**Adverse events**

CTCAE, Version 4.0 grade 4 to 5 toxicities were observed in 2 patients (Table 3). One patients received palliative pelvic RT and died of severe intestinal obstruction after the completion of RT, which was mainly due to intestinal adhesion caused by surgery. Another patient developed grade 4 acute gastrointestinal toxicity and relieved by medication. A total of 29 patients (29/70, 41.4%) experienced grade 1 to 2 acute
gastrointestinal toxicity and 14 (14/70, 20.0%) had grade 1 to 2 hematological toxicity. Only 4 patients displayed grade 3 hematological toxicity. Other adverse reactions related to RT included grade 1 or grade 2 genitourinary toxicity (n = 5) and grade 1 dermatitis (n = 1). Generally, pelvic RT was well-tolerated in most patients and could be performed as previously planned without interruption of RT related toxicity.

Table 3
Radiotherapy-related adverse events

| Toxic effect              | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---------------------------|---------|---------|---------|---------|---------|
| Hematologic toxicity      | 8 (11.4)| 6 (8.6) | 4 (5.7) | 0 (0.0) | 0 (0.0) |
| Colitis                   | 9 (12.9)| 20 (28.6)| 0 (0.0) | 1 (1.4) | 1 (1.4) |
| Cystitis                  | 0 (0.0) | 5 (7.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Radiation dermatitis      | 1 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Discussion

In the current single-center study, 70 cases of OC patients administered with pelvic RT were retrospectively reviewed. Our data revealed that pelvic RT exhibited remarkable antitumor activity in OC patients without unpredictable adverse events. We reported a 2-year OS rate of 69.1% and a 2-year PFS rate of 34.8%, which corroborated with the findings of previous investigations (10, 11). The 3-year LC rate was 75.5%, supporting recent studies documenting that RT yielded satisfying local control outcome in OC patients (10, 12, 13). Besides, in agreement with other researches (14, 15), survival after RT had no correlation with platinum sensitivity at the onset of RT, indicating that RT could serve as an effective modality in the treatment of OC patients irrespective of platinum status.

Univariate and multivariate cox regression models were constructed in an attempt to locate potential beneficiaries of pelvic RT. Concerning histology, we observed that NHGSC was a favorable prognostic factor. Rare histology variants, such as ovarian clear cell carcinoma (OCCC), was particularly chemo-resistant with a clinical response rate to platinum-based CT of merely 18% (16, 17), and chances of curability of this subtype could be enhanced by adjuvant RT (18). Brown AP et al. documented that OCCC patients had a higher 5-year OS rate (88% vs 37%) and PFS rate (75% vs 20%) compared with other patients (10). Among the 5 OCCC patients in our series (Supplementary table 2), 2 patients progressed within 1 year and another patient progressed 36 months after RT. Only 1 patient died 43 months after RT and 4 other patients were still alive at the last follow-up, rendering improved PFS and OS time. Collectively, early and aggressive RT ought to be employed in the management of patients diagnosed with OCCC.

In the current study, early stage disease (FIGO stage I & II) and more CT regimens before RT predicted a longer PFS rate and OS rate. It is a well-acknowledged fact that advanced stage OC patients recurred
after a median interval of 18–24 months and had a poor 5-year OS rate of 31% for stage III, 13% for stage IV (14), respectively, compared with early stage disease. This finding is inconsistent with that of Robert Rome et al. who observed significant correlation between initial stage I & II and disease specific death (19). However, prior investigations have shown that patients with stage III OC could still gain benefit from adjuvant intensity modulated whole-abdominal radiotherapy although more aggressive and accurate local management regimens are in urgent need (7). Regarding numbers of prior CT regimens, our finding is contrary to previous study which suggested that patients exposed to one prior CT regimens showed longer duration of survival than those administered with more prior CT regimens (15). The reason why numbers of CT cycles before RT was identified as a prognostic factor remains uncovered, and further mechanistic research should be undertaken to explore the underlying mechanism. It's highly likely that this result could be a statistical anomaly due to the limited number of patients enrolled in our retrospective study.

Furthermore, adjuvant RT after first relapse could markedly extend PFS period, but the OS benefit had not been observed according to our result. Westhoff et al. also found a prolonged PFS in 10 patients received RT for the first recurrence compared with those received it for subsequent recurrence (20). Additionally, we also reached the conclusion that adjuvant RT improved PFS period for OC patients during initial treatment. However, we didn't compare the toxicity and survival differences between post-operative adjuvant RT, adjuvant CT alone, and sequential chemoradiotherapy at initial treatment, which was in demand for in-depth investigations to confirm and validate these findings. Thus, we are unable to comment on the superiority of adjuvant RT over adjuvant CT for initial treatment from the results obtained in this study.

Several limitations to this study need to be acknowledged. First, it was a single-center experience and the sample size was relatively small. Second, it is possible that the results were biased, given the nature of retrospective design. Selection biases might occur when gynecologic oncologists recommended adjuvant pelvic RT. Finally, patients’ economic conditions and medical literacy would exert a large effect on treatment choice. Hence, definitive large clinical trials are awaited regarding suitable OC patients for adjuvant pelvic RT.

In conclusion, pelvic RT might be a promising treatment option for OC patients, regardless of the platinum-sensitivity status. Patients with early stage disease, NHGSC, experiencing initial treatment and first recurrence, receiving more CT cycles are good candidates for adjuvant pelvic RT. Further investigations are warranted to confirm and validate these factors in terms of choosing treatment for OC patients.

**Declarations**

**Ethics approval and consent to participate**
All the procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Zhongnan hospital of Wuhan University and with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

**Consent for publication**

Not applicable

**Availability of data and materials**

All data generated or analysed during this study are included in this published article and its supplementary information files.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

Study conception and design were performed by HQ & CX. Material preparation and data collection were performed by LH, MC & CY. Analysis was performed by JC. The first draft of the manuscript was written by JC & ZM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Figures**

**Figure 1**

![Graph showing survival rates and number at risk](image-url)
Kaplan-Meier survival curves on OS, PFS, LC of ovary carcinoma patients received pelvic radiotherapy. OS, overall survival; PFS, progression free survival; LC, local control; CI, confidence interval; NR, not reached

**Figure 2**

Forest plot based on the results of multivariate analysis of prognostic factors associated with (A) PFS and (B) OS, PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval;
Figure 3

Kaplan-Meier estimate according to independent risk factors correlated with PFS Patients were divided into 2 subgroups based on the number of risk factors: low risk (0-1 risk factor), high risk (2-4 risk factors). Low risk group patients had a significantly longer PFS than patients in high risk group. PFS, progression free survival

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx