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Involved-field radiation therapy for recurrent ovarian cancer: Results of a multi-institutional prospective phase II trial

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HIGHLIGHTS

- This is the first prospective study that aimed to define the role of involved-field radiation therapy (IFRT).
- Selected patients may achieve protracted progression-free survival after IFRT without toxicity.
- IFRT could increase chemotherapy break in patients with recurrent and persistent epithelial ovarian cancer.

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ABSTRACT

Objective. To evaluate the efficacy and safety of involved-field radiation therapy (IFRT) in patients with locoregionally confined recurrent or persistent epithelial ovarian cancer.

Methods. This study included patients with recurrent epithelial ovarian cancer eligible for IFRT either during diagnosis of the recurrence or after salvage therapies. IFRT was performed at a dose of ≥45 Gy for all tumors with 10–15-mm margins as seen on standard imaging. The primary endpoint was progression-free survival (PFS); the secondary endpoints were safety, response rate, local control, and overall survival (OS).

Results. Thirty patients with a mean number of 5.7 metastatic lesions each were enrolled between 2014 and 2016. Seventeen were treated with 3-D conformal radiation therapy (RT) and 13 with intensity-modulated RT. IFRT was well tolerated in all patients, and acute toxicity ≥ grade 2 was not observed. One case of grade 3 abdominal pain was reported 10 months post-RT. The overall and complete response rates were 85.7% and 50%, respectively. After a median follow-up of 28 (range, 17–42) months, the median PFS was 7 months. The 2-year PFS rate was 39.3%. Six of the 16 patients who developed outfield disease progression after IFRT were successfully treated with repeat IFRT as salvage treatment. The 3-year local control and OS rates were 84.4% and 55.8%, respectively.

Conclusions. Although the primary endpoint was not met, IFRT might be safe and effective for in-field tumor control in patients with persistent epithelial ovarian cancer with a limited number of metastatic foci. We plan to conduct a larger scale multi-center phase II prospective study.

1. Introduction

Most patients with advanced epithelial ovarian cancer experience relapse and thus require additional salvage treatment despite initial therapy such as maximal cytoreductive surgery with platinum-based chemotherapy [1]. The current standard of care for patients with recurrent epithelial ovarian cancer is palliative chemotherapy, endocrine therapy, and cytoreductive surgery when appropriate, with radiation therapy reserved for the management of symptomatic metastases [2]. Although this treatment paradigm yields a prolonged survival rate in a number of patients with recurrent epithelial ovarian cancer, it is not curative [3,4]. An analysis of the outcomes of 976 patients with platinum-sensitive recurrent ovarian cancer who were treated with pegylated liposomal doxorubicin with carboplatin or paclitaxel and carboplatin in the CALYPSO trial showed that approximately <10% remained relapse-

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free 2 years after completion of treatment [4]. These data, along with the accepted curative role of chemotherapy in the adjuvant setting after optimal cytoreduction of epithelial ovarian cancer, imply that current systemic therapies are helpful in controlling micrometastatic spread. However, single-agent or combination chemotherapy may be unlikely to be curative in patients harboring gross disease.

Although whole abdominal radiation therapy showed significant efficacy in a small proportion of patients with complete resection, this treatment has lost its popularity because of late bowel toxicity and post-treatment protracted bone marrow suppression risk. However, in addition to standard chemotherapy, involved-field radiation therapy (IFRT), which targets only localized nodal or extranodal recurrences, has been shown to result in prolonged disease-free intervals and even cure in selected patients [5]. The benefit of IFRT may come from excellent in-field tumor control as well as its capability to prevent known recurrent disease from seeding new metastases. This concept is quite similar to the idea of cytoreductive surgery where complete resection of all macroscopic disease increases overall survival (OS) in a select group of patients with recurrent epithelial ovarian cancer [6]. However, the reported series of IFRT have been primarily single-institutional experiences and retrospective [7–14]. Critics of IFRT argue that the long-term disease-free survival benefit in these studies has more to do with selection bias toward patients with favorable biologic behavior.

Therefore, we conducted a phase II multi-center prospective study (KROG 14-05) to assess whether the hypothesis that IFRT to all macroscopic disease in combination with standard chemotherapy and cytoreductive surgery can substantially affect the clinical outcome of recurrent epithelial ovarian cancer is reproducible in a prospective setting. Secondary endpoints were RT-related toxicity, local control, and OS.

2. Methods

2.1. Study design

This multi-institution study was a non-randomized single-arm phase II trial of IFRT as part of the standard salvage treatment for all gross tumors of recurrent epithelial ovarian cancer. The study design was approved by the review board of the Korean Radiation Oncology Group (KROG) and by the institutional review boards of all participating hospitals. Each patient signed an informed consent form. This study is registered on ClinicalTrials.gov (identifier: NCT02135523).

2.2. Patients

Patients with recurrent epithelial ovarian cancer were eligible for enrollment if they met the following criteria: Measurable disease (≥1) was present with residual tumor following salvage treatment (systemic therapy ± cytoreductive surgery) or recurrent tumor if chemotherapy was impossible or refused by a patient who was amenable to IFRT; and all metastatic disease was located within the localized peritoneum, liver, abdominal-pelvic-mediastinal-neck lymph node, cul-de-sac, vaginal cuff, abdominal wall (e.g., incision site), and lung (≤4). Whether patients would participate in the trial was determined at the multidisciplinary team meeting.

Patients were required to have minimal bone marrow, renal, and hepatic organ function, including absolute neutrophil count ≥ 500/μl, serum creatinine level ≤ 2.0 times the upper limit of normal, and AST and ALT ≤ 2.5 times the upper limit of normal. The initial tumors at diagnosis must have been treated with optimal cytoreductive surgery and adjuvant systemic therapy according to their pathologic stage. Notable exclusions included patients with diffuse peritoneal seeding and brain or bone metastases (Supplementary Fig. 1).

2.3. Treatment

All identified metastases were treated either with external beam RT or with brachytherapy (only for vaginal or vault recurrence). All patients underwent computed tomography (CT) simulation before being treated using 3-dimensional conformal RT (3-D CRT), intensity-modulated RT (IMRT), or brachytherapy. The gross tumor volume included all known tumors as seen on standard imaging. The clinical target volume (CTV) was expanded to 10–15 mm and to adjacent high-risk regions at the discretion of the treating physician. High-risk regions included either the pre-chemotherapy or pre-surgery volume if IFRT was delivered after chemotherapy or surgery, or the involved nodal chain region (e.g., cervical, axillary, mediastinal, paraaortic, iliac, and inguinal) if the involvement of multiple lymph nodes was suspected in the same region. The planning target volume margins were added from the CTV, and at least 45 Gy equivalent to 2 Gy ($\alpha/\beta = 10$) was prescribed. Target agents (e.g., bevacizumab) were permitted during IFRT, but not in cytotoxic chemotherapy.

2.4. Follow-up

The study endpoints were assessed via follow-up every 3 months through history taking and physical examination, standard imaging, and laboratory testing including for cancer antigen 125 (CA-125). Computed tomography (CT) scans encompassing the target lesions were scheduled 1 month after the completion of IFRT, every 6 months for 2 years, and then annually for 1 year. Serum CA-125 was measured 1 month after IFRT, every 3 months for 1 year, and then every 6 months for 2 years. Before enrollment, fluorodeoxyglucose positron emission tomography/CT was mandated, but it was then optionally scheduled annually after treatment for 3 years. The tumor response and disease progression were evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Local failure was defined as tumor progression at the treated site. For patients in whom local failure was determined via serial assessments, the event was documented from the first radiographic appearance of tumor progression.

2.5. Statistical analysis

The primary endpoint of the study was progression-free survival (PFS), and the secondary endpoints were local control, safety, and OS. Using a one-arm survival sample size calculator, the sample size was calculated as 30 patients (median PFS = 9 to 16 months, with alpha = 0.05 and beta = 0.20). PFS was defined as the time from IFRT to subsequent recurrence, progression, or death without disease, whichever comes first. Secondary endpoints were toxicity, response rate, treatment breaks (defined as the intervals between courses of chemotherapy), local control, and OS. The Kaplan-Meier method was used to estimate the OS, PFS, and local failure-free survival. Cox's regression model was used for multivariate analysis of PFS. Statistical significance was set at a 2-sided *P*-value of <0.05.

3. Results

Thirty patients were enrolled in the study between April 2014 and April 2016. The comprehensive patient and treatment characteristics and trial schema are shown in Table 1 and eFigure 1. Before enrollment, patients received a median of 3 courses of chemotherapy (range, 1–7). Six patients had one recurrent site, while the other 24 (80%) had multiple recurrent sites (median 3.5, range 2–19; mean 5.7 ± 4.9). Twelve patients underwent IFRT as first attempted salvage therapy at the time of localized recurrence, while 15 patients underwent IFRT for induced localized recurrence or residual disease after cytoreductive surgery and chemotherapy (median 6 cycles, range 3–11; most (14/15) had platinum-based combination therapy with ($n = 2$) or without ($n =$

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