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ABSTRACT

The role for localized radiation to treat ovarian cancer (OC) patients with locally recurrent vaginal/perirectal lesions remains unclear, though we hypothesize these patients may be salvaged locally and gain long-term survival benefit. We describe our institutional outcomes using intensity modulated radiation therapy (IMRT) +/- high-dose rate (HDR) brachytherapy to treat this population. Our primary objectives were to evaluate complete response rates of targeted lesions after radiation and calculate our 5-year in-field control (IFC) rate. Secondary objectives were to assess radiation-related toxicities, chemotherapy free-interval (CFI), as well as post-radiation progression-free (PFS) and overall survival (OS). PFS and OS were defined from radiation start to either progression or death/last follow-up, respectively. This was a heavily pre-treated cohort of 17 recurrent OC patients with a median follow-up of 28.4 months (range 4.5–33.0). Radiation was well tolerated with 2 (12.0%) experiencing grade 3/4 gastrointestinal/genitourinary toxicities. In conclusion, radiation to treat locally recurrent vaginal/perirectal lesions in heavily pre-treated OC patients is safe and may effectively provide IFC.

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- Localized recurrence
- Oligometastatic recurrence
- Radiation

1. Introduction

Despite recent advances in primary and maintenance therapies for patients with ovarian carcinoma (OC), over 80% will recur and experience treatment-related toxicities. The landscape of therapeutic options in the recurrent setting is driven by platinum response, and most commonly includes systemic therapies such as chemotherapy, biologic targeted therapies, immunotherapy, and even endocrine therapy (NCCN Guidelines, 2020). Prior to the development of effective palliative chemotherapy options, pelvic radiation was used for local control (Firat and Erickson, 2001). However, this modality fell out of favor because it failed to address upper abdominal disease, while whole abdomen radiation produced toxicities that outweighed its limited benefits. Nevertheless, while current guidelines reserve a role for localized radiation to palliate symptoms, (NCCN Guidelines, 2020) it remains unclear who benefits most from this localized treatment modality.

The small, but growing body of literature on radiation for recurrent OC has documented responses in heterogeneous populations with oligometastatic disease (i.e. vaginal/rectal implants vs. localized nodal and extranodal recurrences in the abdomen and/or pelvis) with limited insight into which subgroups experience clinical benefit (Firat and Erickson, 2001; Albuquerque et al., 2016; Chundury et al., 2016;
stratified by pre-radiation platinum status. All tests were two-sided with analysis.

Chemotherapy-free interval (CFI) was evidenced by imaging or initiation systemic therapy, death, or last follow-up at time of analysis. IFC was defined as no recurrence within 12 months vs. ≥12 months. Overall median PFS post-radiation was 11.0 months (range 2.6–27.5). Patients treated with definitive intent (n = 11), had a 13.4 month longer median PFS than those treated with palliative doses (18.6 vs 5.2 months, p = 0.01). PFS did not differ when stratified by platinum status prior to radiation. The 9 patients who were platinum-sensitive prior to radiation had similar median PFS (6.5 vs. 13.4 months, log-rank p = 0.75), but longer OS (71.1 vs 18.8 months, log-rank p = 0.05, Fig. 2) compared to their platinum-resistant counterparts. Excluding patients with low-grade serous histology and those who were treated with palliative intent, the median CFI was 14.2 months (range 4.70–33.0) with no impact on PFS or OS when stratified by CFI < 12 months vs. ≥ 12 months.

Overall radiation was well tolerated with 2 patients experiencing grade 3/4 toxicities. Patient 12 had a vesicovaginal fistula repair 5 months prior to radiation and the fistula recurred during her last week of radiation for multisite disease (vaginal cuff and retroperitoneal adenopathy). Patient 5 was diagnosed with a parastomal hernia and bowel perforation outside of the radiated field approximately 4 weeks after completing palliative pelvic IMRT + HDR brachytherapy for multi-site disease. This was thought to be due to a 10 cm mass eroding into the colon and she eventually succumbed from this event.

4. Discussion

Focused radiation therapy led to durable IFC for most OC patients with recurrence involving the vaginal apex and/or perirectal area. As expected, genitourinary and gastrointestinal side effects were most frequent, but grade 3–4 complications were uncommon. However, OS was determined by platinum sensitivity, suggesting that subsequent chemotherapy plays a role in determining survival. Our results support continuing our ongoing institutional practice to evaluate patients with limited metastatic burden for targeted radiation with the goal of providing treatment breaks from systemic therapy, palliation of symptoms, and effective locoregional control.

Prior studies exploring localized radiotherapy, including our own institutional data from 2016, historically included heterogeneous
populations of OC patients, many with localized nodal and extranodal recurrences in the abdomen and/or pelvis (Albuquerque et al., 2016; Chundury et al., 2016; Westhoff et al., 2016; Kim et al., 2019; Brown et al., 2013; Yahara et al., 2013; Chang et al., 2018; Smart et al., 2019; Onal et al., 2020). Nevertheless, rates of local control at 2 and 3 years after radiation are 80% and 5-year IFC rates as high as 71% (Albuquerque et al., 2016; Brown et al., 2013). More recently, the SABR-COMET trial reported a 5-year OS benefit among patients with metastatic solid tumors (n = 1) or during a secondary cytoreductive surgery (n = 3). Nevertheless, no patients underwent a diverting procedure after radiation completion. Collectively, this data suggests that in carefully selected women with recurrent OC localized to the pelvis and involving the vagina and/or perirectal area, there may be a potential advantage to delivering aggressive local radiation. This can be administered with limited toxicity, and provide heavily pretreated patients treatment breaks from systemic therapy. Furthermore, we show a median CFI post-radiation of 14.2 months, which for platinum-resistant patients, could lead to re-challenge with a platinum or additional agents.

| ID | Age at RT (years) | Race | Histology | Stage | Genetics | Optimally Debulled (<1cm) | Location Treated with RT | Time to RT from Dx (months) | Initial Platinum Status | Pre-RT Platinum Status |
|----|------------------|------|-----------|-------|----------|--------------------------|--------------------------|--------------------------|-------------------------|------------------------|
| 1  | 81               | White| HG Serous | IIb   | Unknown  | No                       | Vaginal apex, Left paraortic LN | 53                       | Sensitive               | Resistant              |
| 2  | 61               | White| HG Serous | IIIc  | Unknown  | No                       | Vaginal apex, Right external iliac LN | 73                       | Sensitive               | Sensitive              |
| 3  | 78               | Asian | Clear cell| Ic    | Negative* | No                       | Vaginal apex, three abdominal & pelvic masses, RP LN | 18                       | Sensitive               | Sensitive              |
| 4  | 49               | White| LG Serous | IVb   | Unknown  | No                       | Vaginal apex, Peritoneum, Serosa, Left inguinal, Mediastinum | 149                      | Sensitive               | Sensitive              |
| 5  | 66               | White| HG Serous | IIIc  | Unknown  | No                       | Vaginal apex (involving bladder & sigmoid colon), Left iliac LN | 74                       | Sensitive               | Resistant              |
| 6  | 79               | White| HG Serous | IIc   | BRCA1    | No                       | Vaginal apex, Left external iliac LN | 148                      | Sensitive               | Sensitive              |
| 7  | 80               | White| HG Serous | IVb   | Unknown  | No                       | Vaginal apex, hila, Inguinal LN | 36                       | Resistant               | Resistant              |
| 8  | 75               | White| LG Serous | IIIc  | Negative* | Yes                      | Vaginal apex, Pelvis | 135                      | Sensitive               | Resistant              |
| 9  | 67               | White| HG Serous | IIIc  | Negative* | BRCA1/2                   | Vaginal apex, L SVC, Lung, Left abdominal wall, LNs: Left PA, Right inguinal, Right external iliac | 113                      | Sensitive               | Sensitive              |
| 10 | 79               | White| HG Serous | IIIc  | Negative* | Yes                      | Vaginal apex | 35                       | Sensitive               | Sensitive              |
| 11 | 53               | White| Gr 3 Endometrioid and HG Ib Serous | IIc | BRCA2 | Yes | Vaginal apex | 81 | Sensitive | Sensitive |
| 12 | 59               | White| Carcinosarcoma | IVa | Negative* | No | Vaginal apex, RP adenopathy | 9 | Refractory | Refractory |
| 13 | 57               | Black| HG Serous | IIIc  | BRCA2    | Yes                      | Vaginal fornix, Spleen, Liver, Left iliac, Peritoneum, Left rectus | 78                       | Sensitive               | Sensitive              |
| 14 | 39               | White| Clear cell | Ic   | MLH1     | Yes                      | Vaginal apex, LNs: RP, Left iliac | 10                       | Resistant               | Resistant              |
| 15 | 56               | White| Carcinosarcoma (HG Serous) | IIIc | Negative* | Yes | Vaginal apex, bladder dome, Left iliac | 75                       | Sensitive               | Resistant              |
| 16 | 74               | White| HG Serous | IIIc  | Negative* | RAD51C                    | Perirectal & Vaginal apex | 87                       | Sensitive               | Sensitive              |
| 17 | 65               | White| Gr 3 Endometrioid and HG Serous | IIIc | Negative* | VUS | Vaginal apex | 139 | Sensitive | Sensitive |

RT: radiation; Dx: diagnosis; HG: high-grade; Gr: grade; LG: low-grade; LN: lymph node; RP: retroperitoneal.

* Patients were screened with a multi-gene panel.
## Table 2
Treatment and outcomes.

| ID | Lines of chemo prior to RT (n) | RT modality | Intent of RT | RT alone | Total RT dosage (cGy) | Dose/Fraction (cGy) | In field failure | Grade 3/4 toxicities | Survival after RT (months) | Status |
|----|--------------------------------|-------------|--------------|----------|-----------------------|---------------------|------------------|-------------------|--------------------------|--------|
| 10 | 2 HDR Brachytherapy (Vaginal cylinder), IMRT | Definitive | Yes | | 1000, 6000 | 500, 200 | Yes | No | 52.6 | Alive with disease |
| 11 | 2 IMRT | Definitive | Yes | | 6000 | 200 | Yes | No | 38.2 | Alive without disease |
| 16 | 3 IMRT | Definitive | Yes | | 5940 | 180 | No | No | 16.6 | Dead |
| 17 | 3 IMRT | Definitive | Yes | | 6000 | 200 | No | No | 7.6 | Alive with disease |
| 5 | 8 HDR Brachytherapy (Vaginal cylinder), IMRT | Palliative | Yes | | 1000, 5040 | 500, 180 | No | Yes | 4.5 | Dead |
| 12 | 1 HDR Brachytherapy (Vaginal cylinder), IMRT | Definitive | Yes | | 1000, 6000 | 500, 200 | No | Yes | 14.0 | Dead |
| 15 | 3 HDR Interstitial brachytherapy, IMRT | Definitive | Yes | | 1800, 5940 | 225, 180 | No | No | 16.5 | Dead |
| 1 | 4 IMRT | Definitive | Yes* | | 5040 | 180 | No | No | 38.0 | Dead |
| 2 | 1 IMRT | Definitive | Yes | | 6000 | 200 | No | No | 69.8 | Dead |
| 3 | 1 IMRT | Palliative | No, concurrent carboplatin & paclitaxel | | 5040 | 180 | No | No | 89.1 | Alive without disease |
| 4 | 5 IMRT | Palliative | Yes | | 5000 | 200 | No | No | 28.5 | Dead |
| 9 | 9 IMRT | Palliative | Yes | | 6000 | 200 | No | No | 28.7 | Dead |
| 13 | 8 IMRT | Palliative | Yes | | 6000 | 200 | No | No | 26.0 | Dead |
| 6 | 1 HDR Brachytherapy (Vaginal cylinder) | Definitive | Unknown | | 2400 | 400 | Yes | No | 166.4 | Dead |
| 7 | 2 HDR Brachytherapy (Vaginal cylinder) | Palliative | No, concurrent bevacizumab/pemetrexed | | 4800 | 800 | No | No | 4.7 | Dead |
| 14 | 1 HDR Brachytherapy (Vaginal cylinder) | Definitive | No, concurrent pembrolizumab | | 4800 | 800 | No | No | 20.6 | Alive without disease |

![Fig. 1. Kaplan-Meier estimates of IFC, PFS, and OS among recurrent ovarian cancer patients treated with radiation.](image-url)
Our case series has several limitations impacting interpretation of data and extrapolation to the recurrent OC patient population at large. Given the small sample size and high rates of complete response to radiation, we were unable to perform subgroup analyses to better understand predictors of complete response to radiation and 5-year IFC. Though platinum status prior to radiation was collected, subgroup analysis was not feasible to further explore the impact of platinum-sensitivity to radiation response and IFC. Our small sample size also did not allow for meaningful comparisons between different radiation modalities (IMRT versus brachytherapy), dose, and volumes for optimal tumor response, nor could we stratify by important clinical characteristics such as tumor number, size, or location (vaginal apex/perirectal area vs other), histology, number of therapies prior to radiation, and genetic status. Additionally, although radiation was generally well tolerated, we do not have quality of life data for this cohort to determine symptomatic benefit from radiation.

Future studies should examine utilization of other modalities to deliver aggressive local radiation to locally recurrent OC patients as employed in this study. Our institution is actively examining stereotactic radiation utilizing MRI-guidance and adaptive treatment planning to test whether this approach can provide patients with shortened treatment times (days instead of weeks) while maintaining desired clinical outcomes for treatment sites throughout the body without increasing adverse events. Additionally, the timing of radiation in relation to chemotherapy should be investigated. At present, there is no consensus regarding initiation of radiation in patients with locoregional recurrence. In our study, time from diagnosis to first round of radiation therapy was >5 years. Potentially, initiation of local therapy earlier in the treatment course could provide greater therapeutic benefit, while simultaneously reducing cumulative treatment-related toxicity and improving quality of life outcomes. Finally, it will be important to identify any clinical (platinum sensitivity, histology, etc.) or genetic markers (tumor mutational burden, BRCA status) within the population that may predispose patients to greater benefit from aggressive local therapy.

In conclusion, our data suggests that utilization of aggressive local therapy with radiation for patients with locoregional pelvic recurrence is safe, provides effective IFC, leading to increased CFI, with minimal gastrointestinal/genitourinary side effects. We propose that radiation should be considered for appropriately selected patients at the time of locoregional pelvic recurrence as it may lead to improved clinical outcomes.

Author Contributions

1. Elizabeth Johns, M.D., M.S.: Lead author who contributed to project design, performed the data collection and entry, and manuscript writing, and approved final submitted version.
2. Jennifer Stanley, M.D., Ph.D.: Assisted with IRB approval, performed the data collection and entry, project design, manuscript writing, and approved final submitted version.
3. Michael Toboni, M.D., M.P.H.: Performed the data collection and entry, project design, and manuscript writing.
4. Julie Schwarz, M.D., Ph.D.: Provided input regarding project design, assisted with manuscript revisions, and approval of final submitted version.
5. Fan Zhang, M.D. Master of Statistics: Assisted with statistical analysis, tables/figures, manuscript revisions, and approval of final submitted version.
6. Andrea Hagemann, M.D., M.S.C.I.: Assisted with manuscript revisions and approval of final submitted version.
7. Katherine Fuh, M.D., PhD.: Assisted with manuscript revisions and approval of final submitted version.
8. Premal Thaker, M.D., Ph.D.: Provided input regarding project design, assisted with manuscript revisions, and approval of final submitted version.
9. Carolyn McCourt, M.D.: Assisted with manuscript revisions and approval of final submitted version.
10. David Mutch, M.D.: Assisted with manuscript revisions and approval of final submitted version.
11. Matthew Powell, M.D.: Assisted with manuscript revisions and approval of final submitted version.
12. Dineo Khabele, M.D.: Assisted with manuscript revisions and approval of final submitted version.
13. Lindsay Kuroki, M.D., M.S.C.I.: Senior author who was directly involved with study design, data clean-up, manuscript writing, and approval of final submitted version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2021.100808.

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