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Radiation therapy for vaginal and perirectal lesions in recurrent ovarian cancer

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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 4.5–166.4) after radiation completion. 52.9% had high-grade serous histology and 4 (23.5%) had isolated vaginal/perirectal disease. Four (23.5%) patients had in-field failures at 3.7, 11.2, 24.5, and 27.5 months after start of radiation, all treated with definitive dosing of radiation therapy. 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 $p = 0.05$) than their platinum-resistant counterparts. Excluding patients with low-grade histology or who were treated with palliative radiation, median CFI was 14.2 months (range 4.7 – 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.

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;

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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). Though the reported incidence of oligometastatic vaginal/perirectal OC recurrences appears low, (Casey et al., 1996) these areas are unique in that they may be salvaged with targeted radiation to improve not only local control and long-term survival, but also to effectively palliate symptoms. Thus, we aimed to better define the patient population with vaginal/perirectal oligometastatic OC recurrences who benefits from radiation and what toxicities may result from this treatment modality. Here, we describe our institutional experience utilizing intensity modulated radiation therapy (IMRT) +/- high dose-rate (HDR) brachytherapy to treat vaginal and perirectal recurrences in OC patients. Our primary objectives were to evaluate complete response rates of targeted lesions after radiation and calculate the 5-year in-field local control (IFC) rate. Secondary objectives were to assess radiation-related toxicities, as well as post-radiation progression-free survival (PFS) and overall survival (OS).

2. Methods

This case series included 17 patients with recurrent OC who received IMRT, HDR brachytherapy, or both for vaginal and/or perirectal recurrences at Washington University School of Medicine from January 2006 to November 2019. Eligible patients were identified from our Radiation Oncology institutional database. Initial treatment planning, simulation, treatment devices, and radiation treatment plans were individualized at the discretion of the treating radiation oncologist. This retrospective review was approved by the Washington University Institutional Review Board (#202005019).

We included patients with recurrent OC, regardless of stage or histology, with a vaginal and/or perirectal recurrence as determined by computed tomography (CT), 18-fluoro-deoxyglucose positron emission tomography (FDG-PET), and/or magnetic resonance imaging (MRI). Patients were subdivided by oligometastatic, defined as 1–5 metastatic lesions, (Lievens et al., 2020) or multi-site recurrence prior to radiation.

Following radiation, patients were seen for 6-week post-radiation exams by either a radiation oncologist or gynecologic oncologist, and thereafter according to systemic treatment schedules, but at least every 3 months. Radiation related toxicities were categorized as acute ($\leq$28 days) or late (>28 days) and graded per common terminology criteria for adverse events (CTCAE) version 5.0 (Cancer Therapy Evaluation Program (CTEP), 2017). All patients were followed until death or time of analysis.

OS was defined from start of radiation to death or last follow-up at time of analysis. PFS was defined from start of radiation to progression (evidenced by imaging or initiation systemic therapy), death, or last follow-up at time of analysis. IFC was defined as no recurrence within the radiated field as determined by PET/CT, CT, MRI, or clinical exam. Those suspected of recurrence following radiation did not require biopsy for histologic confirmation. Chemotherapy-free interval (CFI) was calculated as the time between radiation start and next line of chemotherapy. OS, PFS, and IFC were calculated using Kaplan-Meier method. The log rank test was used to compare PFS and OS after radiation stratified by pre-radiation platinum status. All tests were two-sided with a significance level of 0.05. SAS Version 9.4 (Cary, NC) was used to perform all statistical analyses.

3. Results

A total of 17 patients were included in the analysis, 4 with oligometastatic disease and 13 with multi-site disease. Table 1 summarizes patient clinical characteristics. All but 2 patients were white, the median age at diagnosis was 58 (range 38–77), and most had stage III disease and high-grade serous histology. Of the 12 patients with available genetic testing results, 2 had germline mutations in *BRCA2*, 1 in *BRCA1,* and 1 in *MLH1*. All 4 (23.5%) patients (ID 10, 11, 16, and 17) with oligometastatic disease confined to the vagina/rectum were initially platinum sensitive, but only 3 were platinum sensitive immediately preceding radiation.

Table 2 summarizes treatment characteristics of patients stratified by oligometastatic and multi-site recurrence. Overall, this was a heavily pretreated population. Patients had received a median of 3 lines of chemotherapy prior to radiation (range 1–9), including 3 who received concurrent chemoradiation. Eleven of the 17 patients received definitive radiation; median time for radiation completion was 41 days (range 11–105). One patient (ID 17) experienced extended time to completion of a total of 105 elapsed days—45 days for initial photon treatment, 6000 cGy in 30 fractions, followed by proton boost, 30 cobalt gray equivalents (CGE) in 15 fractions. This plan was specifically individualized for this patient, as she was the only one in our series who received proton therapy. The two patients with the longest CFI after radiation included a *BRCA2* mutation carrier (ID 11) with isolated disease to the vagina, while the other (ID 14) had a mismatch repair deficient (*MLH1)* tumor treated with concurrent radiation and pembrolizumab.

Median follow-up after radiation was 28.4 months (range 4.5–166.4). Fifteen (88.2%) patients achieved a complete response of targetable lesion(s) after radiation. Four (23.5%) patients (ID 8, 6, 11 and 10) had in-field failures at 3.7, 11.2, 24.5, and 27.5 months after start of radiation (Fig. 1). Two were *BRCA* carriers, and 3 received additional radiation to the vaginal cuff/perirectal area. A detailed narrative of these 4 patients and their management strategies are provided in Supplemental Table 1. Eleven women were treated with curative intent, and among them, 7 (64%) were free of disease within the treatment field at last follow-up. Ten patients were evaluable for 5-year follow-up after radiation, contributing to a 5-year IFC rate of 70%.

At the time of this analysis, 3 (17.6%) patients were alive with no evidence of disease, 2 (11.8%) were alive with disease, and 12 (58.8%) were dead of disease. 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. $\geq$ 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

Table 1
Summary of clinical characteristics.

ID	Age at RT (years)	Race	Histology	Stage	Genetics	Optimally Debulked (<1cm)	Location Treated with RT	Time to RT from Dx (months)	Initial Platinum Status	Pre-RT Platinum Status
N = 17	66 (39–81)	White (15)	HG Serous (9) LG Serous (2) Clear Cell (2) Mixed (3) Carcinosarcoma (1)	I (3) II (2) III (9) IV (3)	*BRCA* (3) *MLH1* (1)	Yes (8)	Vaginal apex (17)	75 (9–149)	Sensitive (14) Resistant (2) Refractory (1)	Sensitive (8) Resistant (7) Refractory (1) Unknown (1)
1	81	White	HG Serous	IIIb	Unknown	No	Vaginal apex, Left *para*-aortic 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 Mesenteric implants	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, hilum, Inguinal LN	36	Resistant	Resistant
8	75	White	LG Serous	IIIc	Negative *BRCA1/2*	Yes	Vaginal apex, Pelvis	135	Sensitive	Resistant
9	67	White	HG Serous	IIIc	Negative *BRCA1/2*	No	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 Serous	Ib	*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*	Yes	Perirectal & Vaginal apex	87	Sensitive	Sensitive
17	65	White	Gr 3 Endometrioid and HG Serous	IIIc	*RAD51C* VUS	Yes	Vaginal apex	139	Sensitive	Resistant

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.

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 treated with palliative radiation vs ablative therapy (17.7% vs. 42.3% ,95% CI, 28–56%; p = 0.006), with no new grade 2–5 adverse events or differences in quality of life (Palma et al., 2020). Though this study excluded gynecologic oncology patients, our study results show comparable rates of 5-year in-field control (70%) when targeted local radiation therapy is employed in this patient population. Importantly, due to the anatomic location of tumors in this study, patients experiencing in-field recurrence were frequently salvaged with additional radiation. Of the 17 patients in our case series, four had undergone a diverting ostomy prior to initiation of radiation, either as a part of their upfront staging surgery (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.

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
Oligometastatic disease										
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
Multisite disease: IMRT + HDR Brachytherapy										
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
Multisite disease: IMRT alone										
1	4	IMRT	Definitive	Yes	5040	180	No	No	38.0	Dead
8	4	IMRT#	Definitive	Yes*	5040	180	Yes	No	58.8	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
Multisite disease: HDR Brachytherapy alone										
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

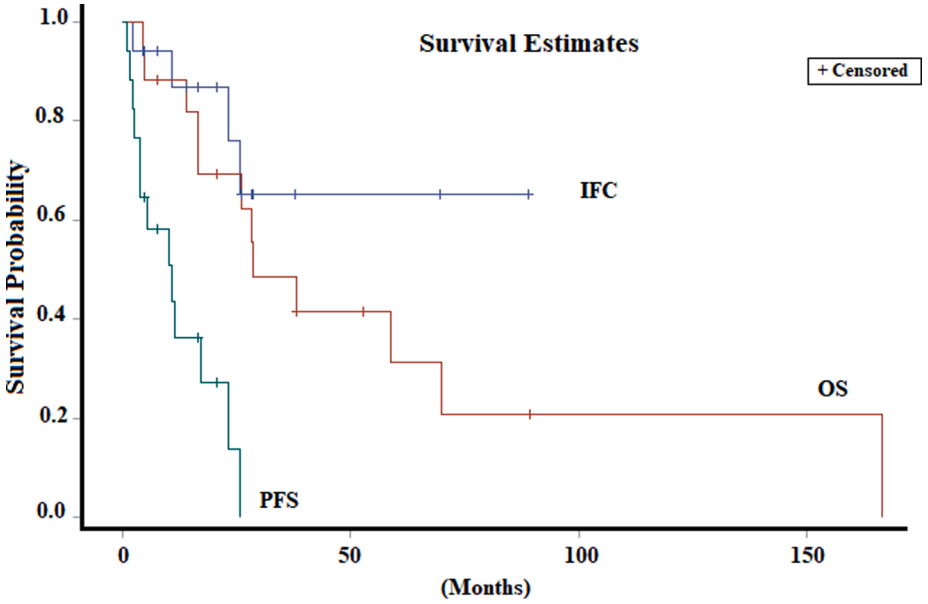

Fig. 1. Kaplan-Meier estimates of IFC, PFS, and OS among recurrent ovarian cancer patients treated with radiation.

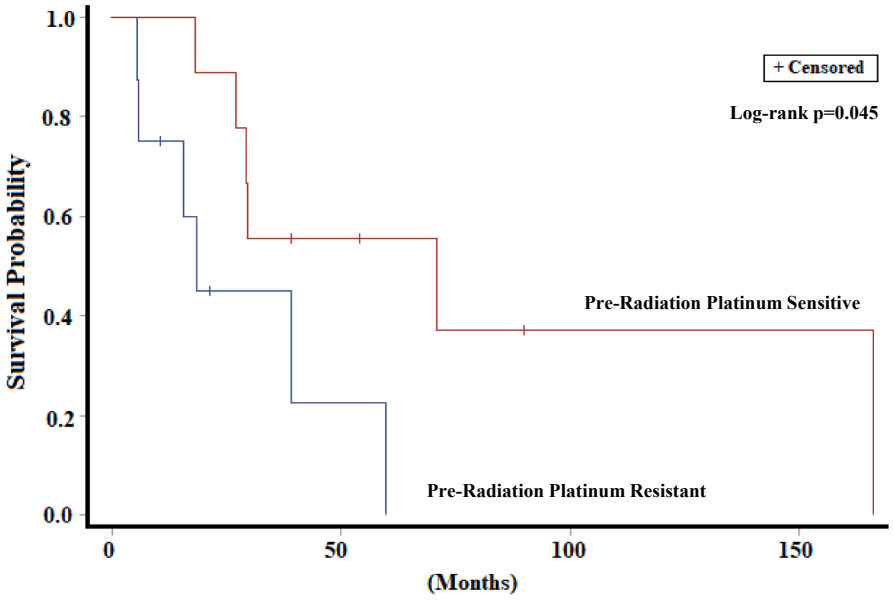

Fig. 2. Kaplan-Meier analysis showing OS after radiation stratified by pre-radiation platinum status.

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., M.S.: 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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