Combining concurrent radiotherapy and immunotherapy for synergistic effects in recurrent endometrial cancer – A case report

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ABSTRACT
Endometrial cancer, also known as uterine cancer, is the second most common cancer affecting women globally and the fourth most prevalent in the United States (US). Treatment often involves a combination of surgery, radiotherapy and chemotherapy depending on the severity. In this case report, we present two patients with relapsed endometrial carcinomas, who responded positively to combined radiotherapy and immunotherapy followed by maintenance immunotherapy.

Given the worsening prognoses associated with recurrent endometrial cancers, these two cases warrant the further exploration of the concurrent administration of immunotherapy and radiation therapy in the context of clinical trials.

1. Introduction

Uterine cancer is the second most common gynecological cancer affecting women globally. According to GLOBOCAN, there were 417,367 new cases and 97,370 deaths worldwide in 2020 (Global, 2021). According to the American Cancer Society, the average age at diagnosis in the US is 60. Despite the scientific strides that have been made in diagnosis and treatment, incidence (21.1 per 100,000) rates in Northern America are the highest in the world and mortality rates (3.2 per 100,000) are the fourth highest globally (NCI, 2021).

The goal of this case report is to share the observed efficacy of the combined administration of radiotherapy and immunotherapy for the treatment of recurrent endometrial carcinomas. Multiple pre-clinical studies have demonstrated that radiotherapy enhances the effects of immunotherapy and other case reports have confirmed these findings (Formenti et al., 2018). However, there are no published studies regarding contemporaneous administration of radiation therapy and immunotherapy (Table 1). These two patient cases endorse the synergistic benefits of combined radiation therapy and immunotherapy followed by maintenance immunotherapy for managing relapsed endometrial carcinomas.

2. Case presentation

2.1. Case 1 narrative

A 58-year-old woman with a history of leiomyomas presented to the clinic with vaginal bleeding. She was diagnosed with FIGO Stage I Grade 1 endometrioid endometrial adenocarcinoma (limited to the polyp and endometrium) after undergoing total laparoscopic hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with morcellation. The malignancy was limited to the polyp and endometrium. No nodal assessment was performed.

Two months later, she began to experience abdominal pain. Six months after diagnosis, a pelvic ultrasound and computed tomography (CT) scan revealed four enhancing masses at the lower abdominal wall...
Table 1
A summary of previous endometrial cancer case reviews that have delivered radiotherapy and immunotherapy sequentially.

| Authors(s)’ Name | Type of Cancer | Number of Patients | Immunotherapy | Radiotherapy | Radiological Response |
|------------------|----------------|--------------------|---------------|--------------|-----------------------|
| Mehnert, J. M. et al., 2016 | pT1b pN0, stage IB, FIGO grade III endometrial adenocarcinoma, high-grade endometrioid type | 1 | Pembrolizumab (10 mg/kg every 2 weeks) administered 2 years after radiotherapy | Extended-field radiotherapy (dosage not specified) | After initially deferring radiation therapy, the patient was treated with extended-field radiotherapy and chemotherapy. Two years later, she developed supraclavicular adenopathy that, when biopsied, revealed recurrent metastatic adenocarcinoma. Following immunotherapy, she experienced rapid clinical improvement, with resolution of lower extremity edema, supraclavicular adenopathy, and a partial response at 8 weeks following treatment initiation, sustained, at the time of the study publication, for over 14 months. She tolerated therapy well, with grade 1 rash, grade 1 liver function test elevation, and grade 2 fever early in her treatment course that resolved spontaneously. |
| Mahmood, S. S. et al., 2018 | Stage IIIIC2 serous carcinoma of the endometrium with one positive right aortic lymph node | 1 | Durvalumab 1500 mg flat dose; Tremelimumab 75 mg flat dose | Intravaginal radiation therapy followed by carboplatin area under the curve (AUC) 5 and paclitaxel | After a 6-month remission following radiation therapy, she was found to have newly metastatic disease, with bilateral pulmonary nodules, a hepatic lesion, and lymphadenopathy. Nearly 4 weeks after initiating immunotherapy, a CT scan revealed numerous metastases to lungs, liver, and bone. The patient eventually developed non-obstructive coronary disease and lymphohistiocytic myocarditis. By the publishing of this study, the patient requires oxygen through nasal canula and cannot perform daily activities on her own. There were 342 disease-free follow-up days with a complete response. |
| Hasumi, K. et al., 2011 | Recurrent or stage IV Uterine cancer | 1 | For the immature dendritic cells (iDC) the first injection consisted of 2.8*10^7(7) cells and the 2nd injection consisted of 2.4*10^7(7) cells. For the activated T-cells (AT), the first injection consisted of 25*10^7 (7) cells and the 2nd injection had 26*10^7(7) cells. The treatment would have iDC injected then AT injected a day later. Then the 2nd injections were ~ 3 days after radiotherapy. | Intensity Modulated Radiotherapy was delivered to each site injected with iDC (41 Gy, 5 fractions). IMRT was administered variably between 8 and 12 days after AT injection | Patient #1: Mixed clear cell and endometrioid (CC/EAC) endometrial cancer, stage IIIA Patient #2: Recurrent/metastatic uterine serous carcinoma (USC) |
| Santin, A. D. et al., 2016 | Patient #1: Mixed clear cell and endometrioid (CC/EAC) endometrial cancer, stage IIIA Patient #2: Recurrent/metastatic uterine serous carcinoma (USC) | 2 | Nivolumab 3 mg/kg biweekly was given 6 weeks after last chemotherapy administration. Patient #2: Off-label trial of nivolumab, intravenous infusions, 3 mg/kg every 2 week | Vaginal cuff radiation (dosage not specified). Patient #2: the article implies the patient also received radiation, but the dosage was not specified. | Patient #1: Patient did well with chemotherapy and radiation until March 2012. Six weeks after initiation on nivolumab single agent therapy, the patient was clinically improved to the point to resume and maintain all her normal activities. After 7 months, the results of a CT scan showed the continued regression of the tumor deposits in the pelvis and abdomen. Patient #2: The patient significantly improved after 3 nivolumab treatments. The patient continued to improve at the publishing of the article. |
| Genç, M. et al., 2015 | Primary malignant melanoma developed from a mature teratoma of ovary while there was a concurrent primary endometrial carcinoma in uterus | 1 | IFN-α 28 5,000,000 U three days per week for two months | In addition, paraaortic and pelvic RT (4500 cGy) was administered for 25 days. | She was still asymptomatic at 12 months at follow-up |
incision site within the rectus abdominus and subcutaneous tissue. CT-guided core biopsy confirmed estrogen (ER) and progesterone receptor (PR) positive metastatic adenocarcinoma. PET/CT scan confirmed multiple hypermetabolic anterior abdominal wall masses. They included a 2.4 × 2 cm mass on the left (L) lateral margin of the rectus muscle (SUV 22), a 2.3 × 1.7 cm right (R) rectus muscle mass (SUV 13), a 4.0 × 4.3 cm R rectus abdominis nodule (SUV 22), and a 1.9 × 1.3 cm sub-serosal mass adjacent to the rectosigmoid colon.

She subsequently underwent debulking of the abdominal wall and rectosigmoid lesions followed by six cycles of carboplatin and paclitaxel with no evidence of recurrent disease upon treatment completion. Unfortunately, about three months later, she began experiencing intermittent left pelvic pain. CT of the abdomen and pelvis revealed a 1.3 × 1.2 R peri-psoas tumor and three subcutaneous masses at the level of the L anterior iliac spine measuring 1.0 × 0.9 cm, 2.5 × 1.3 cm and 1.0 × 0.9 cm. She was also referred for a Radiation Oncology consultation due to the recurrent stage IV disease at the L anterior abdominal wall and right peri-psoas adipose tissue.

She received 45 Gray (Gy) in 25 fractions to the pelvis, 56.7 Gy in 30 fractions to the L abdominal wall, and 54 Gy in 30 fractions to the R peri-psoas tumor implant for one and a half months. The anterior L abdominal wall masses resolved.

Genetic testing revealed pathogenic mutations in CTNNB1 and PTEN genes and high microsatellite instability (MSI-H), the latter making her a potential candidate for immunotherapy.

Five months after the start of radiation therapy, she again developed a 3.2 × 1.3 cm lesion at the L anterior abdominal wall and biopsy was consistent with recurrent endometrial cancer. Of note, squamous metaplasia was noted in the biopsy sample. Following resection of the L abdominal wall nodule, she remained stable and in remission for another seven months (Fig. 1).

Subsequently, PET/CT revealed a large 7.1 × 2.4 cm FDG avid lesion (SUV 15.6) in the subcutaneous fat anterior to the L iliac wing, a new ER and PR positive L anterior apex pulmonary mass measuring 4.3 × 3.1 cm (SUV 12.7) and a slightly enlarged 1.3 × 0.4 cm AP window lymph node without FDG avidity. A L lung core biopsy confirmed a CK7, PAX8, ER and PR positive necrotic adenocarcinoma of endometrioid origin.

Six months after combined radiotherapy (8 Gy × 2 to the lesion anterior to the L iliac wing) and pembrolizumab treatment, the patient had marked improvement. The L anterior apex lung mass shrank from 4.3 × 3.1 cm (SUV 12.7) to 2.6 × 1.2 cm (SUV 2.0). The previously enlarged lymph node had resolved. Although the subcutaneous L iliac wing lesion had decreased slightly to 6.7 × 2.3 cm, its maximum uptake decreased markedly from 15.6 to 3.7 (Fig. 2-A-D).

Follow-up CT scans 21 months after the initiation of the combined immunotherapy and radiation course with subsequent pembrolizumab maintenance, confirmed no evidence of metastatic disease in the chest, abdomen, and pelvis.

### 2.2. Case 2 narrative

A 64-year-old female underwent robotic total laparoscopic hysterectomy (TLH) and bilateral salpingo-oophorectomy (BSO) to address vaginal bleeding. Pathologic analysis revealed FIGO stage 1A, grade 2 endometroid carcinoma, characterized by lymphovascular space invasion, a 5.6 cm tumor, and 48 percent myometrial invasion. Of seven lymph nodes submitted, none were positive for metastatic carcinoma. She was referred for adjuvant radiation therapy and received vaginal brachytherapy (30 Gy in 5 fractions prescribed to the vaginal surface) within two months of her surgery. Six months post radiation therapy (8 months post-surgery/at baseline), she developed persistent lower back pain and vaginal bleeding. An abdomen/pelvis CT scan revealed a pelvic mass while PET-CT confirmed multiple hypermetabolic lesions including within the previously treated vaginal cuff, consistent with metastatic disease. Additional lesions included a left pelvic sidewall mass measuring 2.2 × 1.8 cm (SUV 25.6), 2.5 × 2 cm (SUV 26.4) left vaginal cuff thickening, and a left perirectal fat nodule measuring 1.4 × 0.9 cm (SUV 19.8).

Biopsy of the left pelvic sidewall tumor revealed recurrent endometrial cancer and MSI-H status making her a candidate for immunotherapy.

She started taking megestrol acetate 40 mg and tamoxifen 20 mg twice a day with a mixed response on PET-CT three months later (11 months from baseline). Although the FDG avidity decreased within the L pelvic side wall, L vaginal cuff, L cul-de-sac and R pelvic sidewall nodules, there was a marked increase in the size and FDG avidity of multiple portal and L pelvic wall lymph nodes. For instance, a previously 1.2 × 0.9 cm (SUV 14.0) retrorectal lymph node increased to 2.3 × 1.7 cm (SUV 15.9), while the portocaval lymph node initially measuring 0.5 cm (SUV 6.1) increased to 1.1 × 1.0 cm (SUV 6.4).

A follow up CT scan two months later (13 months from baseline) continued to demonstrate a mixed response. The previously noted L vaginal cuff and R retrocaval metastases decreased slightly in size but the L pelvic side wall mass had grown to 3.21 × 2.13 cm and the portocaval lymph node mass to 2.82 × 2.1 cm, prompting consideration of concurrent immunotherapy and radiotherapy (Fig. 4 A and B).

The patient started pembrolizumab and radiotherapy concurrently (40 Gy in five fractions to the L pelvic wall and portal lymph nodes). A follow-up CT abdomen/pelvis scan two months after radiotherapy concluded (17 months from baseline) revealed partial response marked by the resolution of both the portocaval (Fig. 4C) and previously observed sub-centimeter right external iliac lymphadenopathy. Additionally, the right retrocaval lymph node shrank from 1.4 × 1.2 cm to 0.6 × 0.4 cm while the L pelvic sidewall lymph node decreased from 3.21 × 2.13 cm to 2.8 × 1.7 cm (Fig 4D). There were no new sites of abdominopelvic or pulmonary involvement.

The patient continued maintenance immunotherapy (Fig. 3). Follow up CT scans 24 and 29 months from baseline revealed a stable L pelvic sidewall and sub-centimeter R retrocaval lymph nodes and no new thoracic or abdominopelvic malignancies. She opted to stop treatment.

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**Fig. 1.** Timeline of the treatment course for patient one from baseline to the most recent follow up.
CT of the abdomen and pelvis 34 months from baseline indicated a stable left pelvic sidewall lymph node measuring 3.0 × 1.3 cm with no other lymphadenopathy.

3. Case discussion

Endometrial cancer, also known as uterine cancer, is the most common gynecologic cancer (American College of Obstetricians and Gynecologists (ACOG), 2019). Even though this malignancy is usually detected at an early stage, incidence and mortality rates have continued to rise in recent years, thereby necessitating the need for novel treatment modalities (American College of Obstetricians and Gynecologists (ACOG), 2019). Currently, immunotherapy is approved for advanced endometrial cancer patients who have disease progression following prior systemic therapy. A systematic review of published literature failed to reveal any studies that concomitantly combined immunotherapy and radiotherapy (Mehnert et al., 2016; Hasumi et al., 2011; Genç et al., 2015; Altorki et al., 2021; Hatten et al., 2022 Mar 3). In the vignettes we presented, it is possible that immunotherapy alone may have eradicated the sites of local and distant disease. However, in other malignancies, concurrent administration of high-dose radiotherapy and immunotherapy has led to increased pathologic responses suggesting improved efficacy with simultaneous delivery of these treatment modalities (Altorki et al., 2021). Moreover, the first case may reflect the “abscopal effect” whereby the treatment of one site with radiotherapy generates robust immune-mediated response at untreated metastases distal to the site of radiotherapy (Hatten et al., 2022). Therefore, randomized controlled trials are necessary to probe the synergy of concomitant immunotherapy and radiotherapy in endometrial cancer cases. At present, NRG GY020 is the only trial, to our knowledge, testing the combination of radiotherapy and immunotherapy in early-stage endometrial cancer. Of note, both patients have had durable responses though one opted to stop maintenance treatment and the other continues to receive infusions to date. In future clinical trials, it will be key to determine the optimal duration of maintenance immunotherapy.

4. Conclusion

In summary, in this case report, we present two individuals with successful outcomes following the concurrent use of immunotherapy and radiotherapy for the treatment of metastatic endometrial cancer. These cases demonstrate the potential role of combination treatment in a broader population. However, due to the small sample size, additional clinical trials have to be conducted before this combination therapy is recommended for implementation on a widespread scale.

Patient Consent.

The patients described in the manuscript have consented to the submission of the case report to the journal. No identifying information is included in this article.
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CRediT authorship contribution statement

Luiza Chepkemoi: Data curation, Writing - original draft, Writing - review & editing. Oluwaseyi Ajayi: Data curation, Investigation, Writing - original draft, Writing - review & editing. Nancy Anaboraonye: Data curation, Investigation, Writing - original draft, Writing - review & editing. Onyinye D. Balogun: Conceptualization, Resources, Methodology, Formal analysis, Supervision, Writing - review & editing.

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.

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Fig. 4. A-D (clockwise): CT scans demonstrating the initial portocaval metastasis (upper left) and left pelvic sidewall implant (upper right) prior to immunotherapy and radiotherapy and after treatment (bottom row).

Fig. 3. Timeline of the treatment plan and radiological response for patient two from baseline to the most recent follow up.
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