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Case report

Successful treatment of platinum refractory ovarian clear cell carcinoma with secondary cytoreductive surgery and implantable transponder placement to facilitate targeted volumetric arc radiation therapy

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ABSTRACT

We describe a case of the first successful treatment of platinum refractory clear cell ovarian cancer with secondary cytoreductive surgery and placement of Calypso transponders to facilitate post-operative volumetric arc radiation therapy. In the setting of both primary and recurrent disease, patients with clear cell ovarian cancer are less responsive to standard chemotherapy and those treated with radiation therapy may have improved outcomes compared to the use of other treatment modalities. Volumetric arc radiation therapy with implantable transponders is feasible, and allows for the targeted treatment of sites of metastatic disease while limiting toxicity to surrounding structures and can be considered for patients with recurrent ovarian cancer and oligometastatic disease.

1. Case report

A 52-year-old woman presented to her gynecologist with post-menopausal bleeding. Pelvic ultrasound demonstrated an enlarged, heterogeneous uterus that appeared to contain necrotic or cystic areas and polypoid excrescences. The ovaries were not well-delineated but no adnexal lesions were visualized. She was referred to a gynecologic oncologist and underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymph node dissection. Intraoperatively, a right ovarian mass, measuring 18 × 20 cm was noted. Surgical pathology showed a high grade clear cell ovarian adenocarcinoma arising in the context of endometriosis, in the right ovary and meso-ovarian tissue. Baseline post-operative CT scan of the chest, abdomen, and pelvis was remarkable for a 2.5 × 1.5 cm nodular soft tissue attenuation along the right vaginal cuff which was thought to be post-operative changes. The patient then received six cycles of dose-dense carboplatin and paclitaxel, with a dose reduction in paclitaxel for cycle six secondary to grade 2–3 neuropathy. Multi-gene panel genetic testing of 28 genes associated with hereditary cancer was performed and did not identify any deleterious mutations. Post-treatment CT of the chest, abdomen, and pelvis re-demonstrated the pelvic soft tissue nodule, now measuring 3.5 × 3.9 cm. This lesion was FDG-avid on PET-CT, but there were no other areas consistent with metastatic disease (Fig. 1).

Given her oligometastatic disease on imaging, she underwent robotic-assisted secondary cytoreduction of right pelvic mass, right ureterolysis, and placement of Calypso transponders (Varian Medical Systems, Palo Alto, CA) to assist with radiation targeting (Fig. 2). The mass was densely adherent to the right ureter and hypogastric artery and vein. Although the majority of the mass was resected, the remaining disease was approximately 5 mm in size. No other areas of visible disease were noted intraoperatively. The right pelvic mass contained metastatic adenocarcinoma consistent with her clear cell cancer. The patient then received 60 Gy in 30 fractions with 6 MV photons of Calypso-guided volume-mediated arc therapy (VMAT). The patient tolerated radiation therapy well and did not describe any radiation-related toxicities either during treatment or in post-treatment surveillance. The patient has no evidence of disease 18 months after surgery.

2. Discussion

Oligometastatic recurrent ovarian cancer can be managed with secondary cytoreductive surgery, which is usually followed by chemotherapy (Salani et al., 2007; Bristow et al., 2009). Adjuvant radiation may be employed depending on the location and distribution of disease in select patients, particularly for those with endometriosis-associated ovarian cancer (Brown et al., 2013; Albuquerque et al., 2016; Modesitt

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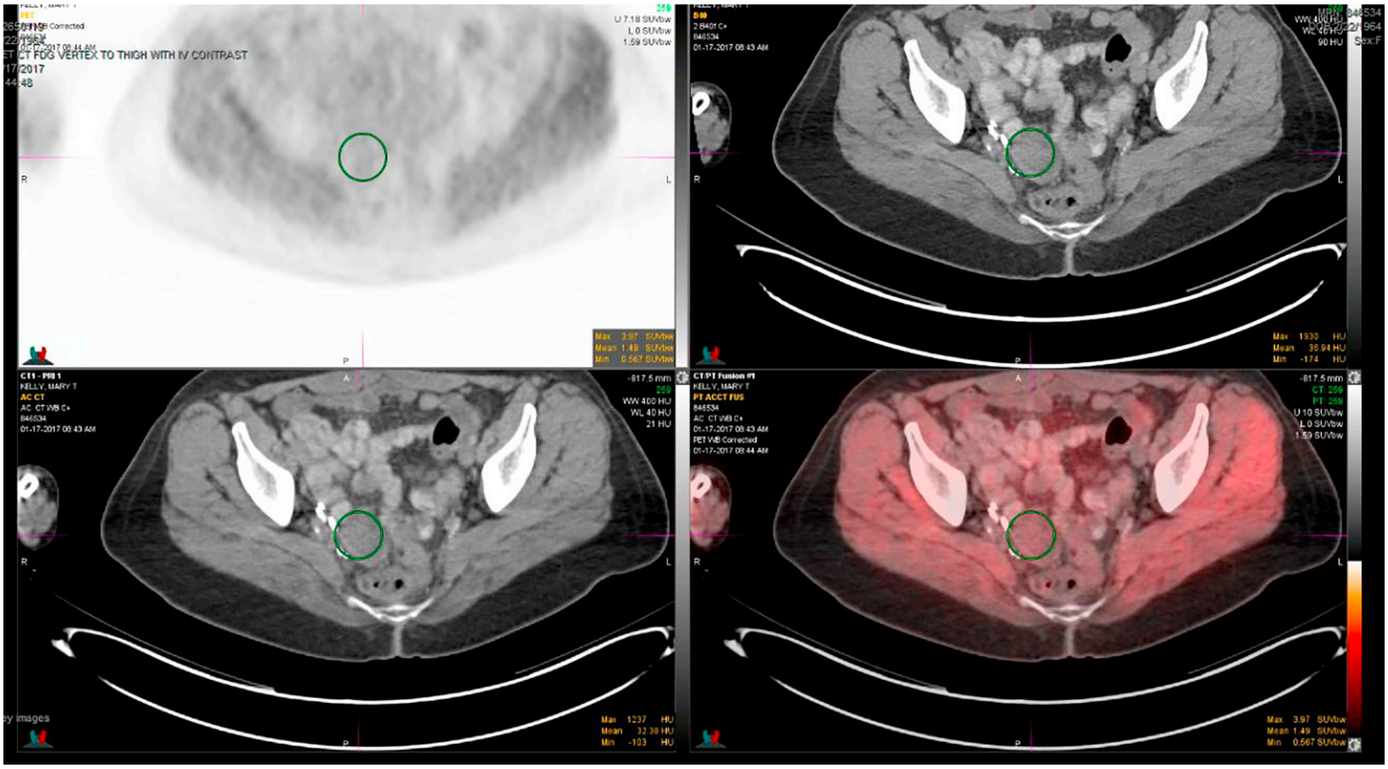

Fig. 1. Fused PET-CT images of pelvic nodule near vaginal cuff with increased FDG-uptake on post-chemotherapy imaging.

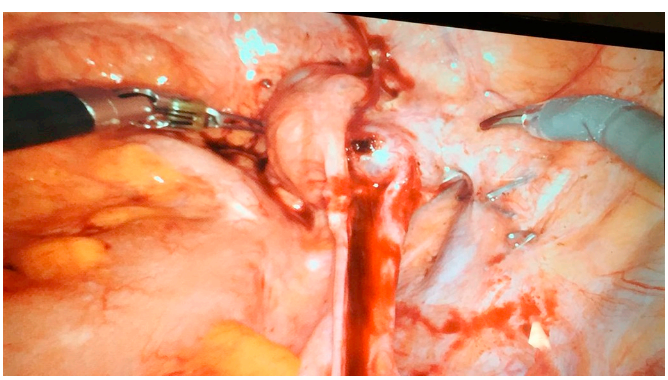

Fig. 2. Intraoperative visualization of right pelvic mass prior to resection.

et al., 2002). Clear cell ovarian cancers may be more responsive to radiation than other histologic subtypes (Hoskins et al., 2012). There is conflicting evidence regarding a survival benefit in patients with stage I-II disease who receive adjuvant radiation therapy, although this has not been studied prospectively (Hoskins et al., 2012; Hogen et al., 2016). In patients with recurrent clear cell ovarian cancer, radiation therapy may be associated with a survival benefit, but this is based on data from retrospective, single institution studies (Brown et al., 2013; Albuquerque et al., 2016).

Concerns regarding the toxicity associated with radiation therapy, including urinary symptoms, scarring leading to the need for ureteral stents, enteritis, proctitis, and small bowel obstruction, have limited its use in recurrent ovarian cancer (Petit et al., 2007; MacGibbon et al., 1999). Localization of therapy, however, can mitigate many of these toxicities. Intensity modulated radiation therapy (IMRT) allows for sparing of normal tissues, decreased toxicity, and improved target volume coverage compared to conventional radiation therapy (Shih et al., 2013; Klopp et al., 2013). Relatively few published studies have utilized IMRT for ovarian cancer apart from single institution series, but these have reported high metabolic response rates on PET-CT and limited radiation-related toxicity (Du et al., 2012; Chundury et al., 2016.).

VMAT uses dynamic modulated arcs to deliver IMRT to target structures and permits the incorporation of transponder-based systems to increase the precision of radiation therapy delivery (Teoh et al., 2011; Macchia et al., 2017). The Calypso 4D System (Varian Medical Systems) utilizes implantable 8 mm electromagnetic transponders, or beacons, to facilitate electromagnetic tracing that allows for localized delivery of radiation therapy via continuous radiofrequency communication between the beacons and the Calypso System (Fig. 3) (Balter et al., 2005; Franz et al., 2014). Each transponder consists of a sealed glass capsule containing an electronic circuit and measures 1.85 mm × 8.7 mm. The introducer needle of the transponder is used to pierce the tissue and the delivery system is fired to secure them in place within the target tissue. Two to three transponders are permanently placed into the target tissue, with post-placement CT obtained for treatment planning. These CT images establish the relationship between the transponders and the radiation treatment isocenter. During radiation therapy treatment, infrared cameras determine the position of an array that generates an electromagnetic field of 300–500 kHz. This field excites the transponders and is used by the Calypso system to monitor the transponder's position relative to the array and the isocenter. Data is transmitted continuously during treatment to a monitoring system that alerts the radiation therapist if the target position exceeds a pre-specified distance from the isocenter, allowing for real-time adjustment of a patient's position to more precisely deliver radiation therapy (Quigley et al., 2009; Shah et al., 2011).

The Calypso system has been most extensively studied in the treatment of prostate cancer, with studies demonstrating an excellent safety profile and similar treatment times with the Calypso system compared to IMRT, accurate treatment localization, and reduced residual treatment planning margins (Quigley et al., 2009; Kupelian et al., 2006; Willoughby et al., 2006; Kupelian et al., 2007; Mayyas et al., 2013). Other studies have demonstrated the feasibility and safety of the Calypso system in patients with lung and pancreatic cancers (Shinohara

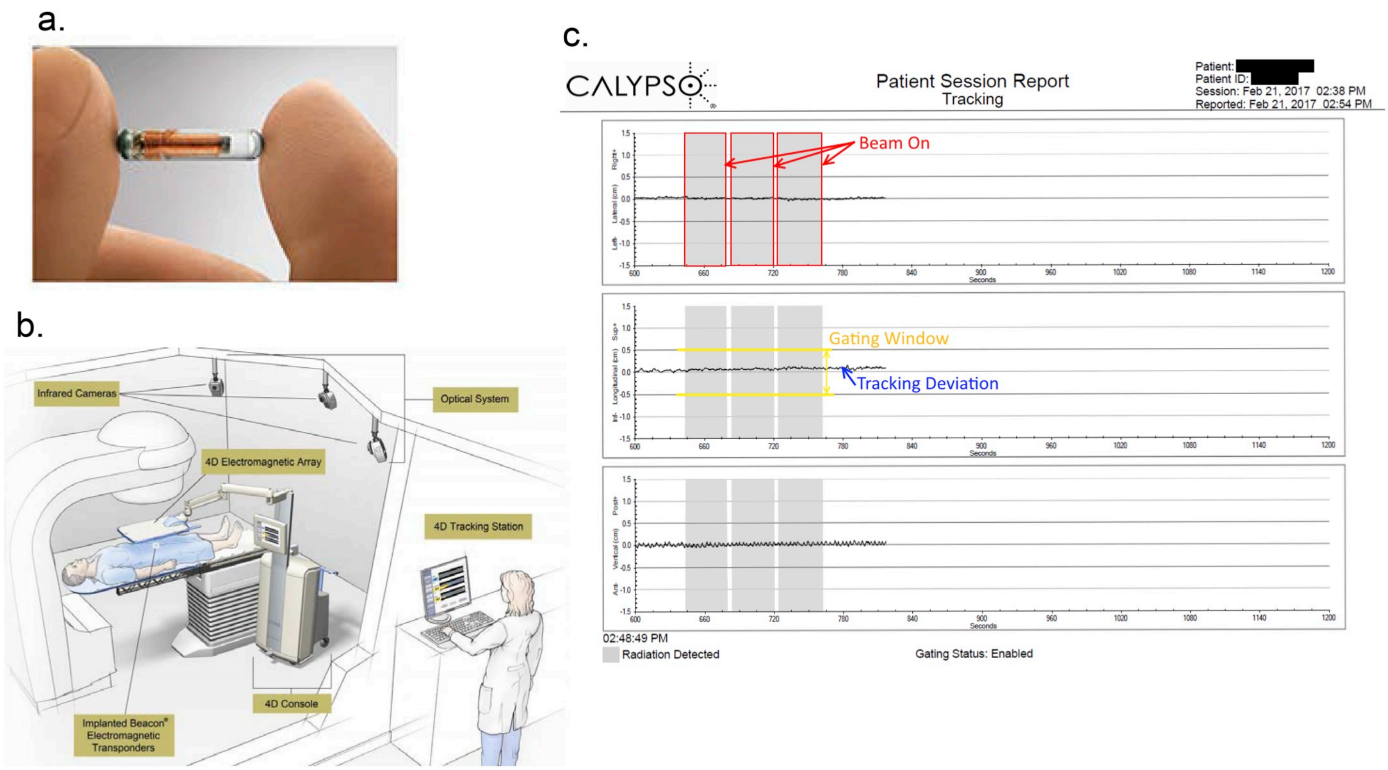

Fig. 3. Transponder, Calypso system schematic, and monitoring during radiation treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

a. Transponder is shown, measuring 1.85 × 8.77 mm; 2–3 transponders are typically implanted.
b. Schematic of Calypso system during treatment. Infrared cameras determine position of a 4D array above patient relative to the isocenter. The 4D array sends/receives radiofrequency signals to/from beacons to triangulate position.
c. Tracking of patient position using Calypso system during treatment. Gray areas indicate when beam is on (indicated in red). Beam is held if any direction tracks outside of gating window (highlighted in yellow).

et al., 2012; Shah et al., 2013). Its published use in gynecologic cancer has been limited to a small series of patients with locally advanced cervical cancer undergoing curative intent chemoradiation and has not been previously described in the management of ovarian cancer (Gatcombe et al., 2010).

3. Conclusion

We describe the successful treatment of platinum refractory clear cell ovarian cancer with secondary cytoreductive surgery and volumetric arc radiation therapy using the Calypso system. Although radiation therapy is not standardly utilized in the treatment of recurrent ovarian cancer, it may have increased efficacy in tumors with clear cell histology. While concerns about the toxicities associated with radiation for recurrent ovarian cancer have limited its use in the past, improved techniques like IMRT and VMAT allow for the delivery of localized radiation therapy while sparing surrounding normal tissue. For patients with limited foci of disease, the Calypso system can successfully facilitate targeted radiation therapy administration and can be considered in the management of patients with oligometastatic, recurrent ovarian cancer.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. No conflicts of interest regarding this case report exist for Drs. Fehniger, Schiff, or Pothuri.

Author contribution

Dr. Fehniger conducted a literature review and summarized the patient's clinical information. Dr. Schiff provided guidance regarding the use of the Varian transponders and treated the patient with radiation therapy. Dr. Pothuri reviewed and edited the case report.

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