# Novel use of adjuvant proton beam therapy in patient with pelvic renal transplant diagnosed with stage IB3 cervical adenocarcinoma

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## ABSTRACT

Cervical adenocarcinoma is the second most common histology of cervical cancer and treatment can involve surgery, radiotherapy, systemic therapy, and any combination of the three. Photon external beam radiation therapy and brachytherapy have been the mainstay of radiation treatment options for cervical cancer. Here, we report a case of a 41-year-old patient who had a prior renal transplant and was diagnosed with early-stage, intermediate-risk adenocarcinoma treated with modified radical hysterectomy plus adjuvant proton-beam therapy and vaginal brachytherapy. Treatment was well tolerated with a disease-free interval of 14-months and preserved renal function.

## 1. Introduction

The mainstay treatment for early-stage, presumed low-risk cervical cancer is radical hysterectomy. Adjuvant radiotherapy improves locoregional control in cases with intermediate risk factors for recurrence per the Sedlis criteria: depth of cervical stromal invasion, lymphovascular invasion, and tumor size (Sedlis et al., 1999; Rotman et al., 2006). In an ancillary analysis of three GOG surgical trials, where patients received no adjuvant therapy, the only factor independently associated with recurrence for adenocarcinoma was tumor size greater than 4 cm. (Levinson et al., 2021). For bulky stage IB or locally advanced cervical cancer, definitive treatment with external beam radiotherapy, brachytherapy, and platinum-containing chemotherapy is standard of care (Eifel et al., 2004; Keys et al., 1999; Peters et al., 2000; Rose et al., 2007; Whitney et al., 1999).

Like squamous cell carcinoma, most cases of endocervical adenocarcinoma are associated with high-risk human papilloma virus (HPV) strains (Hodgson et al., 2019). As a result, protective factors against cervical cancer include early vaccination against HPV, regular cervical cancer screening, and the use of condoms during intercourse (Bowden et al., 2023). Risk factors, however, include tobacco smoking, immunosuppression, long-term usage of oral contraceptives, and behaviors associated with increased risk for HPV infection. (Chelimo et al., 2013).

According to the Organ Procurement and Transplantation Network, in 2022 37.8 % of organ recipients were women, and of those, 16.9 % were women under the age of 34 ("National Data - OPTN", 2024; Transplants, 2022). Most organ transplants require some degree of immunosuppression, posing a risk of persistent HPV infection and HPV-associated cancers, including cervical, post-transplant.

Photon external beam radiotherapy, plus or minus vaginal brachytherapy, is the standard treatment modality for adjuvant treatment of cervical cancers with risk factors for recurrence. Proton therapy has been used to treat a variety of cancers and has been increasingly used in breast and prostate cancers, as it has less off-target effects than photon therapy while preserving tumor coverage (Lin et al., 2016).There have been several dosimetric studies of proton therapy in gynecologic cancers, typically in the post-hysterectomy setting, with demonstration of reduced dose to the small bowel, large bowel, kidneys, spinal cord, pelvic bone marrow, and kidneys (Marnitz et al., 2015; Milby et al. (2012); van de Sande et al., 2016; Vyfhuis et al., 2019; Xu et al., 2018). Clinically, proton therapy has been used to treat patients with uterine, cervical, or vaginal carcinoma post-hysterectomy with adjuvant pelvic or extended field radiotherapy showing promising low rates of acute grade 3 + toxicity and excellent in field disease control. (Arians et al., 2023; Lin et al., 2016; Xu et al., 2018). However, none of the studies of proton therapy reported the use of these treatment modalities in the

context of patient with a pelvic kidney transplant. Here, we present a case of early-stage cervical adenocarcinoma in a 41-year-old woman status post renal transplant on chronic immunosuppression treated with adjuvant proton therapy and vaginal brachytherapy.

## 2. Case

A 41-year-old White G2P0020 female presented with a chief concern of a 2.5-year history of intermittent postcoital vaginal bleeding. Pap smear approximately 7 years prior was positive for high-risk HPV and subsequent colposcopy was normal. Pap 2 years prior to presentation was negative for intraepithelial lesion or malignancy with no HPV testing performed. On pelvic exam, discharge was noted to be coming from cervix and Pap smear showed HPV16-positive adenocarcinoma in situ. Endocervical and endometrial curettage showed fragments of invasive endocervical adenocarcinoma with fragments of secretory endometrium. Subsequent cold-knife conization demonstrated invasive moderately differentiated endocervical adenocarcinoma with deep margins, focal invasion of the ectocervix and lymphovascular space invasion. Fluorodeoxyglucose positron emission tomography (FDG-PET) scan show ed a 5 cm endocervical hypermetabolic mass and bilateral level IIA cervical lymph nodes, favored to be reactive, but otherwise no lymphadenopathy or distant metastatic disease (Fig. 1).

Her past medical history was significant for ulcerative colitis and a living donor kidney transplant in the right pelvis 7 years prior to presentation after developing dialysis-dependent chronic kidney disease secondary to atypical hemolytic uremic syndrome. She was on mycophenolate and tacrolimus for immunosuppression at the time of cervical cancer diagnosis. She was a former social smoker with a 5-pack-year history.

She presented to our institution for further management. Pelvic exam demonstrated a visible 2.5 cm lesion within the central portion of the cervix. Cervix was mobile with no evidence of parametrial extension on bimanual exam. Renal evaluation showed serum creatinine level of 1.45 mg/dL and estimated GFR (eGFR) of 46. Patient was advised on the risks of surgery and the use of frozen pathology to determine extent of disease invasion as well as the possibility of requiring adjuvant radiotherapy and systemic therapy depending on the extent of the disease. Through shared-decision making, patient consented to proceed with modified radical hysterectomy with possible bilateral oophorectomy, if frozen pathology showed intermediate-risk disease or higher given the need for adjuvant radiotherapy in the treatment regimen. She underwent modified radical hysterectomy, bilateral pelvic sentinel lymphadenectomy, and left completion pelvic lymphadenectomy. A transplant surgeon was present during the entire procedure to assist with intraoperative navigation around the transplanted kidney. On frozen section pathology, the tumor was an adenocarcinoma measuring $2 \times 2 \times 5$ cm with a depth of invasion of at least 5 mm. Due to multiple intermediate risk features as indications for adjuvant radiotherapy, a bilateral oophorectomy was performed. Final pathology demonstrated 2018 FIGO Stage IB3 adenocarcinoma, HPV-16 positive, with 3–5 mm depth of stromal invasion confined to the superficial one third of the endocervix (Fig. 2). Surgical margins were negative. There was no parametrial invasion and ovaries and fallopian tubes were benign. Two left and one right pelvic sentinel lymph nodes and an additional 12 left pelvic lymph nodes were negative.

After surgery, the patient was recommended to undergo adjuvant radiotherapy with intensity modulated proton therapy (IMPT). The initial request for proton coverage was denied and peer-to-peer with a board certified radiation oncologist was performed. After a thorough
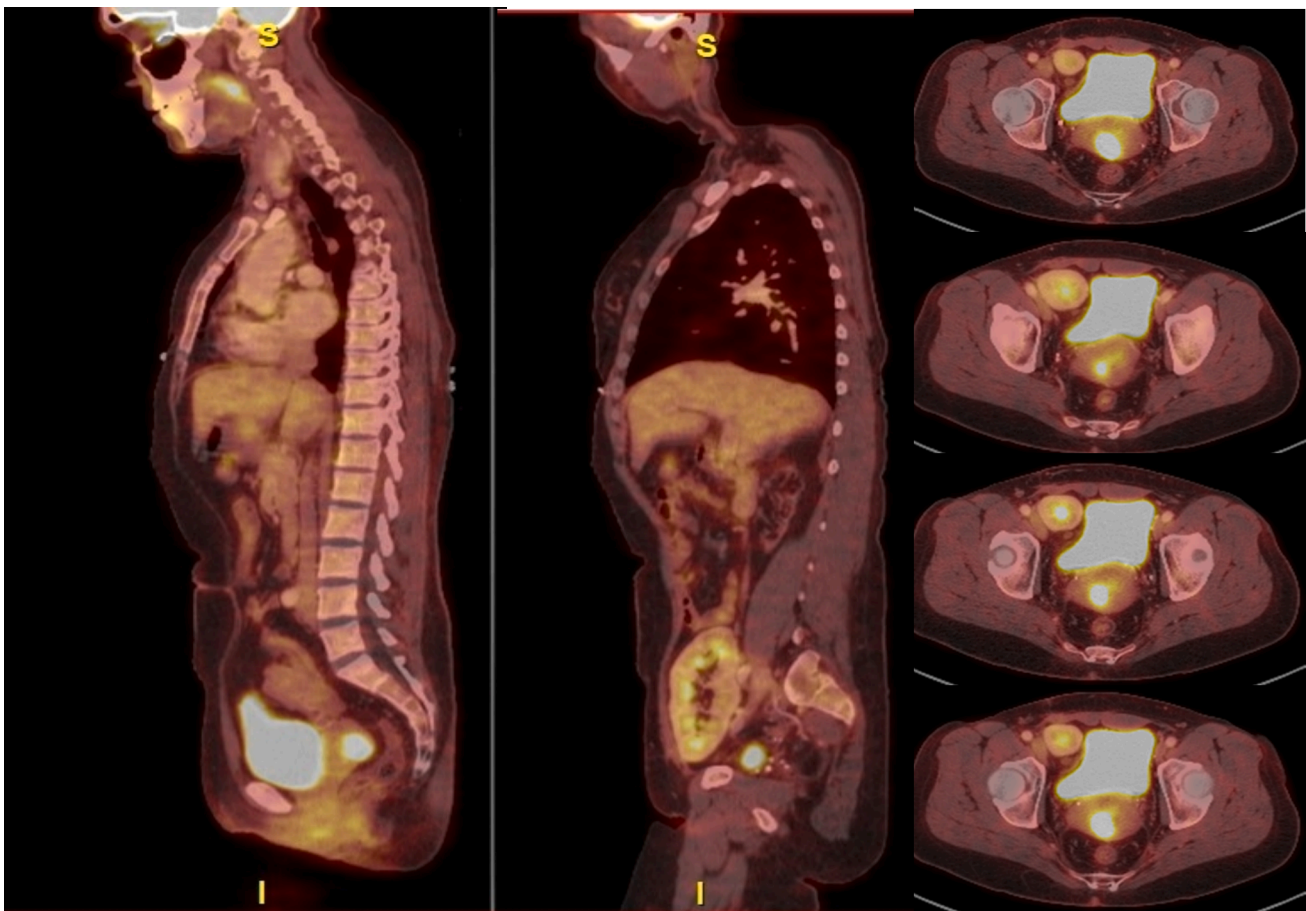


**Fig. 1.** FDG-PET Imaging at Diagnosis. Sagittal and axial sections depicting uptake by tumor, and the distance of tumor to pelvic kidney, respectively.
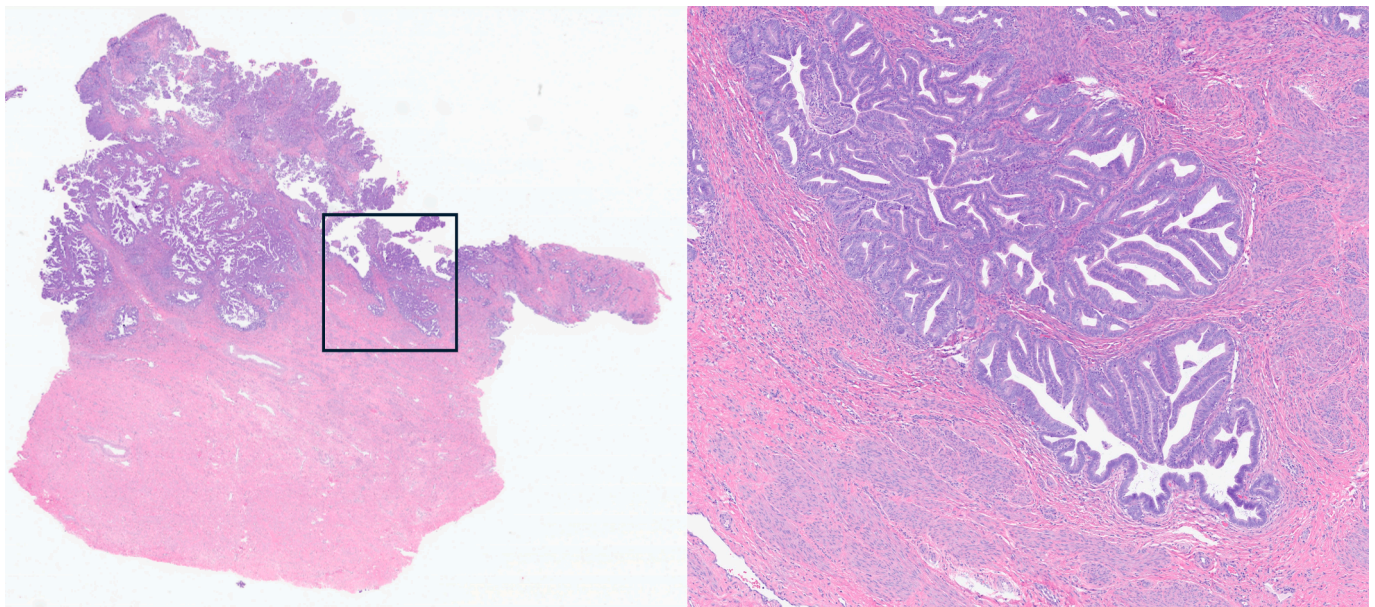
**Fig. 2.** Endocervical Histology. Low-power magnification (left) view depicts intermediate stromal invasion of the tumor relative to the tissue underneath. High-power magnification (right) view from insert box depicts characteristic features of adenocarcinoma, such as prominent hyperchromasia alongside formation of glandular structures.

discussion of the patient's history and dosimetric comparison of her IMRT and proton plans, with particular emphasis on the mean and V20Gy to the right pelvic kidney, the denial was overturned. Clinical target volumes included the vaginal cuff and regional lymph nodes including the bilateral obturator, internal and external iliac, and common iliac lymph nodes. Prescription dose was 4500 cGy in 25 fractions. She also received 1000 cGy in two fractions of vaginal cuff brachytherapy with a multi-channel vaginal cylinder. Planning parameters included dose to 95 % (D95%) of the clinical target volume to receive > 100 % of the prescribed dose and dose to 20 % of the transplanted kidney to receive less than 20 Gy. Dose constraints for the bowel, rectum, and bladder were consistent with cooperative group studies (Klopp et al., 2018). Achieved metrics for the transplanted kidney were D20% of 4.31 Gy and V20Gy of 10.3 %. Fig. 3 shows representative

slices of the dose color wash for IMPT (Fig. 3a) and volumetric modulated radiotherapy (VMAT; Fig. 3b) plans as well as the comparison dose-volume histogram (DVH; Fig. 3c) for the two plans.

During treatment, the patient experienced grade 1 fatigue managed with rest and urinary urgency and dysuria, managed with phenazopyridine and acetaminophen. At her 3-month follow-up, the patient reported transient urinary urgency and dysuria after treatment, but symptoms had resolved by the time of the follow up visit. She had resumed normal sexual activity with no dyspareunia or vaginal bleeding. FDG-PET showed no evidence of residual or recurrent disease; however, there were inflammatory changes in the rectum (Fig. 4). Serum creatinine was 1.20 mg/dL and eGFR 58. Seven months after treatment, the patient reported hematochezia and diarrhea for several weeks consistent with her prior ulcerative colitis flares. Serum
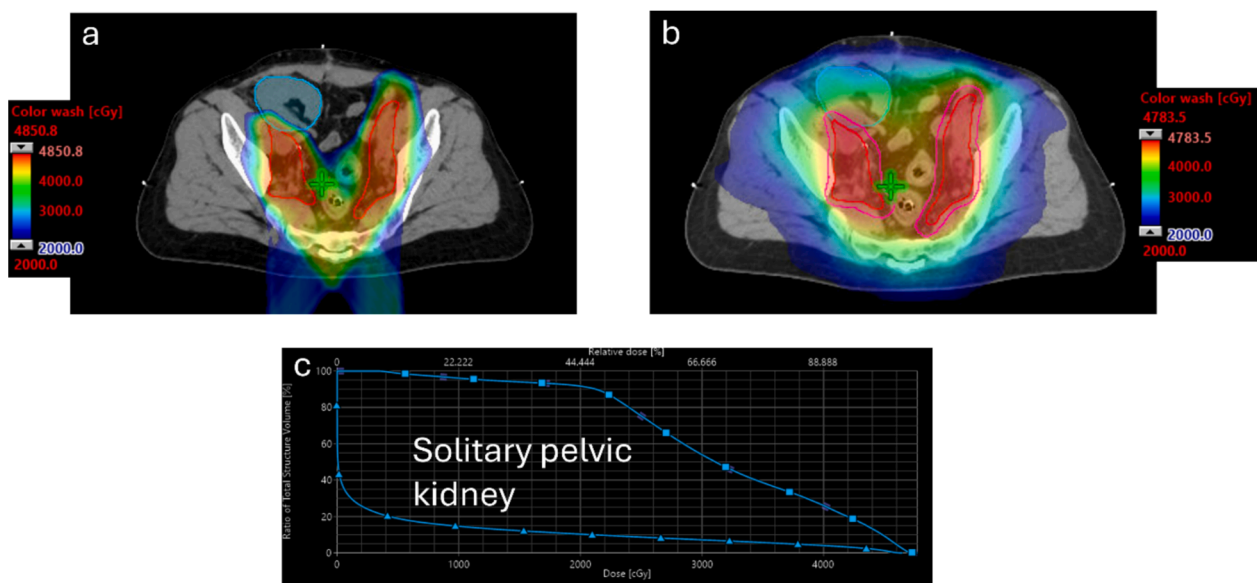


**Fig. 3.** External beam radiotherapy plan details. Representative isodose wash from intensity modulated proton therapy (IMPT) (Fig. 4a) versus volumetric modulated radiation therapy (VMAT) plan (Fig. 4b) showing dose to the clinical target volume (red) and solitary pelvic kidney (cyan). The low dose color wash is set at 2000 cGy for both plans. Fig. 4cis the dose volume histogram (DVH) showing dose to the solitary right pelvic kidney for IMPT (triangle) and VMAT (square) plans.
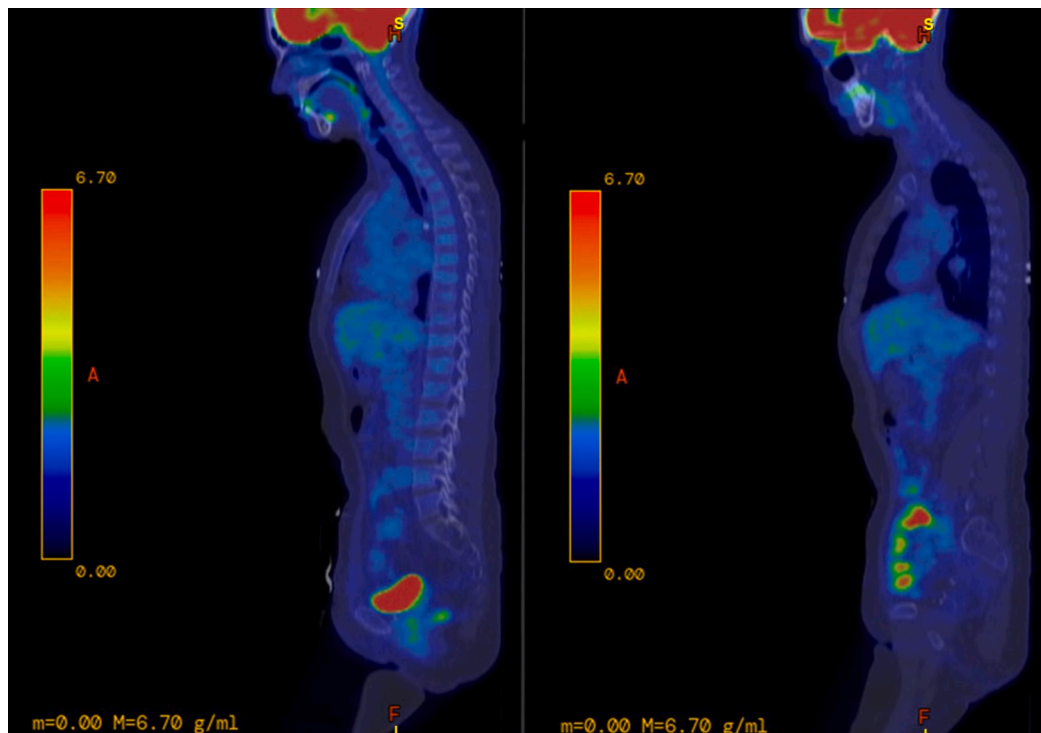
**Fig. 4.** Sagittal slice of positron emission tomography-computed tomography (PET-CT) scan 3 months after treatment showing no residual fluorodeoxyglucose uptake, and anatomical changes consistent with a hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy.

creatinine was 1.36 mg/dL and eGFR 50 mL/min. At subsequent follow-up at 10.5 months after completion of radiotherapy, patient reported near resolution of colitis flare with a 10–12 lb weight gain, but persistent postcoital bleeding. Pelvic exam showed atrophied and friable vaginal mucosa without evidence of recurrent disease. CT abdomen and pelvis was negative for recurrent or metastatic disease. Creatinine was 1.5 mg/dL and eGFR 44 mL/min. At 14 months follow-up, conservative management with systemic and topical estrogen had improved postcoital vaginal bleeding, although it had not completely resolved. Creatinine decreased to 1.26 mg/dLwith an increase in eGFR to 54 mL/min.

### 3. Discussion

Although cervical cancer following kidney transplantation is uncommon, transplanted pelvic kidneys can impose a challenge in the treatment of pelvic cancers requiring surgery and radiotherapy. In the setting of intermediate-risk cervical cancer, definitive treatment would have included pelvic external beam radiotherapy, brachytherapy, and concurrent weekly cisplatin (Chino et al., 2020). However, given the patient's renal transplant, there was a concern of radiation and chemotherapeutic-induced nephrotoxicity with these guideline-suggested treatment modalities. Through shared-decision making, the patient opted for surgery; as if she were to meet low-risk criteria, surgery alone would have been appropriate treatment. Even in the setting of intermediate-risk disease, upfront surgery would offer debulking of disease with possible reduction of risk to the transplanted kidney due to lower radiation dose required in the adjuvant versus definitive settings and avoidance of nephrotoxic chemotherapy used in the definitive approach.

Our patient was initially treated with an open hysterectomy as this surgical approach has been shown to have significantly higher rates of disease-free survival at 4.5 years compared to minimally invasive surgeries in patients with IA2-IIA cervical cancer. (Ramirez et al., 2018). A bilateral salpingo-oophorectomy was performed due to the need for adjuvant radiation as patient's frozen pathology revealed intermediate-risk disease, (Sedlis et al., 1998). As radiation-induced premature ovarian failure can occur in doses as low as 200 cGy (Hilal et al., 2022) and was expected to occur in her case. The histology of the cancer alone also carried a higher risk as adenocarcinoma has been associated with a higher rate of ovarian metastasis than squamous cell carcinoma (Sutton et al., 1992). A series of case reports in patients with incidental, functioning unilateral pelvic kidneys showed that photon therapy at doses required for treatment lead to loss of the pelvic kidney, although these patients had no side effects as their contralateral retroperitoneal kidneys were still functioning (Bakri et al., 1993; Lataifeh et al., 2007; Rosenshein et al., 1980). One case report detailed photon therapy in a renal transplant patient with stage IIB cervical adenocarcinoma, where a modified field that spared the transplanted kidney and common iliac vessels was used (Ripley et al., 1995). The patient eventually suffered from buttock pain due to cancer recurrence and died from disease progression 21 months after completion of radiotherapy.

At least two case reports have detailed allograft autotransplantation to the contralateral area of the pelvis or to the upper abdomen with revascularization of the kidney with the splenic artery in the context of invasive vulvar carcinoma and stage IIB squamous cell cervical carcinoma, respectively (Abouna et al., 1994; DeRoover et al., 2000)- these patients were able to tolerate photon therapy with successful target coverage and preservation of adequate kidney function. Although autotransplantation followed by photon therapy has shown success in some cases, a second surgery would pose risks, be technically complex and impact patient quality of life such as the lifetime use of nephrostomy bags. Alternatively, a case series showed 4 cases of patients with renal transplants who underwent intensity modulated proton therapy for anal cancer, which led to eradication of the cancer with maintenance of functioning kidney (Buchberger et al., 2019).

Protons are positively charged particles that continuously lose energy as they interact with the tissue they traverse and lose a significant amount of energy very rapidly prior to stopping causing the Bragg peak phenomenon (Chhabra et al., 2016). In proton radiotherapy therapy, the Bragg peak is modifiable based on the initial energy of the proton, and any structure distal to the Bragg peak receives negligible radiation exposure. This is in sharp contrast to the traditional photon therapy,

which attenuates exponentially and results in more dose distal to the tumor. Prior authorization for proton therapy in adults poses an administrative burden and significant barrier to timely patient care (Gupta et al., 2019). Fortunately, a peer-to-peer discussion overtuned the initial denial, as the benefit of proton therapy in this unique case was readily apparent. A previous small study analyzed the efficacy of proton beam therapy in patients with gynecological cancers post-hysterectomy and showed that patients receiving proton therapy had reduced gastrointestinal, hematologic, and genitourinary toxicities while maintaining at least the same efficacy as intensity modulated radiation therapy (Lin et al., 2016). Our treatment plan comparisons between proton and photon therapy showed similar findings including larger sparing of the surface area of the kidney parenchyma. (Fig. 3). Although not the primary indication for proton therapy, small bowel dose was lower with proton therapy, which is beneficial given her history of ulcerative colitis as patients with inflammatory bowel disease may be at higher risk for severe acute and late radiation toxicity (Willett et al., 2000). There was no advantage in rectum coverage between our proton and photon treatment plans due to the posterior beam arrangement. A vaginal cuff brachytherapy boost was delivered to optimize local control, as a vaginal cuff recurrence would be difficult to salvage in the setting of a transplanted kidney, while allowing for a lower dose prescription for external beam radiotherapy to minimize dose to the transplanted pelvic kidney.

This case of a 41-year-old patient with history of renal transplant diagnosed with early-stage, intermediate-risk adenocarcinoma highlights the advantage of both shared decision making and use of proton therapy in the treatment of gynecological cancer. Proton therapy was associated with satisfactory therapeutic effects while sparing kidney function, preventing the need for lifelong dialysis or another transplant. The efficacy and advantages of proton therapy in the treatment of gynecological malignancies should be further assessed through prospective trials.

## 4. Consent

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.

### Author Contributions

Pedro Versuti Del Cioppo Vasques was a major contributor in writing the manuscript and compiling the patient's history. Drs. Garda and Bakkum-Gamez were both involved in the patient's care with Dr. Garda being the radiologist oncologist and Dr. Bakkum-Gamez being the primary surgeon in the case. Dr. Dean was the transplant surgeon present during the patient's tumor debulking surgery. Dr. Molligan was the pathologist involved in the case. All authors read and approved the final manuscript.

### CRediT authorship contribution statement

**Pedro Versuti Del Cioppo Vasques:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation, Conceptualization. **Jamie N. Bakkum-Gamez:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Patrick G. Dean:** Writing – original draft, Investigation. **Jeremy F. Molligan:** Writing – original draft, Investigation. **Allison E. Garda:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Bakkum-Gamez is an editor for *Gynecology Oncology Reports* and is an inventor of Mayo Clinic intellectual property licensed to Exact Sciences (Madison, WI), and may receive royalties paid to Mayo Clinic].

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