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Teaching Case

New School Technology Meets Old School Technique: Intensity Modulated Proton Therapy and Laparoscopic Pelvic Sling Facilitate Safe and Efficacious Treatment of Pelvic Sarcoma

Hunter C. Gits, MD, MSc,[a] Eric J. Dozois, MD,[b] Matthew T. Houdek, MD,[c] Thanh P. Ho, MD,[d] Scott H. Okuno, MD,[d] Rachael M. Guenzel, APRN, CNP, DNP,[a] Laura A. McGrath, APRN, CNP, MSN,[a] Alan J. Kraling, CMD, RTT,[a] Jedediah E. Johnson, PhD,[a] and Scott C. Lester, MD[a],*

[a]*Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota;* [b]*Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, Minnesota;* [c]*Department of Orthopedics, Mayo Clinic, Rochester, Minnesota;* [d]*Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota*

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Abstract

Purpose: Small bowel tolerance may be dose-limiting in the management of some pelvic and abdominal malignancies with curative-intent radiation therapy. Multiple techniques previously have been attempted to exclude the small bowel from the radiation field, including the surgical insertion of an absorbable mesh to serve as a temporary pelvic sling. This case highlights a clinically meaningful application of this technique with modern radiation therapy.

Methods and Materials: A patient with locally invasive, unresectable high-grade sarcoma of the right pelvic vasculature was evaluated for definitive radiation therapy. The tumor immediately abutted the small bowel. The patient underwent laparoscopic placement of a mesh sling to retract the abutting small bowel and subsequently completed intensity modulated proton therapy.

Results: The patient tolerated the mesh insertion procedure and radiation therapy well with no significant toxic effects. The combination approach achieved excellent dose metrics, and the patient has no evidence of progression 14 months out from treatment.

Conclusions: The combination of mesh as a pelvic sling and proton radiation therapy enabled the application of a curative dose of radiation therapy and should be considered for patients in need of curative-intent radiation when the bowel is in close proximity to the target.

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*Corresponding author: Scott C. Lester, MD; E-mail: Lester.Scott@mayo.edu

Introduction

Curative-intent radiation therapy often is a necessary component in the management of unresectable abdominal and pelvic malignancies, and small bowel is the

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primary dose-limiting organ.[1] Radiation therapy-induced enteritis and small bowel injuries such as fistulas, strictures, and perforations are related to dose and the volume of the organ exposed.[2,3] Severe toxic effects can be fatal. As a result, although some patients may be placed at higher risk for toxic effects when target coverage is prioritized, patients may more commonly experience greater risk for recurrence when the target is undercovered to protect the bowel. Several noninvasive and invasive methods have been used to displace the small bowel out of the radiation field.[4] Additionally, advanced radiation therapy techniques may be synergistic with displacement methods by enabling dose escalation and dosimetric sparing of close but no longer abutting critical structures. Herein, the authors describe a case of locally invasive pelvic sarcoma in which a pelvic sling was used to retract the small bowel away from the tumor and facilitate definitive intensity modulated proton therapy (IMPT).

Case Presentation

A 66-year-old woman was evaluated in the Department of Radiation Oncology in June 2020 for newly diagnosed high-grade sarcoma likely arising from the distal right external iliac vasculature. Six months previously she had been found to have a deep venous thrombosis of the proximal right common femoral vein on ultrasound and had been initiated on anticoagulation. At the time of evaluation in radiation oncology, the patient was experiencing mild right pelvic pain and increased right lower extremity swelling. Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated a 7.9 × 5.8 × 10.4−cm tumor of the right pelvic sidewall and groin that encased her right external iliac and common femoral vessels with occlusion and invasion of the venous system. The tumor also directly abutted a 23-mm segment of her small bowel with a thin fat plane between the 2 (Fig 1A). Positron emission tomography and CT demonstrated a hypermetabolic lesion without regional adenopathy or distant disease (Fig 2A). The patient's medical history was significant for right-sided ductal carcinoma in situ of breast origin managed with lumpectomy and adjuvant radiation, right-sided renal cell carcinoma managed with partial nephrectomy, active tobacco smoking, and diabetes mellitus.

The patient previously had been evaluated by orthopedic oncology, and surgical resection was predicted to involve resection of right femoral nerve and vascular reconstruction over a long segment with the possibility to include an external hemipelvectomy. Given her medical comorbidities, tobacco use, the extent of surgery, and risk of progression, the patient had been deemed a poor candidate for resection. Definitive radiation therapy was offered as an alternative to surgery, although there was concern for delivering curative-intent dose given the proximity of the small bowel to the tumor. The patient was counseled that with standard techniques, radiation therapy alone likely could be delivered only with palliative intent. To offer a potentially curative approach, the patient was referred to colorectal surgery for laparoscopic placement of mesh to retract the small bowel from the superior extent of the tumor. Mesh placement was selected over other techniques such as tissue expander placement or hydrogel insertion given the unstable location and absence of tissue planes in the inferolateral abdominopelvic cavity. The patient consented to the procedure and subsequent radiation therapy.

The surgical procedure was performed under general anesthesia, and prophylactic cefazolin and metronidazole were administered. Three 5-mm trocars were placed for the camera and 2 working ports, and laparoscopic mobilization of the bowel was performed. To exclude the bowel from the planned radiation field, a 16 × 20−cm absorbable mesh was inserted through a 4-cm low midline incision. The mesh was secured with absorbable suture laterally to the underside of the abdominal wall, superiorly to the retroperitoneum, and medially to the right border of the sigmoid colon and rectum. Care was taken to avoid the iliac vessels and ureter. The procedure and postoperative course proceeded well and without complication. The patient endorsed mild new abdominal pain after her procedure in addition to her baseline right pelvic pain. She otherwise felt well and was discharged 1 day after the procedure.

After 1 week with no apparent complications such as infection or bowel obstruction, the patient was simulated for radiation planning in the supine position using a lower-extremity vacuum bag to immobilize the legs and pelvis. Intravenous contrast was used. The treatment planning CT confirmed that retraction of the bowel had been achieved (Fig 1B). Fluid had layered between the mesh and small bowel, enhancing displacement. The nearest edge of the small bowel was 10 mm away from the gross tumor. The diagnostic MRI was fused to the planning CT to improve target delineation.

Intensity modulated proton therapy to be delivered in 15 fractions was planned, treating the tumor to 6750 cGyE with expansions to cover areas at risk for subclinical disease to 5700 cGyE and 4500 cGyE (Fig 3A). To reduce the risk of incisional dehiscence, care was taken to avoid beams entering through the midline incision and laparoscopic port sites. A 2-field arrangement was used and consisted of ipsilateral posterior-oblique and anterior-oblique beams. Hounsfield unit overrides for the mesh were considered unnecessary owing to the composition, size, and geometry of the mesh material in this plan. Multifield optimization was performed using a pencil beam superposition convolution algorithm and a uniform estimate of 1.1 for relative biologic effectiveness. The plan was designed to be robust to 5 mm of setup uncertainty, 3% range uncertainty, and interfield displacements of 2 mm.

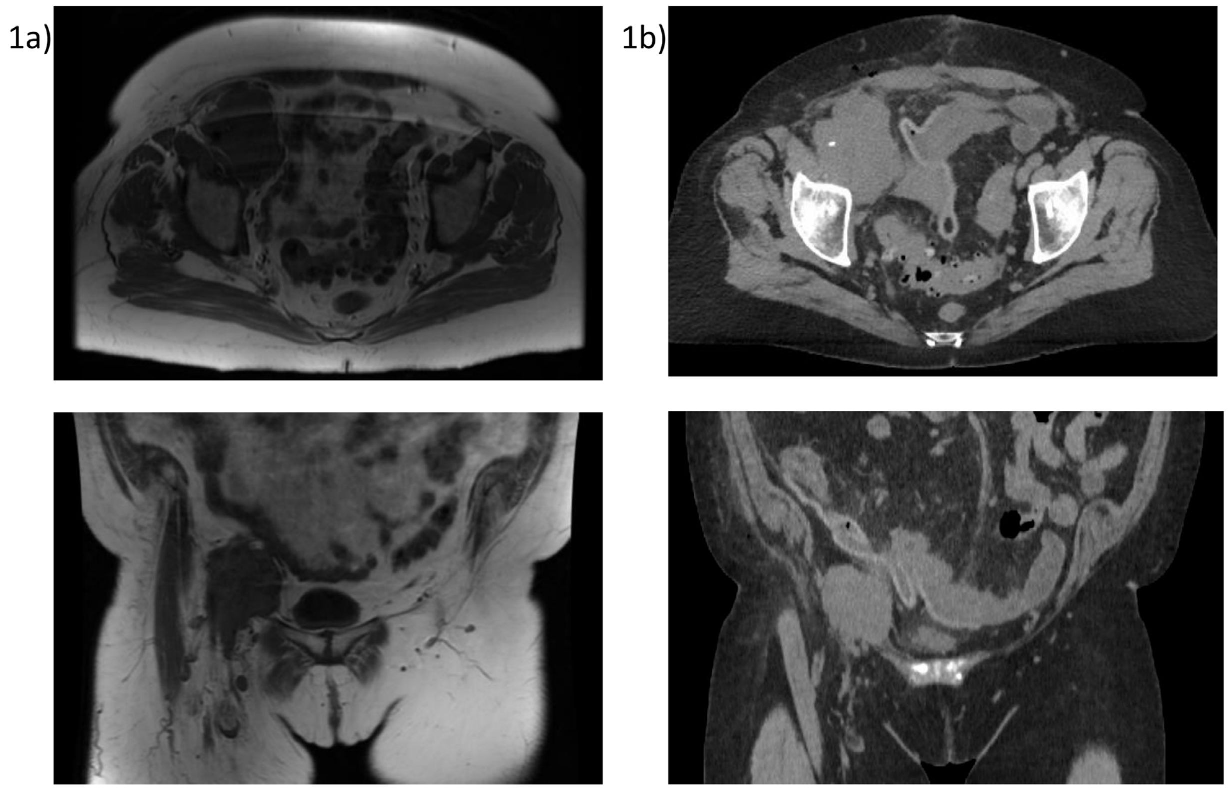

Fig. 1 A, Magnetic resonance imaging before mesh insertion showing direct abutment of the tumor and small bowel over a 23-mm segment. B, Treatment planning computed tomography after mesh insertion, which resulted in 10 mm or more of separation between the tumor and small bowel.

The minimum dose covering 99% of the gross tumor volume (GTV D99%) was 6783 cGyE, and the minimum and maximum point doses were 6257 cGyE and 7766 cGyE, respectively. An internal subvolume was permitted to receive additional dose, and approximately 45% of the gross tumor volume received ≥7500 cGyE. No beam ranged out toward the small bowel. Instead, a crisp lateral penumbra was achieved by using the smallest appropriate spot size of our delivery system for each field, and this was leveraged to maximize small bowel sparing. A 4.5-cm range shifter attached to the end of the treatment nozzle was needed for the anterior oblique beam to cover the proximal regions of the target, whereas no range shifter was required for the posterior oblique field. The small bowel maximum dose to 0.03 cc (D0.03 cc) was 4397 cGyE, maximum dose to 1 (D1) cc was 3553 cGyE, and volume receiving 3000 cGyE (V3000 cGyE) was 2.77 cc. Other organs at risk OAR were well spared with all plan normal-tissue constraints met. Additionally, the final plan dose was recomputed using an in-house developed Monte Carlo dose calculation engine.[5,6] This system also generates the nonuniform effective biological dose by combining the physical dose with a model of proton relative biologic effectiveness that is based on the calculated distribution of

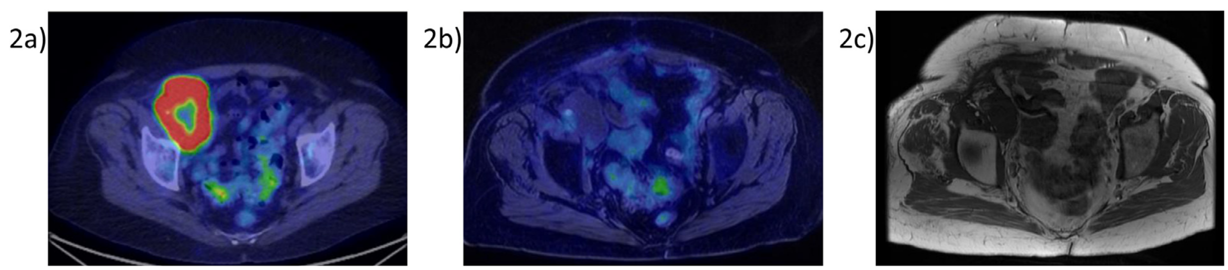

Fig. 2 A, Positron emission tomography−computed tomography at diagnosis showing a large, centrally necrotic right pelvic mass. B, Follow-up positron emission tomography−magnetic resonance imaging at 3 months posttreatment demonstrating complete metabolic response and decreased size of the mass with no evidence of locoregional progression or distant metastasis. C, Follow-up MRI at 14 months posttreatment redemonstrating no evidence of progression.

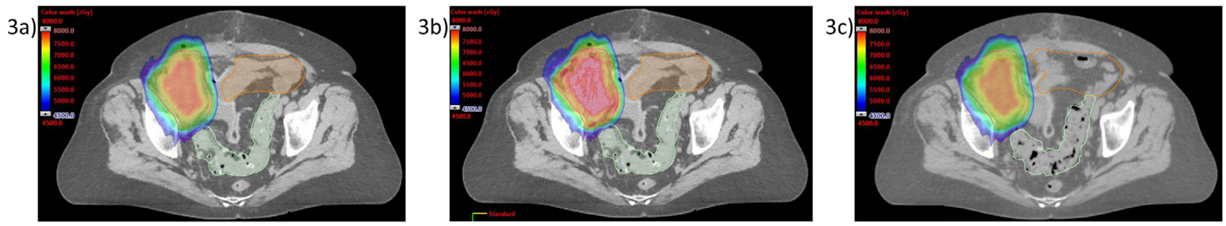

Fig. 3 Radiation therapy plan treating the gross tumor to 6750 cGyE with expansions to 5700 cGyE and 4500 cGyE to cover areas at risk for subclinical disease; the target is contoured in magenta, the small bowel in green, and the large bowel in orange. A, Treatment planning computed tomography using a uniform estimate of 1.1 for relative biologic effectiveness. B, Treatment planning computed tomography using an in-house 9model estimate of nonuniform relative biological effectiveness. C, Verification computed tomography using a uniform estimate of 1.1 for relative biological effectiveness.

linear energy transfer (Fig 3B). These Monte Carlo dose calculations confirmed that the small bowel D0.03 cc was consistent with treatment goals of less than 4500 cGyE.

The patient commenced radiation therapy 3 weeks after placement of the mesh, and treatment was completed without interruption. Weekly CT verification scans demonstrated consistent displacement of the small bowel from the high-dose radiation region (Fig 3C). Throughout radiation therapy the patient experienced expected mild decreased appetite, nausea, fatigue, and dermatitis, all of which resolved shortly after completing radiation.

Positron emission tomography and MRI performed 3 months after completion of radiation therapy demonstrated a complete metabolic response with decreased size of the mass (6.7 × 4.9 × 9.5 cm), absence of restricted diffusion and contrast enhancement, and no evidence of locoregional progression or distant metastasis (Fig 1B). The patient reported resolution of her pain as well as no new bowel-related toxic effects. Imaging surveillance of the pelvis, most recently with MRI at 14 months after completion of radiation therapy (Fig 1C), demonstrated continued decreased size of the mass (now 5.1 × 2.9 × 5.9 cm) and no evidence of locoregional progression. Clinically, the patient remains on anticoagulation and experiences mild discomfort associated with fluctuating right lower-extremity lymphedema. No bowel-related toxic effects were reported at follow-up.

Discussion

For curative-intent radiation therapy, it is incumbent upon the radiation oncologist to identify and, when possible, overcome barriers to safely achieving a curative-intent dose to gross disease. For disease abutting a critical, radiosensitive organ, the options to undertreat disease or exceed the tolerance of the organ can lead to suboptimal outcomes. However, in some circumstances the radiosensitive organ can be displaced using interventional or surgical methods to provide curative-intent dosing while minimizing toxic effects. A common example is the insertion of a hydrogel spacer for displacement of the rectum from the prostate.[7] Combined modality therapy often can leverage complementary features of surgery and radiation to maximize the chance for success. A relevant example is the use of radiation therapy to facilitate limb-persevering surgery for soft-tissue sarcomas. The key difference is that whereas radiation often is used to improve the outcomes of curative-intent surgery, this report highlights an example of using surgery to improve curative-intent radiation therapy.

Although small bowel mobility in the pelvis may ameliorate toxic effects from expected high dose exposure over short segments, extended segments and/or doses far exceeding tolerance remain concerning, particularly if the at-risk section of the bowel is not freely mobile. Various techniques have been used to exclude the small bowel from the abdominal and pelvic radiation fields, including noninvasive measures such as prone positioning, use of a bellyboard, and bladder filling. The effectiveness of these techniques is limited, leading to innovation of invasive methods to displace the bowel, such as insertion of mesh, tissue expanders, and/or silicon prostheses as well as generation of a pelvic sling from native peritoneum or omentum.[4,8-13] A theoretical downside of any invasive technique is the development of adhesions, which may restrict small bowel mobility. A short duration between procedure and radiation treatment could mitigate this concern, particularly with adequate displacement such that the small bowel cannot be fixed in high-dose regions.

Placement of mesh before radiation therapy is discussed most in the literature, and the Table 1 highlights the diseases, organs that have been displaced, and select outcomes.[4,8,13-19] Mesh placement has been shown to improve radiation therapy dosimetry with superior small bowel sparing compared with before insertion.[14] Traditionally, mesh was placed using a laparotomy, which is generally well tolerated but carries risks of complications including pelvic infection or abscess, wound dehiscence, and small-bowel obstruction, herniation, and fistula formation.[15-17,20]Laparoscopic surgical techniques permit insertion to be performed in a minimally invasive

Table 1 Selected studies of mesh used to retract the small bowel before radiation therapy in the management of pelvic and abdominal malignancies

Reference	Patients, No.	Primary histologies	Organ(s) excluded	Median follow-up, mo	Radiographic exclusion of small bowel, %	Toxic effects possibly related to mesh placement	Rate of radiation enteritis, %
Soper et al, 1985[18]	6	Cervical, endometrial	Small bowel	5	100	None	0
Devereux et al, 1988[8]	60	Rectal, gynecologic	Small bowel	28 (mean)	N/a	None	0
Feldman et al, 1988[4]	16	Rectal, sacral chordoma	Small bowel	15 (mean)	81	Fungal infection	0
Sener et al, 1989[17]	8	Colorectal, urologic	Small bowel	12	N/a	Pelvic abscess, wound dehiscence, small bowel herniation, small bowel obstruction × 2	12
Dasmahapatra and Swaminathan, 1991[16]	45	Rectal	Small bowel	34	100	Small bowel obstruction × 2	0
Rodier et al, 1991[19]	60	Cervical, endometrial, rectal, bladder, retroperitoneal sarcoma, ovarian, vulvar	Small bowel	18 (mean)	93	Small bowel obstruction × 5	7
Beitler et al, 1997[15]	20	Rectal	Small bowel	18 (mean)	N/a	Pelvic abscess, perineal seroma, toxic perineal wound, pulmonary embolus, lower extremity deep venous thrombosis	7
Joyce et al, 2009[14]	6	Prostate, bladder	Small bowel	N/a	100	Pulmonary edema	N/a
Yoon et al, 2013[13]	5	Retroperitoneal sarcoma, pelvic sarcoma, Wilms tumor	Small bowel, colon, ureter, bladder, pancreas	18	100	Lower extremity deep venous thrombosis	0

Abbreviation: N/a = not applicable.

manner, which reduces operative morbidity and decreases recovery times.[14,21] Although the risks are modest, displacing small bowel through invasive techniques may be of most value when otherwise there are unacceptably high risks of small-bowel toxic effects or treatment failure.[13,22] The technique of using mesh as a pelvic sling is nearly 4 decades old and was pioneered during previous eras that lacked access to modern highly conformal radiation therapy techniques and high-quality image guidance.[10] In this patient's situation, no radiation technology yet exists that safely could deliver a definitive radiation dose to a sarcoma abutting the small bowel without additional measures.

The risk of radiation-induced enteropathy increases significantly at 4500 to 5000 cGy, which can be dose-limiting when treating tumors of the pelvis.[23] Herein the authors describe a case of definitive treatment of a radioresistant tumor with previously immediately adjacent small bowel to an equivalent dose in 200 cGyE fractions of over 10000 $cGyE_3$ and 8000 $cGyE_{10}$.[24-26] Insertion of the mesh provided some physical separation between the tumor and bowel, whereas IMPT permitted a sufficiently steep dose gradient to achieve small-bowel D0.03 cc of less than 5300 $cGyE_3$. Previously, IMPT has been shown to provide clinically relevant dose reductions of pelvic organs at risk relative to photon therapy and may have significant utility in situations in which abrupt dose fall-off is crucial.[27] More widely available intensity modulated radiation therapy could be used in similar settings with sufficient anatomic separation for dose fall-off. Owing in part to the challenge of achieving a high target dose, soft-tissue sarcoma uncommonly is treated with curative-intent radiation therapy alone. Retrospective analysis of definitive radiation therapy for soft-tissue sarcoma suggests improvement in clinical outcomes with doses of 6300 cGy or higher, achieving 60% local control and 52% overall survival at 5 years in this group.[28] In the plan from this case, the intermediate dose-volume in this case was prescribed to more than 6500 $cGyE_{10}$. The patient's active smoking and diabetes mellitus placed her at increased risk of radiation-induced complications.[29] Despite her comorbidities, radiation therapy was delivered safely without significant early or late toxic effects to date. At 14 months since radiation therapy, locoregional control has endured with no distant metastases.

High-quality modern proton radiation therapy is essential to provide the optimal plan, and an experienced multidisciplinary team is needed. The penumbra increases as protons traverse greater distances of matter owing to increased multicoulomb scattering[30]; thus, thoughtful beam arrangements and weighting are essential. Beam spot size further drives the sharpness of the lateral penumbra in pencil-beam scanning.[31] In this case, the smallest beam spots were used in the region where the target and primary OAR are in closest proximity to maintain a crisp lateral penumbra in this region. In addition to careful beam arrangements, the planned dose was evaluated using both analytical and Monte Carlo dose calculations to ensure that the dose modeling was sufficiently accurate. Furthermore, a biological dose model was used to analyze and correct via reoptimization for regions of excessively high biological dose caused by the combination of high physical dose and the increased linear energy transfer of end-of-range protons. Robust optimization should be used routinely to ensure adequate target coverage and OAR protection. Lastly, verification scanning is critical to assess for changes in target, organs at risk OARs, and patient habitus that could perturb the radiation plan. This was particularly important in this case, as fluid within the sling was partly responsible for the displacement and certainly could have changed. This patient's tumor and small bowel position were stable throughout verifications, and the dose distribution remained true to plan.

Conclusions

In a case of locally invasive high-grade sarcoma of the pelvis, a mesh was placed laparoscopically without complication and was used to retract small bowel that previously abutted the tumor, permitting definitive high-dose IMPT to be delivered with excellent dose metrics, no late bowel-related toxic effects, and locoregional control at 14 months from treatment. This combination of an established surgical technique and modern proton radiation therapy should be considered in the setting of definitive radiation therapy, particularly for patients with anatomically unfavorable tumor locations and/or increased risk of bowel toxic effects.

References

1. Green N. The avoidance of small intestine injury in gynecologic cancer. *Int J Radiat Oncol Biol Phys*. 1983;9:1385–1390.
2. Chen SW, Liang JA, Yang SN, et al. Radiation injury to intestine following hysterectomy and adjuvant radiotherapy for cervical cancer. *Gynecol Oncol*. Oct 2004;95:208–214.
3. Sher ME, Bauer J. Radiation-induced enteropathy. *Am J Gastroenterol*. 1990;85:121–128.
4. Feldman MI, Kavanah MT, Devereux DF, Choe S. New surgical method to prevent pelvic radiation enteropathy. *Am J Clin Oncol*. 1988;11:25–33.
5. Wan Chan Tseung H, Ma J, Beltran C. A fast GPU-based Monte Carlo simulation of proton transport with detailed modeling of nonelastic interactions. *Med Phys*. 2015;42:2967–2978.
6. Beltran C, Tseung HWC, Augustine KE, et al. Clinical implementation of a proton dose verification system utilizing a GPU accelerated Monte Carlo engine. *Int J Part Ther*. 2016;3:312–319.
7. Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: Final results of a phase III trial. *Int J Radiat Oncol Biol Phys*. 2017;97:976–985.

8. Devereux DF, Chandler JJ, Eisenstat T, Zinkin L. Efficacy of an absorbable mesh in keeping the small bowel out of the human pelvis following surgery. *Dis Colon Rectum*. 1988;31:17–21.
9. Hoffman JP, Sigurdson ER, Eisenberg BL. Use of saline-filled tissue expanders to protect the small bowel from radiation. *Oncology (Williston Park)*. Jan 1998;12:51–54. discussion 54, 60, 62, passim.
10. Kavanah MT, Feldman MI, Devereux DF, Kondi ES. New surgical approach to minimize radiation-associated small bowel injury in patients with pelvic malignancies requiring surgery and high-dose irradiation. A preliminary report. *Cancer*. 1985;56:1300–1304.
11. Sezeur A, Martella L, Abbou C, et al. Small intestine protection from radiation by means of a removable adapted prosthesis. *Am J Surg*. 1999;178:22–25. discussion 25-26.
12. Vasilev SA, McGonigle KF, Spencer-Smith EL. Intestinal peritoneal sling as an adjunct to radical pelvic operation and pelvic irradiation. *J Am Coll Surg*. 1995;180:568–572.
13. Yoon SS, Chen YL, Kambadakone A, Schmidt B, DeLaney TF. Surgical placement of biologic mesh spacers prior to external beam radiation for retroperitoneal and pelvic tumors. *Pract Radiat Oncol*. 2013;3:199–208.
14. Joyce M, Thirion P, Kiernan F, et al. Laparoscopic pelvic sling placement facilitates optimum therapeutic radiotherapy delivery in the management of pelvic malignancy. *Eur J Surg Oncol*. Apr 2009;35:348–351.
15. Beitler A, Rodriguez-Bigas MA, Weber TK, Lee RJ, Cuenca R, Petrelli NJ. Complications of absorbable pelvic mesh slings following surgery for rectal carcinoma. *Dis Colon Rectum*. 1997;40:1336–1341.
16. Dasmahapatra KS, Swaminathan AP. The use of a biodegradable mesh to prevent radiation-associated small-bowel injury. *Arch Surg*. 1991;126:366–369.
17. Sener SF, Imperato JP, Blum MD, et al. Technique and complications of reconstruction of the pelvic floor with polyglactin mesh. *Surg Gynecol Obstet*. 1989;168:475–480.
18. Soper JT, Clarke-Pearson DL, Creasman WT, et al. Absorbable synthetic mesh (910-polyglactin) intestinal sling to reduce radiation-induced small bowel injury in patients with pelvic malignancies. *Gynecol Oncol*. 1988;29:283–289.
19. Rodier JF, Janser JC, Rodier D, et al. Prevention of radiation enteritis by an absorbable polyglycolic acid mesh sling. A 60-case multicentric study. *Cancer*. 1991;68:2545–2549.
20. Patsner B, Mann Jr WJ, Chalas E, Orr Jr. JW. Intestinal complications associated with use of the Dexon mesh sling in gynecologic oncology patients. *Gynecol Oncol*. 1990;38:146–148.
21. Jarrett TW, Pardalidis NP, Silverstein M, Sweetser PM, Smith AD. Laparoscopic enterolysis and placement of an intestinal sling before radiation therapy for the treatment of prostate cancer. *Urology*. 1995;45:326–328.
22. Chan DKH, Cheo T, Cheong WK. Successful use of tissue expander and pelvic sling to exclude small bowel for high-dose pelvic irradiation. *Int J Colorectal Dis*. 2019;34:1043–1046.
23. Kinsella TJ, Bloomer WD. Tolerance of the intestine to radiation therapy. *Surg Gynecol Obstet*. 1980;151:273–284.
24. Stacchiotti S, Collini P, Messina A, et al. High-grade soft-tissue sarcomas: Tumor response assessment—Pilot study to assess the correlation between radiologic and pathologic response by using RECIST and Choi criteria. *Radiology*. 2009;251:447–456.
25. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998;16:197–203.
26. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol*. 1989;62:679–694.
27. van de Sande MA, Creutzberg CL, van de Water S, Sharfo AW, Hoogeman MS. Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy? *Radiother Oncol*. 2016;120:397–403.
28. Kepka L, DeLaney TF, Suit HD, Goldberg SI. Results of radiation therapy for unresected soft-tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 2005;63:852–859.
29. Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. *J Clin Oncol*. 2002;20:3651–3657.
30. Rana S, Zeidan O, Ramirez E, Rains M, Gao J, Zheng Y. Measurements of lateral penumbra for uniform scanning proton beams under various beam delivery conditions and comparison to the XiO treatment planning system. *Med Phys*. 2013;40: 091708.
31. Kraan AC, Depauw N, Clasie B, Giunta M, Madden T, Kooy HM. Effects of spot parameters in pencil beam scanning treatment planning. *Med Phys*. 2018;45:60–73.