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PTCOG Gastrointestinal Subcommittee Lower Gastrointestinal Tract Malignancies Consensus Statement

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ABSTRACT

Purpose: Radiotherapy delivery in the definitive management of lower gastrointestinal (LGI) tract malignancies is associated with substantial risk of acute and late gastrointestinal (GI), genitourinary, dermatologic, and hematologic toxicities. Advanced radiation therapy techniques such as proton beam therapy (PBT) offer optimal dosimetric sparing of critical organs at risk, achieving a more favorable therapeutic ratio compared with photon therapy.

Materials and Methods: The international Particle Therapy Cooperative Group GI Subcommittee conducted a systematic literature review, from which consensus recommendations were developed on the application of PBT for LGI malignancies.

Results: Eleven recommendations on clinical indications for which PBT should be considered are presented with supporting literature, and each recommendation was assessed for level of evidence and strength of recommendation. Detailed technical guidelines pertaining to simulation, treatment planning and delivery, and image guidance are also provided.

Conclusion: PBT may be of significant value in select patients with LGI malignancies. Additional clinical data are needed to further elucidate the potential benefits of PBT for patients with anal cancer and rectal cancer.

Introduction

Lower gastrointestinal (LGI) tract malignancies arise from the rectum and anal canal. There will be an estimated 46,050 rectal cancers (RC) and 9760 anal cancers (AC) diagnosed in the United States (U.S.) in 2023.[1] Standard definitive management of nonmetastatic rectal adenocarcinoma involves surgery, radiation therapy (RT) and chemotherapy, and concurrent chemoradiotherapy (CRT) for anal squamous cell carcinoma, with 5-year local control (LC) and overall survival (OS) rates from 85% to 92% and 68% to 80%, respectively, for RC,[2–4] and 68% to 87% and 65% to 74%, respectively, for AC.[5–7]

Despite advances in photon RT with intensity-modulated RT (IMRT) that have reduced toxicities compared with 2-dimensional conformal RT (3DCRT) planning, toxicity remains high. Abdominopelvic organs-at-risk (OARs) are susceptible to acute and late gastrointestinal (GI), genitourinary, dermatologic, and hematologic toxicities, all impacting quality of life (QoL).[8]

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There is limited but growing evidence demonstrating safe and effective proton beam therapy (PBT) application for LGI malignancies.[9–11]. The unique stopping power of proton beams, with essentially zero exit dose, allows for significant OAR sparing.[12] For LGI malignancies, unintended radiation exposure reduction could theoretically decrease acute- and long-term toxicities, minimize the impact on QOL, and allow for safer dose escalation and hypofractionation. Additionally, in several circumstances, including reirradiation and genetic predisposition to malignancy, PBT may provide disproportionate value.

With the growing number of proton centers internationally, the appropriate application of this technology in the treatment of patients with LGI malignancies is of burgeoning interest. A body of evidence and clinical experience has emerged in recent years that will begin to inform scenarios in which PBT may be considered as a treatment option. The Particle Therapy Cooperative Group (PTCOG) Gastrointestinal Subcommittee presents a consensus statement of PBT use for LGI malignancies. Clinical scenarios with supporting evidence, areas for further investigation, and technical guidance and best practices for LGI PBT are discussed.

Methods and materials

Following disclosure of potential biases, financial relationships, or conflicts of interest to exclude panel member participation, 12 radiation oncologists ($n = 9$) and physicists ($n = 3$) within the PTCOG GI Subcommittee with expertise in PBT for LGI malignancies contributed. A systematic literature review was conducted using PubMed/MEDLINE. Searches were limited to English language, peer-reviewed, scientific articles without date restrictions. Searched keywords included "rectal," "anal," "anorectal," or "lower gastrointestinal" and "proton" or "particle." Additional targeted literature searches were conducted to identify additional relevant articles. Articles deemed not pertinent, with ≤ 3 patients, or with insufficient information on patient selection, study methodology, or results were excluded. All articles were screened for suitability.

The ASTRO Clinical Practice Guidelines were referenced to determine the methodology used to determine panel consensus for recommendations, assign strength of recommendation (SoR), assess literature quality of evidence grade, and assign the level of evidence.[13] Panel recommendations required $\geq 80\%$ consensus (90% if based on expert consensus). For recommendations reaching consensus, SoR was assigned: strong or conditional.[13]

Literature supporting each recommendation was assessed for overall quality of evidence grade: High Moderate, Low, or Expert Opinion.[13] Levels of evidence were also assessed for each recommendation. Based on the Oxford Center for Evidence-Based Medicine Levels of Evidence,[14] score definitions include 1 = systematic review/meta-analysis; 2 = randomized trial/observational study with dramatic effect; 3 = nonrandomized, controlled cohort/follow-up study; 4 = case series/case-control/historically-controlled study; 5 = mechanism-based reasoning.

Data and rationale—disease sites

Rectal cancer

Standard neoadjuvant CRT and total mesorectal excision for locally advanced rectal cancer (LARC) achieve LC > 90%.[2] Total neoadjuvant therapy regimens, including short-course RT (SCRT) or long-course CRT and multiagent chemotherapy, achieve pathologic complete response rates 20% to 30%.[15,16] Despite favorable oncologic outcomes, pelvic RT can cause severe toxicities, including anastomotic leak, fistula formation, bowel obstruction, bladder scarring, erectile dysfunction, dyspareunia, premature ovarian failure, pelvic insufficiency fracture, and secondary malignancy.[17] Late toxicities can significantly impact QOL. The PROSPECT trial, a multicenter, noninferiority, randomized trial of standard concurrent CRT vs neoadjuvant FOLFOX alone in rectal cancer patients who were candidates for sphincter-sparing surgery, demonstrated no difference in disease control but showed mixed results in patient-reported outcomes (PROs).[18,19] Strategies such as the use of advanced radiation techniques to reduce toxicity through maximal OAR avoidance while maintaining excellent control and survival rates are highly desirable.[20,21]

Several treatment-planning studies have demonstrated PBT significantly reduces bone marrow (BM) V5 (volume receiving ≥ 5 Gy), V10, V15, and V20, small bowel V10 and V20, and bladder V40 compared to photon-based RT.[22–25] Small bowel V15 reduction may be clinically meaningful given a strong dose-volume relationship of this metric with grade 3+ acute small bowel toxicity in RC.[26] PBT can also improve conformality indices, spare genitalia,[21] and be particularly beneficial for larger tumors.[25]

Although prospective and retrospective data exist describing outcomes after PBT for recurrent, previously irradiated RC,[27–29] data for newly diagnosed RC are sparse. Jeans et al used pencil beam scanning (PBS)-PBT to deliver 5 Gy (relative biological effectiveness [RBE]) x 5 fractions for 11 patients preoperatively[9] using single-field optimization (SFO) with right and left posterior oblique beams. PBT achieved significant dose reductions to small and large bowel, bladder, pelvic BM, and femoral heads compared with IMRT or 3DCRT. After a median 10.5-month follow-up, there were no grade 2+ (G2+) toxicities and no local failures. With SCRT likely to play a larger role in the preoperative treatment of LARC, this study showed the feasibility of safe, effective, and robust PBT SCRT.

PRORECT is a currently enrolling phase II prospective, randomized Swedish trial comparing photon- and proton-based SCRT followed by 4 months of chemotherapy and resection assessing G2-5 toxicities, PROs, chemotherapy completion, tumor regression score, and cost-effectiveness.[30]

Large treatment volumes for RC overlap surrounding OARs, often resulting in exceeding dose constraints. In addition, sparing normal tissues from low doses could be significant for bone marrow and younger patients at higher risk for secondary malignancies.

Anal cancer

Definitive CRT for AC results in significant acute and chronic morbidity. RTOG 0529 compared IMRT to historical outcomes of 3DCRT, and while the primary endpoint was not met, did demonstrate meaningful toxicity reductions using IMRT.[8] However, toxicities were still frequent, with 73% G2+ hematologic, 21% G3+ GI, and 23% G3+ dermatologic toxicities. Further toxicity mitigation is needed.

PBS-PBT has dosimetric advantages over IMRT for AC (Figure 1). Ojerholm et al found PBT significantly reduced low-dose radiation to nearly all OARs compared with IMRT, including external genitalia, potentially impacting long-term sexual health.[31,32] PBS also reduced BM volume irradiated, potentially impacting hematologic toxicities.[33]

Despite dosimetric advantages, the clinical benefit of PBT for AC remains unproven. In a prospective multi-institutional feasibility study, Wo et al showed PBS-PBT can safely treat AC patients,[34] with similar disease control and toxicity (G3+ dermatologic toxicity 24% vs 23%; G3+ GI toxicity 36% vs 21%) rates to those in RTOG 0529. The Proton Collaborative Group REG001-09 prospective multi-institutional registry found PBT achieved a meaningful reduction in acute GI toxicities compared to IMRT.[35]

A large multi-institutional retrospective review comparing 208 AC patients treated with PBS-PBT or IMRT[36] showed dosimetric advantages to PBS-PBT, without significant differences between G3+ acute toxicities (IMRT 68% vs intensity-modulated proton therapy (IMPT) 67%, $P = .96$) or 2-year G3+ late toxicities (3.5% vs 1.8%, $P = .88$).

While limited available data do not show a clear benefit with PBT for AC, further prospective study is needed to determine whether toxicity differences exist between PBT and IMRT. Patients receiving

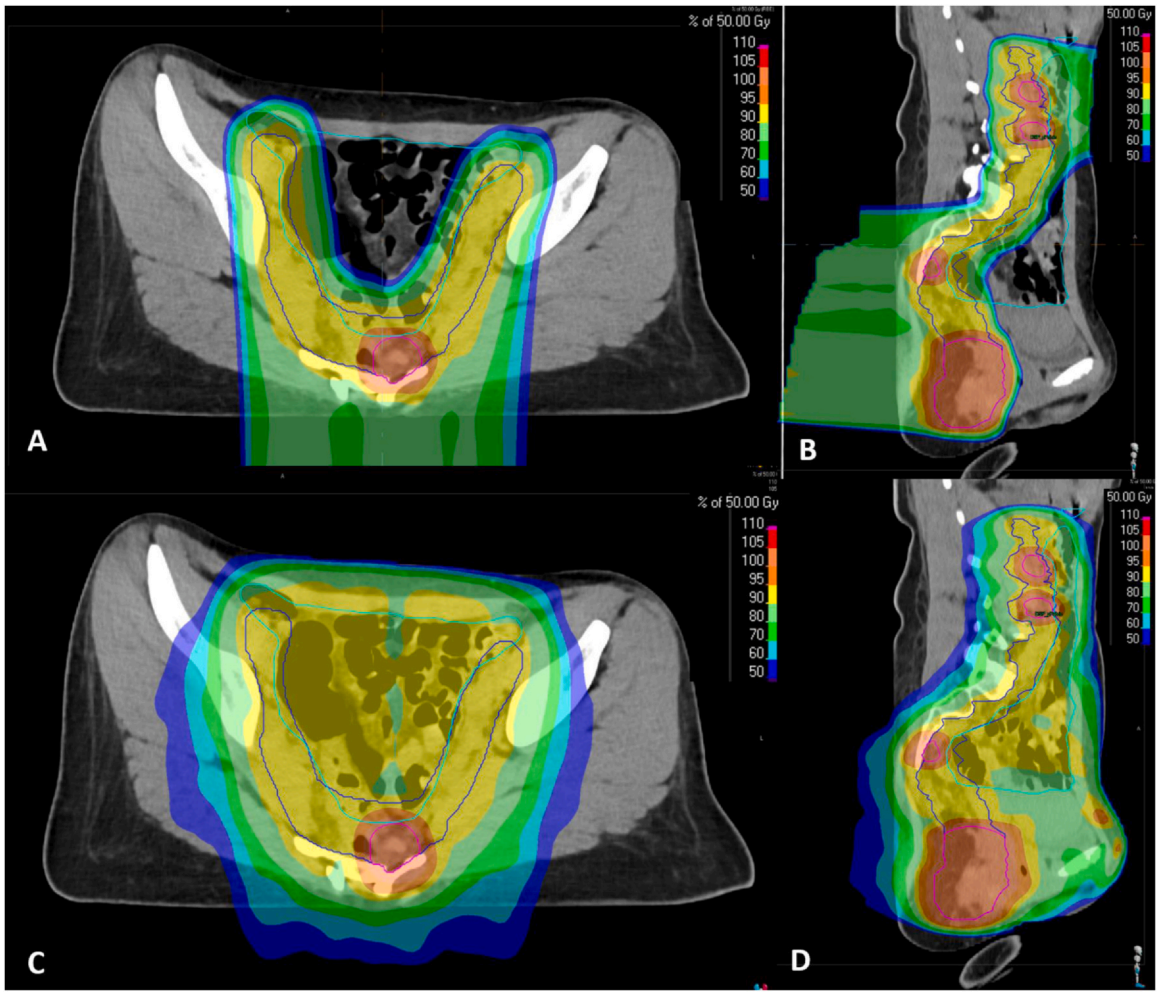

Figure 1. 41-year-old female with p16+, moderately-differentiated anal SCCa, cT2N1M1 (para-aortic LNs), who received definitive SIB-IMPT to 45 Gy(RBE)-50 Gy (RBE) in 25 fractions and concurrent capecitabine/mitomycin-C (MMC). Proton and VMAT axial (A,C) and sagittal (B,D) representative cross-sections. Dose threshold of 50% prescription dose (blue). Low-dose CTV (blue outline), high-dose CTV (pink), bowel (cyan).

concurrent CRT may particularly benefit from PBT, as suggested in a 1483-patient comparative effectiveness study of concurrent CRT for locally advanced cancer, including AC.[37] Despite older age and less favorable Charlson-Deyo comorbidity scores in the PBT group, fewer G2/3+ adverse events and decline in performance status were seen with PBT. Greater therapeutic gains and toxicity reduction may come from tailored radiotherapy dose and systemic therapy regimens, concepts actively being tested by the Eastern Cooperative Oncology Group in a randomized study assessing de-intensified chemotherapy and RT regimens[38] and the PLATO United Kingdom trial assessing multiple treatment de-escalation risk strategies,[39] neither of which specifically study PBT.

Data and rationale–clinical indications

Given still limited access to PBT, it is important to understand which patients may benefit most from PBT. Herein, we discuss clinical situations in which PBT should be considered, along with published evidence supporting these consensus recommendations (Table 1).

Reirradiation (strength of recommendation (SoR = Strong)

Locoregional recurrences or new primary LGI tract tumors within previously-irradiated fields present a treatment challenge. Salvage treatment options are limited and often involve a combination of surgical resection, systemic therapy, and reirradiation. However, salvage surgery is technically difficult and associated with substantial morbidity, and reirradiation is challenging to deliver safely without exceeding OAR constraints.

Multiple experiences have been published utilizing photon-based planning for RC reirradiation. Valentini et al conducted a 59-patient prospective evaluation of sequential twice-daily reirradiation to 30 Gy to gross disease + 4 cm and 40.8 Gy sequential boost to gross disease + 2 cm.[3] Overall response rate was 44%, with a modest 5% G3 GI toxicity rate. 51% of the patients underwent resection, and 53% maintained 36-month local control.

PBT can provide a unique opportunity to improve reirradiation safety by reducing cumulative doses to abdominopelvic OARs[40] (Figure 2). A systemic review of GI PBT reirradiation demonstrated few high-grade complications,[41] similar to reports in gynecologic reirradiation.[42]

Initial clinical experiences are limited by small sample size and delivery with passive scatter technology but demonstrate OAR dose reduction with PBT. Berman et al reported on 7 RC patients receiving reirradiation to a median 61.2 Gy(RBE).[27] PBT reduced bowel V10Gy (6.9% vs 46.2%, $P = .02$) and V20Gy (5.8% vs 12.8%, $P = .02$) versus photon plans. Six patients (85%) had complete metabolic responses, and all with pain had at least partial improvement; there were 3 (42%) late G3 toxicities. A 15-patient experience of pelvic passive scattering proton therapy (PSPT) reirradiation to 39 to 45 Gy(RBE) in 1.5 Gy BID[28] reported no G4+ toxicities at 14-month follow-up. BM (eg, V10Gy 18.6% vs 46.7%, $P < .01$, V20Gy 13.1% vs 27.2%, $P < .01$) and bowel (V30Gy 3.9% vs 16.1%, $P = .02$) doses were lower with PBT versus IMRT.

Table 1
Patient selection recommendations and strength of recommendation for the use of proton therapy in the treatment of lower GI cancer.

Subcommittee recommendation	Strength of recommendation	Overall quality of evidence grade	Level of evidence
Patients requiring reirradiation for local-regional recurrence.	Strong	Moderate	3
Patients in whom critical structure dose constraints cannot be met with other radiation modalities.	Strong	Expert Opinion	5
Patients with pelvic or transplanted kidneys within or near the target volume.	Strong	Expert Opinion	4
Adolescent and young adult (AYA)/young patients.	Strong	Low	4
Patients with active inflammatory bowel disease (Crohn's, ulcerative colitis, etc.)	Strong	Low	4
Patients with genetic syndromes predisposing them to development of radiation-induced secondary malignancy, making total volume of radiation minimization crucial.	Strong	Low	4
Patients enrolled on a prospective clinical trial.	Strong	Expert Opinion	-
Patients who need to preserve ovarian function and fertility.	Strong	Expert Opinion	5
Patients with advanced local regional disease, particularly with gross lymph nodes in the para-aortic or high pelvic areas requiring extended nodal irradiation.	Conditional	Expert Opinion	5
Patients with active connective tissue disorder.	Conditional	Expert Opinion	5
Patients at high risk for bowel complications such as those with multiple prior abdominal surgeries.	Conditional	Expert Opinion	5

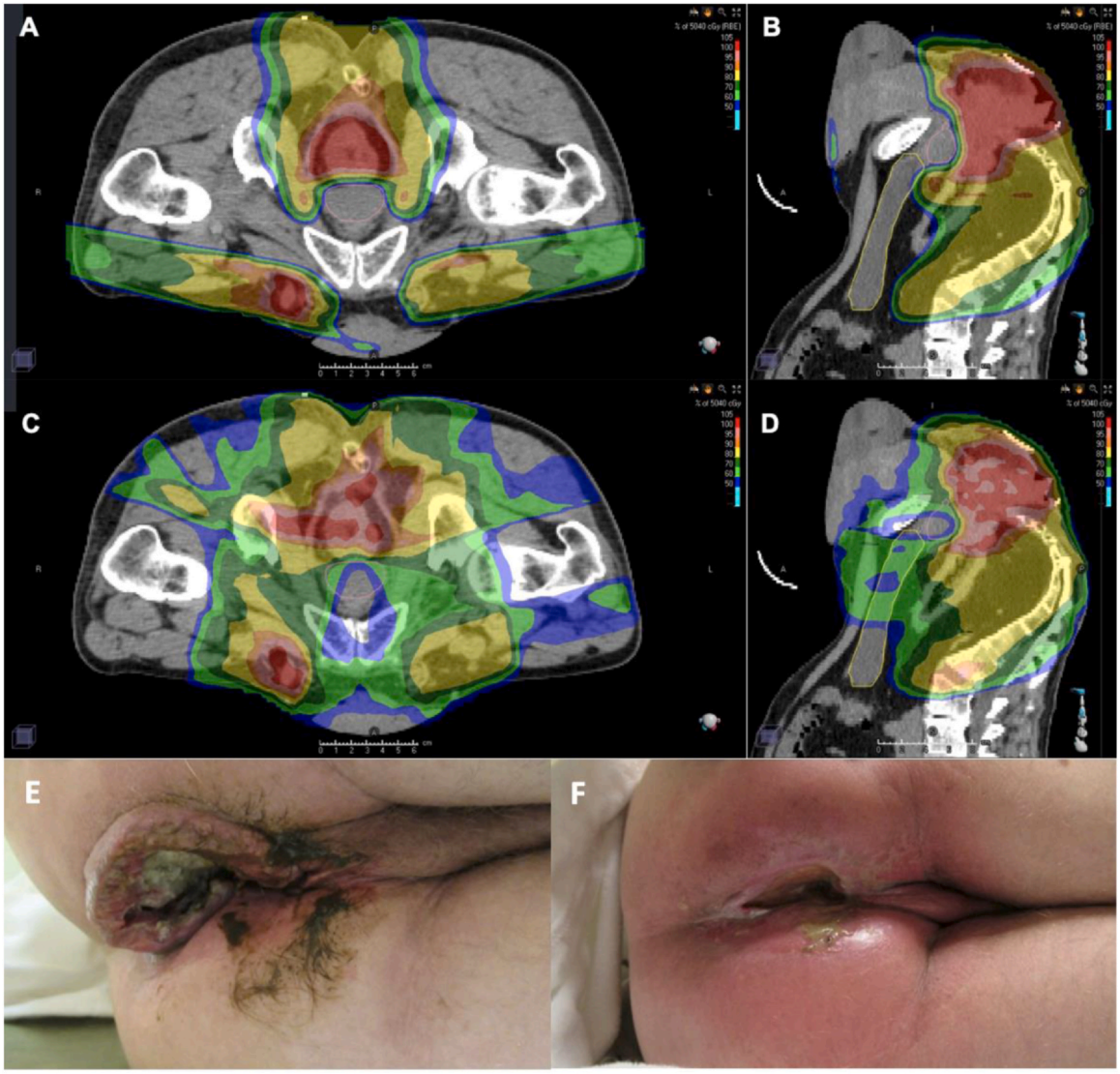

Figure 2. 49-year-old male with HIV and recurrent anal intraepithelial neoplasia (AIN) treated with local excisions followed by salvage definitive RT to 55.8 Gy (RBE). Twelve years later, he developed T3N1aM0 invasive anal SCCa. SIB-PBS-PBT to 42 Gy(RBE)-50.4 Gy(RBE) in 28 fractions with concurrent capecitabine/MMC was delivered. Proton and VMAT axial (A,C) and sagittal (B,D) representative cross-sections. The dose threshold of 50% prescription dose. Low-dose PTV (blue), prostate (salmon), bladder (yellow). (E-F) Significant tumor response from pre-treatment baseline (E) to end-of-treatment (F) after PBT.

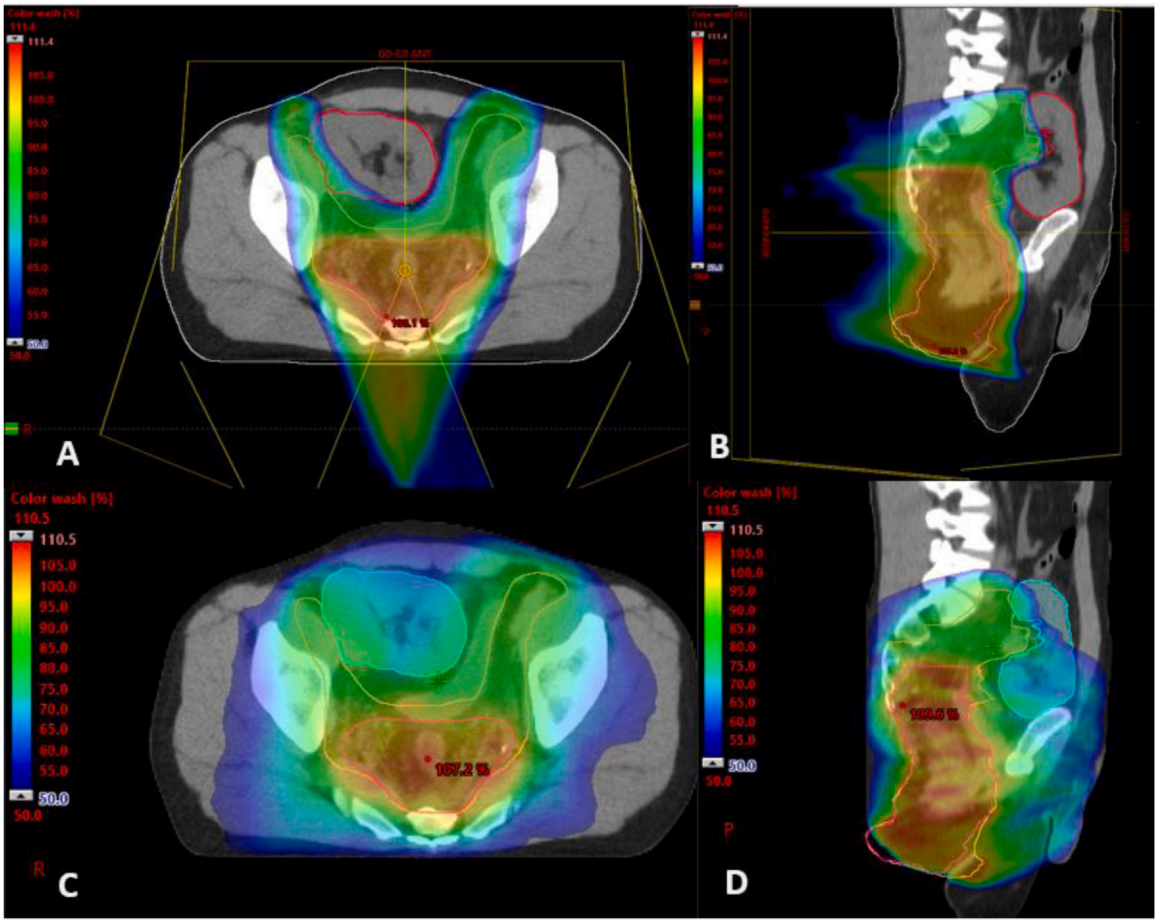

Figure 3. 46-year-old male with glomerulonephritis and kidney failure status-post renal transplant with keratinizing anal/distal rectal SCCa, well-differentiated, cT3N0M0. He received concurrent capecitabine/MMC and SIB-PBT to 58 Gy(RBE)-47 Gy(RBE) in 29 fractions. The mean transplanted kidney dose with PBT and comparative VMAT plan was 0.7 Gy and 29.6 Gy, respectively. Proton and VMAT axial (A,C) and sagittal (B,D) representative cross-sections. Dose threshold of 50% of the prescription dose (blue). Low-dose CTV (yellow), high-dose CTV (red-orange), pelvic transplanted kidney (protons = red; photons = cyan). Abbreviation: VMAT, volumetric modulated arc therapy.

Koroulakis et al reported on 28 patients treated with PBS-PBT re-irradiation to a median 44.4 Gy(RBE).[29] G3+ acute and late toxicities occurred in 3 (10.7%) and 4 (14.2%) patients, respectively. Two-year LC and OS were 47% and 71%, respectively. While outcomes of these series are heterogeneous, all 3 treated to higher biologically effective doses than are typically used with photons[3] and included a less favorable patient cohort including multiply recurrent pelvic malignancies.

Overall, PBT affords improved dose conformity in patients at high risk of toxicities and significantly decreases doses to bowel and BM, which are often more critical in the reirradiation setting. Further reports are necessary to optimize treatment and reirradiation composite dose constraints.

Inability to meet critical structure dose constraints with other radiation modalities (SoR = Strong)

OAR constraints for photon therapy are well-described.[43] OAR constraint modifications from RTOG 0529 have been incorporated into daily practice with modern photon techniques such as IMRT and volumetric modulated arc therapy.[8] For anorectal malignancies in which these constraints cannot be met without target volume coverage compromise, PBT should be strongly considered.

Pelvic kidney transplant and other kidney dysfunction (SoR = Strong)

In 2020, 22,817 kidney transplants were performed, representing the 10th consecutive year of record-breaking numbers.[44] These patients are chronically immunocompromised and at increased risk for developing cancer, specifically Human Papillomavirus-mediated squamous cell carcinoma, including AC.[45–50] Patients with pelvic kidney transplant, one functional kidney, or other kidney dysfunction requiring definitive RT for RC/AC may uniquely benefit from the conformality of PBT (Figure 3).

Per Quantitative Analysis of Normal Tissue Effects in the Clinic guidelines, bilateral kidney dose-volume constraints for an estimated nephropathy risk of $< 5\%$ include a mean kidney dose < 18 Gy, V20Gy $< 32\%$, and V6Gy $< 30\%$.[43,51] Acute, subacute and chronic kidney injury can manifest as subclinical and clinical sequelae such as hypertension, weight gain, edema, dyspnea, nausea, fatigue, confusion, coma and even death.[51] In a series of 4 patients with transplanted pelvic kidneys and AC receiving concurrent definitive PBS-PBT and 5-FU/mitomycin-C, the transplanted kidney mean dose was < 1 Gy(RBE) in 3 patients and 3.6 Gy(RBE) in one patient, max V20Gy 5.79%, and max V6Gy 18.26%, well below accepted kidney constraints and what would be achievable with photons.[52] While long-term follow-up data will provide more insight into the impact of radiation dose sparing achievable with PBT, optimal transplanted kidney sparing and integral dose mitigation with PBT should be offered when available.

Early-onset disease/adolescent or young adult (AYA) patients (SoR = Strong)

The median age of rectal and AC diagnoses is 63 and 62 years, respectively.[53,54] Early-onset colorectal cancer is increasing, with

colorectal cancer now the second most common cancer diagnosis and the third leading cause of cancer mortality in age < 50 years in the U.S.[54,55] For RC alone, 15% occur in patients 18 to 49 years old. Risk factors include obesity, physical inactivity, and smoking.[56] Additionally, 25% of AC cases occur in patients < 55 years of age.

The adolescent or young adult (AYA) population, variably defined as 15-18 years to 28-39 years, are 8 times more likely to be affected by cancer than patients < 15 years and 2 to 3-times increased risk of developing a subsequent primary cancer after any initial cancer.[57] Cancer is the leading disease-related cause of death in young adults in the U.S.[58] Thus, this vulnerable population is at significant risk of not only developing cancer but also experiencing long-term sequelae of curative therapy, including secondary malignancies.

The integral dose delivered with RT is decreased with PBT, which may reduce secondary malignancies risk. In a 4392-patient cohort study for childhood solid cancers, a significant association between the development of secondary malignancy and integral dose was observed.[59] In a National Cancer Database analysis of 450,373 patients treated with 3DCRT (33.5%), IMRT (65.2%), or PBT (1.3%) for primary nonmetastatic cancer, second cancer risk was increased for IMRT versus PBT ($P \leq .0001$).[60] The potential for PBT to decrease secondary cancer risk for AYA patients highlights a therapeutic advantage that should be harnessed for this vulnerable population.

Sexual health considerations in this population are also of particular concern. Vaginal canal and genitalia sparing may be more feasible with IMPT, potentially leading to improved long-term sexual health outcomes.[61,62] Other potential options for sexual function preservation across age groups, and particularly of concern in the AYA population, may also include neoadjuvant FOLFOX for patients with LARC who are candidates for sphincter-sparing surgery, thereby avoiding radiotherapy, which has traditionally been a planned component of standard neoadjuvant therapy. In the recent publication of the PROSPECT trial, neoadjuvant FOLFOX was demonstrated to be noninferior in disease control outcomes (disease-free survival, overall survival, local recurrence rate) compared with standard concurrent CRT with 5-FU and radiotherapy, and also resulted in improved sexual function at 12 months.[18] However, fertility was not assessed on this trial, so this important endpoint will require further study; in addition, the relative incidence of other toxicities and PROs was mixed between the 2 groups.[19]

Inflammatory bowel disease (SoR = Strong)

Patients with inflammatory bowel disease (IBD), including ulcerative colitis or Crohn's disease, are at increased risk of severe acute and late RT-induced complications. In one series of 28 patients with IBD (Crohn's = 10; ulcerative colitis = 18) who underwent abdominopelvic RT, 46% developed severe toxicity: 21% required treatment cessation for acute toxicity and 29% required hospitalization or surgical intervention for late toxicity.[63] In a second series including 28 patients with IBD (Crohn's = 13; ulcerative colitis = 15) receiving external beam RT of brachytherapy for a pelvic malignancy, 11% of the patients developed G3 or 4 acute GI toxicity.[64] In this study, rectal IBD location ($P = .016$) and low body mass index ($P = .012$) were associated with more severe IBD activity within or after 6 months following RT. Concurrent chemotherapy and prior abdominal surgery may further increase GI toxicity risk, specifically acute diarrhea and late small bowel obstruction.[65] Therefore, patients with IBD should be strongly considered for PBT to maximally spare abdominopelvic OARs, especially small and large bowel.

Genetic predisposition to secondary cancer (SoR = Strong)

Patients with genetic mutations carrying elevated risks of developing malignancy or increased RT sensitivity should be strongly considered for PBT to avoid unnecessary normal tissue exposure. Radiation exposure in the setting of Li-Fraumeni syndrome, TP53 mutations, and dysregulated DNA damage response and cell cycle regulation result in increased susceptibility to secondary cancers.[66–70] Similarly, patients with familial retinoblastoma and accompanying germline mutations in the Rb gene are also at elevated risk of radiation-induced second cancers, particularly sarcomas, with an up to 10.7-fold risk increase in tissues receiving > 60 Gy.[71–74] Mutations in the MutL Homolog I gene are linked to radiation-induced cancers due to upregulation of inflammatory molecular pathways leading to carcinogenesis.[75]

Given the low prevalence of these mutations and historic avoidance of RT in patients carrying these gene aberrations, the robust study of therapeutic RT in these patients is limited. However, as PBT has been modeled to reduce secondary cancers for abdominopelvic organs in patients without underlying genetic mutations,[76] and given biologic principles underlying the genetic mutations and RT mechanism of action, avoidance of unnecessary radiation to nontarget tissue with PBT is likely particularly advantageous.

Enrollment on a prospective clinical trial (SoR = Strong)

The appropriate utilization and optimal treatment approach of PBT for LGI tumors is under active investigation. While treatment planning studies,[22–25,31,32] and several retrospective and prospective evaluations[9,10,35,36] have been performed, data are limited. Further elucidation with prospective clinical trials is needed to better characterize the value of PBT for LGI tumors and, concomitantly, improve access to patients benefitting from PBT. Ongoing prospective studies evaluating PBT for anorectal cancers are included in Table 2. For patients enrolled in ongoing and future prospective clinical trials, including multicenter prospective registry trials, PBT should be strongly considered.

Fertility preservation (SoR = Strong)

RC incidence is increasing in patients aged < 50 years, and one-quarter of AC is diagnosed in patients aged < 54 years; moreover, ~two-thirds of AC cases are diagnosed in women.[1,77] As such, fertility preservation presents an important and increasingly prevalent component of QOL. Options include ovariopexy, cryopreservation of oocytes, cryopreservation of ovarian tissue, and use of GnRH analogs, the latter 2 which are considered experimental. Avoidance of reproductive structures with PBT may be beneficial, especially in the setting of ovariopexy, to further minimize dose and potentially improve the likelihood of future successful fertility attempts (Figure 4).

Advanced local-regional disease with high pelvic/para-aortic nodal involvement (SoR = Conditional)

Patients with LGI malignancies can present with nodal disease beyond lymphatic basins encompassed in the definition of regional disease, including high pelvic and para-aortic lymph nodes (LNs). These patients are often treated with curative intent despite technically having M1 disease. In these cases, the radiotherapy field is extended superiorly to include involved and intervening LN basins at risk. The bowel may fall near or even abut the superior LN stations in these cases. PBT may provide improved conformality around the lymphatic clinical target volume (CTV) with dramatically reduced low-to-moderate bowel dose, potentially resulting in reduced acute GI toxicities given the strong association of small bowel V15 with acute grade 3+ GI toxcity.[26] Also, for escalated boost dose delivery to involved LNs that is often preferred but challenging due to bowel dose constraints, PBT may allow dose escalation and the higher likelihood of tumor control while also mitigating morbidity risk to surrounding OARs, and thus should be considered in these circumstances.

Table 2
Current active and/or recruiting clinical trials assessing the use of proton therapy for anal cancer or rectal cancer internationally as indicated on clinicaltrials.gov.

Trial name (NCT)	Country	Study design	N	Intervention	Inclusion	Primary endpoint
Rectal Cancer						
Pencil Beam Proton Therapy for Pelvic Recurrences in Rectal Cancer patients Previously Treated With Radiotherapy (ReRad II) (NCT04695782)	Denmark	Phase 2, nonrandomized, single arm	65	Dose escalated pencil beam PBT 55 Gy(RBE)/44fx BID -65 Gy (RBE)/52fx BID	Locally recurrent rectal cancer, prior pelvic RT (> 30 Gy EQD2)	Neoadjuvant treatment: Rate of pathological complete resection (R0) Definitive treatment: Local control at 1 year
Preoperative Short-Course Radiation Therapy With PROtons Compared to Photons in High-Risk RECTal Cancer (PRORECT) (NCT04525989)	Sweden	Phase 2, randomized	254	Preoperative PBT versus photon therapy; 5 Gy x 5 fx	Newly diagnosed locally advanced rectal adenocarcinoma	Acute grade 2-5 GI toxicity
Hypofractionated Pencil-Beam Scanning Intensity-modulated Proton Therapy (IMPT) in Recurrent Rectal Cancer (IMPARC) (NCT04827732)	USA	Nonrandomized	20	Intensity-modulated PBT in 5 daily fractions at increasing dose levels	Adenocarcinoma of the rectum, anus or rectosigmoid junction of any stage with recurrent disease in the pelvis, one prior course of radiation therapy to the pelvis for rectal cancer	Maximum tolerated dose of reirradiation using hypofractionated intensity-modulated PBT
Prospective Evaluation of Pencil Beam Scanning Proton Therapy for Previously Irradiated Tumors (NCT05313191)	USA	Phase 2, nonrandomized	55	Intensity-modulated PBT	Recurrent or new primary nonmetastatic rectal or anal cancer with history of radiation therapy for rectal or anal cancer, overlap of 50% isodose line	Rate of grade 3 or worse treatment-related acute or late adverse events within 1 year of reirradiation completion
Anal Cancer						
Re-Rad III. Pencil Beam Proton Therapy for Recurrences in Anal Cancer Patients Previously Treated With Radiotherapy (ReRad III) (DACG 5) (NCT05055635)	Denmark	Phase 2, nonrandomized, single arm	55	Dose escalated pencil beam PBT 55 Gy(RBE)/44fx BID -65 Gy (RBE)/52fx BID	Recurrent anal cancer, prior RT (> 30 Gy EQD2)	Local control at 12 months
Proton Therapy in Reducing Toxicity in Anal Cancer (NCT03018418)	USA	Phase 2, single arm	14	Standard chemoradiation with 5-FU, Mitomycin, and pencil beam PBT	Squamous or basaloid carcinoma of the anal cancer, stage T2-4 with any N category	Acute (< 3 months) grade 3 or greater hematologic, GI, GU, and dermatologic toxicity
Proton Versus Photon Therapy in Anal Squamous Cell Carcinoma (SWANCA) (NCT04462042)	Sweden	Phase 2, randomized	100	Intensity-modulated PBT versus photon radiotherapy (VMAT/IMRT/HT)	Previously untreated squamous cell carcinoma of the anal canal	Acute (< 3 months) grade > 2 hematological side effects
Prospective Evaluation of Pencil Beam Scanning Proton Therapy for Previously Irradiated Tumors (NCT05313191)	USA	Phase 2, nonrandomized	55	Intensity-modulated PBT	Recurrent or new primary nonmetastatic rectal or anal cancer with history of radiation therapy for rectal or anal cancer, overlap of 50% isodose line	Rate of grade 3 or worse treatment-related acute or late adverse events within 1 year of reirradiation completion

Abbreviations: BID, twice daily; fx, fractions; GI, gastrointestinal; GU, genitourinary; HT, helical TomoTherapy; IMRT, intensity-modulated radiation therapy; PBT, proton therapy; RBE, relative biological effectiveness; USA, United States; VMAT, volumetric modulated arc therapy.

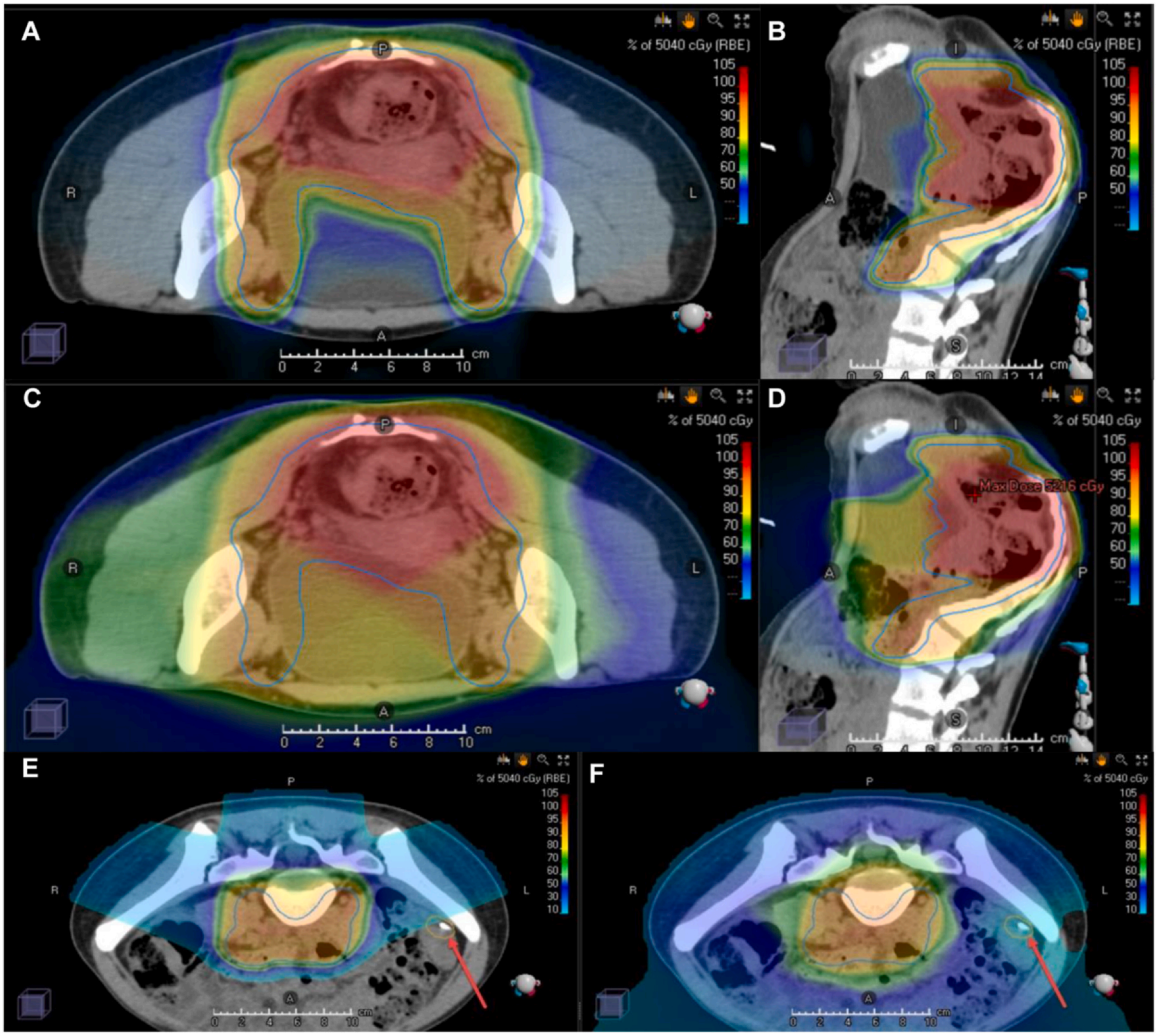

Figure 4. 31-year-old female with cT4bN2M0 mid-rectal adenocarcinoma status-post ovarian transposition. She received preoperative concurrent capecitabine and PBT for ovarian function preservation using SIB to 45.64 Gy(RBE)-50.4 Gy(RBE) in 28 fractions. Proton and VMAT axial (A,C; D,F) and sagittal (B,E) representative cross-sections. The dose threshold set at 50% of the prescription dose, A-D (blue). Low-dose CTV (blue), transposed left ovary (yellow, red arrows, E-F).

Connective tissue disorder/collagen vascular disease (SoR = Conditional)

RT has historically been avoided in patients with collagen vascular disorder or connective tissue disease, such as scleroderma or systemic lupus erythematosus. Similar to concerns for the increased baseline propensity to develop complications from RT in IBD, concerns in patients with collagen vascular disorder are underlying risks of fibrosis and inflammation that may place patients at increased risk of development severe acute and late radiation toxicities.[78–80]

Multiple prior surgeries (SoR = Conditional)

Patients with a history of prior abdominal surgeries are at higher risk of bowel complications due to scar tissue formation that can lead to bowel obstruction, fistula, and stricture formation. In the setting of prior abdominopelvic surgery, RT risks may be increased, as peritoneal adhesions developing from surgery can lead to bowel fixation or adhesion.[81] This can decrease variability in bowel location during radiation which can be favorable to avoid exposing the same area of the bowel to full radiation dose. Minimizing bowel exposure to RT with PBT may be beneficial to avoid serious bowel complications.

Considerations for treatment planning and delivery

Simulation

The trajectory of proton beams through tissue is highly sensitive to anatomical variation and, therefore, reproducibility of patient setup and rectum, bowel, and bladder geometry are of paramount importance. Diet protocol and bowel preparation before simulation and each treatment are advised to increase reproducibility, including low-gas diet, anti-foaming/anti-gas agents beginning several days before simulation, and instructions to empty bowel and bladder upon arrival and drinking 16 oz. of water ~30 to 60 minutes prior to appointments.

Patients can be simulated either supine or prone with the aim of minimizing the effects of anatomical and setup variabilities. Prone setup may be challenging in the setting of large pannus or large breasts, but a belly board may increase patient comfort stability and enable the bowel to move anteriorly and superiorly away from the CTV. Prone setup also allows for immobilization of the gluteal cleft with a thermoplastic mold, preventing gluteal muscle contour changes. The supine position, however, is typically more comfortable and reproducible, important when planning complex geometries with PBS to optimize robustness. For inguinal treatment, supine positioning with a

comfortably full bladder is preferred. Nonmetallic radiopaque markers may be used to mark the anal verge/tumor near the anal verge. Genitalia should be reproducibly positioned out-of-field for males, and vaginal dilators considered for females for anterior vaginal wall and urethral sparing.[61,62]

If significant rectal distention is present at simulation, verification scans may be useful early in treatment with replanning as necessary. Enema with repeat simulation may be considered. CT simulation should use 2 to 3 mm slice thickness from mid-femur to L2-3 or 5 cm above the superior-most extent of nodal disease. An empty bladder CT simulation scan for robustness evaluation can be considered should full bladder be challenging to maintain as treatment progresses; similarly, a pre-emptive scan without a vaginal dilator could be obtained should dilator use need to be discontinued.

Proton ranges for pelvic irradiation vary from < 1 cm for inguinal nodes to 20 cm for pelvic nodes and rectum and ~ 30 cm in obese patients. A significant contribution to uncertainty in proton range calculation is attributed to planning CT data. To reduce range uncertainties, CT numbers (Hounsfield units (HU)) are mapped to proton relative stopping power using stoichiometric calibration.[82] Despite this, overall range uncertainty is typically 2.7% to 3.5%,[83–86] translating to ~ 1 cm for a 30 cm range in water. Li et al demonstrated range uncertainty may be further reduced to about 2.2% by use of Dual-Energy CT simulation imaging.[87]

Image reconstruction artifacts caused by metallic implants like hip prostheses degrade the accuracy of the HU, with possible additional range inaccuracies of > 1 cm for centrally located pelvic targets with a double hip prosthesis.[88–90] While CT manufacturers provide algorithms to reduce metal artifacts (Metal Artifact Reduction reconstruction), performance varies across vendors.[91,92] Therefore, careful Metal Artifact Reduction reconstruction accuracy evaluation through simulated plans using phantoms with metallic implants is needed. Using megavoltage CT and overriding HU to known values may also mitigate metal artifacts. The megavoltage CT approach can produce accurate results[93–95] but is not commonly used and requires its own calibration curve in the treatment planning system. Overriding HU is practical, but range uncertainties must be carefully calculated. Users should avoid any beam traversing or passing near hip implants due to their uncertain dimension given imaging artifacts.[90]

MRI and/or PET/CT may help with target delineation, with rigid or deformable registration to the planning CT for contouring.

Treatment planning

The impact of range uncertainty, anatomical variability, and patient setup reproducibility on dosimetric robustness needs consideration when selecting beam angles.[96] Robust beam angles for most anorectal targets are left-posterior obliques and right-posterior obliques, which avoid variable bowel gas regions and minimize bowel and bone marrow dose, although they are subject to gluteal cleft variations, rotational asymmetries, and rectal distensibility.[97] Lateral fields are also used, are robust, but do not effectively spare bone marrow. For inguinal nodes, anterior-posterior or left-anterior oblique/right-anterior oblique beams may be used. Treatment planning margins around the CTV should incorporate proton-specific margins distal to the target along each beam direction for range uncertainty (beam-specific planning target volumes (bsPTV)).[98] Typical margins for bsPTV: distal margin along beam axis of 3.5% distal target depth + 1 mm; the lateral margin in the plane perpendicular to the beam axis of 3 to 5 mm for set-up uncertainty.

PSPT fields require larger distal margins than PBS fields due to the range compensator material in the beam path to shape the beam distal edge. PSPT plans are somewhat more robust to variable bowel gas, but beam angles should be chosen to avoid such variations regardless. PSPT does not allow for proximal conformity, precluding skin sparing.

PBS-based planning involves inverse optimization of individual beamlets within a scanned treatment field. By optimizing positioning and weight distribution of proton Bragg peaks (spots), maximal OAR sparing is achievable.[99–102] Treating anorectal tumors involves careful delineation of planning structures and complex optimization methods.[101] Two optimization methods used for PBS-PBT include SFO and multifield optimization (MFO).[102]

With SFO, spot-weight distribution within each individual treatment field is optimized independent of other fields, reducing spot-weight modulation in the beam's-eye view. This reduces the gradients generated between multiple fields, resulting in near-uniform dose across the target. SFO-based plans are generally highly robust and less sensitive to setup and range errors but less effective at sparing OARs wrapped around or abutting the target volume.[99,102]

MFO involves optimization of the spot-weight distribution from all treatment fields simultaneously, allowing IMPT distributions to be delivered. Individual treatment fields are heavily modulated longitudinally and laterally across the beam's-eye view, whereas the composite distribution from all fields may be homogeneous and highly conformal. IMPT is recommended for complex volumes with extensive nodal involvement for pelvis sparing and when SFO cannot adequately spare OARs. MFO-based methods are more sensitive to minor perturbations in patient positioning and internal anatomical variation.

While some of these uncertainties may be accounted for with bsPTV margins, highly modulated MFO distributions can significantly degradation plan quality within the target itself, with dose heterogeneities due to sharp inter-field dose gradients.[100–104] These dosimetric effects may be mitigated with *robust optimization* techniques.[105–107]

A modified form of MFO, individualized-field simultaneous optimization, involving split target-based field weight distribution, is being increasingly used for improving bowel and bladder sparing.[98]

The robustness of each PBS treatment plan should be evaluated to set up and proton range uncertainties to ensure acceptable dose coverage for all scenarios. Often a metric of D95 with 95% target coverage under the worst-case scenario is used for plan evaluation.[98,107] Contemporary treatment planning systems provide tools for robustness analysis.

Biological uncertainty at the end of the range of a proton beam is an additional consideration. Left-posterior obliques and right-posterior oblique beams, for example, are directed toward the small bowel. As linear energy transfer (LET) increases at the end of the range, so does the number of ionizations per unit distance. The subsequent DNA damage clusters and increases in beam RBE place distal OARs at greater risk. Only alternative beam angle selections can mitigate this risk with PSPT, but PBS allows for LET-based optimization approaches to be considered that may remove the higher LET peaks away from the OAR.

Image-guidance and delivery

Daily image guidance should be used to ensure reproducible patient positioning. Contemporary PBT systems include on-board cone-beam CT (CBCT),[108] which can minimize inter-fractional pelvic rotation variation.[109] In systems without volumetric image guidance, orthogonal planar images can align patients, but patient rotational errors should be assessed, and these systems cannot be relied on to make 6-DoF corrections.[110] Regular repeat CT image datasets, typically every 2 weeks during treatment or minimally halfway throughout treatment, should be acquired during treatment to evaluate the impact of anatomical change like weight loss and/or tumor shrinkage. If volumetric image guidance is not available, more frequent repeat CT datasets may be needed to confirm internal soft tissue anatomy. Offline adaptive replanning should be performed as necessary. For SCRT in 5 fractions, verification CT scans on days 1 and 2 can be considered, without repeat assessments if acceptable. CBCT datasets may be useful for adaptive planning strategies; deformable registration of the planning CT to the daily CBCT may allow for more regular evaluation of the need for adaptive replanning.[111]

Conclusion

There are well-described dosimetric advantages of PBT compared to other radiation modalities for LGI cancers. While all patients will not equally benefit from PBT, those at especially high risk of toxicity from photon therapy should be most strongly considered for PBT. As such, the PTCOG GI Subcommittee provides current recommendations for when practitioners should consider PBT for LGI cancers.

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Author Contributions

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Declaration of Conflicts of Interest

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