Lower Gastrointestinal Malignancies

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16.1 Introduction

Lower GI cancers present a particular problem for multidisciplinary care. Concurrent chemoradiotherapy is the standard of care, but with it comes a host of treatment-related toxicities. For rectal cancer, preoperative chemoradiation with 5-fluorouracil-(5-FU)-based treatment followed by total mesorectal excision results in the best local control. For anal squamous cell cancer (SCC), definitive chemoradiation with two sensitizing agents has allowed curative treatment without the need for surgery.

Fortunately, lower GI cancers are curable, but survivors may face not only acute but also late toxicities including the bowel, bladder, bone marrow, and sexual function toxicities as well as an increased risk for second malignant neoplasms. Acute toxicities are significant in these diseases as they dictate how fit patients are as they head into surgery (for rectal adenocarcinomas) or the likelihood of finishing treatment within a narrow package time (for anal SCCs). One of the major treatment-limiting acute toxicities is bowel toxicity, usually manifest as diarrhea. Because 5-FU, which can cause bowel mucositis, is frequently combined with pelvic radiation, treatment-related diarrhea is common. Historically, dosimetric planning parameters for bowel have focused on the maximum radiation dose. Even as recently as the "failed" RTOG 0822 trial for rectal cancer using IMRT in combination with capecitabine and oxaliplatin, volumetric small bowel limits were set for V35, V40, and V45 [1]. However, more recent retrospective data have suggested that the volume of bowel, in particular small bowel, that receives low to medium doses of radiation is most predictive of clinically significant diarrhea during concurrent chemoradiation. Doses ranging from 15 to 25 Gy are the most predictive of acute GI toxicity regardless of how the bowel is contoured (tight individual loops or a peritoneal structure) [2–6]. Another important acute toxicity during lower GI chemoradiation is bone marrow toxicity. This is particularly important when marrow-toxic agents like mitomycin C are employed, as is standard for anal SCC. Even for rectal adenocarcinoma, most patients will proceed to adjuvant chemotherapy with regimens like FOLFOX, so marrow preservation is an important goal. Sexual function after combined modality treatment for lower GI cancers can certainly suffer. Protection of gonads, the vagina, and the external genitalia has been difficult to achieve in the 3DCRT era, but modern techniques may improve on this. Son et al. showed that mean dose (<43 Gy) and generalized equivalent uniform dose (<35 Gy) to the vagina are important predictors of vaginal stenosis [7]. Attention to vaginal dose, starting with contouring the vagina as an avoidance structure, may help reduce the negative quality of life impact of chemoradiation. The role of proton therapy (PT) in GI cancers has been reviewed [8], but there is a paucity of clinical data published for lower GI cancers.

16.2 Rectal Adenocarcinoma

PT is currently being used for rectal cancers in some centers. Early comparative dosimetry studies showed an advantage for PS PT over three-dimensional conformal radiotherapy (3DCRT) photons with respect to the small bowel, bladder, and femoral heads in the postoperative setting [9] and for unresectable rectal cancers with dose

escalation [10]. More recent studies comparing IMRT and PS PT have also shown dosimetric improvements with proton therapy with respect to the bladder, bowel, testes, and bone marrow [11, 12]. In particular, passive scattering (PS) PT had lower small bowel V10–V20 volumes, which is predicted to correlate to acute diarrhea with 5FU-based chemoradiation [11]. A comparison of intensity-modulated radiation therapy (IMRT) with pencil beam scanning (PBS) PT using lateral beams in the preoperative setting showed that PBS PT could deliver much lower small bowel V15 (66 cc vs. 286 cc), lower bladder, and lower femoral head doses [13]. In a retrospective series comparing 39 patients treated with IMRT and 26 patients treated with PBS PT in the neoadjuvant setting with concurrent chemotherapy, there was significantly less grade ≥ 2 diarrhea in PBS PT patients (12% vs. 39%, $p = 0.022$) [14]. Proton therapy has also been explored in the reirradiation setting for rectal cancer with superior bowel dosimetry and feasible treatment in a small number of patients [15].

16.3 Simulation, Target Delineation, Radiation Dose, and Fractionation

The first major decision with regard to positioning is whether to simulate the patient in the supine or prone position. When using 3DCRT for rectal cancer, prone positioning with a "belly board" can displace pelvic loops of small bowel away from the target volume. However, this position is not always comfortable for the patient and is generally less stable than the supine position. Precise positioning is more critical for robust proton therapy delivery, so supine positioning has its advantages. The decision for prone versus supine positioning for rectal cancer should be individualized to the patient and the intended proton technique.

In general:

- CT simulation should be performed with a comfortably full bladder (when possible to displace small bowel from the target volume), with intravenous iodinated contrast (when not contraindicated) to facilitate elective nodal anatomical delineation. Pelvic floor immobilization is required in the supine position (knee and ankle support). For the purposes of dose calculation, a non-contrast CT needs to be employed in planning proton therapy. Standard oral contrast agents need to be overridden and can cause artifacts that can make proton planning more complicated. A negative contrast agent with Hounsfield units close to tissue, such as VoLumen®, can help with bowel definition without needing to be overridden.
- A vaginal cylinder can be used to displace the anterior vagina away from the target volume. We have found that an empty bladder is more reproducible than a variably full bladder for consistent vaginal cylinder position during treatment (personal communication, James M. Metz MD).
- MRI and/or PET/CT may be helpful for accurate delineation of the extent of the primary tumor and involved lymph nodes [16, 17].
- The GTV and involved nodes should be defined using all imaging modalities and these should be registered to planning CT for accurate delineation. Registering over the area of interest should be considered to minimize uncertainties.

- The CTV (elective nodal area) should include internal iliac lymph nodes, mesorectal, and presacral space. If appropriate, ischiorectal fossa should be included. The Radiation Therapy Oncology Group (RTOG) elective nodal anorectal atlas [18] has high-resolution pictorial details and instructions regarding elective nodal contouring.
- The PTV should be created from CTV with expansion according to institutional standard accounting for setup and delivery uncertainties and mainly used for dose recording and reporting purposes (ICRU 78).
- The following organs at risk (OAR) are segmented:
  Small bowel: Contouring should include all individual small bowel loops to at least 2 cm above the superior extent of both PTVs. It may be helpful to initially delineate the large bowel +/− endometrium to exclude these from subsequent delineation of small bowel.
  External genitalia: Delineation of the male genitalia should include the penis and scrotum. In woman it should include the clitoris and labia majora and minora out to the inguinal creases. Superior border in both sexes should lie midway through the symphysis pubis. A planning structure that defines the "perineal skin" may also be helpful to avoid inadvertent hot spots in the skin folds.
  Bladder: From dome to the neck including outer bladder wall.
  Right and left femoral heads: To be contoured separately on each side, including the ball of the femur, trochanters, and proximal shaft to the level of the bottom of ischial tuberosities.
  Vagina: Soft tissue extending from the vaginal meatus to the inferior aspect of the uterus [7].

16.4 Passive Scattering Treatment Planning

Treatment planning for anorectal cancers is complex due to concerns related to inconsistent patient positioning (especially the pelvic tilt) and varying patterns of bowel gas both in and outside of the mesorectal target. PS PT is limited by the maximum field size and the lack of proximal target conformality. The latter in particular can lead to high-skin doses, especially in the gluteal cleft which is prone to desquamation. However, compared to pencil beam scanning, PS PT is generally more robust with regard to the aforementioned uncertainties regarding positioning and bowel gas.

To account for the range uncertainties from multiple sources such as energy fluctuation of the delivery machine (~1 mm), compensator manufacturing (2 mm), and translation of the CT Hounsfield number into proton's stopping power (~3.5% of depth of CTV), distal and proximal margins are added to the CTV along beam direction to ensure sufficient target coverage. For PS technique, the distal margin is calculated by 3.5% distal CTV depth plus 3 mm, while proximal margin is 3 mm plus 3.5% of proximal CTV depth [19]. The same CTV to PTV expansions are applied to the other directions.

For patients with "simple" target volumes, namely, patients who do not have indications to treat the external iliac or inguinal nodes, high-quality PS plans can be generated that compare favorably to PBS plans with respect to avoiding OARs. In Fig. 16.1, both PS and PBS plans deliver minimal dose to the bowel, in part due to favorable bowel anatomy even in the supine position.

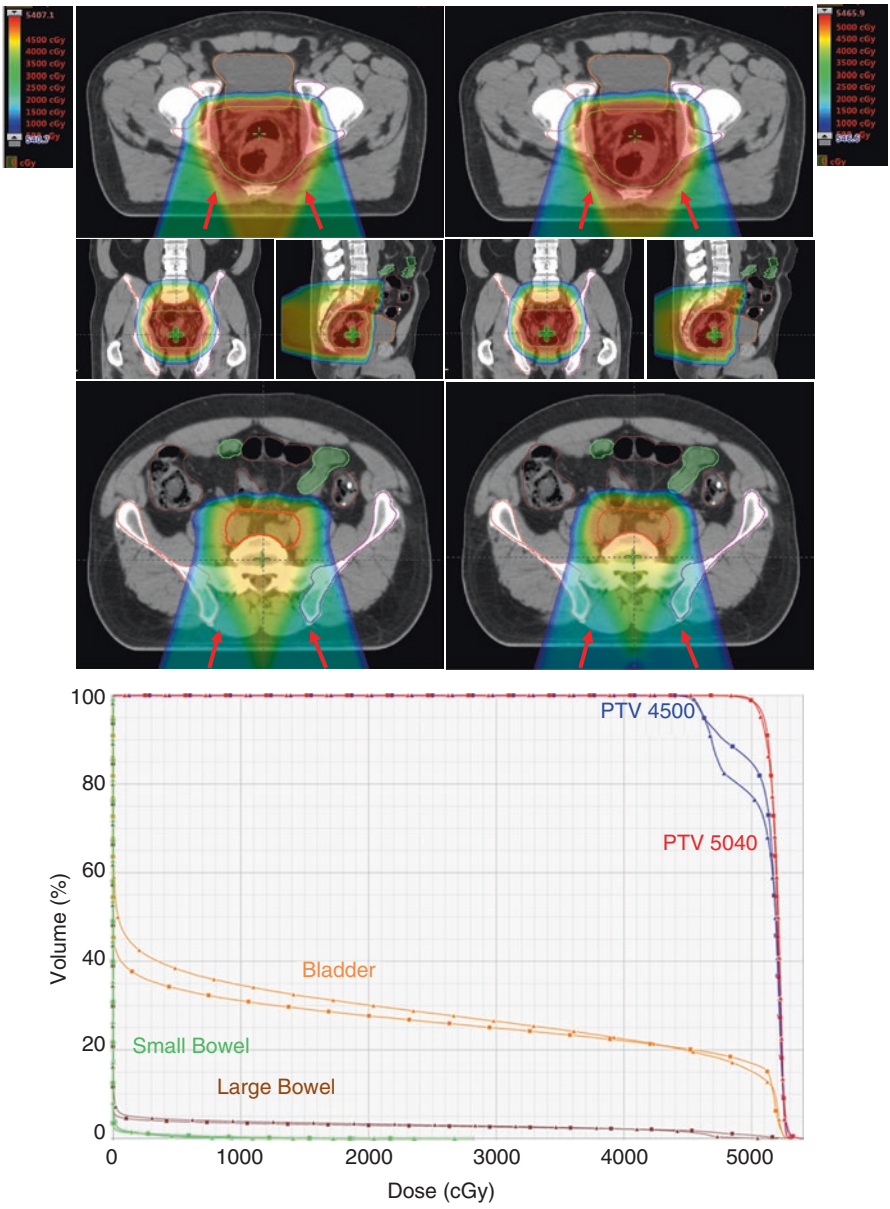

Fig. 16.1 Comparison of PS and PBS for a "simple" rectal adenocarcinoma target volume. This young man with T3 N1 rectal adenocarcinoma was treated with preoperative chemoradiation using PS PT in the supine position using standard target volumes that did NOT include external iliac or inguinal nodes. Panel A and B show comparative color washes for PS (*left*) and PBS (*right*) using posterior oblique fields (*red arrows*) at different viewing planes. Panel C shows the comparative dose-volume histogram. CTV_4500 (*red*), CTV_5040 (*green*), the bladder (*orange*), small bowel (*light green*), large bowel (*brown*), and bone marrow (*pink*) are contoured, and the bowel and bladder are displayed on the dose-volume histogram, where the PS (*square*) and PBS (*triangle*) plans are compared

16.5 Pencil Beam Scanning

In contrast to PS, the distal and proximal margins are both reduced by 2 mm for PBS planning as no compensator is used (3.5% of CTV depth plus 1 mm). Beam-specific PBS target volumes (PBSTV) are created using those proximal and distal margins of each beam as well as the same CTV to PTV expansions in the directions perpendicular to the beam. PBSTV or PTV, which is larger, is used for plan optimization. Usually, PBSTV is adopted. For cases with serious CT artifacts, increase on distal and proximal margin should be considered to ensure target coverage.

16.5.1 Irregular Targets

Generally speaking, PBS offers a potential advantage over passive scattering when targets are irregular. In the case of rectal adenocarcinomas, the target volumes become more complex when nodal volumes are extended more anteriorly to include external iliac nodes (e.g., T4 tumors involving anterior structures) and/or inguinal nodes (e.g., extensive involvement of the anal sphincter). These types of target volumes are more similar to anal SCC target volumes, discussed in more depth below.

Another strategy using PBS to target simpler rectal adenocarcinoma target volumes is to use opposed laterals. The ability to conform proximally allows for sparing of femoral heads while simultaneously keeping skin dose negligible (Fig. 16.2). We have used this technique to treat some patients who need external iliac nodal volumes included as well.

16.5.2 Robustness Planning

Planning margins do not protect against unpredictable changes that occur during the course of treatment. Proton dose distributions are sensitive to changes of tissue density or position of tissue interfaces. To ensure the target coverage, air cavities in bowel or rectum are often overridden with proper HU, as shown in left panel of Fig. 16.3. If the air cavity in this patient shown in Fig. 16.3 was filled during daily treatment, the target will still be covered. However, there would be significant “overshoot” when the air cavity presents during treatment. Therefore, lateral beams would be less likely to unpredictably deposit dose into more sensitive anterior structures (as opposed to muscle and fat lateral to the target volume).

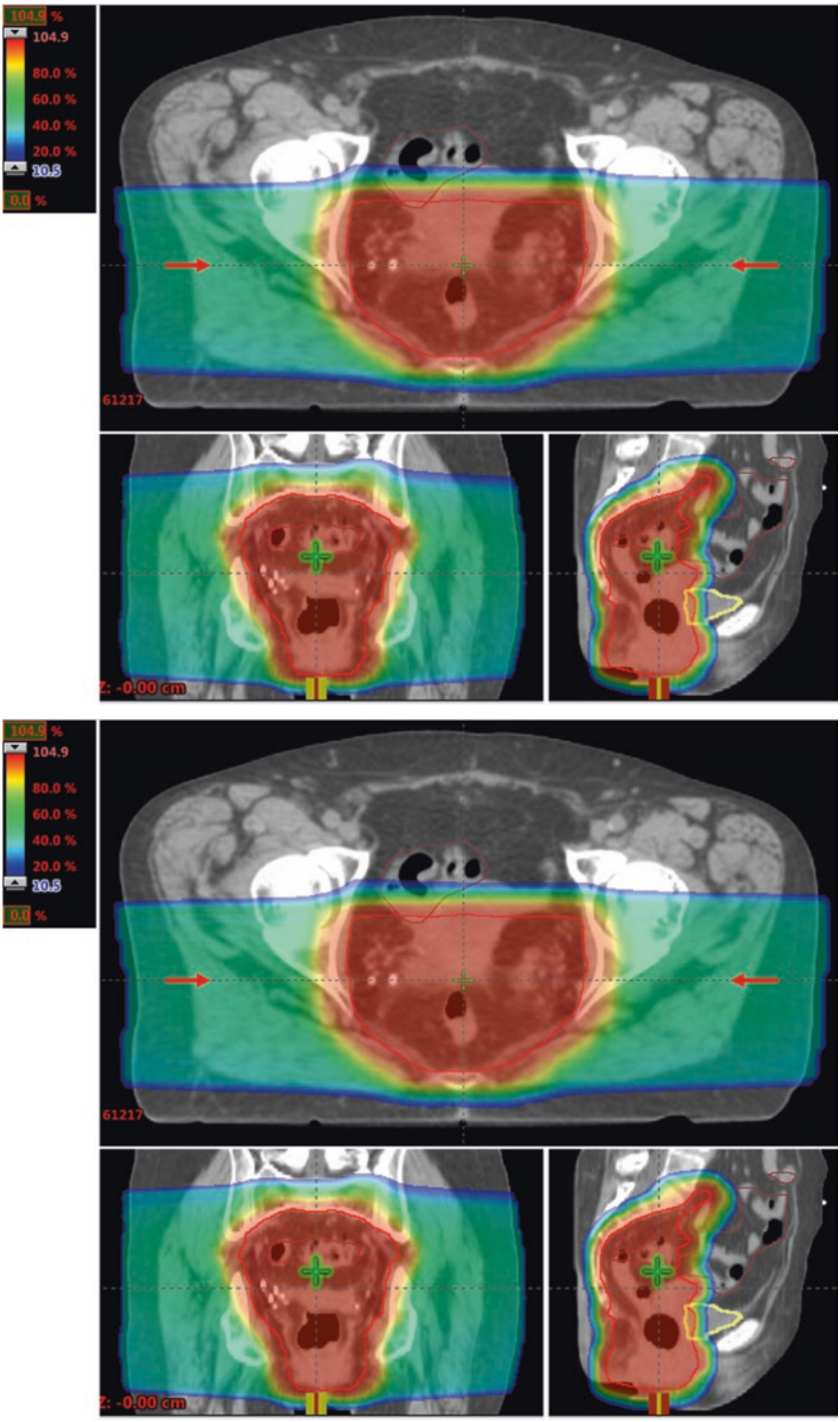

Fig. 16.2 Opposed lateral PBS fields (*red arrows*) for rectal adenocarcinoma. Dose color wash with CTV_4500 (*red*), bladder (*yellow*), and bowel (*brown*) contoured

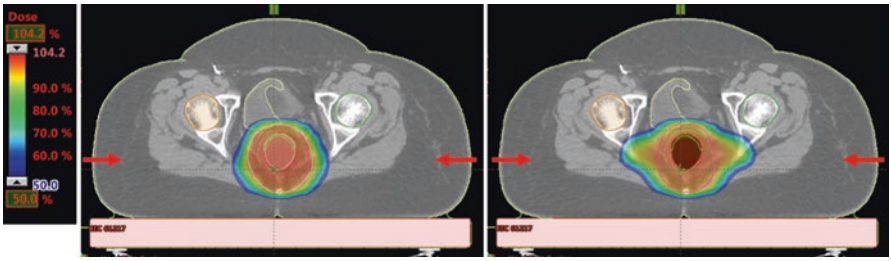

Fig. 16.3 Effect of air in rectum on proton dose distribution. This patient with a rectal lymphoma has significant air in the rectum at the time of simulation treated with opposed lateral PBS beams (*red arrows*). The left panel shows the dose distribution when the air is overridden with tissue equivalent (assuming case of empty rectum). The right panel shows the dose distribution without overriding the air. Both dose color washes are set to 50% of the prescription dose. If posterior beams were used, the "overshoot" would have gone into the bladder instead of the muscle and fat

16.6 Anal Cancer

Special consideration is given to treatment of anal SCC compared to rectal adenocarcinoma. The concurrent chemotherapy is more aggressive, the treatment volumes are larger and more complex, and skin toxicity is a much more significant issue. These clinical considerations are reflected in the more complex technical requirements for anal SCC proton therapy.

16.6.1 Simulation, Target Delineation, Organ at Risk Delineation, and Radiation Dose/Fractionation

- Given the complexity of the treatment volume in anal cancer compared to rectal cancer, CT simulation generally should be performed supine with a comfortably full bladder.
- MRI is helpful for accurate delineation of the extent of anal tumor and involved lymph nodes. PET may also be helpful in identification of involved nodal areas and primary tumor segmentation.
- As in rectal cancer, the GTV and involved nodes should be defined using all imaging modalities, and these should be registered to planning CT for accurate delineation. A further isotropic margin of at least 2 cm should be added to GTV, depending on tumor stage, while respecting anatomical boundaries. Attention must be given, especially for anal verge and perianal lesions, that a 2-cm radial and caudal margin is used to ensure coverage of perianal skin.
- The CTV (elective nodal area) should include inguinal lymph nodes, external and internal iliac lymph nodes, obturator, mesorectal, and presacral space. If appropriate, ischiorectal fossa should be included. The AGITG consensus atlas [20] and the Radiation Therapy Oncology Group (RTOG) elective nodal anorectal atlas [18] are both excellent resources.

– The PTV should be created from CTV as above, but with the larger, more complex target volume, larger expansions may be considered for anal CTV.
– Organs at risk (OAR) is segmented as in rectal cancer with the following additions:
  Due to the myelotoxic concurrent chemotherapy agents used in anal cancer, the total pelvic bone marrow—composed of iliac, lower pelvic, and lumbosacral subdivisions—should be outlined as described by Mell et al. [21].
  In addition, careful attention should be paid to skin dose in anal cancer as radiation dermatitis may be a limiting toxicity for timely completion of therapy. We also use an avoidance structure called "perineal skin" to limit excessive dose to sensitive regions.
  The recommended dosing and fractionation vary depending on the clinical scenario: tumor stage, whether an excisional biopsy has been performed, and the use of a simultaneous integrated boost technique vs sequential boost technique (Table 16.1).

The use of concurrent chemotherapy is standard of care; unless there are medical contraindications to systemic treatment when a higher radiation dose could be considered.

16.6.2 Patient Positioning, Immobilization, and Treatment Verification

Setup accuracy should ideally be ascertained with daily orthogonal X-ray imaging matched to the bony pelvis or volumetric imaging, if available. For advanced stage with bulky disease (primary or lymph nodes), imaging and clinical examination should be considered during the course of treatment (every 1 or 2 weeks) to assess for potential changes in anatomy, as they could have potential impact in dose distribution. Additionally, weight should be monitored as weight loss could lead to overshooting target volumes using proton therapy.

Table 16.1 Recommended radiation doses

Stage	Technique	Elective nodal dose	GTV dose
T1 and non-bulky T2	SIB	42Gy(RBE) in 28F	50.4 Gy(RBE) in 28F
Bulky T2, T3 and T4	SIB	45 Gy(RBE)	54 Gy(RBE) in 30F
Involved nodes	SIB	n/a	50.4–54 Gy(RBE)
Any	Sequential	30–36 Gy(RBE)	Boost to macroscopic 50.4–60 Gy (RBE)

16.7 3D Proton Passive Scattering vs Pencil Beam Scanning Planning

16.7.1 Passive Scattering

There are no reports using PS for anal cancer, therefore principles for treatment of the pelvis (gynecologic, prostate) could be applied. The target volumes for anal cancer are complex compared to rectal cancer since the inguinal nodes are included. Generally, matched fields would be required. Care should be taken to avoid placing match lines on organs at risk (OARs) and any colostomy. Match line feathering can be utilized to reduce excessive hot spots at the match line level.

16.7.2 Pencil Beam Scanning

PBS plans can consist of left- and right-posterior oblique fields to cover volumes encompassing the primary tumor, pelvic nodes, and inguinal nodes [22]. Figure 16.4 shows a plan using right- and left-posterior oblique SFUD (single-field uniform dose or single-field optimization (SFO)) fields in a woman. Of note, a vaginal cylinder was used to maximize sparing of at least the anterior vaginal wall. If a sequential cone down is used for the primary tumor, skin sparing can be

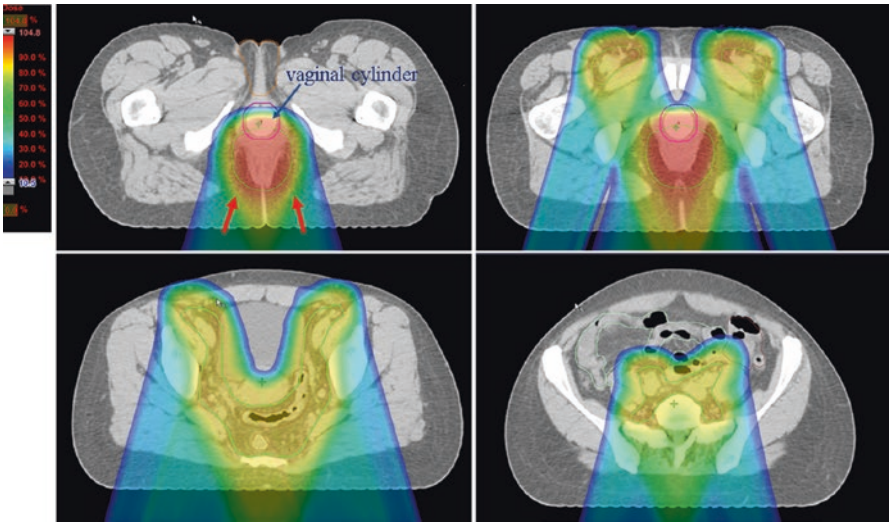

Fig. 16.4 Pencil beam scanning plan using posterior oblique (*red arrows*) SFUD fields for anal cancer. Several axial slices are shown with dose color wash for the initial fields treated to 42 Gy and 50.4 Gy with a simultaneous infield boost. The CTV_4200 (*green contour*) is shown as well as the small bowel (*light green*), large bowel (*brown*), external genitalia (*orange*), and vagina (*pink*). A vaginal cylinder was inserted at the time of simulation and for daily treatments in an effort to spare concentric dose to the entire vagina

achieved using opposed lateral beams. Plans can be optimized using the SFUD technique, allowing each field to uniformly cover the target in order to increase plan robustness.

Alternately, posterior and anterior SFUD fields can be used with an internal "gradient match" where the external iliac volume connects the inguinal nodes and the internal iliac nodes. This fields matching method using volumetric gradient dose optimization (GDO) has been routinely used on craniospinal irradiation for proton PBS technique without match line changes [23]. The GDO involves the use of multiple fields such that in the overlapped junction area, the dose contribution decreases in one field, while this decrease is compensated by increasing dose contribution from the adjacent field. Challenges still exist for opposing beam sets due to the fact of range uncertainties of proton therapy. Cold-dose buffer in the junction has to be deliberately created to prevent potential overlaps between beam sets. To investigate the worst case scenario, often the robustness of the plan is studied by manually introducing setup and range uncertainties. Although this technique may be more sensitive to changes in body weight and position, it can help with challenging volumes, such as a hip replacement as shown in Fig. 16.5.

16.7.3 Dosimetric and Toxicity Comparison

To date there are no data regarding outcomes of patients with anal cancer treated with PT. There are two in silico modeling studies, Ojerholm et al. [22] and Anad et al. [25], reporting that PT offers significant reduction in doses to the small bowel, bladder, and genitalia when compared to seven field IMRT in eight cases [22] and volumetric arc therapy (VMAT) in eight cases [25]. This reduction is more substantial in doses <30 Gy across all organs. Furthermore both studies have shown significant reduction in the pelvic bone marrow dose of clinical relevance.

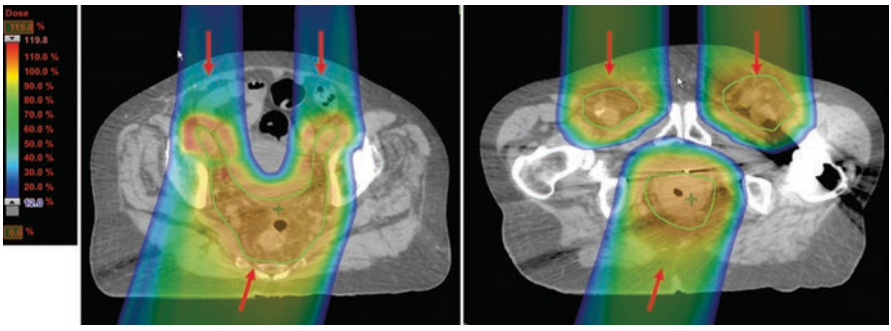

Fig. 16.5 Pencil beam scanning plan for a patient with hip replacement using GDO for anterior and posterior matched fields (*red arrows*). CTV is shown in light green contour

Table 16.2 Recommended dose constraints to organs at risk when using proton beam therapy anal cancer are listed

Organ at risk	Recommended dose constraint
Small bowel	Max dose 54 Gy 120 cc < 15 Gy
Bladder	50% < 35 Gy 35% < 40 Gy 5% < 50 Gy
Femoral heads	Max dose = 50 Gy 50% < 30 Gy 35% < 40 Gy 5% < 44 Gy
Genitalia	50% < 20 Gy 35% < 30 Gy 5% < 40 Gy

These recommendations are adapted from RTOG 0529 protocol [24]. As additional data are accumulated, these constraints will continue to be refined. In clinical practice, the planner should make every effort to achieve the lowest dose possible for all normal tissues while maximizing coverage.

16.7.4 Future Developments

It is crucial that prospective data collection (in a trial or registry) of clinical toxicity and long-term PROMs are undertaken to aid establishing the benefit of protons. MGH currently is running a multi-institutional trial for anal cancer (NCT01858025) to determine the feasibility of PBS with concurrent 5-fluorouracil and mitomycin C. Proton radiotherapy will be considered feasible if grade 3+ skin toxicity seen on this protocol is less than 48% (reported grade 3+ dermatologic toxicity from RTOG 98–11).

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