Carcinoma of the Anal Canal

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13.1 Introduction

There will be an estimated 8200 cases of anal canal cancer in 2017 with an estimated 1100 deaths from the disease [1]. Although uncommon, the relative incidence of anal cancer has been increasing over the last 20 years, largely due to infection by the human papillomavirus (HPV) [2]. Historically, the treatment of squamous cell carcinoma of the anal canal has been surgery with abdominoperineal resection (APR). This produced overall survival rates of approximately 50%, but resulted in a permanent colostomy and high locoregional recurrence [3, 4]. In an effort to improve these results, Nigro and colleagues, over three decades ago, pioneered a preoperative regimen combining pelvic radiation therapy and chemotherapy with 5-fluorouracil (5-FU, 25 mg/kg continuous infusion [CI]) and mitomycin (MMC, 0.5 mg/kg bolus) [5]. Radiation was prescribed to 30 Gy in 15 fractions and calculated at the central axis mid-plane. Treatment was delivered using anterior and posterior opposed fields to the true pelvis and inguinal lymphatics. Surgery followed chemoradiation 4–6 weeks later. In a report of their first 28 patients treated with this combined modality approach, 26 patients underwent either APR or local excision following chemoradiation [6]. Eighty percent of patients were found to have pathologic complete response. In a subsequent series of 38 patients treated with chemoradiation alone as definitive therapy, an 84% clinical complete response rate was achieved [5]. Following these promising results, randomized clinical trials have sought to validate sphincter-preserving chemoradiation as the primary treatment for anal cancer.

13.1.1 Combined Modality Therapy

The Nigro regimen was empirically derived. As such, subsequent clinical trials have critically examined components of this regimen. The question of the relative benefit of chemoradiation compared to radiation alone was assessed in two separate studies: the European Organization for Research and Treatment of Cancer (EORTC) 22861 trial and the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) ACT I trial [7, 8]. In the EORTC trial, 110 patients from 1987–1994 were randomized between radiation alone or radiation with 5-FU (750 mg/m^2 CI days 1–5 and days 29–33) and MMC (15 mg/m^2 bolus on day 1). Inclusion criteria encompassed T3-T4 primary or any tumor stage with node-positive disease. Pelvic radiation was delivered using a 3 or 4 field technique to 45 Gy in 25 fractions followed by a 6-week rest period. Patients then underwent a boost of 15 Gy if achieving a complete clinical response or 20 Gy if achieving a partial response, which was delivered by electrons, photons, or iridium 192 implant. Compared to radiation alone, combined modality treatment led to an improvement in clinical complete response (80% vs. 54%), 5-year local control (68% vs. 50%, $P = 0.02$), and 5-year colostomy-free survival (72% vs. 40%, $P = 0.02$) [8]. The overall survival for the entire cohort was 56% with no difference between the two arms, likely due to patients undergoing successful salvage APR.

In a similar design, the UK ACT I trial accrued 585 patients (51% clinical T3 disease, 20% positive nodes) between 1987 and 1994 to radiation alone or radiation with 5-FU (750–1000 mg/m^2 CI days 1–5 and days 29–33) and MMC (12 mg/m^2 bolus on day 1). Radiation was prescribed to 45 Gy using anterior (AP) and posterior (PA) opposed fields followed by a 6-week rest period. Patients with less than a 50% clinical response underwent surgical resection. Patients with more than a 50% clinical response received a boost of 15–25 Gy delivered by electrons, photons, or an iridium implant [8]. Six weeks after completion of the primary radiation treatment, there were comparable rates of patients with greater than 50% response (92% in both arms). Early morbidity, including hematologic, skin, gastrointestinal, and genitourinary toxicity, was significantly worse with the addition of chemotherapy (48%) vs. radiation alone (39%), $P = 0.03$. With a median follow-up of 13 years, patients in the combined modality arm had lower rates of local failure (32% vs. 57%, $P < 0.001$) without improvements in overall survival (53% vs. 58%, $P = 0.12$). However, there was an increased rate of anal cancer-specific survival in patients receiving combined modality therapy compared to radiation alone (70% vs. 58%, $P = 0.004$). Late morbidity did not differ between concurrent therapy and radiation alone (42% vs. 38%, $P = 0.39$).

13.1.2 Evaluating the Benefit of Mitomycin and Additional Chemotherapy

Despite the benefits of combined modality therapy observed in the UK ACT I and EORTC trials, the acute toxicity was significant. In the UK ACT I trial, six patients died of chemotherapy-related hematologic toxicity [7]. The U.S. Intergroup (Radiation Therapy Oncology Group [RTOG] 8704/Eastern Cooperative Oncology Group [ECOG] 1289) trial directly evaluated whether MMC was an essential component of combined modality therapy [9]. Between 1988 and 1991, 310 patients were randomized to radiation therapy with 5-FU (1000 mg/m^2 CI days 1–4 and days 28–31) or radiation with 5-FU (same regimen) and MMC (10 mg/m^2 bolus on days 1 and 28). Any tumor or nodal stage was allowed to enroll, with 85% of patients having T2-T4 disease and 17% clinically node-positive. Radiation was delivered using large anterior and posterior opposed fields to 45 Gy in 25 fractions with shrinking AP-PA fields after 30.6 Gy. Patients received an additional 5.4 Gy boost for persistently palpable tumor. At 4 years, patients receiving 5-FU and MMC experienced a lower colostomy rate (9% vs. 22%, $P = 0.002$) and higher disease-free survival (73% vs. 51%, $P = 0.0003$). There was no statistical difference in overall survival in the 5-FU/MMC arm compared to 5-FU alone (76% vs. 67%, $P = 0.31$). Despite improvements in disease-specific outcomes, toxicity was increased in the MMC arm with 23% of patients experiencing a grade 4 or 5 toxicity compared to 7% of patients receiving 5-FU alone ($P < 0.001$).

The RTOG 9811 trial also evaluated whether MMC could be eliminated from the standard chemoradiation backbone. Rather than a direct substitution of MMC, the trial evaluated whether two cycles of induction cisplatin/5-FU followed by

cisplatin/5-FU-based chemoradiation would offer improved disease-free survival compared to the standard regimen of chemoradiation with mitomycin/5-FU [10, 11]. From 1998–2005, 682 patients were randomized among the two arms. Inclusion criteria comprised T2-T4 primaries of any nodal status, with 35% having T3-T4 primary disease and 26% being node-positive. The control arm was treated akin to the 5-FU and MMC arm from RTOG 8704. The experimental arm included two cycles of induction chemotherapy using CI 5-FU 1000 mg/m^2/day days 1–4, 29–32, 57–60, and 85–88 with bolus cisplatin 75 mg/m^2 on days 1, 29, 57, and 84, and then a substitution of bolus cisplatin instead of MMC during chemoradiation. For both arms, radiation was administered as 45 Gy in 25 fractions with AP-PA or multiple field techniques. The initial fields encompassed the pelvis (mesorectum/iliacs), anus, presacral region, and inguinal nodes with the superior border at L5-S1 and inferiorly 2.5 cm below the anus and tumor. After 30.6 Gy, the superior border was reduced to the bottom of the sacroiliac joints and the pelvis was boosted to 45 Gy. For patients with T3-T4 primaries, positive inguinal nodes, or T2 with residual disease, an additional radiation boost of 10–14 Gy at 2 Gy/fraction was delivered. In contrast to the prior randomized trials discussed, there was no planned radiation break between the pelvic 45 Gy and the tumor boost. Although the initial report observed no difference in the primary endpoint of disease-free survival, three-year colostomy rates were significantly worse with cisplatin (10% vs. 16%, $P = 0.02$) [11]. There was also no difference in acute grade 3–4 non-hematologic side effects between the arms (74% for both arms), although acute grade 3–4 hematologic toxicity was significantly worse with MMC (62% vs. 42%, $P < 0.001$). In the 5-year update, cisplatin was found to be detrimental in terms disease-free survival (68% vs. 58%, $P = 0.006$), overall survival (78% vs. 71%, $P = 0.026$), and colostomy-free survival (72% vs. 65%, $P = 0.05$) [10]. Differences in locoregional failure (20% vs. 26%, $P = 0.087$) and colostomy rates (12% vs. 17%, $P = 0.074$) did not reach statistical significance. Late grade 3 and 4 side effect rates were comparable over time (13% MMC vs. 11% cisplatin, $P = 0.35$). As such, chemoradiation with concurrent 5-FU and MMC remains the standard of care in the United States.

The UK ACT II trial evaluated a more direct comparison of whether MMC could be substituted for cisplatin during chemoradiation with a primary endpoint of clinical complete response at 26 weeks, as well as whether maintenance chemotherapy with cisplatin would improve progression-free survival beyond chemoradiation alone [12]. Between 2001-2008, 940 patients were randomized to radiation with 5-FU (1000 mg/m^2/day CI days 1–4 and 29–32) and MMC (12 mg/m^2 bolus on day 1), or radiation with 5-FU and cisplatin (60 mg/m^2 bolus on days 1 and 29). In a 2 × 2 factorial design, a second randomization evaluated the benefit of adjuvant 5-FU/cisplatin chemotherapy (an additional two cycles of 5-FU days 71–74 and 92–95 and cisplatin days 71 and 92). T3-T4 primaries made up 46% of patients and 32% had involved nodes. Radiation was prescribed to 50.4 Gy using an AP/PA filed design, with a field reduction at 30.6 Gy. Treatment was given continuously without a planned break, in contrast to the UK ACT I trial. The cisplatin and MMC arms demonstrated similar rates of clinical complete response at 26 weeks (89.6% vs. 90.5%, $P = 0.64$). With a median follow-up of 5 years, there also was no difference

in progression-free survival by maintenance (74%) vs. no maintenance (73%), $P = 0.7$. The rates of any grade 3 or 4 toxicities were similar in both the MMC and cisplatin arms (72 vs 73%), but the MMC arm had higher rates of grade 3 or 4 hematologic toxicity (26% vs. 16%, $P < 0.001$). The authors concluded that 5-FU/MMC-based chemoradiation remains the standard of care due to fewer cycles of chemotherapy, similar toxic effects, fewer non-chemotherapy drugs, less infusion time, and lower costs. However, cisplatin-based chemotherapy may be considered as an alternative regimen in patients who would not tolerate the hematologic toxicity associated with MMC.

In contrast to RTOG 9811, the UK ACT II trial did not include induction chemotherapy within the cisplatin containing arm. One hypothesis regarding the inferiority of the cisplatin regimen in RTOG 9811 is that the overall treatment time was extended in this arm, potentially leading to accelerated repopulation and inferior oncologic outcomes. In a pooled analysis from RTOG 8704 and RTOG 9811, the overall treatment time had a detrimental effect on local failure and colostomy-free survival. Patients with overall treatment times greater than 53 days had nearly a two times higher risk of local failure compared to patients with treatment times less than 53 days (HR = 1.86, 95% CI 1.31–2.64, $P = 0.0006$) [13]. Retrospective studies have also observed similar detrimental effects from prolonged treatment time [12, 14].

13.2 Radiation Treatment Approaches

The existing randomized controlled trial data previously discussed all utilized older 2-dimensional or 3-dimensional conformal RT (3D-CRT) techniques. In either approach, orthogonal beams of radiation covering the gross tumor and pelvic and inguinal nodal regions generally use an AP/PA field arrangement that indiscriminately delivers homogeneous high doses of radiation to large volumes of normal surrounding bowel, bone, bladder, genitalia, and skin, leading to treatment-associated morbidity. In 2D planning, the design of the radiation field borders and blocking of normal organs are based on known correlations between bony anatomy and the tumor and nodal targets. The surrounding adjacent normal tissues cannot be spared, limiting the radiation dose that can be safely administered. 3D-CRT techniques utilize an initial CT simulation of the patient in the treatment position (discussed later in this chapter); yet, the degree of planning can vary widely. For example, some radiation oncologists use a 3D approach to have confidence that the tumor volume is accurately covered by the radiation fields. Gross tumor volume is contoured on each CT slice, but the fields and blocks may still be based on bony landmarks akin to the 2D technique. However, with a more optimal 3D approach, one could also contour the clinical target volume (gross tumor volume and draining nodal regions) and the normal organs on each CT slice. Radiation dose is prescribed to the target volume, and dose constraints are placed on normal tissues. Treatment accuracy, delivery, and dose quantification with a highly conformal 3D-CRT approach are superior to the 2D technique, but even with an excellent 3D plan,

adjacent normal tissues cannot be adequately spared, as these techniques use uniform, static fields for radiation therapy delivery.

Since there is inherent difficulty in sparing the critical surrounding tissue with 2D or 3D radiation delivery techniques, chemoradiation is associated with significant acute toxicity including hematologic, dermatologic, and gastrointestinal. In RTOG 9811, the rate of acute non-hematologic grade 3 or 4 toxicity was 74% in both the MMC and cisplatin groups, with a rate of grade 3 or 4 hematologic toxicity of 62% in the standard 5-FU/MMC arm [11]. In the UK ACT II trial, rates of grade 3 or 4 non-hematologic toxicity were 62% in the 5-FU/MMC arm, with a rate of grade 3 or 4 hematologic toxicity of 26% (of note, only one dose of MMC day 1 is administered in the UK in contrast to two doses given days 1 and 28 in the US) [12].

13.2.1 3D-CRT Technique

3D-CRT uses a sequential cone down technique with an AP/PA or 4-field arrangement [11]. Initial pelvic fields are treated to 30.6 Gy at 1.8 Gy per fraction from the L5/S1 interspace to at least 2.5 cm inferior to the anal tumor or bottom of the anal canal. The lateral borders of the AP fields include the inguinal lymph nodal compartments. At 30.6 Gy, the superior border is reduced to the greater sciatic notch for an additional 14.4 Gy to a total dose of 45 Gy at 1.8 Gy per fraction. Subsequently, the primary tumor is treated with a 2–2.5 cm margin for the final boost to a total of 54–59 Gy. Grossly involved pelvic lymph nodes are also included in the final boost phase if small bowel could be sufficiently avoided. For a 4-field technique, the inguinal lymph nodes are included in the AP and lateral fields, but not the PA field to allow femoral head sparing. Anterior electron fields matched to the exit of the PA fields provide additional dose to supplement the inguinal lymph node targets. For involved inguinal lymph nodes, the entire inguinal space is treated to 45 Gy with a boost to 54–59 Gy to the gross disease. Representative 3D-Conformal fields are illustrated in Fig. 13.1.

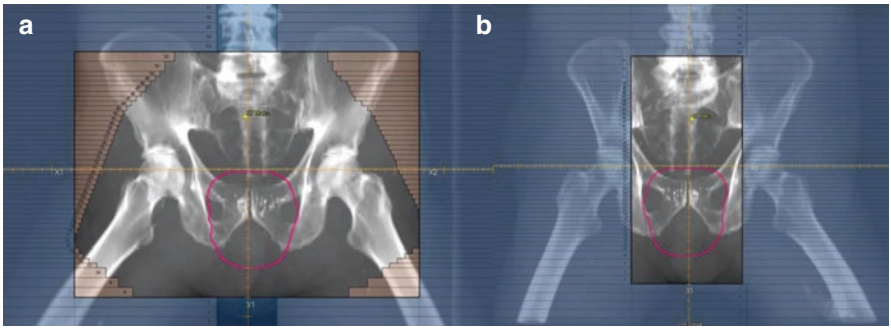

Fig. 13.1 3D-Conformal technique using AP (**a**) and PA (**b**) fields. The PA field is reduced laterally to spare the femoral heads. Additional dose is provided to the inguinal lymph nodes with electrons

13.2.2 The Potential of Intensity-Modulated Radiation Therapy

Intensity-modulated radiotherapy (IMRT) is a form of advanced, photon-based therapy that uses inverse planning with a computer-optimized algorithm to create radiation-beam characteristics to meet stringent tumor and target volume coverage directives and normal tissue constraints. The IMRT plan conforms the radiation dose to the tumor and target volumes with a steep dose gradient, allowing for decreased radiation dose to the surrounding normal organs. Thus, IMRT has the potential to reduce the acute and late toxicities from 5-FU/MMC chemoradiation for anal canal cancer. In turn, the use of IMRT may also reduce treatment breaks that negatively influence outcomes and allow for radiation dose escalation in trials for high-risk, locally advanced patients. In contrast to the 2–4 fields used for 2D or 3D-CRT radiation delivery, IMRT allows for the modulation of radiation intensity and often relies on nine or more radiation fields. IMRT can be dynamic, in which collimating leaves move across an active radiation field, or step-and-shoot, in which leaves sculpt the field shape while the beam is off. More recently, volumetric-modulated arc therapy (VMAT) has been utilized, in which intensity-modulated techniques are performed in the setting of continuous gantry rotation.

13.2.3 Clinical Experience Using Intensity-Modulated Radiation Therapy

Retrospective dosimetric comparative studies assessing 3D-CRT compared to IMRT have all demonstrated a reduction in radiation dose to the normal organs at risk. Compared to traditional techniques, IMRT reduces dose to the small bowel, genitalia, and bladder [14, 15]. Early experiences with IMRT appear to achieve similar local control and improved toxicity compared to historical experiences [15, 16]. In the first multicenter trial assessing the use of IMRT for anal cancer, Salama and colleagues reported their retrospective experience of 53 patients who underwent IMRT with concurrent 5-FU and MMC [15]. Patients treated at the University of Chicago received 45 Gy in 1.8 Gy fractions to nodal regions at risk and to gross disease followed by a sequential IMRT boost plan to 54 Gy to gross disease. A separate cohort from the Mayo Clinic was treated using a simultaneous integrated boost technique to three different target dose levels (50 Gy, 45 Gy, and 41.25 Gy) in 25 fractions. The rate of grade 3 or higher gastrointestinal (GI) and dermatologic toxicity was 15% and 38%, respectively. Eighteen-month colostomy-free survival, overall survival, and freedom from local failure were 84%, 93%, and 84%, respectively. These data suggested improved treatment tolerance with IMRT and similar efficacy when compared to the 5-FU and MMC arm of RTOG 9811.

Kachnic et al. reported their results of 43 patients treated with a single phase dose-painting static IMRT technique [16]. In this multi-institutional retrospective review, the prescription dose varied depending on the stage of the disease. In patients with T2N0 cancer, the primary tumor received 50.4 Gy in 1.8 Gy per

fraction, and the elective nodal planning target volume (PTV) was treated to 42 Gy in 1.5 Gy per fraction. For patients with T3/T4 N0-3 disease, the primary tumor received 54 Gy in 1.8 Gy per fraction, and the elective nodal PTV received 45 Gy in 1.5 Gy per fraction. IMRT was delivered with 8–10 static fields. Grade 3 or higher skin toxicity was observed in 10% of patients, while grade 3 or higher GI toxicity was noted in 7% of patients. These toxicity rates compared favorably to those observed in the standard 5-FU/MMC arm of RTOG 9811 (49% grade 3 or higher dermatologic events and 36% grade 3 or higher GI toxicity). Two-year local control, overall survival, colostomy-free survival, and metastasis-free survival were 95%, 94%, 90%, and 92%, respectively. The proportion of patients requiring a treatment break was 40%, which was similar to the IMRT series by Salama and colleagues in which 42% of patients required a treatment break. Both IMRT studies observed reduced rates of treatment breaks compared to the 62% of patients who required a break in the standard 5-FU/MMC arm of RTOG 9811 [11, 15, 16].

RTOG 0529 is the only prospective trial for the use of IMRT in patients with squamous cell carcinoma of the anal canal [17]. The rationale for this phase II trial was to evaluate whether reduced dose to the organs at risk with IMRT could result in a reduction in acute toxicity. The primary end point of the study was grade 2 or higher GI or genitourinary (GU) events as compared to historical controls on the standard arm of RTOG 9811. A total of 52 patients were evaluable on the trial. Eligible patients included patients with T2-T4 disease with any N category. Treatment was provided using a dose-painting technique with differential prescriptions based on the tumor stage. Similar to the series by Kachnic and colleagues above, patients with T2N0 disease received 50.4 Gy to the primary tumor and 42 Gy to the elective nodal volumes in 28 fractions. Patients with T3/T4N0-3 disease received 54 Gy to the primary site and 45 Gy to the elective nodal volume in 30 fractions. Involved lymph nodes were treated to 54 Gy if greater than 3 cm or 50.4 Gy if less than or equal to 3 cm in 30 fractions. All patients received 5-FU (1000 mg/m^2/day, 96 h CI) and MMC (10 mg/m^2 IV bolus) days 1 and 29. Compared to the historical control arm from RTOG 9811, there were no differences in grade 2 or higher GI/GU morbidity (77% vs. 77%, $P = 0.50$). However, in the patients treated with IMRT, there was a significant reduction in combined grade 3 or higher GI events (21% vs. 36%, $P = 0.0052$), grade 3 or higher dermatologic toxicity (23% vs. 49%, $P = 0.0052$), and grade 2 or higher hematologic events (73% vs. 85%, $P = 0.032$). In addition, treatment breaks due to toxicity were needed in 49% of IMRT-treated patients compared with 62% on the 5-FU/MMC arm of 9811 ($P = 0.09$), with a median duration of radiotherapy of 42.5 days (range: 32–59) using IMRT, compared with 49 days (range: 0–102) on RTOG 9811 ($P < 0.0001$). A recent update of this study showed that this IMRT approach

Table 13.1 Grade 3+ acute toxicity sparing with IMRT

Series	Patient #	Hematologic (%)	Dermatologic (%)	Gastrointestinal (%)	Genitourinary
RTOG 9811 [11] 5-FU/MMC	325	62	4	36	3%
RTOG 0529 [17]	52	58	23	21	2%
Salama [15]	53	59	38	15	0%
Defoe [18]	78	13	29	18	NR
Kachnic [16]	43	51	10	7	7%
Chuong [19]	52	29	12	10	0%
Han [20]	58	41	46	9	0%
Franco [21]	54	17	13	8	2%
Call [22]	152	41	20	11	0%

also yielded similar 2-year disease-related outcomes compared with the 5-FU/MMC arm of RTOG 9811 [22]. Table 13.1 reviews the grade 3 and higher acute toxicity rates of the 5-FU/MMC arm of RTOG 9811 [11] as compared to several IMRT series [15, 16, 18–22] and RTOG 0529 [17]. Collectively, with the reduction in GI and dermatologic acute adverse events, improved treatment tolerance, and similar outcomes, IMRT-based chemoradiation has become the standard of care in the definitive treatment of anal cancer [23].

13.2.4 Proton Therapy

There is emerging interest in the use of intensity-modulated proton therapy (IMPT) for treatment of anal cancer. Dosimetric studies have shown reduced dose to bowel, bladder, genitalia, and bone marrow with IMPT as compared to IMRT, with preserved PTV coverage [34, 35]. With use of IMPT, a common approach is a 3-field Multi Field Optimized (MFO) split target technique. A posterior field is used to cover the primary tumor and posterior pelvic lymph nodes. Two anterior oblique fields are used to cover the inguinal lymph nodes and anterior pelvic lymph nodes. Given the limited number of beam paths and reduced exit dose with proton therapy, this technique allows for sparing of the anterior structures (bowel/bladder) and lateral pelvic bone structures without compromise in the PTV coverage. Representative IMPT and IMRT plans are shown in Fig. 13.2. The feasibility of pencil beam scanning proton therapy techniques for anal cancer is the subject of ongoing trials (NCT03018418, NCT01858025).

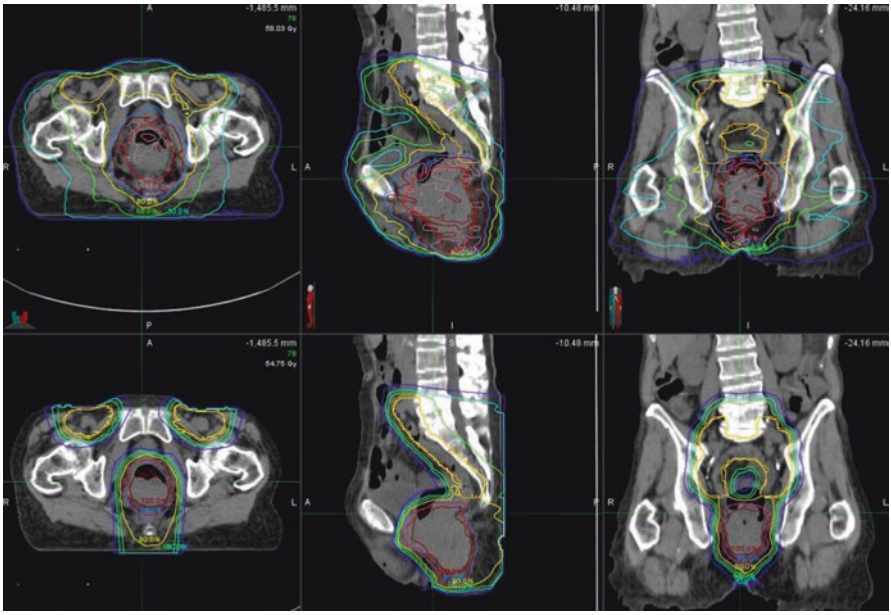

Fig. 13.2 Representative comparison plans and isodose distributions for IMRT (*top*) and IMPT (*bottom*)

13.3 IMRT Planning

13.3.1 Considerations in Work-Up Prior to Planning

It is important to consider the cause of the anal cancer. Order HIV testing (in patients with established risk factors) and obtain p16 expression on anal pathology (if an HPV panel was not already performed). If the patient does have a history of high-risk HPV infection in the anus, it is important to then consider evaluation of the cervix, vulva, or penis to rule out any synchronous disease before proceeding with standard IMRT contouring. Local extent of disease is evaluated with physical examination, which typically includes anoscopy for enhanced visualization and histological confirmation. Evaluation for distant metastatic disease and locoregional inguinal and pelvic lymph node involvement require radiographic imaging. Contrasted CT imaging is routinely used for this purpose, but is considered inferior to physical examination for evaluation of primary anal tumors. MRI may be useful in certain cases for further characterization of primary tumors, especially when local invasion is suspected, but in general has not been demonstrated

Table 13.2 AJCC nodal staging for anal cancer, eighth edition (2016)

Regional LYMPH nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

additional benefit over the use of CT for routine staging of anal cancer. Positron emission tomography (PET) and PET-CT are now routinely integrated into the staging algorithm for patients. PET-CT appears to have a higher sensitivity than conventional imaging (CT and/or magnetic resonance imaging [MRI]) for detecting regional lymph node metastases, and as such, has been found to change IMRT dose-painting design [24].

It is also important to note that there are changes to the new 2016 edition of the American Joint Commission on Cancer (AJCC) staging system. The major change in this Eighth Edition is a revision of the nodal staging [25]. Based on the recent analysis of the impact of TN category of disease on the outcomes of RTOG 9811, there were no notable outcome differences beyond nodal positivity [26]. The location or amount of lymph node disease was not prognostic. Thus, patients should now be staged as N0 or N1, and the N1 category is further subdivided by the nodal regions involved, Table 13.2.

Lastly, although wide local excision is not considered standard in the treatment of anal canal cancer, it is sometimes performed in the initial evaluation or management of early stage small tumors without evidence of anal sphincter or nodal involvement. Even with adequate staging, the risk of recurrence remains high enough following local excision to warrant definitive chemoradiation, which is considered the standard of care for the treatment of carcinoma of the anal canal.

13.3.2 CT Simulation Techniques

Patients may undergo CT simulation in a supine/frog leg position or a prone position on a bowel displacement device (“belly board”). Advantages of supine position include allowing for a frog leg position and direct visualization of the inguinal lymph node targets. Prone position with use of a belly board may be particularly advantageous for patients with a larger body habitus to improve small bowel sparing

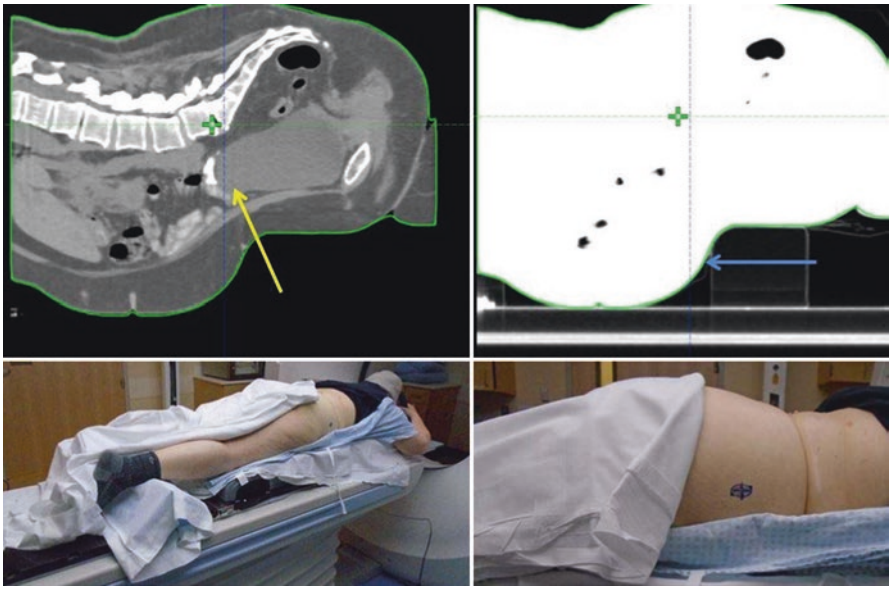

Fig. 13.3 Prone CT simulation using a belly board. *Blue arrow* delineates the gap in the prone belly board that allows for geometric displacement of small bowel. *Yellow arrow* shows that bladder filling may provide additional small bowel displacement

(Fig. 13.3). At the time of simulation, visible disease should be noted and marked with a radiopaque wire to ensure adequate dose coverage (Fig. 13.4). Placement of a radiopaque anal marker may also be useful to determine the distance of the disease from the verge for contouring purposes. Use of bolus may be required to achieve adequate dose coverage for patients with superficial tumors extending outside of the verge (Fig. 13.4). Oral contrast is given approximately 30 min prior to simulation for better small bowel visualization. Intravenous contrast may be useful in visualizing and contouring the elective nodal vessels, particularly in patients who are thin; however, more commonly, these authors utilize fusion with the patient's CT with contrast staging study if needed. For additional small bowel sparing, bladder filling may also be utilized, but remember to reproduce filling prior to each treatment (Fig. 13.3). Once the patient is appropriately positioned, CT images at 3 mm intervals from the upper lumbar spine to the mid-femur) should be obtained.

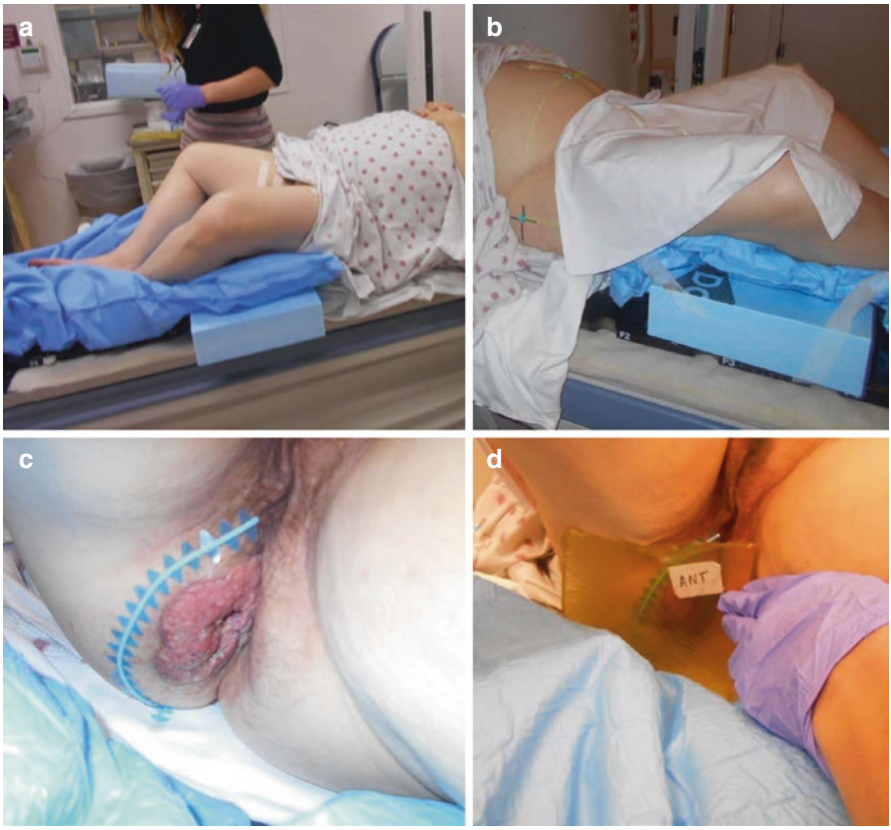

Fig. 13.4 Supine CT simulation for a patient with extension of the anal canal tumor outside of the verge onto skin. The patient underwent simulation in the frog leg position. The gross tumor outside of the verge was marked with a wire (2c), and bolus was applied (2d) for daily treatments

13.3.3 Importance of Accurate Target Delineation

Careful attention to target delineation (including gross disease, elective nodal volume, and normal structures) is essential for conformal treatment of anal cancer, respective of the treatment technique employed. The RTOG 0529 trial of IMRT included prospective radiation planning quality assurance as a component of the trial. A review of the quality assurance data revealed that 81% of cases required plan revisions prior to treatment; 46% required multiple revisions, and four plans did not pass. Reasons for not passing included incorrect contouring of gross tumor (21%), miscontouring of elective nodal volumes (mesorectum 55%, presacrum 43%, inguinal fossa 33%, iliac nodal groups 31%), and/or misidentification of normal structures (small bowel 60%, large bowel 45%) [21].

13.3.4 Target Volumes

According to the International Commission on Radiological Units 50 guidelines, all target and normal tissue structures are contoured on the planning CT slices. Multiple consensus atlases now exist from the RTOG, [27] Australasian Gastrointestinal Trial Group [28], and the United Kingdom [29] which illustrate target definitions with representative case examples. A detailed comparison of these atlases is reviewed in Table 13.3. For IMRT planning and delivery, the most common approach is the use of a dose-painting IMRT technique (as demonstrated in RTOG 0529) with simultaneous differential daily doses to the gross target volume (GTV) and the elective nodal volume. The total dose to the primary tumor as well as gross lymphadenopathy is determined by the maximum size of each respective target. The total elective nodal dose will vary depending on the prescription dose to the primary tumor using a simultaneous integrated boost technique. While we will review this dose-painted approach that is widely used in the Unites States, an initial IMRT comprehensive field followed by a sequential IMRT boost is also acceptable.

When contouring the GTV, one should use all available clinical and radiographic information including radiopaque wires/markers at the time of simulation. Endoscopy reports may also be helpful. Contouring of the GTV may be aided by registration of the diagnostic PET, PET-CT, or MRI in the treatment planning system. An MRI (T2-weighted sequences) may be particularly useful in patients with advanced disease with invasion of nearby organs (Fig. 13.5). Gross lymphadenopathy should be contoured and noted as separate structures when using an IMRT simultaneous integrated boost technique.

Construction of the clinical target volume (CTV) of the primary tumor is performed by an isotropic expansion of 1.5–2 cm from the GTV. The primary tumor CTV should include the entire GTV as well as the entire anal canal and anal sphincter muscles. This structure should be modified to account for the natural barriers of bone and muscle if the tumor does not involve these structures. An elective dose volume should be constructed that includes the primary and nodal CTVs as well as the entire mesorectum, internal iliac, external iliac, presacral, and bilateral inguinal lymph node regions. Common errors in contouring the elective nodal volume include failure to correctly contour the entire extent of the mesorectum as well as insufficient inguinal lymph node delineation. When contouring the inguinal lymph node region, a 5–7 mm isotropic expansion around the femoral vessels will *not* adequately cover the inguinal lymphatics at risk [30]. Instead, the entire inguinal compartment bounded by musculature should be contoured. Table 13.3 depicts the gross tumor and elective target delineations and prescription doses depicted in the three published IMRT atlases. Of note, these authors have slightly modified the RTOG 0529 anal primary CTV recommendations, and now use a 1.5–2.0 cm isotropic expansion with a 5 mm expansion for the PTV (provided that daily image guidance is used). Excellent definitions of elective nodal volume contouring may be found in the Australasian Gastrointestinal Trial Group [28]. In contouring of the normal pelvic organs at risk (OARs), the small bowel, left femoral head, right

Table 13.3 Target definitions and dose prescriptions from contemporary anal cancer atlases

	RTOG 0529/NRG oncology atlas [27]	Australasian gastrointestinal trials group atlas [28]	United Kingdom atlas [29]
Primary tumor GTV; GTVp Node-positive GTV; GTVn+	Use all clinical and imaging information; contoured separately	Use all clinical and imaging information	Use all clinical and imaging information
Primary tumor CTV; CTVp	2.5 cm isotropic expansion around anal primary GTV, modified to avoid overlap into natural barriers to tumor infiltration (non-target muscles or bone); includes the entire anal canal	Includes the GTV, entire anal canal from the anorectal junction to the anal verge, and the anal sphincters and an additional 2 cm isotropic expansion modified for anatomic boundaries	1.5 cm isotropic expansion of around anal primary GTV; manually enlarge to include anal canal from anorectal junction (4 cm from anal verge marker); include sphincters and exclude bone and muscle if free from tumor
Primary tumor PTV, PTVp	1.0 cm isotropic CTV expansion	1.0 cm isotropic CTV expansion 0.5–0.7 cm if daily image guidance	1.0 cm isotropic CTV expansion with daily image guidance
Primary tumor dose	Tumors > 5 cm (T3, T4) or any T, N positive—54 Gy at 1.8 Gy per fraction; PTVp_5400 Tumors < 5 cm (T2) and N negative—50.4 Gy at 1.8 per fraction; PTVp_5040	54 Gy at 1.8 Gy per fraction for most tumors; consider 50.4 Gy at 1.8 Gy per fraction for T1 or non-bulky T2 tumors	Tumors > 5 cm (T3, T4) or any T, N positive—53.2 Gy at 1.9 Gy per fraction Tumors < 5 cm (T1, T2) and N negative—50.4 Gy at 1.8 Gy per fraction
Gross nodal CTV; CTVn+	Gross lymph node +1 cm CTV avoiding non-target muscle/bone	Gross lymph node +1–2 cm CTV avoiding non-target muscle/bone	Gross lymph node +0.5 cm CTV avoiding non-target muscle/bone
Gross nodal PTV; PTVn+	1.0 cm isotropic CTV expansion	1.0 cm isotropic CTV expansion; 0.5–0.7 cm with daily image guidance	0.5 cm isotropic CTV expansion with daily image guidance
Gross nodal dose	50.4 Gy at 1.8 Gy per fraction if ≤3 cm; PTVn+_5040 54 Gy at 1.8 Gy per fraction if >3 cm; PTVn+_5400	50.4–54 Gy depending on size at 1.8 Gy per fraction	50.4 Gy at 1.8 Gy per fraction
Elective nodal dose	T2 N0: 42 Gy at 1.5 Gy per fraction; PTVn_4200 T3/T4 or N+: 45 Gy at 1.5 Gy per fraction; PTVn_4500	42 Gy at 1.5 Gy per fraction if primary dose is 50.4 Gy in 28 fractions 45 Gy at 1.5 Gy per fraction if primary dose is 54 Gy in 30 fractions	40 Gy at 1.43 Gy per fraction (28 fractions) for all patients

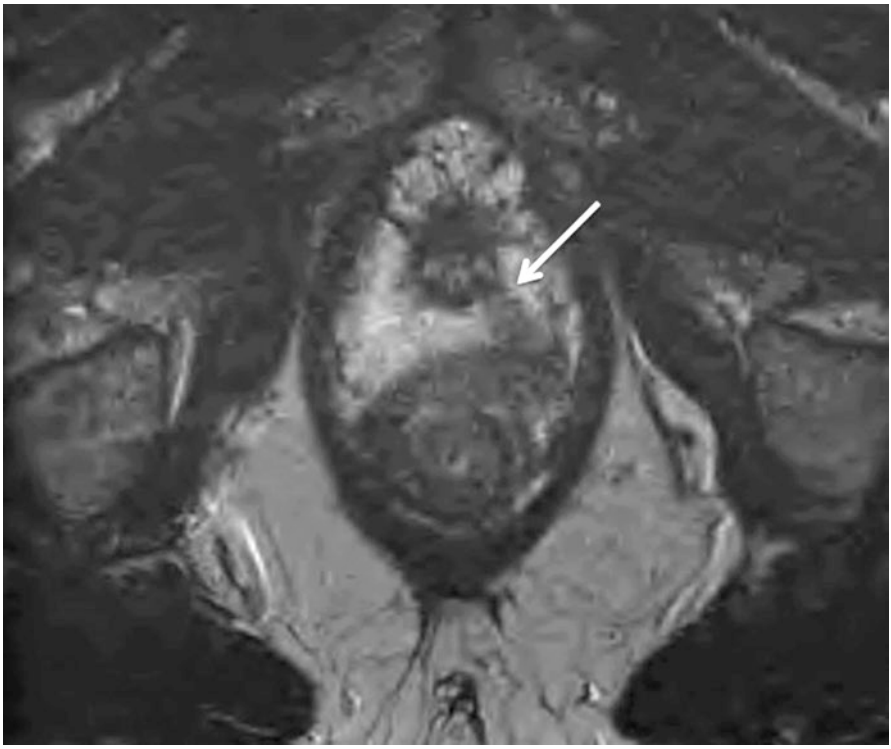

Fig. 13.5 Axial T2-weighted MRI image showing invasion of the anal canal cancer into the prostate with abutment of the urethra (*white arrow*) indicating T4 disease

femoral head, genitalia, bladder, pelvic bones, large bowel, and skin should all be outlined on each axial CT slice. The external contours of all pelvic bones, including iliacs, lumbosacral spine, and lower pelvic bones, should be contoured together as a surrogate for pelvic bone marrow. Bowel should be drawn as individual loops without the intertwining mesentery or as a bowel bag delineated from L4-5 down. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue. The RTOG atlas for normal pelvic tissues may be useful for contouring normal organs [31]. A representative IMRT plan and radiation targets are shown in Fig. 13.6.

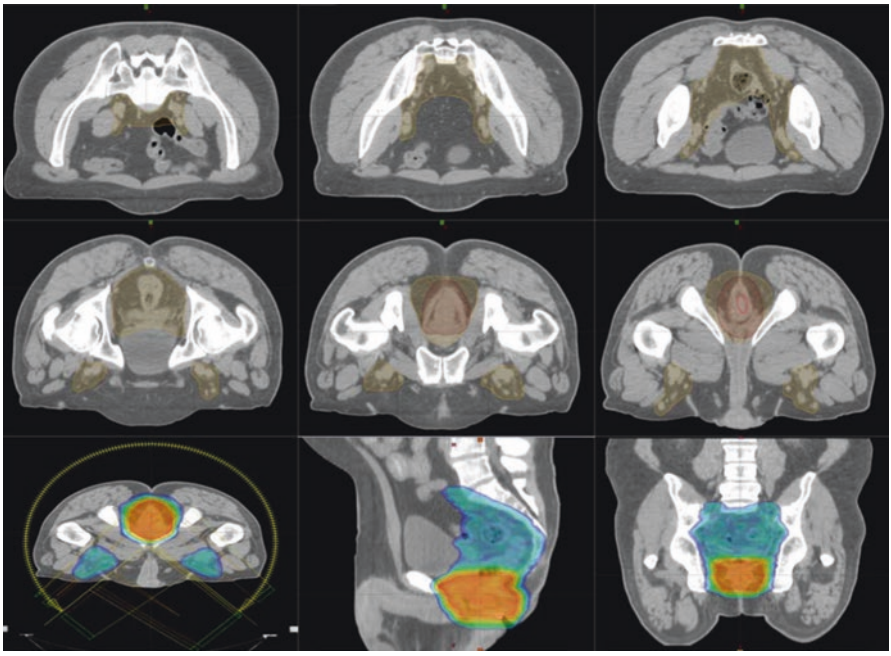

Fig. 13.6 Representative IMRT CTV contouring axial slices (GTVp_5040 in *red*; CTVn_4200 in *orange*) and treatment plan for a male patient with Stage II—T2N0M0 anal cancer. The patient was positioned prone on a bowel displacement device and treated with an IMRT plan using Volumetric Arc Therapy (VMAT). This VMAT plan utilized 10 MV beams and 270° arcs with gantry start/stop angles similar to those used with a 7-field IMRT technique in order to cover the anterior elective nodal volume and spare entrance dose to anterior organs at risk. The primary PTV (PTVp_5040) received 50.4 Gy (*Red*) and the elective nodal PTV (PTVn_4200) received 42 Gy (*blue*) in 28 fractions

13.3.5 IMRT Dosimetric Planning and Delivery

IMRT planning allows for differential doses to the gross disease, elective nodal regions, and the OARs. The OARs used in optimization typically include the small bowel, femoral heads, genitalia, bladder, pelvic bones, and large bowel. In addition, all PTVs should spare non-target skin surfaces manually or automatically trimmed by 3–5 mm (unless there is skin involvement). For bone marrow sparing, pelvic bones including the iliac crests, lumbosacral spine, and lower pelvic bones should be contoured together as a surrogate for pelvic bone marrow. Representative dose constraints based on RTOG 0529 and the UK NICE guidance for IMRT are outlined in Table 13.4. For IMRT optimization in patients enrolled on RTOG 0529, major violations included greater than 5 cc small bowel receiving more than 50 Gy, any point dose small bowel higher than 54 Gy, and greater than 5% femoral heads receiving more than 44 Gy [17]. All other dose constraint deviations were considered minor violations, but were acceptable for treatment.

Table 13.4 Normal organs at risk treatment planning parameters for anal cancer IMRT

Organ at risk	Representative constraints (RTOG 0529 [31] and UK NICE guidance for IMRT [33])
Small bowel	V45Gy < 20 cc V35Gy < 150 cc V30Gy < 200 cc
Femoral heads (L&R)	V44Gy [%] ≤ 5 V40Gy [%] ≤ 35 V30Gy [%] ≤ 50
Bladder	V50Gy [%] ≤ 5 V40Gy [%] ≤ 35 V35Gy [%] ≤ 50
Genitalia	V40Gy [%] ≤ 5 V30Gy [%] ≤ 35 V20Gy [%] ≤ 50
Large bowel	V45Gy < 20 cc V35Gy < 150 cc V30Gy < 200 cc
Bone marrow	V50Gy [%] ≤ 5 V40Gy [%] ≤ 35 V30Gy [%] ≤ 50

Treatment planning priorities should be considered in order of decreasing importance:

1. PTVp—covering 95% of the PTV.
2. PTVn+—covering 95% of the PTV.
3. PTVn (elective nodes)—covering 95% of the PTV.
4. Small bowel.
5. Femoral heads.
6. External genitalia.
7. Bladder.
8. Pelvic bone marrow.
9. Large bowel.

For IMRT plans, patient-specific quality assurance (QA) is highly recommended. QA is performed by delivering the plan onto a phantom or portal imager to measure the 2D/3D dose. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

Patients should receive daily KV images for setup and treatment verification. Bone should be used as the surrogate. Corrections should be made for shifts of 1 mm or greater and recorded. Cone beam CT images, if available, may also be helpful to evaluate the relationship of the CTV to the bladder/rectum, to verify male genitalia position, and to evaluate weight loss or tumor volume reduction that may necessitate adaptive re-planning.

For IMRT systems where isocenter is not defined (e.g., tomotherapy), setup verification images may consist of a series of axial CT images (megavoltage or kilovoltage) obtained over at least 5 cm length, to be compared with simulation CT images. It is recommended that there be an option to display target structures on the simulation images. It is also recommended that the setup verification images be obtained at levels where cephalocaudad positioning, as well as transverse positioning, can be verified. Appropriate levels would include either around the mid to upper sacrum or around the upper border of the acetabulae.

13.3.6 Radiation Dose Considerations

The dose required for locally advanced lesions remains an area of active investigation. An analysis of locoregional failures by T and N stage was performed for patients enrolled in RTOG 9811 [30]. In patients treated with 5-FU and MMC, the three-year colostomy failure rates were 9% (T2N0), 12% (T3N0), 20% (T4N0), 4%(T2N1-3), 19% (T3N1-3), and 28% (T4N1-3). Higher failure rates in high-risk patients raise the question of whether the radiation dose should be escalated. The intended dose for T3, T4, or node-positive patients enrolled on RTOG 9811 was 45 Gy followed by a boost to 55–59 Gy in 30–32 fractions administered over 5.5–6.5 weeks.

Dose escalation was assessed in a randomized design in the French Action Clinique Coordonnées en Cancérologie Digestive (ACCORD-03) trial [32]. In this 2 × 2 factorial study, the roles of two cycles of cisplatin/5-FU induction chemotherapy and dose-escalated radiation were both evaluated. Radiation was delivered using conventional AP/PA or 4-field box techniques to 45 Gy followed by a 3-week break for primary tumor assessment. Patients in the standard boost arms received an additional 15 Gy (60 Gy total dose) using external beam or low dose-rate brachytherapy. Patients in the high-dose boost arms received an additional 25 Gy (total 70 Gy) if there was less than an 80% response at the primary tumor and 20 Gy (total 65 Gy) if there was greater than an 80% response. Patients with no change or progression were recommended to undergo abdominoperineal resection. After a median follow-up of 50 months, there was no advantage in the high-dose boost arms in regard to local control or colostomy-free survival. The addition of induction chemotherapy (which was also found to have no improvement on outcomes) and the inclusion of a three-week treatment gap between external beam radiation and the boost phase may have confounded the interpretation of dose escalation utility in this trial.

Radiation dose will be evaluated in the international PLATO trial (Personalizing Radiotherapy Dose in Anal Cancer) using dose-painted IMRT [33]. This umbrella trial will assess radiation dose intensification in high-risk patients and dose de-escalation in favorable patients. Patients with T1/T2N0 tumors $\leq$ 4 cm will be enrolled on the phase II ACT IV trial and will be randomized to 50.4 Gy in 28 fractions or 41.4 Gy in 23 fractions. Enrollment is planned at 162 patients with a 2:1 randomization. Patients with tumors that are greater than 4 cm or node-positive

will be randomized on the Phase II/III ACT V trial to 53.2 Gy in 28 fractions, 58.8 Gy in 28 fractions, or 61.6 Gy in 28 fractions with standard chemotherapy. Only one of the dose-escalated arms (58.8 Gy or 61.6 Gy) will be evaluated for the phase III component. The primary endpoint for each trial is three-year locoregional failure.

13.4 Toxicity Management

Definitive chemoradiation for anal canal cancer may be one of the most difficult treatments for patients to complete. Acute side effects of chemoradiation may result in treatment breaks, which can compromise the local control of the disease [13]. Table 13.5 summarizes the acute and late side effects of chemoradiation for patients with anal cancer. Patients with anal cancer require close multidisciplinary care. Attention in weekly management visits is warranted with frequent skin exams and query of the patient's GI, genitourinary, nutritional, and overall status. Patients should also have close hematologic monitoring. Those with cytopenias must be counseled for neutropenic fever, which may necessitate inpatient admission for IV antibiotics. In patients with severe acute mucosal toxicity (skin or GI) that occurs early in the course of therapy, the treating physician should consider

Table 13.5 Acute and late toxicities associated with chemoradiation for anal cancer

Organ system	Acute effects	Late effects
Skin	Dermatitis Skin desquamation	Telangectasias Hyperpigmentation Skin dryness
Bone marrow	Neutropenia Lymphopenia Thrombocytopenia Anemia Neutropenic sepsis	Not applicable
Gastrointestinal	Nausea/anorexia Diarrhea Frequent bowel movements Fecal leakage Fecal urgency Tenesmus	Radiation enteropathy Chronic anorectal dysfunction Chronic urgency/leakage Chronic diarrhea/alternating constipation Small bowel obstruction Rectal bleeding Rectovaginal fistula
Genitourinary	Urinary frequency Dysuria	Hematuria
Sexual/reproductive	Vaginal pain	Vaginal stenosis Vaginal dryness Infertility Erectile dysfunction in men
Musculoskeletal	Not applicable	Decreased bone density Insufficiency fractures of the sacrum or femoral heads

dihydropyrimidine dehydrogenase (DPD) deficiency. DPD-deficient patients hypometabolize 5-FU or capecitabine chemotherapy, which may result in effective overdosing of the drug with heightened toxicity. This likely will necessitate a dose reduction or discontinuation of any additional fluoropyrimidine-based chemotherapy.

13.4.1 Dermatitis

The perianal and inguinal skin should be evaluated at least weekly as patients progress through therapy. Even with highly conformal techniques, perianal skin reactions are often seen due to close proximity to the high-dose PTV. Limiting the PTV to 3–5 mm from the uninvolved skin surface may reduce skin effects with modern IMRT techniques. This may be particularly beneficial in the region of elective nodal coverage. Early during treatment, barrier creams should be instructed for skin lubrication and comfort. Barrier creams may be particularly useful in patients with frequent or loose bowel movements to avoid direct contact of stool to the affected skin. Sitz baths may also provide symptomatic relief throughout treatment. As patients develop desquamation of the skin, topical lidocaine ointments and silver sulfadiazine creams can provide symptom relief and healing. Application of Domeboro-soaked gauze may also be useful in patients with moist desquamation by helping to cleanse the skin of exudative debris. Following gauze removal, patients can then apply a topical silvadene and lidocaine mixture to the clean surface. This may be repeated 2–3 times per day.

13.4.2 Hematologic Toxicity

Bone marrow suppression following chemoradiation with 5-FU and MMC-based chemotherapy continues to be a challenge. The rate of grade 3 or 4 hematologic toxicity was 61% in the standard arm of RTOG 9811, which used concurrent 5-FU/MMC and 3D-conformal techniques [11]. In the RTOG 0529 trial using an IMRT technique, hematologic toxicity rate of grade 3 or higher was 58% [17]. The concept of bone marrow sparing using IMRT or IMPT is an area of active investigation. Bazan and colleagues have described a normal tissue complication probability model (NCTP) in anal cancer patients undergoing chemoradiation [36]. This model suggests that, despite the cytotoxic effects of 5-FU/MMC, a dose-response relationship exists between radiation dose to the pelvic bone marrow and hematologic toxicity. Based on this data, the authors conclude that reductions in mean bone marrow dose <22.5 Gy and <25 Gy can reduce rates of grade 3 or higher hematologic toxicity to <5% and <10%, respectively.

Much like the liver, bone marrow is a synthetic organ with functional subunits arranged in parallel. An absolute volume of liver has been found to be a useful treatment planning parameter in liver SBRT [37]. Similar volume-based parameters may also predict for hematologic toxicity. Investigators recently evaluated this concept

in a cohort of 57 patients with anal cancer receiving chemoradiation [38]. In patients with >700 cc of pelvic bone spared 30 Gy, the incidence of grade 3 or higher hematologic events was 5% during chemoradiation compared to 54% if the volume of marrow spared 30 Gy was less than 700 cc ($P < 0.01$). There is also emerging interest in identifying metabolically active regions of pelvic bone marrow using FDG-PET imaging, which may preferentially be spared during treatment planning [39, 40]. The optimal treatment planning parameters for sparing hematologic toxicity remains an active area of investigation.

13.4.3 Gastrointestinal Toxicity

Patients with anal cancer often have bowel symptoms that can be quite challenging to manage during and after therapy. Avoidance of organs at risk during treatment planning is the primary preventative strategy. This may be assisted with prone treatment position, bladder filling, and IMRT. Several studies have evaluated dosimetric predictors of acute GI toxicity during chemoradiation for anal cancer. Investigators from the University of Pittsburgh reviewed 58 patients undergoing IMRT [41]. Bowel was contoured using the bowel bag technique that extends from the anterior abdominal wall to include the entire peritoneum. The volume of bowel receiving 30 Gy and 40 Gy were significant predictors of grade 3 or higher GI toxicity. In patients with V30 Gy > 310 cc, the rate of toxicity was 39% compared to 9% if the V30 Gy < 310 cc ($P = 0.016$). In patients with V40 Gy < 70 cc, the rate of toxicity was 6% compared to 36% if the V40 Gy > 70 cc ($P = 0.045$). In a similar analysis that also included grade 2 adverse events, a V30 Gy of >450 cc resulted in grade 2 or higher GI toxicity in 33% compared to 8% of patients with a V30 Gy < 450 cc ($P = 0.003$) [42].

During treatment, loose and frequent bowel movements may exacerbate perineal skin reactions. Dietary modification is a useful first step in management and prevention. Patients should adhere to a low-fat, lactose-free, and low-residue diet. Consultation with a dietician should be arranged for a detailed review of potential trigger food and meal planning. Antidiarrheal agents will often be required for refractory, frequent, and loose stools despite dietary modification. A common approach is to start medical therapy with loperamide, which is readily available over the counter. This may be given as needed if symptoms are infrequent. For persistent symptoms, a second agent such as atropine/diphenoxylate may be added to the regimen. The etiology of diarrhea in patients undergoing radiation therapy may also be in part due to bile acid malabsorption [43, 44]. For that reason, bile acid binders such as cholestyramine powder may also aid in symptom relief.

Potential late GI toxicities include rectal bleeding and fecal incontinence. Rectal bleeding, often a result of RT-induced telangiectasia development, is initially

managed with endoscopic evaluation followed by bowel habit optimization and medical therapy including sucralfate enemas and oral metronidazole with or without concurrent formalin [45, 46]. Fecal incontinence is generally managed with pelvic floor exercises, bulking agents, dietary modification, antidiarrheal medications, biofeedback techniques, surgical sphincter repair, and sacral nerve stimulation [44, 46].

13.4.4 Genitourinary Toxicity

Urinary symptoms, which may include urinary frequency and dysuria, are often problematic for patients undergoing definitive treatment for anal cancer. Dosimetric parameters for urinary toxicity mitigation in patients with anal cancer are less defined compared to other organs at risk. It is important to illicit a detailed history regarding the urinary symptoms. Signs of infection, especially early in treatment, should prompt a urinalysis with appropriate use of antibiotics as indicated. Patients with dysuria that occur early on in the urinary stream may be related to periurethral irritation. The physical exam may also reveal periurethral acute reactions. In these patients, a peri-bottle may provide symptom relief. The patient should be instructed to use the bottle to cleanse the skin during and after the urinary stream. Suprapubic pain at the end of the urinary stream, often described as cramping, may imply cystitis. Anti-spasmodics or phenazopyridine may offer symptomatic relief. The risk of late effects has not been well-reported likely due to total mean dose being relatively low as compared to radiation for prostate cancer.

13.4.5 Sexual and Bone Late Effects

Following completion of treatment, patients should be counseled on sexual function and the potential late effects of radiotherapy. Data from quality of life series have demonstrated high rates of long-term sexual toxicity with over 50% of patients reporting decreased interest, dyspareunia, erectile dysfunction, and loss of feeling attractive [47]. For women, vaginal stenosis is common after chemoradiation for anal cancer, causing grade 2 or higher stenosis in over 60% of patients [48]. Young age at diagnosis, treatment during an earlier era, and higher dose to the primary tumor were all associated with higher grades of vaginal stenosis. Efforts to both prevent and treat these symptoms center on combination usage of vaginal dilators, topical estrogen, moisturizers/lubricants, and sexual health counseling [49]. Female patients should be instructed on vaginal dilator use to mitigate vaginal stenosis. No randomized data exist that clearly demonstrate reduction in vaginal stenosis with dilator use. However, a prospective study assessing vaginal dilator use in patients

with rectal or anal cancer noted that patients with less than 40% compliance had higher rates of vaginal stenosis [50]. A typical recommendation for dilator use is 10 min at least three times per week. For men, phosphodiesterase inhibitors are typically used to improve sexual function.

Other late effects of treatment include insufficiency fractures of the sacrum or femoral heads. In a cohort of 492 rectal cancer patients undergoing pelvic radiation therapy, the incidence of sacral insufficiency fracture was 7%. Increasing age, osteoporosis, and female sex were found to be independent predictors of sacral insufficiency fracture [51]. The incidence of insufficiency fractures in anal cancer patients is less well-described. In a cohort of 24 anal cancer patients receiving IMRT, nine (37%) were noted to have pelvic insufficiency fractures at a median time of 15 months following completion of treatment [52]. For patients who develop insufficiency fractures, consider consultation with orthopedics and therapy with anti-inflammatories, vitamin D, and calcium supplements.

13.5 Follow-Up Recommendations

Immediately following completion of chemoradiation, patients should be observed closely to evaluate for resolution of acute toxicities with aggressive supportive care measures as needed. A clinical response assessment should be made monthly following completion of treatment. If residual tumor remains, the patient should be followed closely to evaluate regression. It may take up to 6 months for a complete clinical response to be observed. In the UK ACT II trial, 90% of patients ultimately obtained a complete response at 6 months in the 5-FU/MMC arm [12].

Additionally, the authors generally recommend anoscopy and PET to evaluate for complete response at approximately 3 months post-completion of chemoradiation. A complete metabolic response on a posttreatment PET scan has been observed to be prognostic following chemoradiation for anal cancer [53]. In a series of 53 patients with pretreatment and posttreatment PET scans (median 2 months), the two-year cause-specific survival was 94% in patients with a complete metabolic response compared to 39% in patients with a partial metabolic response [53]. Biopsies should not be performed routinely prior to 6 months due to the risk of radionecrosis, unless there is concern for tumor progression. Once a complete response has been obtained, a regular follow-up regimen should be established that includes digital rectal exam and inguinal lymph node evaluation every 3–6 months for 5 years, anoscopy evaluation every 6–12 months for 3 years, and CT imaging at least annually for high-risk patients (lymph node involvement, T3/T4). Patients with biopsy-proven local recurrence should be referred for abdominoperineal resection (Fig. 13.7).

13.6 Summary

Radiation therapy with 5-flourouracil and mitomycin remains the standard of care for squamous cell carcinoma of the anal canal. This approach highlights an early success in organ-preserving therapy. Despite this success, toxicity remains high in these patients. Conformal radiation planning and delivery with IMRT has been useful in reducing morbidity. However, careful adherence to standardized treatment volume definitions, attention to published dose-volume limits, quality assurance, and image guidance during treatment delivery are all important components in optimizing IMRT outcomes. Ongoing trials are investigating the safety of treatment regimens using IMRT to escalate the dose of radiation for high-risk patients in an attempt to improve local control.

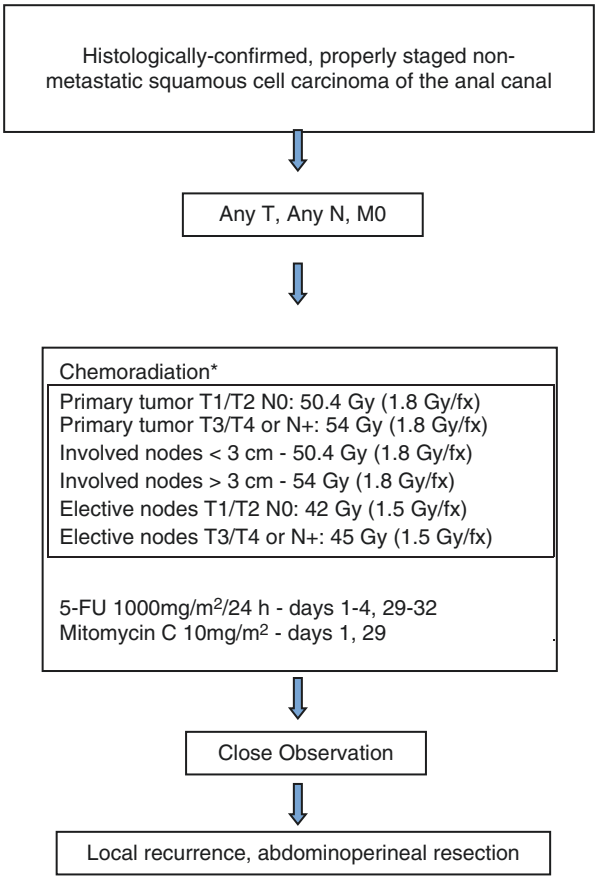

Fig. 13.7 Treatment algorithm. *IMRT radiation is preferred; 3D-CRT is considered an option; proton therapy is under investigation

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