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REVIEW

# Carcinoma of the anal canal

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**Abstract** There are around 5,000 new cases of anal canal cancer each year in the United States. It is of particular risk in HIV-positive populations. Many cases are related to persistent infection with human papillomavirus (HPV). The treatment of anal cancer has progressed from abdominoperineal resection mandating permanent colostomy in the 1940s through the 1970s to modern chemoradiation with sphincter preservation in around 80% of patients, even with locally advanced disease. The evolution of the treatment paradigm of this disease is a model for the treatment of malignant disease with organ preservation. Multiple randomized trials have been conducted to guide this evolution. Technological developments in the delivery of radiotherapy and anti-cancer pharmaceuticals harbor hope for further improvements in outcomes with possible reductions in toxicity and increases in tumor control. Perhaps most inspiring is the recent development of HPV vaccines that may significantly decrease the incidence of this cancer.

**Keywords** HPV · Anal canal cancer · Chemoradiation · Organ preservation

## Introduction

Cancer of the anal canal represents a success story in the management of malignant disease and organ preservation. The treatment paradigm has progressed from requiring a mandatory abdominoperineal resection (APR) with permanent colostomy until the 1970s to combined chemotherapy and radiotherapy with sphincter preservation today, even for locally advanced disease. Concurrent chemoradiation results in a 5-year survival of approximately 75% along with avoidance of a permanent colostomy in approximately 80–90% of patients [1]. However, divergent from the improvement in organ preservation, the incidence of this cancer has been increasing, possibly due to its relationship with human papillomavirus (HPV) [2–4]. In the United States, approximately 4,650 new cases occurred in 2007 with approximately 690 deaths from anal cancer [5]. In 2008, projections are for approximately 5,070 new cases and 680 deaths [6].

## Etiology

Human papillomavirus is considered a major causative agent of ano-genital cancers [2–4, 7]. The classic relationship is that of HPV with carcinoma of the cervix, initially described by zur Hausen [8]. zur Hausen shared the 2008 Nobel Prize in Medicine for his discovery that HPV caused cancer of the uterine cervix. HPV is a common sexually transmitted virus and has been identified by polymerase chain reaction (PCR) in 93% of HIV-positive men who have sex with other men, 60% of HIV-negative men who have sex with other men, 76% of HIV-positive women, and 42% of high-risk HIV-negative women [3]. Promiscuous heterosexual activity, anal intercourse, and other sexually transmitted diseases have also been linked to the development of anal canal cancers [9]. One study of sexually active male university students in the United States revealed that 35% of the subjects tested positive for

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HPV infection by PCR [10]. Trauma associated with anal intercourse may increase transmission of HPV, but is not required for anal canal infection with HPV or the development of cancer [11]. Infection with HPV can be identified in >70% of anal cancer cases but not all [4, 7, 12]. Anal cancer development is a multistep process in which HPV infection and transmutation is a common step, similar to that seen in squamous cell carcinoma of the cervix [2, 7].

The transition zone present at the anal canal–rectal junction, in which squamous metaplasia is common in the columnar epithelium at that site, may have increased susceptibility for malignant transformation via HPV infection [7]. HPV types 16 and 18 are the most frequently detected in anal canal and cervical cancers, but other types have been implicated as well [2, 4]. While HIV infection is a risk factor for HPV infection [13] and anal cancers, there is no consistent evidence of any increased risk of developing anal canal cancer within the first 2 years of HIV infection [9]. But with the advent of effective highly active antiretroviral therapies (HAART), HIV long-term survivors are at increased risk, possibly due to the malignant transformation of the anal mucosa over this time period [14]. Any form of immunosuppression is a risk factor for developing anal canal cancer, including organ transplantation such as kidney transplantation [15]. Smoking has also been shown to increase the risk of developing an anal canal cancer, independent of other risk factors [12].

## Anatomy

The anal canal is limited by the rectum proximally and the perianal skin distally. The anal verge forms the junction of the anal canal with the hair-bearing, keratinized, perianal skin. The mucosa of the distal anal canal, sometimes called the anoderm, is composed of non-keratinized squamous epithelium. A transitional zone forms the junction of the anal canal with the distal rectum (Fig. 1). The transitional zone is formed by a mixture of the columnar epithelium of the rectum and the squamous epithelium of the remainder of the anal canal along with scattered transitional/urothelial epithelium left as remnants of the common embryological origin of the anus and bladder [16]. The transitional zone extends distally for about 1 cm. At this level, the mixed epithelium of the transition zone gives way to stratified squamous epithelium of the anoderm of the lower canal. The columns of Morgagni are "pleats" of rectal mucosa, as described by Dujovny et al., which are formed by the rectal mucosa as it joins the anal canal in the transitional zone. At the base of these pleats are the ducts from the anal glands that secrete mucous [16]. The columns of Morgagni form a dentate or pectinate appearance, and thus this juncture of

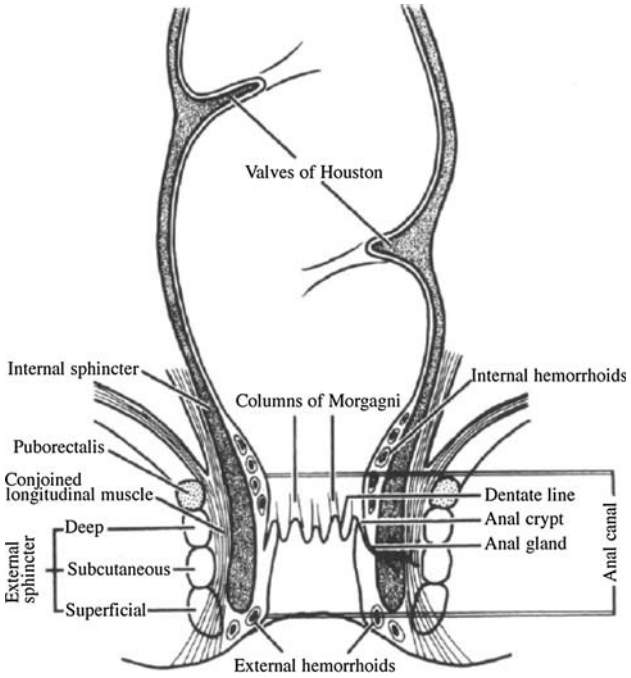


**Fig. 1** Anatomy of the anal canal (used with permission [11])

the transitional zone and the anoderm is called the dentate or pectinate line. Cancers of the perianal skin are also referred to as anal margin cancers. These cancers are those tumors originating in the hair-bearing skin external to the anal verge within 5 cm of the anal verge [17]. Cancers centered in perianal skin that clearly extend into the anal verge are considered anal canal cancers.

The anal canal is surrounded by the sphincter muscles, with the anorectal ring, composed of the encircling puborectalis muscle, palpable at the proximal extent of the canal on digital rectal exam. From the level of the anorectal ring, the internal anal sphincter is continuous with the circular muscle of the rectum and extends distally to below the dentate line. The external sphincter surrounds the internal sphincter and is under voluntary control. Lymphatic drainage of anal canal tumors depends on the location of the tumor. Lymphatic drainage of the anal canal below the dentate line and perianal skin is primarily to the inguinal and femoral lymph nodes, and subsequently to the external iliac groups. Tumors involving the transitional zone may initially spread directly to the inferior hemorrhoidal/rectal, and middle hemorrhoidal/rectal first echelon nodal basins and subsequently drain to the internal iliac chains. Tumors extending more proximally to the distal rectum may initially drain directly to the perirectal and superior hemorrhoidal nodes and subsequently the inferior mesenteric chains [18]. There may be extensive crossover between these pathways [19, 20] especially if the primary drainage path is obstructed by tumor [16].

## Histopathology

Most anal canal cancers are squamous cell carcinomas. Squamous cell carcinomas include keratinizing and non-keratinizing types. The non-keratinizing types typically arise from the transitional zone and include what were formerly referred to as cloacogenic carcinomas, basaloid carcinoma, and transitional cell cancers [17]. There is no significant difference in the treatment and outcomes between these subtypes and keratinizing squamous cell carcinomas [15]. Adenocarcinomas of the anal canal can also arise from the columnar mucosa of the transitional zone and the anal glands present in the canal. Other less common histology of anal canal tumors include melanoma, small cell carcinomas, sarcoma, lymphoma, and very rarely, metastasis from other primary tumors [21–24].

## Clinical presentation

The median age at presentation is around 58–65 years [18, 24–26], although HIV patients with anal cancers tend to be younger, 42–48 years of age [14, 27]. Most patients present with a history of rectal bleeding and many have a history of troublesome hemorrhoids, fissures, or fistulas [24, 28]. In a study of 305 patients reported by Deniaud-Alexandre et al., three-fifths of patients presented with any one or combination of the following: occasional bleeding, minimal pain, or minimal incontinence [25]. Only 7% of patients in this study presented with no pain, no bleeding, and no fecal incontinence. More than a quarter of the patients in this study presented with at least one of the following: >4 loose stools daily, persistent daily bleeding, intermittent pain, or intermittent incontinence. Tumors may spread via direct extension into the adjacent structures including the sphincters to cause total fecal incontinence, but this is rare at initial presentation. Tumors may spread via the lymphatic pathways described above. Risk of nodal involvement increases with size [29], T-stage [30], grade [29], and depth of invasion [28]. In clinically staged patients, around one-fifth of patients present with detectable nodal disease [25, 31]. Up to an additional 26% may have subclinical pelvic or inguinal nodal involvement, based on surgically staged patients [29]. Around 10% present with clinically detectable inguinal nodes [25, 26, 31]. Up to 5% of patients present with distant metastases, usually to lung, liver, bone, or para-aortic lymph nodes [29].

## Workup and staging

The history obtained from anal canal cancer patients should include assessment of risk factors for immunosuppression and HPV infection, including HIV infection and risky sexual behavior. Physical examination should include palpation of inguinal nodes, visual inspection of the anus, and digital rectal exam. The examiner should carefully note location and extent of the primary tumor, i.e. extent out onto the perianal skin, proximal extension from the anal verge, and extent of circumferential involvement. The position (i.e. supine, prone, lateral decubitus, etc.) of the patient should be clearly described in the medical record, so as to maintain proper orientation of the lesion for all members of a multidisciplinary care team. Females require complete pelvic examination including Pap smear of the cervix. Biopsy of the primary tumor and clinically suspicious lymphadenopathy is mandatory. The anal canal needs direct visualization with anoscopy or proctoscopy. This may be best performed under general anesthesia if the exam is too painful. Endoscopic ultrasound is often used to gauge depth of invasion and to analyze perirectal and pelvic lymph node status [32]. Staging by ultrasound can supplement standard TNM staging and has been found to be as predictive as other methods of staging [33]. CT scan of the abdomen and pelvis is necessary to assess status of pelvic and inguinofemoral lymph nodes and may sometimes help to assess the primary tumor. PET, and especially PET fused with CT, is useful in determining extent of disease and directing biopsies of suspicious lymph nodes [34, 35]. CT chest or a simple chest X-ray may be used to evaluate lung metastases. Blood tests should include a complete blood count, and a comprehensive metabolic panel to evaluate liver and renal function. HIV testing should also be considered depending on risk factors for this disease. For known HIV-infected patients, CD4 counts should be assessed as well, as a CD4 count below 200 may predict increased toxicity to treatment [14, 27, 36]. The current staging system is from the American Joint Commission on Cancer staging system, sixth edition [17], as seen in Tables 1 and 2.

## Treatment

Early stage, T1N0 may be resected with a wide local excision (WLE) and no adjuvant therapy with high expectations for cure [29]. If this approach is contemplated, endoscopic ultrasound may provide valuable pre-operative information on depth of invasion and the depth of resection necessary to clear the cancer with an adequate margin [33]. If WLE would likely result in sphincter compromise or if APR would be required for adequate margins, then definitive radiation alone for T1N0 [25, 26, 29] or chemoradiotherapy as discussed below should be strongly considered. Endoscopic ultrasound may help to determine which lesions are most suitable to WLE or radiation alone.

**Table 1** AJCC staging system for anal canal cancers, sixth edition [17]

| Primary tumor (T) | | Regional lymph nodes (N) | |
|---|---|---|---|
| TX | Cannot be assessed | NX | Cannot be assessed |
| T0 | No evidence of primary tumor | N0 | None |
| Tis | Carcinoma in situ | N1 | Metastasis in perirectal nodes |
| T1 | ≤2 cm | N2 | Metastasis in unilateral internal iliac and/or inguinal nodes |
| T2 | >2 to ≤5 cm | N3 | Metastasis in perirectal and inguinal nodes, and/or bilateral internal iliac and/or inguinal nodes |
| T3 | >5 cm | | |
| T4 | Invasion of vagina, urethra, prostate, bladder | | |

**Table 2** AJCC stage grouping for anal canal cancers, sixth edition [17]

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage IIIA | T1–T3 | N1 | N0 |
| | T4 | M0 | M0 |
| Stage IIIB | T4 | N1 | M0 |
| | Any T | N2-3 | M0 |
| Stage IV | Any T | Any N | M1 |

If endoscopic ultrasound reveals involvement of the external sphincter or lymph node involvement, then WLE or radiation alone will likely provide poor results and chemoradiation should be considered [33]. WLE or radiation alone for T1N0 lesions results in local control rates of ≥90% and overall survival of approximately 100% at 5 years [25, 26, 29, 37].

More advanced lesions can also be treated with surgery, but likely require APR with permanent colostomy to clear the tumor. Nodal disease, if addressed surgically with no adjuvant therapy, requires bilateral inguinal and pelvic nodal dissection. APR was the standard treatment for anal canal carcinoma from the 1940s through the 1970s, until Dr. Norman Nigro and colleagues at Wayne State University attempted to improve on outcomes with surgery by adding neoadjuvant chemoradiation with continuous infusion 5-fluorouracil (5FU) and bolus mitomycin-c (MMC) with pelvic radiotherapy (30 Gy in 15 fractions) [20] prior to APR. Two of three initial patients were found to have no evidence of viable tumor in their pathological specimens from the APR after chemoradiation. One additional patient, who had a complete clinical response after chemoradiation, refused surgery and showed no sign of relapse 14 months later. This inspired a more formal protocol of chemoradiation followed by surgery for anal canal carcinoma patients. Nigro et al. reported the results of a study of 19 patients treated with chemoradiation followed by surgery in the 1970s. Fifteen of 19 patients had a pathological complete response (pCR). Twelve patients had an APR and 7 of these 12 had a pCR. The other seven patients had a WLE and all of these patients were found to have had a pCR [38]. These results begged the question of whether or not surgery was needed following a complete response to chemoradiation.

## Chemoradiation

Mitomycin-c was first discovered in the late 1950s, at roughly the same period as 5FU was being developed [39, 40]. This novel antitumor antibiotic had demonstrated activity against a number of solid tumors throughout the following decade and was one of the few readily available agents in the early 1970s to combine with other agents (i.e. 5FU) and/or modalities (i.e. EBRT). It does have significant hematologic toxicity with prolonged thrombocytopenia. Moreover, MMC can cause life-threatening hemolytic uremia syndrome [41]. Cisplatin, a superior radiosensitizer and an agent with reproducible greater activity against squamous cell histology solid tumors, was not discovered to have antitumor properties until the late 1960s and did not become commercially available until well after the initial Nigro report. By that time, confirmatory data had emerged that documented the efficacy of the combination of MMC, 5FU, and EBRT [20, 42, 43]. In addition, the recognition of infusional 5FU (short course for 96–120 h or protracted infusion over a more extended period) as a preferred schedule to maximize this agent's radiosensitizing properties was also not widely appreciated initially.

The early reports by Nigro and colleagues inspired other groups to investigate the role of chemotherapy as a component of sphincter-preserving therapy. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial, launched in 1987, randomized 585 patients to 45 Gy of radiotherapy in 20–25 fractions, or the

same radiotherapy combined with 5FU (1,000 mg/m$^2$/day × 4 days) and MMC (12 mg/m$^2$ × 1 dose). Patients were assessed for 6-week response after completion of radiotherapy. Patients in whom there was a <50% response went to radical surgery. Patients in whom there was >50% response (89% of assessable patients) were recommended to receive a radiotherapy boost. Eighty-one percent of all assessable patients received either a 15 Gy external beam boost or a 25 Gy brachytherapy boost. The addition of chemotherapy to radiotherapy was shown to decrease local failures (61% without chemotherapy vs. 36% with chemotherapy at 3 years, $P < 0.0001$) and cancer-specific mortality (39 vs. 28%, $P = 0.02$). Acute toxicity was significantly worse with chemoradiation ($P = 0.03$) but late toxicity was similar. Overall survival was not significantly improved with chemoradiation (65 vs. 58%, $P = 0.25$) [44].

In 1997, the European Organization for the Research and Treatment of Cancer (EORTC) reported the results of a smaller multi-institutional randomized trial. This trial included 110 patients with stage ≥T3 or ≥N1 disease. Patients were randomized between radiotherapy alone or chemoradiotherapy. All patients received 45 Gy in 25 fractions to the pelvis and inguinal lymph nodes. Patients randomized to chemoradiotherapy received the same radiation regimen with continuous infusion 5FU at 750 mg/m$^2$ on days 1–5 and 29–33, and MMC 15 mg/m$^2$ on day 1. Six weeks after completion of treatment, each patient was evaluated for response. Patients with a clinical complete response (cCR) received a boost of an additional 15 Gy. Patients with a partial response received a 20 Gy boost. Boosts were delivered via electrons, photons, or Ir-192 low-dose rate brachytherapy. Those patients with no response underwent APR. Results of this trial showed that chemotherapy improved cCR rate (80 vs. 54%), local-regional control rate (70 vs. 50%, $P = 0.02$), and colostomy-free survival (75 vs. 40%, $P = 0.002$). However, overall survival was not improved with chemotherapy (56% in both groups) [45].

Due to significant hematologic toxicity associated with MMC, multiple investigators have evaluated the benefit of the addition of MMC to 5FU regimens. In a combined effort of the Radiation Therapy Oncology Group (RTOG) and the Eastern Oncology Group (ECOG), an intergroup trial was conducted and reported by Flam et al. in 1996. This study, RTOG 87-04/ECOG 1289, randomized 310 patients to receive chemoradiation of 45–50.4 Gy (with no planned treatment break) with 5FU (continuous infusion, 1,000 mg/m$^2$/day × 4 days in the first and fourth week of treatment) with or without MMC (10 mg/m$^2$ with each cycle of 5FU). All patients had full thickness biopsies at 4–6 weeks after completion of chemoradiation. If the biopsy was negative, no further treatment was given. If the biopsy was positive at that time, the patient was given 9 Gy of additional radiotherapy with 5FU in the same dose and schedule as before and 100 mg/m$^2$ of cisplatin on the second day of 5FU administration. If renal function was inadequate for cisplatin administration, MMC was given for salvage instead. Results of the study showed that the addition of MMC to 5FU chemoradiation decreased the need for colostomy at 4 years (9% with MMC vs. 23% without MMC, $P = 0.002$), especially in larger tumors, and improved disease-free survival (73 vs. 51%, $P = 0.0003$). Overall survival was not improved ($P = 0.31$) with MMC. Complication rates were higher with MMC than without (23% grade 4 toxicity with MMC vs. 7% without, $P < 0.001$). In addition, there were five treatment-related deaths in the MMC arm and only one in the arm without MMC [46].

In efforts to minimize the hematologic toxicity of chemoradiation, cisplatin has been evaluated as a substitute for MMC. While cisplatin also has risks of significant toxicity (namely nausea/vomiting, renal toxicity, and hearing loss), it has less hematologic toxicity than MMC. Multiple single institution reviews have investigated the possibility of replacing MMC with cisplatin. For example, Gerard et al. reported in 1998 the results of a single institution review of 98 patients, most with advanced stage, all treated with 5FU and cisplatin with radiotherapy. The radiotherapy consisted of 39–51 Gy with 5FU (800–1,000 mg/m$^2$ continuous infusion over 96 h) and cisplatin (20–25 mg/m$^2$) on days 1–4. External beam radiotherapy dose was 30–39 Gy in 3 Gy fractions and was followed by an Ir-192 low-dose rate implant boost of 19 Gy at ~100 cGy/h, or an external beam boost of 10–16 Gy if unable to perform implant. Inguinal node dissection was performed for N2-3 disease [47]. Five-year local control was 80%, and with a surgical salvage rate of 70%, ultimate local control was 93%. Eighty-two percent of patients avoided colostomy. Six percent of patients required colostomy for treatment-related causes without tumor recurrence (severe bleeding or necrosis), and there was one treatment-related death. Five-year overall survival was 90% for T1, T2, and T4 lesions and 70% for T3 lesions. Other institutions have also reported excellent results substituting cisplatin for MMC combined with 5FU chemoradiation [26, 48].

More recently, the RTOG compared a cisplatin-based chemoradiotherapy regimen with a MMC-based regimen. This study (RTOG 98-11) randomized 598 patients with anal canal carcinoma between immediate chemoradiation with 5FU and MMC (arm 1) and induction 5FU and cisplatin chemotherapy followed by chemoradiation with 5FU and cisplatin (arm 2) [1]. Arm 1 consisted of concurrent 5FU (1,000 mg/m$^2$ on days 1–4 and 29–32), MMC (10 mg/m$^2$ on days 1 and 29) and 45–59.4 Gy radiotherapy with radiotherapy starting on day 1. Arm 2 consisted of

induction chemotherapy with 5FU (1,000 mg/m$^2$ on days 1–4 and 29–32) and cisplatin (25 mg/m$^2$ on days 1 and 29) followed by concurrent chemoradiation with the same cisplatin and 5FU with 45–59.4 Gy radiotherapy starting on day 57. Five-year estimates of disease-free survival were 60% in the immediate chemoradiation/MMC arm and 54% in the induction chemotherapy/cisplatin arm ($P = 0.17$). Colostomy rates at 5 years were lower in the MMC arm (10 vs. 19%, $P = 0.02$). There was no statistically significant difference in overall survival between the two groups (75% with MMC vs. 70% with cisplatin, $P = 0.1$). Overall toxicity was similar but hematologic toxicity was significantly higher in the MMC arm ($P < 0.001$). This trial demonstrates that induction chemotherapy with 5FU and cisplatin followed by chemoradiation with cisplatin and 5FU is not superior to immediate concurrent chemoradiation with 5FU and MMC. The study has been criticized for not directly evaluating immediate chemoradiotherapy with cisplatin and 5FU to immediate chemoradiotherapy with MMC and 5FU [49]. The question of whether or not cisplatin can replace MMC in 5FU chemoradiotherapy regimens for the treatment of anal canal carcinoma has not yet been answered. Until it is, MMC and 5FU remain the standard to which other regimens should be compared, but cisplatin with 5FU is a reasonable alternative, particularly for patients who may not tolerate the increased hematologic toxicity of MMC.

## Radiation time–dose effects

Multiple retrospective studies have evaluated a dose response for radiotherapy in the management of anal canal carcinoma [50, 51]. A retrospective study reported by Hughes et al. has demonstrated improved local control for doses ≥55 Gy, continuous course, with 5FU-based chemoradiation [50]. The intergroup trial discussed above (RTOG 87-04/ECOG 1289) evaluated 45–50 Gy of radiotherapy, in continuous fashion without a planned treatment break, combined with 5FU and MMC. Biopsies were performed at 4–6 weeks after the initial phase of chemoradiation. If patients had a partial response, additional chemotherapy was given with a 9 Gy radiotherapy boost as an "immediate salvage" regimen. If there was no response or progression at 6–8 weeks after the initial course, an APR was performed. In this study, the 4-year local failure rate was 16% with continuous course radiotherapy to 45–50 Gy with 5FU and MMC, with 10 of 146 patients in this arm receiving immediate salvage chemoradiation of 9 Gy [46]. Subsequently, RTOG 92-08 was conducted evaluating higher dose radiotherapy delivered in a split course fashion with the same chemotherapy as the MMC arm in the intergroup trial (RTOG 87-04/ECOG 1289) [52]. Forty-six patients received continuous infusion 5FU for 5 days and bolus MMC with 59.4 Gy at 1.8 Gy per fraction with a planned 2-week break during the course of radiotherapy. Preliminary results revealed that local control was not improved compared to the intergroup trial MMC arm, despite the higher total dose, and the colostomy rate was higher with the split course regimen. The study was temporarily closed, but later reopened to evaluate the same treatment regimen without the planned break. An additional 20 patients were treated on the "no break" regimen. In 2008, long-term results of this trial were published [53]. Statistical analysis revealed no difference in OS or local-regional failure when compared to the MMC arm of the intergroup trial. However, within the 92-08 patients, the 5-year estimates of local failure and distant failure were lower in the "no break" group than those in the mandatory break group, and the OS and disease-free survival were higher in the "no break" group as well; although it should be noted that the trial was not designed to compare the two arms of 98-02 to each other, and therefore no statistical analysis was performed to that end. Available data from randomized trials and retrospective reviews suggest that radiotherapy doses should be at least 45 Gy to T1 lesions. For more advanced lesions and lesions with nodal involvement, chemoradiation is advised with radiotherapy doses of 30.6–45 Gy to subclinical disease and >54–55 Gy to gross disease. Planned breaks are no longer recommended.

## Radiotherapy technique

External beam radiotherapy is typically delivered via a four field box approach using anteroposterior (AP), posteroanterior (PA), and right and left lateral fields (Fig. 2). Modern treatment planning techniques should be used to ensure adequate coverage of the nodal beds and the primary site. CT-based planning with beam's eye view field design should be used. The ability to contour the nodal basins using CT planning allows the clinician to minimize dose to normal tissues while ensuring adequate coverage of target tissues. There are a number of ways to achieve these goals. AP:PA fields can be used with the PA field being designed more narrow than the AP field so as to reduce the dose to the femoral heads (Figs. 3, 4, 5). If this is done, then the inguinal nodes have to be brought up to the desired dose by adding anterior boost fields, most often with electrons. This may be difficult to do with large patients as the nodes may be too deep to deliver effective doses without over-treating the skin (Fig. 5). In addition, exit dose from high dose electrons or photon fields may negate the beneficial effect of a narrow PA field on femoral head dose. Again, CT

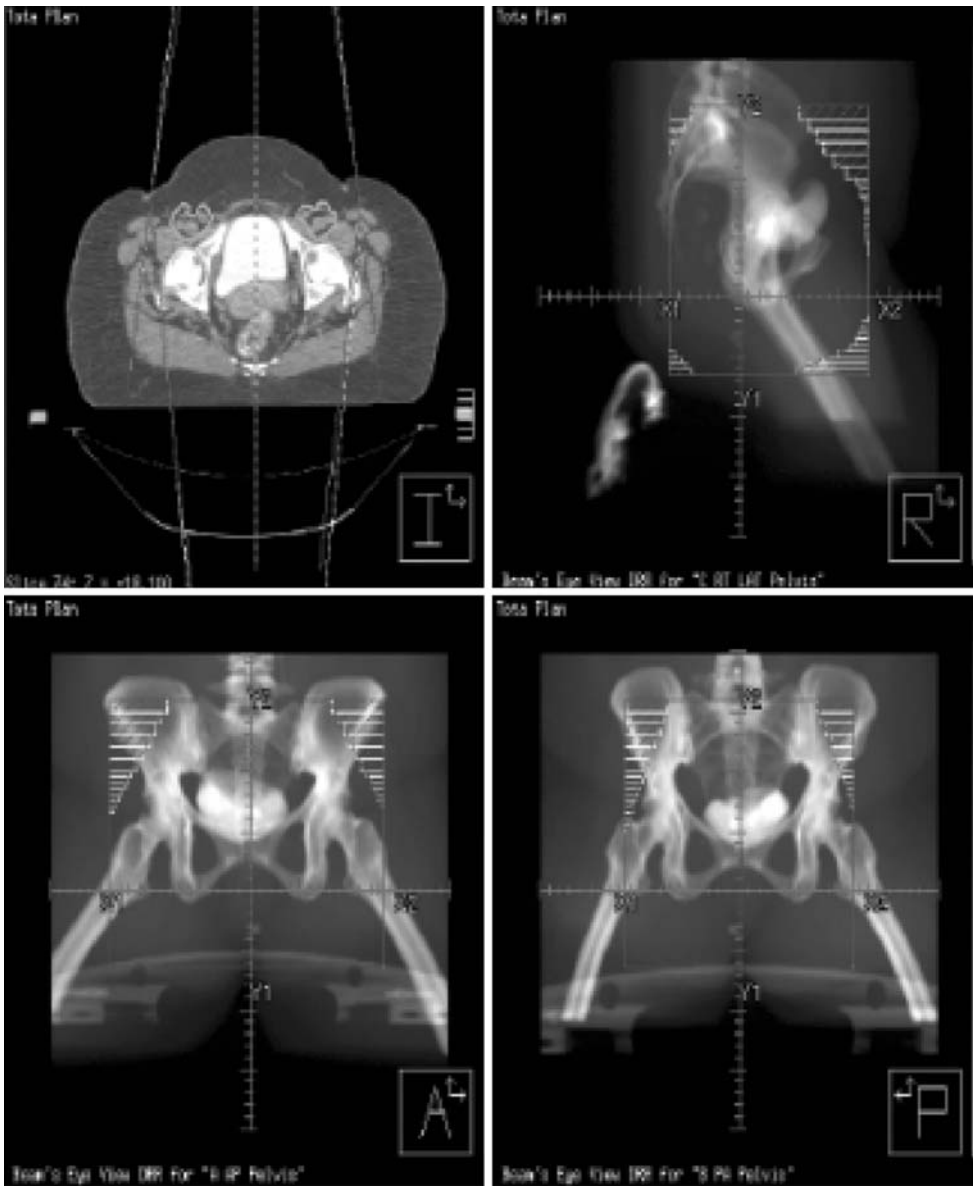

**Fig. 2** Four field box field arrangement for pelvic external beam radiotherapy

planning is extremely helpful to ensure that adequate dose to the lymph nodes at depth is achieved. The addition of lateral fields to a simpler AP:PA approach allows a reduction in dose to the small bowel and may eliminate the need for anterior nodal boost fields. The pelvic nodes are taken to 30–45 Gy at 1.8–2.0 Gy per fraction. A reduction off the superior pelvic lymph nodes after 30 Gy has been included in the chemoradiation regimens of the RTOG trials [1, 46]. The nodes below the level of the sacroiliac joints, including the inguinal nodes, are typically given 45 Gy. The RTOG trials have allowed a reduction of clinically negative inguinal nodes after 36 Gy. Gross disease, including the primary tumor and any clinically suspicious lymph nodes are generally given $\geq$55 Gy, although T1–2, N0 tumors have been given 45–50 Gy in some protocols with good local control [46]. It should be noted that, as discussed above, these lower dose protocols typically plan further chemoradiotherapy if a clinical CR is not achieved, and for patients that do achieve a CR, biopsies of the primary site are considered after 4–6 weeks after the completion of initial chemoradiation with further chemoradiotherapy if the biopsy is positive for residual disease. The final boost can be delivered via external beam or an interstitial implant.

Papillon and colleagues in Lyon, France, pioneered a simple brachytherapy technique that has shown to be effective and deliverable at multiple institutions [26, 31, 54, 55]. A small acrylic template is used to space a semi-circle of hollow needles in place and are after loaded with Ir-192 to deliver 10–15 Gy at 1 Gy/h to a depth of 0.5 cm as a boost to the anal canal primary site (Fig. 6). This allows the boost treatment to be delivered after the peak

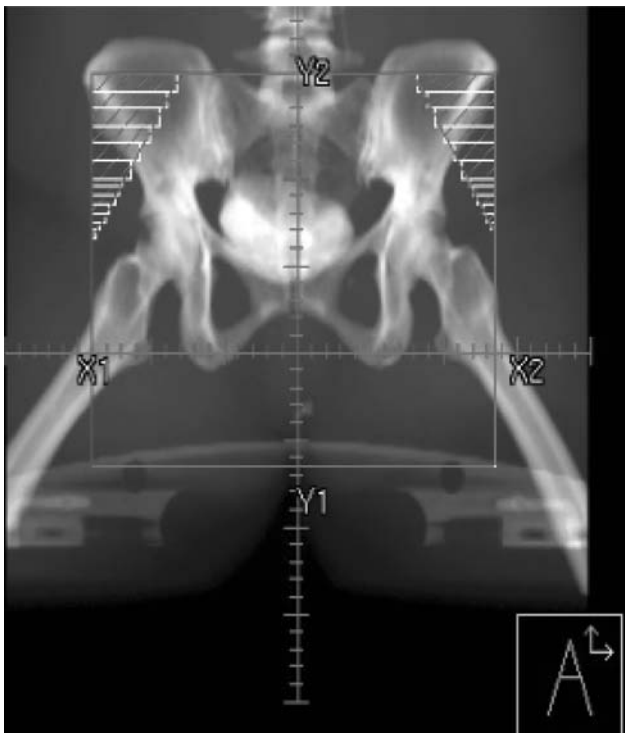


**Fig. 3** Initial anterior–posterior field for pelvic external beam radiotherapy

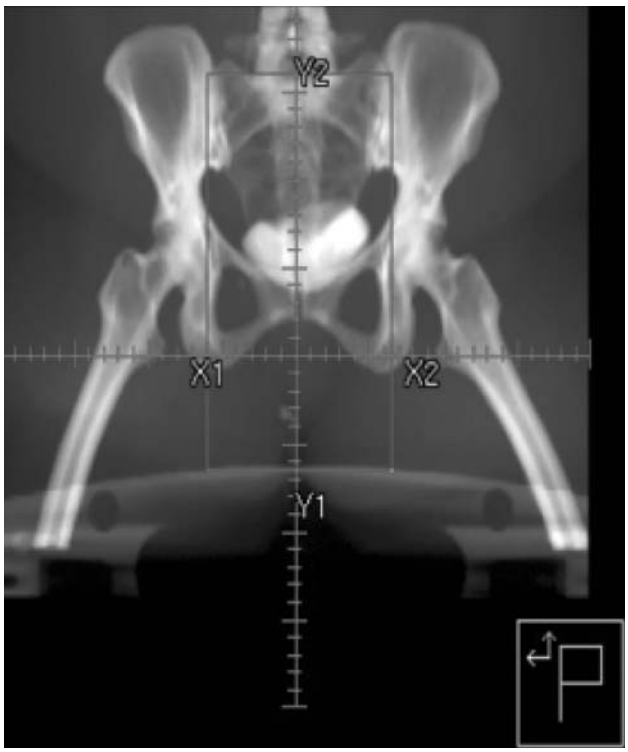


**Fig. 4** Initial narrow posterior–anterior field for pelvic external beam radiotherapy, sometimes used to reduce dose to the femoral heads

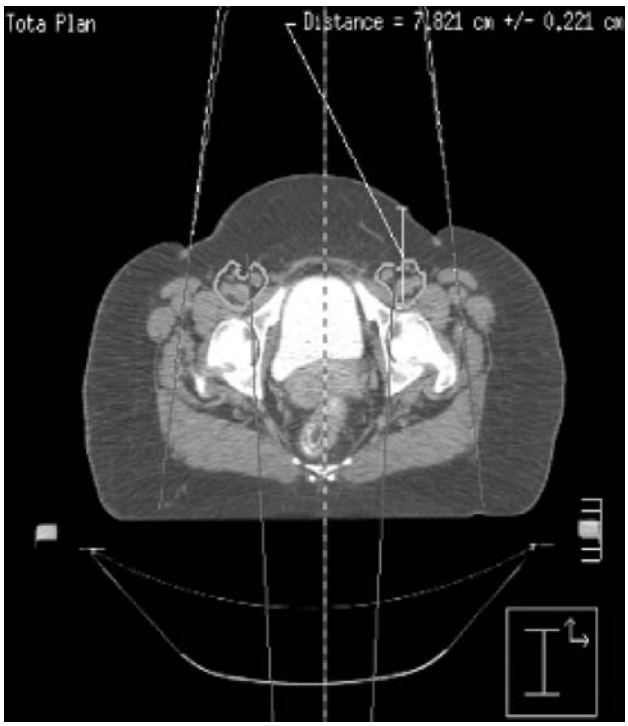


**Fig. 5** Axial CT scan showing diverging edges of the anterior–posterior and posterior–anterior beams from Figs. 3 and 4, and the depth of the inguinal nodes at that level

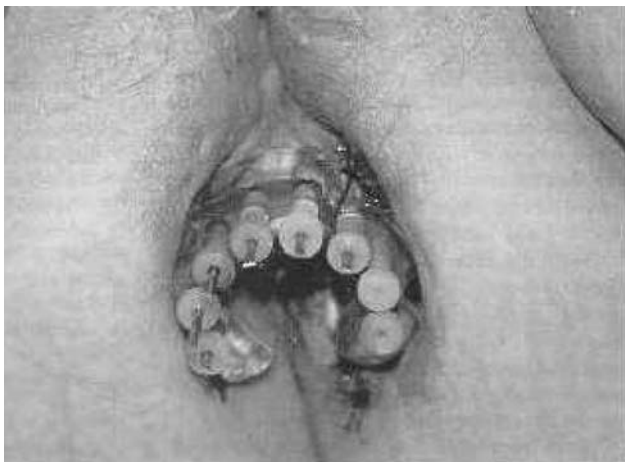

**Fig. 6** Image of a Papillon style implant of the anal canal (used with permission [26]) for brachytherapy boost to the primary site

acute proctitis and skin reaction from external beam has diminished somewhat, and the 10–15 h it takes to deliver the boost makes this approach logistically straightforward. This approach is limited to lesions that are less than 4 cm long, and less than half the circumference of the anus. External beam boosts are also effective and allow treatment of gross nodal disease simultaneous with the primary tumor.

## Results of treatment

Early lesions may be treated successfully with local therapy. As discussed above, WLE or radiation alone for T1N0 lesions results in local control rates of ≥90% and overall survival of approximately 100% at 5 years [25, 26, 29, 37]. For more advanced disease, T2 or greater or node positive, modern treatment approaches with continuous infusion 5FU and MMC chemotherapy with continuous course radiotherapy yield local control rates of 87–90% [1, 53]. In the most recent RTOG trial, 98-11, regional/nodal failures occurred as the first site of failure in <10% of patients. The 5-year local-regional recurrence and distant metastasis rates were 25 and 15%, respectively, in the MMC arm [1]. APR is successful as salvage therapy in about 50% of patients that present with a local-only recurrence. The salvage rate is very poor in patients that have positive nodes at initial presentation, nodal relapses, or persistent/relapsed disease at the primary site that is fixed to the pelvic sidewall [21, 56–59].

## Complications of treatment

More than 75% of patients will suffer at least one grade 3 or higher toxicity during modern chemoradiotherapy regimens [1]. The most common acute toxicities are fatigue, nausea, diarrhea, thrombocytopenia, neutropenia, and skin breakdown in the treatment field. Twelve percent of patients in RTOG 87-04/ECOG 1289 required an unplanned break in treatment due to acute toxicity. Toxic deaths occur up to 2% in randomized trials [44–46] although none were reported in either arm of RTOG 98-11 [1]. Around 5–10% of patients suffer severe long-term toxicity after chemoradiation [1, 26, 50, 53], with around 5% requiring colostomy for treatment-related problems rather than tumor recurrence [26, 44, 45, 47]. Late toxicity may include chronic diarrhea, anal stenosis, incontinence (particularly if the sphincter was involved by tumor), chronic pelvic pain, hip fracture, and sexual dysfunction [60].

## Anal canal carcinoma in HIV patients

As discussed above, as HIV patients have gained longer life expectancy through the use of HAART, their risk of developing anal canal cancers has increased. While cancer of the uterine cervix is an AIDS-defining illness, cancer of the anal canal is not [61]. HIV patients with anal canal cancer present at a younger age, and with earlier stage disease, and are more often male than non-HIV patients [14, 27]. Some investigators have reported worse outcomes in patients with HIV compared to those who are HIV-negative [14, 27]; however, others have shown similar cancer control outcomes regardless of HIV status [62, 63]. Most studies do suggest that HIV patients are more likely to suffer significant acute toxicity from chemoradiation, particularly hematologic toxicity associated with MMC [14, 27, 62, 64]. Some authors have related low CD4 counts (<200–350 cells/mL) to increased acute toxicity [65] or worse cancer-specific survival [62], while others have shown no correlations between worse toxicity [14, 62–64] or cancer control-related outcomes [14, 63, 65] and CD4 counts. It should be noted that the most recent reports that show less influence of CD4 counts on outcomes, both cancer control and toxicity related, have evaluated HIV-positive patients treated with HAART [14, 62, 63]. HAART has been found to increase mucosal toxicity of chemotherapy [66] and increase radiosensitivity in some cancer cells [67]. These findings suggest that HAART potentially could increase toxicity of treatment but could also improve cancer response. Stadler and colleagues compared outcomes of HIV-positive patients with anal canal cancers and receiving chemoradiation with HAART to those who did not receive HAART. Their findings suggested a trend for better survival in patients treated with HAART to those that did not receive HAART ($P = 0.0524$) [68]. Toxicity seemed similar between the two groups. It has been suggested that all HIV-positive patients with anal canal carcinoma should be considered for HAART [36, 62, 68, 69]. In general, HIV-positive patients should be treated with chemoradiation similar to HIV-negative patients although some investigators have substituted 5FU/cisplatin regimens for 5FU/MMC regimens, in order to decrease hematologic toxicity [63, 64, 68]. Others advocate for new approaches to improve disease control and reduce toxicity in this population [14, 62]. One such approach is the National Cancer Institute-sponsored AIDS Malignancy Consortium's phase II study (AMC 045) of chemoradiation consisting of cisplatin (75 mg/m$^2$ on days 1 and 29), 5FU (1,000 mg/m$^2$ CI on days 1–4 and 29–32) and cetuximab (400 mg/m$^2$ on days 8, 15, 22, 29, 36, and 42) with radiotherapy to 45–59.4 Gy (depending on stage) at 1.8 Gy per fraction with no planned breaks [70] (registered at http://ClinicalTrials.gov as NCT00324415).

## New directions

There are a number of exciting new developments concerning multimodality treatment of malignancies, including anal canal cancers. Technological improvements in radiotherapy have brought about a flood of new approaches for delivering radiation. Intensity-modulated radiotherapy (IMRT) allows for the delivery of tumoricidal doses of

radiotherapy to the target tissues while allowing for more normal tissue sparing. IMRT has been implemented in some institutions for anal canal carcinoma [71]. The difficulty in this approach lies in the details. Instead of drawing fields to the shape desired for each radiotherapy beam, a very straightforward approach, the different target and normal (avoidance) tissues are contoured in the treatment planning computer (Fig. 7). Then dose constraints and objectives are fed into the treatment planning computer system. The planning program then tries to develop the best solution to the problem presented. This is called inverse treatment planning. In this way, constraints on dose to the femoral heads, uninvolved skin, genitalia, bladder, small bowel, and proximal rectum/sigmoid colon can be entered into the treatment planning system. Similarly, minimum dose objectives for elective nodal regions as well as higher doses for areas of gross disease can be prescribed. From these input data, the computer program attempts to find a solution that fulfills all the requirements. While using IMRT may spare normal tissues radiation dose, this approach is absolutely dependent on the radiation oncologist to be very knowledgeable of anatomy, tumor location and extent, and draining lymphatic pathways for appropriate contouring, or the computer may not target the correct area. Figure 8 illustrates a typical beam arrangement for an IMRT approach for anal cancer. The RTOG recently completed enrollment for a phase II trial of IMRT for anal canal cancers (RTOG 0529) and has developed an anatomical atlas to assist in appropriate treatment planning (http://www.rtog.org/anoratlas/main.html) [72]. The results of RTOG 0529 have not yet been published.

IMRT is capable of producing very sharp dose fall-off, such that normal tissues close to target areas may be spared radiation dose. This can make set-up accuracy very important in order to ensure that the target is appropriately treated and not missed or under-dosed. Image-guided radiotherapy (IGRT) is another recent tool that has been developed to help improve accuracy of patient set-up and treatment. In general, IGRT is the use of pre-treatment imaging with the patient in the treatment position on the treatment table. Orthogonal X-ray images or "cone-beam" CT using a kV X-ray head and electronic X-ray detector built on the gantry of the linear accelerator allow for these images to be taken to verify the proper position of the patient immediately prior to treatment. Computer software systems then allow for millimeter adjustments in patient positioning to improve accuracy of treatment set-up to $\leq$5 mm. IGRT can be used with standard external beam radiotherapy but is most beneficial when IMRT is implemented, since set-up accuracy may be of greater importance. Helical tomotherapy has also been applied to anal canal cancers [73]. This approach is another form of

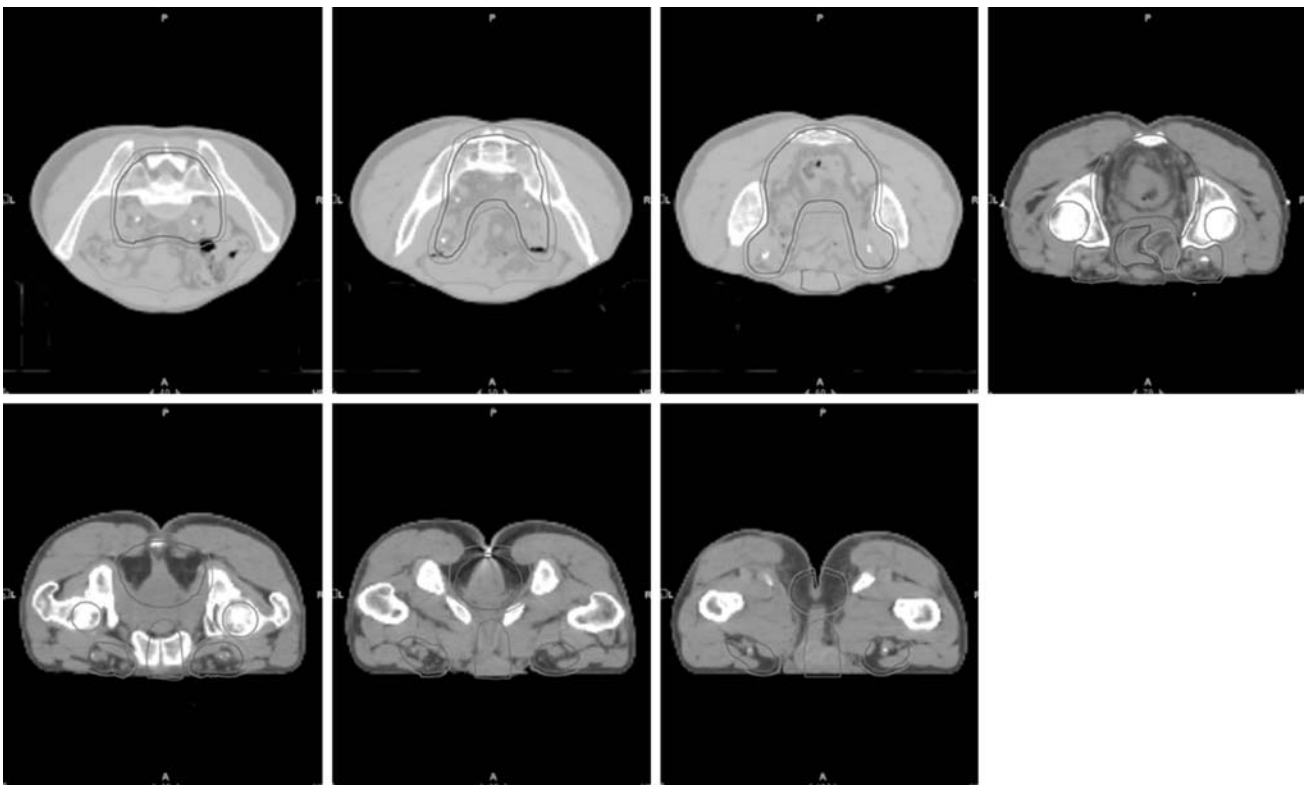

**Fig. 7** Target volume delineation required to deliver intensity-modulated radiotherapy for anal canal cancer

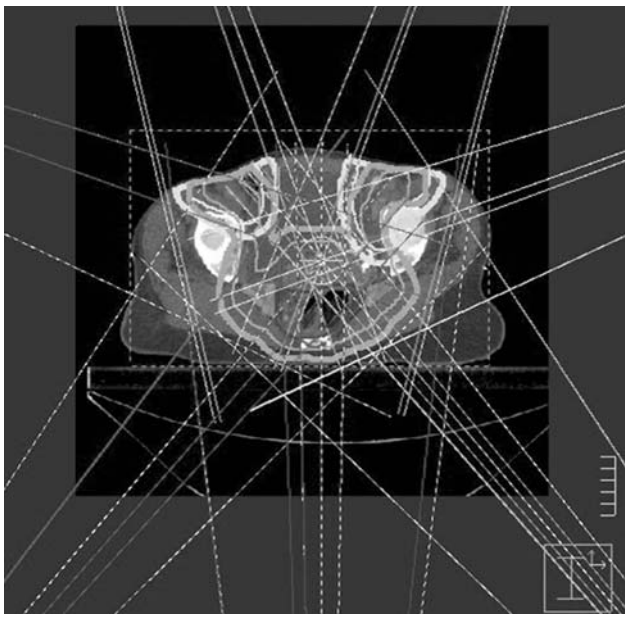

**Fig. 8** Typical beam arrangement used for intensity-modulated radiotherapy for anal canal cancer

IMRT using a Tomotherapy® unit that allows for the delivery of radiotherapy over 360° of rotation around the patient. It also includes an integrated megavoltage CT scanner that can provide for IGRT similar to the cone-beam CT described above for IGRT [74]. Figure 9 illustrates an IMRT dose distribution achieved using helical tomotherapy.

Multimodality cancer treatment has also benefited from the development of new anti-cancer pharmaceuticals. "Small molecule" therapies, such as tyrosine kinase inhibitors and in particular epidermal growth factor receptor (EGFR) inhibitors, have become more prevalent for squamous cell carcinomas and some are being investigated for anal canal cancer. Cetuximab is a monoclonal antibody against the EGFR. It has been shown to be effective in squamous cell cancers of the head and neck when combined with radiotherapy [75] or chemotherapy [76] and is now being evaluated against anal cancers in the trial mentioned above for HIV-positive patients (AMC 045). There are other small molecule kinase inhibitors under investigation as well as anti-angiogenic agents, anti-inflammatory agents, and other novel approaches being investigated for other squamous cell carcinomas [77]. Eventually, these agents may find a place in the treatment of anal canal cancers through integration into clinical trials. Current clinical trials for anal canal cancers listed on the National Cancer Institute's web site include a four-arm United Kingdom trial comparing 5FU/MMC chemoradiation

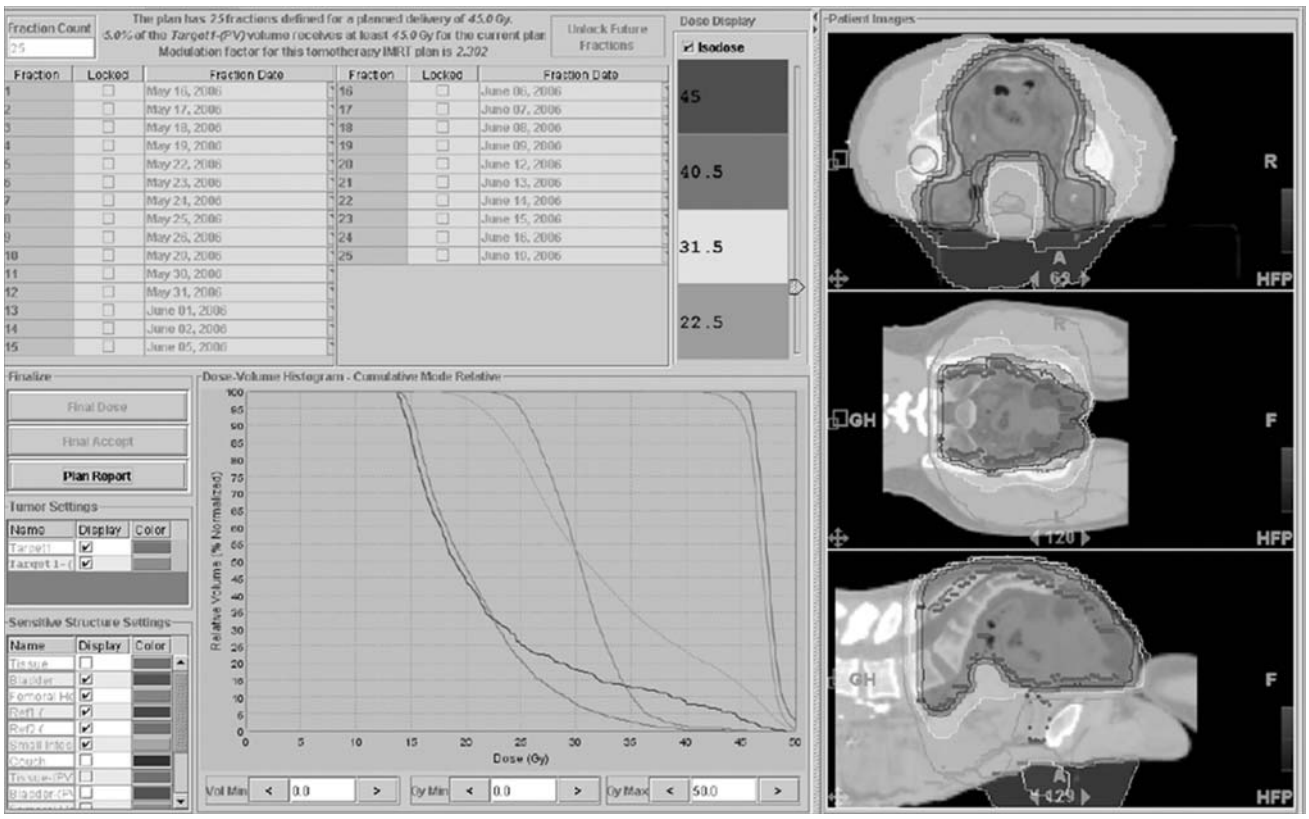


**Fig. 9** Example of a dose distribution from helical tomotherapy for anal canal cancer

to 5FU/cisplatin chemoradiation, with or without adjuvant 5FU/cisplatin chemotherapy after chemoradiation (registered at http://ClinicalTrials.gov as NCT00025090). Another active clinical trial is evaluating capecitabine and oxaliplatin combined with radiation therapy at the M.D. Anderson Cancer Center in Houston (registered at http://ClinicalTrials.gov as NCT00093379).

Preventing a cancer is always better than having to treat one. One major development in the prevention of cancer that is likely to affect the impact of anal canal cancer is the HPV vaccines. There are two vaccines that have undergone large randomized trials. Both vaccines present the L1 protein as a target for immune response. The L1 protein composes the majority of the viral capsid that makes up the main component of the viral shell. The first vaccine (Ceravix®) is a bivalent vaccine designed against HPV types 16 and 18. The other vaccine (Gardasil®) is a quadrivalent vaccine against HPV types 6, 11, 16 and 18. These two vaccines have been shown in randomized trials to decrease the rate of persistent infection in young women as well as to prevent cervical cancer [78–80]. The quadrivalent vaccine has been approved by the US FDA for use in females aged 9–26 for the prevention of cervical cancer and genital warts. Data recently presented have shown that quadrivalent vaccine decreased the rate of persistent HPV infection [81] and genital warts [82] in males, although these results have not yet been published. Their effect on the risk of anal cancer in any population has not yet been tested. However, most anal canal cancers involve persistent HPV infection. It seems reasonable to assume that any decrease in persistent HPV infection rates in a high-risk population may decrease the incidence of anal canal cancer. These vaccines also have not been shown to protect against diseases caused by HPV types with which the patient was infected before vaccination. Patients are protected against HPV types in the vaccines with which the patient was not infected before vaccination.

## Conclusions

Anal canal cancers are diagnosed in approximately 5,000 people each year in the United States. Recent progress in HPV vaccines may herald a decrease in the incidence of anal cancers in the future if ways to implement them in high-risk populations are developed. In terms of treatment of anal cancer, great gains in organ preservation have been made over the last three decades. Local excision or radiotherapy alone yields high cures for early-stage disease. With combined chemotherapy and radiotherapy, survival rates without colostomy are around 80–90% with disease-free survival in the range of 60% at 5 years for locally advanced disease. New approaches to reduce toxicity of therapy and increase efficacy are needed, particularly in HIV-positive patients.

**Conflict of interest statement** The authors declare that they have no conflict of interest to the publication of this article.

## References

1. Ajani JA, Winter KA, Gunderson LL et al (2008) Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 299:1914–1921
2. Welton ML, Sharkey FE, Kahlenberg MS (2004) The etiology and epidemiology of anal cancer. Surg Oncol Clin N Am 13:263–275
3. Scarpini C, White V, Muralidhar B et al (2008) Improved screening for anal neoplasia by immunocytochemical detection of minichromosome maintenance proteins. Cancer Epidemiol Biomark Prev 17:2855–2864
4. Gervaz P, Hirschel B, Morel P (2006) Molecular biology of squamous cell carcinoma of the anus. Br J Surg 93:531–538
5. Jemal A, Siegel R, Ward E et al (2007) Cancer statistics. CA Cancer J Clin 57:43–66
6. Jemal A, Siegel R, Ward E et al (2008) Cancer statistics. CA Cancer J Clin 58:71–96
7. Steenbergen RD, de Wilde J, Wilting SM et al (2005) HPV-mediated transformation of the anogenital tract. J Clin Virol 32(Suppl):S25–S33
8. zur Hausen H (1977) Human papillomaviruses and their possible role in squamous cell carcinomas. Curr Top Microbiol Immunol 78:1–30
9. Frisch M (2002) On the etiology of anal squamous carcinoma. Dan Med Bull 49:194–209
10. Weaver BA, Feng Q, Holmes KK et al (2004) Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis 189:677–685
11. Rousseau DL Jr, Thomas CR Jr, Petrelli NJ, Kahlenberg MS (2005) Squamous cell carcinoma of the anal canal. Surg Oncol 14:121–132
12. Daling JR, Madeleine MM, Johnson LG et al (2004) Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 101:270–280
13. Palefsky JM, Holly EA, Efirdc JT et al (2005) Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS 19:1407–1414
14. Oehler-Jänne C, Huguet F, Provencher S et al (2008) HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol 26:2550–2557
15. Longacre TA, Kong CS, Welton ML (2008) Diagnostic problems in anal pathology. Adv Anat Pathol 15:263–278
16. Dujovny N, Quiros RM, Saclarides TJ (2004) Anorectal anatomy and embryology. Surg Oncol Clin N Am 13:277–293
17. American Joint Committee on Cancer (2002) AJCC cancer staging manual. Springer, New York
18. Abeloff MD et al (2008) Abeloff's clinical oncology. Churchill Livingstone/Elsevier, Philadelphia
19. Rouviere H (1938) Anatomy of the human lymphatic system. A compendium translated from the original Anatomie des Lymphatiques Des L'Homme, and rearranged for the use of students and practicioners, by M.J. Tobias. Edwards Brothers, Ann Arbor

20. Nigro ND, Vaitkevicius VK, Considine B Jr (1974) Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum 17:354–356
21. Longo WE, Vernava AM III, Wade TP et al (1995) Rare anal canal cancers in the US veteran: patterns of disease and results of treatment. Am Surg 61:495–500
22. Paterson C, Musselman L, Chorneyko K et al (2003) Merkel cell (neuroendocrine) carcinoma of the anal canal: report of a case. Dis Colon Rectum 46:676–678
23. Ragnarsson-Olding BK, Nilsson PJ, Olding LB, Nilsson BR (2008) Primary ano-rectal malignant melanomas within a population-based national patient series in Sweden during 40 years. Acta Oncol 19:1–7
24. Klas JV, Rothenberger DA, Wong WD, Madoff RD (1999) Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. Cancer 85:1686–1693
25. Deniaud-Alexandre E, Touboul E, Tiret E et al (2003) Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. Int J Radiat Oncol Biol Phys 56:1259–1273
26. Mitchell SE, Mendenhall WM, Zlotecki RA, Carroll RR (2001) Squamous cell carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 49:1007–1013
27. Kim JH, Sarani B, Orkin BA et al (2001) HIV-positive patients with anal carcinoma have poorer treatment tolerance and outcome than HIV-negative patients. Dis Colon Rectum 44:1496–1502
28. Frost DB, Richards PC, Montague ED et al (1984) Epidermoid cancer of the anorectum. Cancer 53:1285–1293
29. Boman BM, Moertel CG, O'Connell MJ et al (1984) Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. Cancer 54:114–125
30. Gerard JP, Chapet O, Samiei F et al (2001) Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. Cancer 92:77–84
31. Grabenbauer GG, Kessler H, Matzel KE et al (2005) Tumor site predicts outcome after radiochemotherapy in squamous-cell carcinoma of the anal region: long-term results of 101 patients. Dis Colon Rectum 48:1742–1751
32. Martellucci J, Naldini G, Colosimo C, Cionini L et al (2008) Accuracy of endoanal ultrasound in the follow-up assessment for squamous cell carcinoma of the anal canal treated with radiochemotherapy. Surg Endosc [Epub ahead of print]
33. Giovannini M, Bardou VJ, Barclay R et al (2001) Anal carcinoma: prognostic value of endorectal ultrasound (ERUS). Results of a prospective multicenter study. Endoscopy 33:231–236
34. Nguyen BT, Joon DL, Khoo V et al (2008) Assessing the impact of FDG-PET in the management of anal cancer. Radiother Oncol 87:376–382
35. Cotter SE, Grigsby PW, Siegel BA et al (2006) FDG-PET/CT in the evaluation of anal carcinoma. Int J Radiat Oncol Biol Phys 65:720–725
36. Kauh J, Koshy M, Gunthel C et al (2005) Management of anal cancer in the HIV-positive population. Oncology (Williston Park) 19:1634–1638
37. Rabbani A, Zlotecki R, Morris C, Mendenhall W (2008) Tumors of the anal canal: organ preservation with radiotherapy. Int J Radiat Oncol Biol Phys 72:S273–S274
38. Nigro ND, Seydel HG, Considine B et al (1983) Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 51:1826–1829
39. Kanamori H, Shima T, Morita C, Hata T (1957) Studies on antitumor activity of mitomycin. J Antibiot (Tokyo) 10:120–127
40. Shiraha Y, Sakai K, Teranaka T (1958–1959) Clinical trials of mitomycin C, a new antitumor antibiotic; preliminary report of results obtained in 82 consecutive cases in the field of general surgery. Antibiot Annu 6:533–540
41. Thomas CR Jr, Stelzer KJ, Douglas JG et al (1994) Common emergencies in cancer medicine: infectious and treatment-related syndromes. Part II. J Natl Med Assoc 86:839–852
42. Rosenberg B, VanCamp L, Trosko JE, Mansour VH (1969) Platinum compounds: a new class of potent antitumour agents. Nature 222:385–386
43. Harder HC, Rosenberg B (1970) Inhibitory effects of anti-tumor platinum compounds on DNA, RNA and protein syntheses in mammalian cells in vitro. Int J Cancer 6:207–216
44. UKCCCR Anal Cancer Trial Working Party, UK Co-ordinating Committee on Cancer Research (1996) Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, mitomycin. Lancet 348: 1049–1054
45. Bartelink H, Roelofsen F, Eschwege F et al (1997) Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 15:2040–2049
46. Flam M, John M, Pajak TF et al (1996) Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 14:2527–2539
47. Gerard JP, Ayzac L, Hun D et al (1998) Treatment of anal canal carcinoma with high dose radiation therapy and concomitant fluorouracil–cisplatinum. Long-term results in 95 patients. Radiother Oncol 46:249–256
48. Hung A, Crane C, Delclos M et al (2003) Cisplatin-based combined modality therapy for anal carcinoma: a wider therapeutic index. Cancer 97:1195–1202
49. Musio D, Codacci-Pisanelli G (2008) Chemotherapy and radiotherapy for anal canal carcinoma. JAMA 300:1410–1411
50. Hughes LL, Rich TA, Delclos L et al (1989) Radiotherapy for anal cancer: experience from 1979–1987. Int J Radiat Oncol Biol Phys 17:1153–1160
51. Constantinou EC, Daly W, Fung CY et al (1997) Time–dose considerations in the treatment of anal cancer. Int J Radiat Oncol Biol Phys 39:651–657
52. John M, Pajak T, Flam M et al (1996) Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. Cancer J Sci Am 2:205–211
53. Konski A, Garcia M Jr, John M et al (2008) Evaluation of planned treatment breaks during radiation therapy for anal cancer: update of RTOG 92-08. Int J Radiat Oncol Biol Phys 72:114–118
54. Papillon J (1974) Radiation therapy in the management of epidermoid carcinoma of the anal region. Dis Colon Rectum 17:181–187
55. Papillon J, Montbarbon JF, Gerard JP et al (1989) Interstitial curietherapy in the conservative treatment of anal and rectal cancers. Int J Radiat Oncol Biol Phys 17:1161–1169
56. Pocard M, Tiret E, Nugent K et al (1998) Results of salvage abdominoperineal resection for anal cancer after radiotherapy. Dis Colon Rectum 41:1488–1493
57. Ellenhorn JD, Enker WE, Quan SH (1994) Salvage abdominoperineal resection following combined chemotherapy and radiotherapy for epidermoid carcinoma of the anus. Ann Surg Oncol 1:105–110
58. Mullen JT, Rodriguez-Bigas MA, Chang GJ et al (2007) Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. Ann Surg Oncol 14:478–483

59. Schiller DE, Cummings BJ, Rai S et al (2007) Outcomes of salvage surgery for squamous cell carcinoma of the anal canal. Ann Surg Oncol 14:2780–2789
60. Papadopoulos K, Thomas CR (2007) Role of combined modality therapy for anal cancer. Gastrointestinal oncology: evidence and analysis, Informa Healthcare, London, pp 199–210
61. (1992) 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 41
62. Wexler A, Berson AM, Goldstone SE et al (2008) Invasive anal squamous-cell carcinoma in the HIV-positive patient: outcome in the era of highly active antiretroviral therapy. Dis Colon Rectum 51:73–81
63. Blazy A, Hennequin C, Gornet JM et al (2005) Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of highly active antiretroviral therapy. Dis Colon Rectum 48:1176–1181
64. Edelman S, Johnstone PA (2006) Combined modality therapy for HIV-infected patients with squamous cell carcinoma of the anus: outcomes and toxicities. Int J Radiat Oncol Biol Phys 66:206–211
65. Hoffman R, Welton ML, Klencke B et al (1999) The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Radiat Oncol Biol Phys 44:127–131
66. Sparano JA, Wiernik PH, Hu X et al (1998) Saquinavir enhances the mucosal toxicity of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma. Med Oncol 15:50–57
67. Pajonk F, Himmelsbach J, Riess K et al (2002) The human immunodeficiency virus (HIV)–1 protease inhibitor saquinavir inhibits proteasome function and causes apoptosis and radiosensitization in non-HIV-associated human cancer cells. Cancer Res 62:5230–5235
68. Stadler RF, Gregorcyk SG, Euhus DM et al (2004) Outcome of HIV-infected patients with invasive squamous-cell carcinoma of the anal canal in the era of highly active antiretroviral therapy. Dis Colon Rectum 47:1305–1309
69. Ryan DP, Clark JW (2005) Review: management of anal cancer in the HIV-positive population. Oncology (Williston Park) 19:1638–1645
70. Remick SC (2005) Review: management of anal cancer in the HIV-positive population. Oncology (Williston Park) 19:1645–1648
71. Kachnic L, Tsai H, Willins J et al (2008) Early clinical outcome in patients treated for anal canal cancer using dose-painted intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 72:S260
72. Myerson R, Garofalo M, El Naqaet I et al (2008) Elective clinical target volumes for conformal therapy in anorectal cancer: an RTOG consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 72:S71
73. Han C, Chen Y, Liu A et al (2007) Dosimetric study and in vivo dose verification for conformal avoidance treatment of anal adenocarcinoma using helical tomotherapy. Med Dosim 32:33–37
74. Welsh JS, Lock M, Harari PM et al (2006) Clinical implementation of adaptive helical tomotherapy: a unique approach to image-guided intensity modulated radiotherapy. Technol Cancer Res Treat 5:465–479
75. Bonner JA, Harari PM, Giralt J et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567–578
76. Vermorken JB, Mesia R, Rivera F et al (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359:1116–1127
77. Le Tourneau C, Siu LL (2008) Molecular-targeted therapies in the treatment of squamous cell carcinomas of the head and neck. Curr Opin Oncol 20:256–263
78. Ault KA (2007) Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 369:1861–1868
79. Villa LL, Costa RL, Petta CA et al (2006) High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer 95:1459–1466
80. Paavonen J, Jenkins D, Bosch FX et al (2007) Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 369:2161–2170
81. Palefsky J, Giuliano A (2008) Efficacy of the quadrivalent HPV vaccine against HPV 6/11/16/18-related genital infection in young men. Nice, France. http://www.eurogin.com/2008/EUROGIN2008_LastMinuteAbstracts.pdf
82. Giuliano A, Palefsky J (2008) The efficacy of quadrivalent HPV (types 6/11/16/18) vaccine in reducing the incidence of HPV-related genital disease in young men. Nice, France. http://www.eurogin.com/2008/EUROGIN2008_LastMinuteAbstracts.pdf