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REVIEW ARTICLE

Management of locally advanced anal canal carcinoma with intensity-modulated radiotherapy and concurrent chemotherapy

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Abstract

The best curative option for locally advanced (stages II–III) squamous-cell carcinomas of the anal canal (SCCAC) is concurrent chemo-radiotherapy delivering 36–45 Gy to the prophylactic planning target volume with an additional boost of 14–20 Gy to the gross tumor volume with or without a gap-period between these two sequences. Although 3-dimensional conformal radiotherapy led to suboptimal tumor coverage because of field junctions, this modality remains a standard of care. Recently, intensity-modulated radiotherapy (IMRT) techniques improved tumor coverage while decreasing doses delivered to organs at risk. Sparing healthy tissues results in fewer severe acute toxicities. Consequently, IMRT could potentially avoid a gap-period that may increase the risk of local failure. Furthermore, these modalities reduce severe late toxicities of the gastrointestinal tract as well as better functional conservation of anorectal sphincter. This report aims to critically review contemporary trends in the management of locally advanced SCCAC using IMRT and concurrent chemotherapy.

Keywords Squamous-cell carcinoma · Anal canal, Cancer · Chemo-radiotherapy · Intensity-modulated radiation therapy · Volumetric modulated arc therapy · Helical tomotherapy

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Introduction

Squamous-cell carcinoma of the anal canal (SCCAC) is a rare malignancy representing 0.4% of new cancer cases per year in the United States with a predominance in women [1]. Over the past three decades, SCCAC's incidence has been rising due to human papilloma virus (HPV) and acquired human immunodeficiency virus (HIV), particularly among middle-aged men [2]. SCCAC's management represents a double challenge: ensuring high local tumor control and prolonged survival while preserving sphincter function in order to maintain the best quality of life.

The anal canal measures 3–5 cm and is located in the distal part of the digestive tract between the rectum and the anal margin. The most common histology is squamous-cell carcinoma representing 95% of cases. Less frequently, other forms could be diagnosed: adenocarcinoma, small-cell carcinoma, undifferentiated carcinoma, sarcoma, lymphoma, or melanoma. The latest WHO classification distinguishes three subtypes within SCCAC: large keratinizing cell carcinoma, large non-keratinizing cell carcinoma, and basaloid cell carcinoma [3]. Among all newly diagnosed SCCAC, between 25 and 35% present lymph node involvement [4]. Lymphatic pathways are the following: an ascending one to the perirectal (mesorectal), internal iliac, and pre-sacral lymph nodes for lesions arising above the dentate line; a second one, anterior, to the external inguinal and iliac lymph nodes for lesions infiltrating below the dentate line. Only 5% of patients are metastatic at diagnosis [5].

In the 1970s and 1980s, the mainstay of treatment was surgery and consisted in an abdominal-perineal amputation. In the 1980s, the radiosensitivity of SCCAC was demonstrated, leading to the reduction of surgical indications in favor of definitive radiotherapy (±concurrent chemotherapy) [6–11]. Currently, the treatment of SCCAC depends upon the stage of disease and can include chemotherapy, radiation therapy, or surgery. Locally advanced SCCAC is usually treated with concurrent chemotherapy and radiotherapy [12]. Abdominal-perineal surgery is generally reserved for recurrent or residual disease following first-line chemo-radiation [12, 13]. Treatment should be started as soon as possible after validation in a multidisciplinary tumor board, preferably in a reference center with known expertise in treating SCCAC.

The aim of this report is to critically review contemporary trends in the management of locally advanced SCCAC (stages II and III) using modern radiotherapy techniques and concurrent chemotherapy.

Epidemiology

Risk factors associated with SCCAC are HPV infection, HIV-positive status, anal intercourse, multiple sexual partners, chronic immunosuppression, age, and tobacco use [14]. The relationship between oncogenic HPV infection and incidence of SCCAC has been investigated. On the one hand, high rates of HPV-DNA up to 88% are detected in SCCAC or in most precancerous lesions. On the other hand, HPV vaccination reduces the rate of intraepithelial neoplasia in the anal canal. These results argue for a causal issue between the oncogenic viral infection and the development of SCCAC [15, 16]. Several studies have shown that expression of oncogene p16 was associated with HPV in SCCAC [17]. Early reports have suggested a more favorable outcome in patients with markers indicative of HPV infection [18, 19]. Among a HIV-positive population factors favoring the appearance of SCCAC are a persistent HPV infection and a low CD4 count [20, 21]. Unfavorable prognostic factors include male gender [22], lymph node involvement [22], tumor size superior to 5 cm [23], ulcerated tumor [24], and absence of HPV-DNA or expression of p16 [19].

Prevention of SCCAC is based on the following: detection of early HPV-induced lesions, HPV vaccination, detection and treatment of HIV infection in high-risk populations, and smoking cessation. In a randomized trial of 4065 males aged from 16 to 26 years, a quadrivalent HPV vaccine demonstrated a significant reduction in external genital lesions compared with placebo [25]. In a subset analysis, the quadrivalent vaccine was associated with a 50% incidence reduction of intraepithelial neoplasia which has led to an approval by the US Food and Drug Administration of the quadrivalent vaccine (Gardasil; Merck, Readington Township, NJ) to prevent SCCAC [26].

Pre-therapeutic assessment

SCCAC symptoms occur lately, and are generally non-specific, reflecting tumor size and/or infiltration; 45% of patients present with anorectal bleeding, 30% with anorectal with pain or fullness, and 20% are asymptomatic. Physical exam specifically includes a digital rectal (and vaginal in women) examination specifying tumor size and location as well as adjacent anatomic structure involvement, a detailed evaluation of the sphincter function, and a perineal skin and anal margin inspection. Careful palpation of inguinal and supraclavicular lymph nodes is systematic and can be supplemented by an ultrasonography (US) if necessary.

A complete gynecological examination including a cervical smear (Papanicolaou (PAP) test) is recommended in

women to detect dysplasia/neoplasia of the cervix, vagina, or vulva. For men, a penile examination should also be systematic. Anuscopy and rectoscopy with biopsies are mandatory for histopathologic analyses, to evaluate anal canal involvement and to detect concurrent high-grade precancerous lesions. Excisional biopsies and/or tumor cytoreduction surgery are not recommended due to the risk of sphincter lesions. Last but not least, patients' performance status, medical co-morbidities, and tobacco consumption should be assessed. Laboratory analyses should test for relevant infections such as HIV and pre-chemotherapy evaluation such as renal and hepatic function and complete blood count [13].

Two staging classifications are commonly used based on physical examination and radiographic imaging. First, the UICC TNM classification (8th edition) takes into account tumor stage (size and invasion of adjacent structures), lymph node involvement (location), and presence of metastasis. Second, the US-TNM classification evaluates the depth of the tumor lesion by endoscopic US. This one allows a better distinction between the T2 and T3 stages [27, 28].

Radiographic imaging includes magnetic resonance imaging (MRI) of the anal canal to assess the local extent to the neighboring anatomical structures, particularly the sphincter-related musculature and the lymph nodes with a special attention for the mesorectum [29]. Computed tomography (CT) scans of the chest, the abdomen, and the pelvis can detect distant metastases. Fluorodeoxyglucose positron emission tomography (FDG-PET) is recommended for advanced tumors or for patients with a high suspicion of lymph node involvement. FDG-PET has a high sensitivity (about 93%) and a moderate specificity (about 76%) in immunocompetent patients that were classified negative on CT [30, 31]. HIV-positive patients, however, may present with a high incidence of false-positive FDG-PET-inguinal lymph nodes, ranging from 25 to 57% [32]. Although inflammatory lymph nodes may present with hypermetabolic activity on FDG-PET, biopsies are recommended for all suspicious inguinal lymph nodes in order to avoid unnecessary over-irradiation. Moreover, FDG-PET imaging has shown high sensitivity rates (93–100%) in the initial detection of primary tumor in situ [31].

The impact of FDG-PET on patient management reveals a marked trend for upstaging after identifying occult nodal disease. T2–T4 stages are more likely to get their final stage reconsidered. As a consequence, eight studies have reported on modified treatment plans (in 12.5–59.3% of patients) based on FDG-PET findings, mostly changes in radiotherapy dose or field adjustments [31].

Management should not be modified based on HIV-positive status or age with good performance status. Ideally, the viral load should be < 10.000, and CD4 > 200 [33, 34] though for patients with CD4 < 250 chemotherapy should be discussed on a case-by-case basis. The risk of a unique hematological toxicity from mitomycin C (MMC) in the elderly and HIV + patients recommends a thorough monitoring of these frail patients during chemotherapy [35, 36].

Chemotherapy for locally advanced stages

The standard for locally advanced SCCAC is concurrent chemo-radiotherapy [13]. The reference chemotherapy regimen consists in prescribing 2 cycles of a continuous intravenous infusion of 1 000 mg/m^2/day of 5-fluorouracil (5-FU) (day 1 to 4 and 29 to 32) associated with 10 mg/m^2 of intravenous MMC (days 1 and 29) administrated in 28-day intervals [13, 37, 38]. Historically, the *United-Kingdom Coordinating Committee for Cancer Research* trial conducted the first randomized trials that proved higher local–regional control using concurrent chemo-radiotherapy with MMC and 5-FU (64%) versus radiotherapy alone (41%) [39]. The benefit of concurrent chemotherapy was confirmed after 13-year of follow-up [22]. Later on, the *European Organization for Research and Treatment of Cancer* (EORTC) published similar results in terms of loco-regional control and lower colostomy rates with the adjunction of concurrent 5-FU and MMC [40]. The role of MMC was questioned because of a marked treatment-related hematologic toxicity [41]. The *RTOG 87-04* trial showed lower colostomy rates and increased disease-free survival at 4 years with the association of MMC and 5-FU compared to 5-FU alone when combined to radiotherapy even though high-grade toxicity rates were more prevalent with MMC [42]. Therefore, MMC prescription may be reconsidered for unfit patient or if hematologic toxicity is expected. In addition, Glynne-Jones et al. observed minimal toxicity and an acceptable compliance when replacing the usual 4-day intravenous perfusion of 5-FU by capecitabine (825 mg/m^2/twice daily) on each radiation day and MMC 12 mg/m^2 only on day 1 [43]. For that reason, capecitabine remains nowadays an accepted option in substitution of 5-FU in association with MMC.

Alternative chemotherapy strategies have turned out so far to be disappointing. Indeed, cisplatin (with 5-FU) has been tested as induction, concomitant, or maintenance schedules. No evidence of improvement has been observed in terms of disease-free or colostomy-free survival after induction [23, 44, 45]. Moreover, MMC-5FU is associated with better colostomy and disease-free survival rates compared to cisplatin-5FU regimens [23, 44]. Cisplatin-based concurrent chemo-radiotherapy did not exhibit lower adverse effects or better complete tumor responses, colostomy, or progression-free survival rates [46].

Epidermal growth factor receptors (EGFR) are overexpressed in 80–90% of SCCAC, whereas KRAS and BRAF mutations, determinants for an anti-EGFR antibody

resistance, are less common than in colorectal cancer [47, 48]. Although preliminary reports suggested a potential activity of anti-EGFR agent trials combining cetuximab, 5-FU, and cisplatin, such studies were condemned to an early shutdown due to unexpected severe adverse event rates [49–53]. However, a phase II trial testing Panitumumab (NCT01285778), a human monoclonal antibody targeting EGFR, completed recruitment in 2017. Results of safety and efficacy of concurrent radiotherapy with MMC, 5-FU, and Panitumumab are awaited.

Three-dimensional conformational radiotherapy (3D-CRT)

In the 1990s–2000s, six phase III trials defined concurrent chemo-radiotherapy as the "gold standard" treatment for locally advanced stages [39, 40, 42, 45, 54, 55]. Radiation therapy aimed to deliver a total dose of 45 Gy in 1.8–2 Gy daily fractions to the pelvic planning target volumes (PTV), followed by an additional dose (boost) of 14–20 Gy to a reduced volume including the tumor and the macroscopically involved lymph nodes. Large volumes of normal tissues and organs at risk were irradiated as most studies used 2D or 3D-CRT techniques. This technical limitation was associated with high rates of adverse events: > 70% of grade 3–4 acute toxicities, 15% of treatment breaks or early treatment completion of radiation therapy, and 10% of grade 3–4 late toxicities [42, 54].

A rest between the pelvic and the reduced boost volume irradiation phases was considered mandatory to better manage acute grade 3–4 toxicity events from 3D-CRT (e.g., perineal epithelitis, rectitis, diarrhea, nausea, and hematologic toxicities) that compromised compliance. The *Radiation Therapy Oncology Group* (RTOG) 92-08 study suggested a deleterious effect on local control of a two-week gap during radiotherapy. A comparison of 2 trials found that overall survival and disease-free survival of patients treated with a gap ($n = 20$) were worse than those irradiated without planned interruptions ($n = 46$) after a follow-up of 8 years (43% vs. 73%, and 34% vs. 63%, respectively). As expected, however, acute toxicity rates were higher for patients treated without a gap (i.e., grade 3–4 hematologic (78%), dermatologic (78%), digestive (28%), and infectious (17%) toxicities) [56]. A shorter treatment-free interval correlated best with a better 5-year loco-regional control [57]. Short potential doubling times and fast accelerated repopulation of SCCAC may explain their clinical response to continuous compared to protracted treatments. Indeed, treatment interruptions may favor tumor repopulation [58].

There is no wide consensus around the doses to be prescribed to both the subclinical and the gross tumor and/or nodal volumes. Indeed, dose escalation strategies, such as the ACCORD 03 trial, that evaluated a dose escalation of the boost dose from 15 Gy to 20–25 Gy failed to demonstrate any major benefit [45]. The high-dose boost in this trial did not improve the 5-year colostomy-free survival. Besides, radiosensitive healthy organs exposed to high doses of radiation, such as the gastrointestinal tract, presented with a marked risk increase of late toxicity with dose escalation [59]. For instance, fecal incontinence which progresses over 1–3 years following radiotherapy is common among SCCAC survivors (43%) lowering patients' quality of life [60]. Recent retrospective studies tend to confirm the absence of a relevant benefit of escalation dose over 59 Gy on overall survival or local control [61]. The RTOG 92-08 evaluated prospectively a boost of 59.4 Gy with a mandatory 2-week treatment break. In comparison to the RTOG 87-04 which delivered a boost of 50.4 Gy, no statistical difference was shown, possibly due to the limited number of patients [56].

IMRT versus 3D-CRT

The first dosimetric studies comparing IMRT with 3D-CRT for SCCAC were published in 2005. IMRT significantly reduced doses delivered to OARs while providing satisfactory tumor coverage and homogeneous PTV dose distribution [62–64]. Unfortunately, RTOG 05-29 trial was not conclusive because the primary endpoint, a 15% reduction in acute grade-2 toxicity with IMRT compared to 3D-CRT, was not achieved. Nonetheless, skin and digestive grade-3 toxicity events with this trial were significantly reduced with IMRT, though in terms of efficacy, 2-year overall survival rates were not statistically different between the two groups [65]. With dose constraints to the pelvis (iliac bones), hematological toxicity was also reduced after dosimetric optimization [66]. Table 1 summarizes studies comparing IMRT versus 3D-CRT for the management of locally advanced SCCAC.

IMRT reduces, in addition, late toxicity rates. Vieillot et al. observed late genito-urinary and cutaneous toxicity rates (grade-1/2) of 14% and 3%, respectively, and late gastrointestinal toxicity rate (≥ grade-3) of 7% in a series of 39 patients [70]. Pollom et al. reported that IMRT was associated with reduced hospitalization events at 3 and 6 months (hazard ratio, 0.70; 95%CI 0.58–0.84) compared to 3D-CRT [71].

Compared to 3D-CRT, arc therapy and helical tomotherapy present the following advantages: lower doses to the organs at risk with lesser risk for acute and late toxicity events; possibility of skipping the irradiation-free gap; and reduce intermediate and high doses to normal tissues [72, 73]. Joseph et al. reported on quality of life in a prospective study with patients treated with helical tomotherapy and concurrent chemotherapy. The impairment of functions and

Table 1 Comparison of 3-dimensional conformal versus intensity-modulated radiotherapy for the management of squamous-cell anal canal carcinoma

Author Year	Patient number	Stage	Pelvic dose (Gy)	Total boost dose (Gy)	Treatment days	Concurrent chemotherapy	Treatment break	Overall survival	Local control	Acute toxicity Grade ≥ 3	Late toxicity Grade ≥ 3
Bazan [67] 1993–2009 Retrospective	46 IMRT: 29 3DCRT: 17	I IMRT: 7% 3DCRT: 24% **II** IMRT: 59% 3DCRT: 29% **III** IMRT: 34% 3DCRT: 47%	*Upper pelvic* **30.6–39.6** (Gy) IMRT: 38% 3DCRT: 76% **45** (Gy) IMRT 41% 3DCRT: 12% *Lower pelvic* **30.6–39.6** (Gy) IMRT: 0% 3DCRT: 35% **45** (Gy) IMRT: 97% 3DCRT: 59%	Median IMRT: 54 3DCRT: 54 **50–55** (Gy) IMRT: 69% 3DCRT: 53% **> 55** (Gy) IMRT: 28% 3DCRT: 29%	Median IMRT: 40 3DCRT: 57 ($p < 0.0001$)	45 patients (98%) IMRT: 100% 3DCRT: 94%	Median (days) IMRT: 1.5 3DCRT: 12 ($p < 0.0001$) % IMRT: 34.5% 3DCRT: 88% ($p < 0.0001$)	At 3 years IMRT: 88% 3DCRT: 52% ($p < 0.01$)	At 3 years IMRT: 92% 3DCRT: 57% ($p < 0.01$)	IMRT: 21% 3DCRT: 65% ($p = 0.003$) **Intestinal** IMRT: 7% 3DCRT: 29% **Skin** IMRT: 21% 3DCRT: 41% **Hematologic** IMRT: 21% 3DCRT: 29%	-
Chuong [68] 2000–2011 Retrospective	89 IMRT: 52 3DCRT: 37	**I** IMRT: 19% 3DCRT: 13.5% **II** ($p = 0.001$) IMRT: 35% 3DCRT: 65% **III** IMRT: 46% 3DCRT: 22%	36 or 45	Median IMRT: 56 3DCRT: 59.4 ($p = 0.038$)	Median IMRT: 38.5 3DCRT: 49 ($p < 0.0001$)	7 patients (8%) IMRT: 2% 3DCRT: 16%	Median (days) IMRT:8 3DCRT: 12 ($p = 0.6$)	At 3 years IMRT: 86% 3DCRT: 91% ($p > 0.1$)	At 3 years IMRT: 92% 3DCRT: 91% ($p > 0.1$)	IMRT: 21% 3DCRT: 59.5% ($p < 0.0001$) **Intestinal** IMRT: 9.5% 3DCRT: 30% ($p = 0.06$) **Skin** IMRT: 11.5% 3DCRT: 65% ($p < 0.0001$) **Hematologic** ($p > 0.1$)	**Intestinal** IMRT: 6% 3DCRT: 24% ($p = 0.01$) **Hematologic** ($p > 0.1$)

Table 1 (continued)

Author Year	Patient number	Stage	Pelvic dose (Gy)	Total boost dose (Gy)	Treatment days	Concurrent chemotherapy	Treatment break	Overall survival	Local control	Acute toxicity Grade ≥ 3	Late toxicity Grade ≥ 3
Weber [69] 1992–2014 Retrospective	103 VMAT: 17 3DCRT: 86	**I** VMAT: 6% 3DCRT: 13% **II** VMAT: 41% 3DCRT: 53.5% **III** VMAT: 53% 3DCRT: 33.5%	50.4 (Gy)	50.4 (Gy) (1.8 (Gy) per fractions)	–	96 patients (93%) VMAT: 94% 3DCRT: 93%	–	–	At 2 years VMAT: 100% 3DCRT: 80% ($p=0.7$)	VMAT: 35% 3DCRT: 53.5% ($p<0.05$) **Intestinal** VMAT: 12% 3DCRT: 9% ($p=0.2$) **Skin** VMAT: 29% 3DCRT: 44% ($p=0.1$) **Hematologic** VMAT: 12% 3DCRT: 17% ($p=0.9$)	–
For IMRT Kachnic [65] 2006–2008 RTOG 0529 Phase II trial *For 3DCRT* Ajani [44] 1998–2005 RTOG 9811 Phase III trial	IMRT: 52 3DCRT: 325	**I** IMRT: 0% 3DCRT: 47% **II** IMRT: 54% 3DCRT: 19% **III** IMRT: 46% 3DCRT: 10%	IMRT 42–45 (Gy) 3DCRT 45 (Gy)	IMRT 50.4–54 (Gy) 3DCRT 55–59 (Gy)	Median IMRT: 43 3DCRT: 49 ($p<0.0001$)	IMRT: 100% 3DCRT: 100%	Median (days) IMRT: 0 3DCRT: 3 ($p=0.0047$) % IMRT: 49% 3DCRT: 62% ($p=0.09$)	–	–	IMRT: 83% 3DCRT: 87% ($p=0.23$) **Intestinal** IMRT: 21% 3DCRT: 36% ($p=0.0082$) **Skin** IMRT: 23% 3DCRT: 49% ($p<0.0001$) **Hematologic** IMRT: 58% 3DCRT: 62% ($p=0.29$)	–

IMRT static or dynamic intensity-modulated radiation therapy, *3DCRT* 3-dimensional conformal radiotherapy, *VMAT* volumetric intensity-modulated arc therapy

symptoms was temporary for most patients and recovered 3 months after treatment completion [74]. The potential drawbacks of arc therapy and helical tomotherapy are also important: numerous entrance gates of the beams around the body (360° rotation) with a widely spread-of integral low dose; long linac- and MLC-related quality control times; long preparation times (e.g., delegation, dosimetry, quality control); high-dose gradients within the target volume; an accurate delineation of organs at risk; and time-consuming daily IGRT. Tubiana et al. reported on the importance of intermediate and high doses, as well as on the major impact of dose per fraction and dose distribution in the risk of second cancer induction [75].

To summarize, IMRT is a significant technical innovation that has led to better acute and medium-term tolerance of radiotherapy. It allows an optimization of the distribution of doses resulting in an improved hematological tolerance of chemo-radiotherapy. Nevertheless, it has not demonstrated any superiority in terms of efficacy compared to a conventional 3-dimensional technique.

Table 2 Differences between the French, American, and Australian/Asian Atlases regarding target volumes and expansion margins

Referential	CTV T	CTV N	Prophylactic or "low-risk" PTV	Boost or high-risk PTV
French Intergroup [12]	GTV T + anal canal + 10 (mm)	Vessels + 7 (mm) excluding muscles and bones	CTV T and N + 7 (mm)	GTV T and N + 15 (mm)
American (RTOG) [79]	GTV T + canal anal + 20 (mm)	Vessels + 7–8 (mm) excluding muscles and bones	CTV T and N + 7–10 (mm)	GTV T and N + 20 (mm)
Australian (AGITG) [78]	GTV T + canal anal + 20 (mm)	Vessels + 7 (mm) excluding muscles and bones	CTV T and N + 10 (mm) CTV T and N + 5–7 (mm) in case of daily IGRT	GTV T + 20 (mm) GTV N + 10–20 (mm)

CTV clinical target volume, *T* tumor, *N* lymph node(s), *PTV* planning target volume, *GTV* gross tumor volume, *IGRT* image-guided radiotherapy

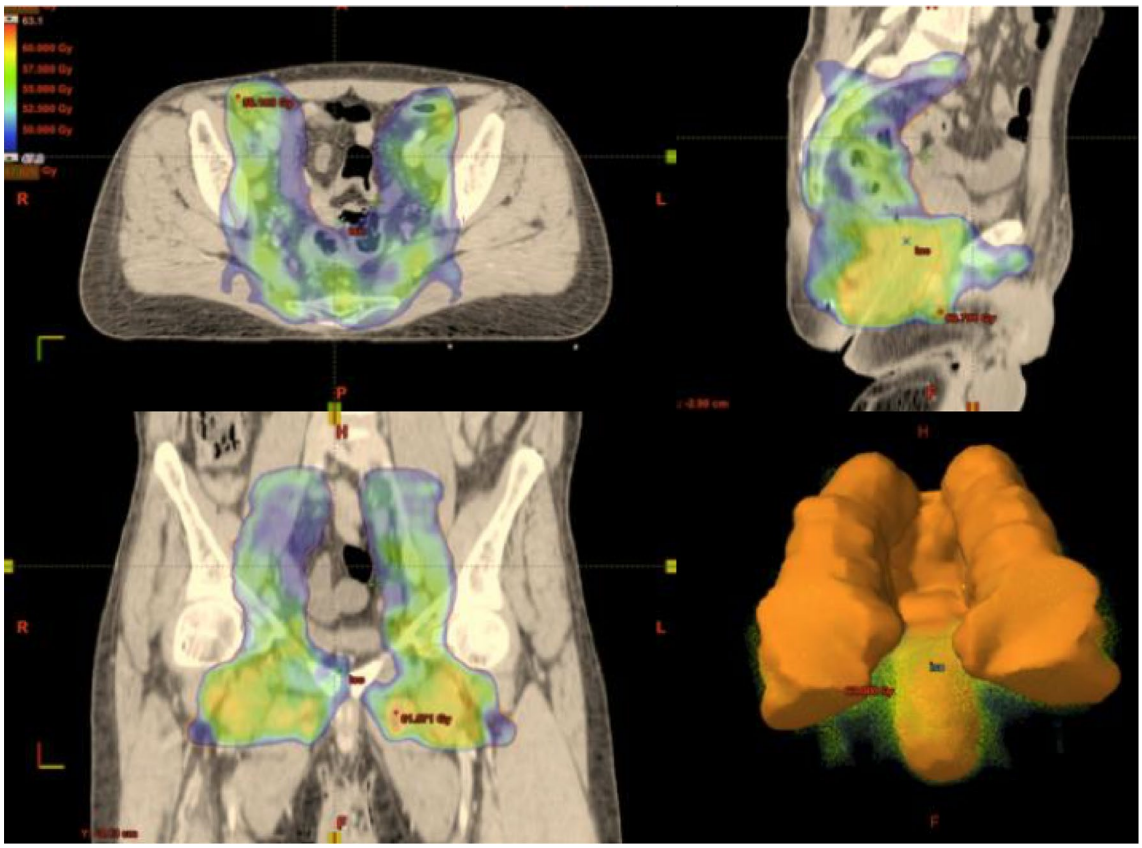

Fig. 1 Coverage of the prophylactic planning target volume by the 95% isodose (47 Gy) with intensity-modulated radiation therapy for locally advanced anal canal carcinoma (T2N3, bilateral nodes)

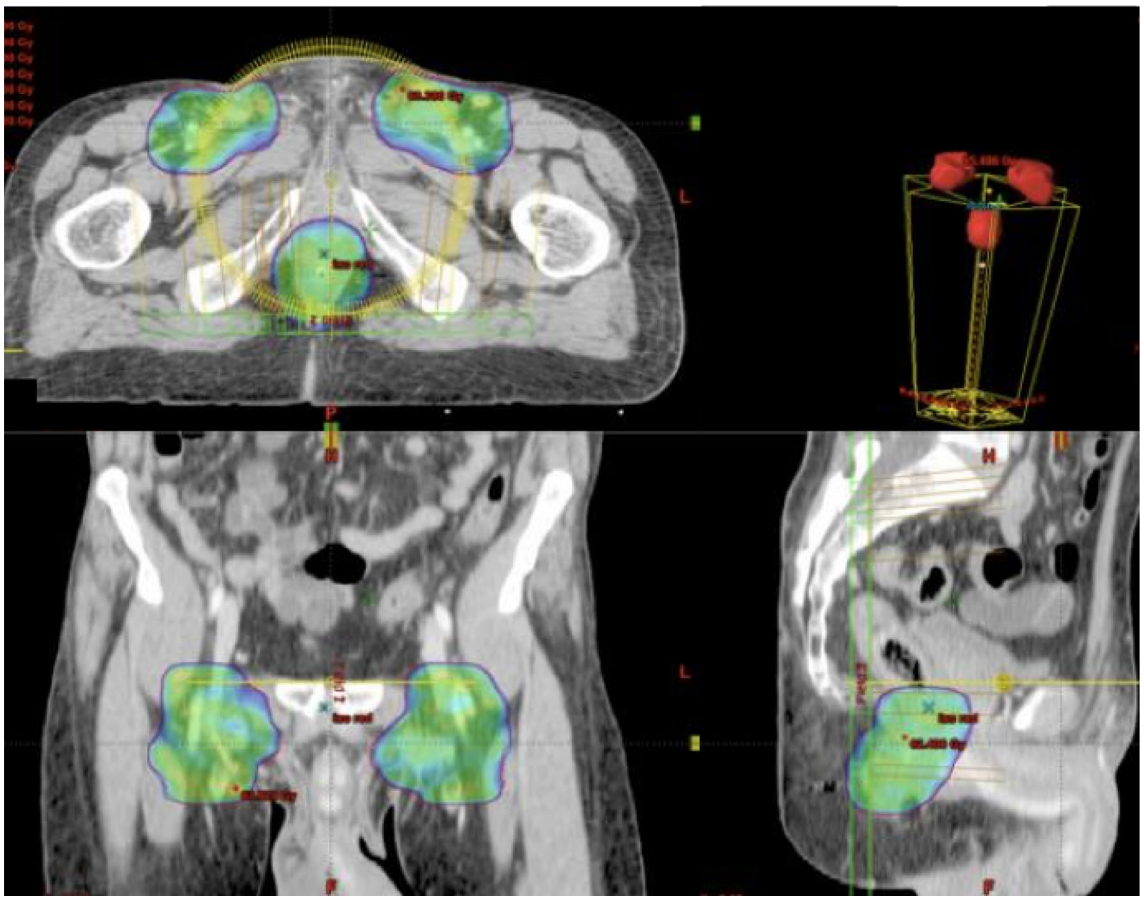

Fig. 2 Coverage of the boost planning target volume by the 95% isodose (56.4 Gy) with intensity-modulated radiation therapy for locally advanced anal canal carcinoma (T2N3, bilateral nodes)

Volumes and doses using IMRT

The extent of the gross tumor volume (GTV) is determined from physical examination, imaging, and endoscopic findings. The delineation of target volumes may be optimized by co-registration between the planning CT scan and a FDG-PET, and/or a strict axial cross-section pelvic MRI [76]. Lymph node involvement looks related with the size and invasion extent of the primary tumor (i.e., 0–10% for T1–T2 vs. 40–50% for T3–T4) [77]. The risk of recurrence is highest in the first three years mostly in the pelvic region (50% in the anorectal region and less often in the common iliac and the pre-sacral regions).

Three atlas guidelines are currently available for delineation [12, 78, 79]. Differences between these guidelines are summarized in Table 2. The superior extent of the low-risk volume (or subclinical disease treatment volume) is commonly the sacral promontory (or L5-S1 interface); the inferior one is 3 cm below the GTV. The definition of subclinically involved lymph node clinical target volume systematically includes bilateral internal and external iliac, obturator, pre-sacral, and mesorectal lymph nodes. Ischiorectal and common iliac regions are added in patients with advanced-stage disease (T3–T4 or N+). Historically, the risk of metachronous inguinal metastases has been reported to be low (7–8%) in clinically node-negative patients at initial staging without inguinal irradiation [80, 81].

Ortholan et al. assessed the benefit of prophylactic bilateral inguinal irradiation with 45 Gy. They were able to show a lower 5-year cumulative rate of inguinal recurrence in the irradiated group (2% vs. 16%, $p=0.006$). The benefit was particularly relevant in patients irradiated with T3–T4 tumors (0% vs. 30%, $p=0.003$), though non-significant in patients irradiated with T1–T2 tumors (3% vs. 12%, $p=0.17$) [82]. Similar findings were observed in a cohort of 116 patients with T2 node-negative tumors, with only a 4.7% rate of inguinal relapses in patients treated without inguinal irradiation [83]. In summary, published data are consistent to recommend the inclusion of the inguinal regions in the low-risk irradiation volume only in patients with advanced local disease (T3–T4) or infiltration below the dentate line. No decisional consensus exists, however, for patients with

Table 3 Literature review of intensity-modulated radiotherapy with simultaneous integrated boost (SIB) modality for the management of squamous-cell anal canal carcinoma

Author Year Technique	Patient HIV positive p16 positive	Stage	Pelvic dose Fraction (fr)	Boost dose Fraction (fr)	Treatment time	Concurrent chemo-therapy	Treatment break	Overall survival	Local control	Acute toxicity Grade ≥ 3	Late toxicity Grade ≥ 3
Kachnic [65] 2006–2008 IMRT	52 patients HIV: 0% p16: NA	**II** 54% **III** 46%	(*1.5 Gy/fr*) **T2N0** 42 (Gy) 28 (fr) **T3/4N0** 45 (Gy) 30 (fr) **N+ < 3 cm** 50.4 (Gy) 30 (fr) (*1.68 Gy/fr*) **N+ > 3 cm** 54 (Gy) 30 (fr) (*1.8 Gy/fr*)	(*1.8 Gy/fr*) **T2N0** 50.4 (Gy) 28 (fr) **T3/4N0** 54 (Gy) 30 (fr) **N+** 54 (Gy) 30 (fr)	Median 43 days Range 32–59	100%	Median 0 days Range 0–12 days 49%	–	–	**Intestinal** 21% **Skin** 23% **Hematologic** 58% **Urinary** 2%	–
Yates [87] 2008–2011 IMRT	42 patients HIV: 7% p16: NA	**I** 12% **II** 41% **III** 45%	(*1.5 Gy /fr*) **T2N0** 42 (Gy) 28 (fr) **T3/4N0** 45 (Gy) 30 (fr) **N+ < 3 cm** 50.4 (Gy) 30 (fr) (*1.68 Gy/fr*) **N+ > 3 cm** 54 (Gy) 30 (fr) (*1.8 Gy/fr*)	(*1.8 Gy/fr*) **T2N0** 50.4 (Gy) 28 (fr) **T3/4N0** 54 (Gy) 30 (fr) **N+** 54 (Gy) 30 (fr)	Median 43 days	100%	Median 5 days Range 2–10 days 19%	At 3 years 92%	At 3 years 94%	**Intestinal** 14% **Skin** 33% **Hematologic** 19%	–
Belgioia [88] 2009–2014 TOMO	41 patients HIV: 5% p16: 85%	**I** 5% **II** 32% **III** 63%	(*1.8 Gy /fr*) **T1N0: 5%** 41.4 (Gy) 23 (fr) **T2N0: 24%** 43.2 (Gy) 24 (fr) **≥T3/N+: 71%** 45 (Gy) 25 (fr)	(*2.2 Gy/fr*) **T1N0: 5%** 50.6 (Gy) 23 (fr) **T2N0: 24%** 52.8 (Gy) 24 (fr) **≥T3/N+: 71%** 55 (Gy) 25 (fr)	Median 35 days Range 30–40	39 patients (95%)	Median 1 day Range 1–3 days 7.3%	At 2 years 93%	At 2 years 92%	**Intestinal** 7% **Skin** 5% **Hematologic** 7%	**Intestinal** 4% **Urinary** 4%

Table 3 (continued)

Author Year Technique	Patient HIV positive p16 positive	Stage	Pelvic dose Fraction (fr)	Boost dose Fraction (fr)	Treatment time	Concurrent chemo-therapy	Treatment break	Overall survival	Local control	Acute toxicity Grade ≥ 3	Late toxicity Grade ≥ 3
Joseph [89] 2008–2016 TOMO	57 patients HIV: 0% p16: NA	**II** 48% **III** 52%	(*1.5 Gy/fr*) 45 (Gy) 30 (fr)	(*1.8 Gy /fr*) 54 (Gy) 30 (fr)	–	56 patients (98%)	Median (days) NA 9%	At 3 years 91%	–	**Intestinal** 24% **Skin** 10.5% **Hematologic** 46% **Urinary** 3.5%	**Intestinal** 5% **Urinary** 2% **Gynecologic** 9%
Franco [90] 2007–2013 IMRT 74% VMAT 13% TOMO 13%	54 patients HIV: 6% p16: NA	**II** 54% **III** 46%	**T2N0** 42 (Gy) 28 (fr) (*1.5 Gy /fr*) **T3/4N0** 45 (Gy) 30 (fr) (*1.5 Gy/fr*) **N + < 3 cm** 50.4 (Gy) 30 (fr) (*1.68 Gy/fr*) **N + > 3 cm** 54 (Gy) 30 (fr) (*1.8 Gy/fr*)	**T2N0** 50.4 (Gy) 28 (fr) (*1.8 Gy/fr*) **T3** 54 (Gy) 30 (fr) (*1.8 Gy/fr*) **T4** 60 (Gy) 30 (fr) (*2 Gy/fr*)	Median 44 days Range 37–55	52 patients (96%)	Mean 4 days 17%	At 4 years 78%	At 4 years 85%	**Intestinal** 8% **Skin** 13% **Hematologic** 11% **Urinary** 2%	*Grade 2* **Intestinal** 14% **Urinary** 2% **Gynecologic** 4%
Franco [91] 2007–2013 VMAT	39 patients HIV: 8% p16: NA	**I** 5% **II** 67% **III** 28%	**T2N0** 42 (Gy) 28 (fr) (*1.5 Gy /fr*) **T3/4N0** 45 (Gy) 30 (fr) (*1.5 Gy/fr*) **N + < 3 cm** 50.4 (Gy) 30 (fr) (*1.68 Gy/fr*) **N + > 3 cm** 54 (Gy) 30 (fr) (*1.8 Gy/fr*)	**T2N0: 33%** 50.4 (Gy) 28 (fr) (*1.8 Gy/fr*) **T3/T4: 67%** 54 (Gy) 30 (fr) (*1.8 Gy/fr*)	Median 43 days Range 38–54	100%	Mean 2 days 30%	At 2 years 85%	–	**Intestinal** 5% **Skin** 18% **Hematologic** 13% **Urinary** 2%	–

Table 3 (continued)

Author Year Technique	Patient HIV positive p16 positive	Stage	Pelvic dose Fraction (fr)	Boost dose Fraction (fr)	Treatment time	Concurrent chemo-therapy	Treatment break	Overall survival	Local control	Acute toxicity Grade ≥ 3	Late toxicity Grade ≥ 3
Tomasoa [92]	106 patients	**I**	*(1.5 Gy/fr)*	*(1.8 Gy/fr)*	–	87 patients (82%)	6%	At 4 years	At 4 years	**Intestinal**	**Intestinal**
2006–2012	HIV: NA	4%	49.5 (Gy)	59.4 (Gy)				77%	79%	14%	4%
IMRT	p16: NA	**II**	33 (fr)	33 (fr)						**Skin**	
		33%								62%	
		III								**Hematologic**	
		55%								7%	

IMRT static or dynamic intensity-modulated radiation therapy, *TOMO* helical tomotherapy, *VMAT* volumetric intensity-modulated arc therapy

T1–T2 tumors. Prophylactic groin irradiation will be recommended on a case-by-case basis and based on the location and size of the primary tumor and on whether a lymph node evaluation is undertaken.

Two clinical target volumes (CTV) may be distinguished for SCCAC irradiation: a low-risk volume including mesorectal, pelvic, and inguinal lymph nodes; and a high-risk volume corresponding to the primary tumor and the involved lymph nodes. A margin of 7–8 mm is generally recommended around the iliac vessels, excluding muscles and bony structures. The margin around the femoral vessels may be ≥ 7 mm to include all surrounding lymph nodes. The RTOG and the *Australasian Gastrointestinal Trials Group* guidelines recommend an additional 10-mm margin anterior to the mesorectal CTV, accounting for rectal motion [84]. International IMRT guidelines suggest a wide range of CTV to PTV margins, ranging from 5 to 10 mm in the prophylactic setting [51, 65, 78].

The PTV margins surrounding the GTV may range from 10 to 20 mm [78, 79, 84]. Figures 1 and 2 illustrate the coverage of the PTV by the 95% isodose using IMRT for a T2N3 SCCAC with bilateral nodes.

Too tight margins may ease a geographical miss in areas with an increased motion; too loose margins may be highly toxic if large volumes of normal tissues or organs at risk are included in the irradiation fields. Chen et al. reported on patients treated with a tight 5-mm margin and IGRT (pelvic bones auto-match on CBCT) for verification and concluded that those margins sustained by daily IGRT controls adequately covered the pelvic volumes reducing simultaneously the dose to the organs at risk [85]. Durrant et al. assessed the motion around the inguinal nodes and the local tumor region using an online CBCT protocol. The estimated 3D margins needed to compensate for random displacements in the lateral, longitudinal, and vertical axes around the inguinal nodes and the primary tumor were, respectively, 1.5 mm, 2.7 mm, and 2.8 mm and 4.6 mm, 8.9 mm, and 5.2 mm [86]. Indeed, the ongoing PLATO trial (ISRCTN88455282) will assess the safety of individualized radiotherapy doses considering reduced margins around the targets. PLATO comprises 3 independent phase II trials which evaluate the radiation dose based on low-, intermediate- or high-risk SCCAC. Locally advanced SCCAC (high-risk group) are randomized between a standard dose of 53.2 Gy in 28 fractions and two escalation doses of 58.8 Gy in 28 fractions or 61.6 Gy in 28 fractions. The primary outcome is loco-regional failure at 3 years.

Three issues have to be considered before scheduling the treatment. The first one is the total dose to be delivered to the low-risk PTV, 36 or 45 Gy in most studies, followed by a sequential boost of 14–23.4 Gy to the high-risk PTV (local tumor and involved lymph nodes) [12, 37]. Although these are the most frequently followed guidelines, there is no

Table 4 Low-dose elective nodal intensity-modulated radiation therapy schedule in the literature for squamous-cell carcinoma of the anus management

Author Year Technique	Patient	Stage	Pelvic dose Fraction (fr)	Boost dose Fraction (fr)	Treatment time	Concurrent chemo-therapy	Treatment break	Overall survival	Lymph node local control (LNLC) Tumor control (TC)	Acute toxicity Grade ≥ 3	Late toxicity Grade ≥ 3
Henkenberens [93] 2009–2014 3D-CRT 63% IMRT 37%	30 patients	**T1** 27% **T2** 63% **T3** 10%	(*1.8 Gy /fr*) 39.6 (Gy) 22 (fr)	**T1** 50 (Gy) **T2** 55.8 (Gy) **T3** 59.4 (Gy)	–	27 patients (90%)	–	At 3 years 90%	At 3 years LNLC = 100% TC = 93%	**Intestinal** 3% **Skin** 23% **Hematologic** 7%	**Intestinal** 0% **Urinary** 0%
Lepinoy [94] 1996–2013 3D-CRT 73% IMRT 27%	142 patients	**I** 2% **II** 55% **III** 43%	(*1.8 Gy /fr*) 36 (Gy) 20 (fr)	(*1,8 Gy/fr*) 59.4 (Gy) 33 (fr)	Median 59 days	100%	Median 14 days Range 14–28 100% (planned)	At 5 years 75%	At 5 years LNLC = 96% TC = 81.5% Inguinal = 98.5% 4 (3%) infield 1 (1%) outfield	**Intestinal** 1% **Skin** 2% **Hematologic** 2%	–
Lestrade [95] 2006–2014 TOMO 57% IMRT 34% VMAT 9%	35 patients	**T1** 54% **T2** 46%	(*1.8 Gy /fr*) 36 (Gy) 20 (fr)	(*1.8 Gy/fr*) 59.4 (Gy) 33 (fr)	Median 56 days Range 48–71	28 patients (80%)	Median 10 days Range 5–26 86% (planned)	At 4 years 93%	At 4 years LNLC = 100% TC = 96.6%	**Intestinal** 11% **Skin** 11% **Hematologic** 3%	–
De Bari [98] 2007–2015 TOMO 64% IMRT 26% VMAT 10%	151 patients	**I** 18% **II** 40% **III** 40%	(*1.8 Gy /fr*) 36 (Gy) 20 (fr)	(*1.8 Gy/fr*) 59.4 (Gy) 33 (fr)	Median 57 days Range 52–59	138 patients (91%)	Median 11 days Range 5–26 81% (planned)	At 4 years 82%	At 4 years LNLC = 96% TC = 82% Inguinal = 100%	**Intestinal** 7% **Skin** 16.5%	**Intestinal** 2%

3D-CRT 3-dimensional conformal, *IMRT* static or dynamic intensity-modulated radiation therapy, *TOMO* helical tomotherapy, *VMAT* volumetric intensity-modulated arc therapy; radiotherapy

consensus regarding on the low-risk PTV dose prescription. The RTOG 9811 trial aimed to deliver 45 Gy to the prophylactic volume in 25 daily fractions, followed by a sequential boost of 10–14 Gy in 2 Gy fractions [23]. The second issue to be considered is fractionation which is conventional (1.8 Gy/fraction/day, 5 times a week). The third issue to be taken in account is overall treatment time which should be as short as possible, ideally between 6 and 8 weeks (59–65 Gy in 33–36 fractions of 1.8 Gy).

The conventional scheme is a sequential plan. Sequential treatment modalities usually deliver 36–45 Gy in 20–25 fractions of 1.8 Gy, 5 times a week, to the low-risk PTV followed by a boost of 14.4–23.4 Gy in 8–13 fractions of 1.8 Gy to the high-risk region. If radiotherapy is carried out using simultaneous integrated boost (SIB) modality, the low-risk PTV shall receive a total dose ranging from 43.2 to 49.5 Gy, in 24–33 fractions of 1.5–1.8 Gy, five days a week, thus a normalized total dose (NTD1.8 Gy) of 48.2 Gy, with an alpha/beta = 10 Gy. The high-risk PTV, however, may be boosted up to a dose of 52.8–60 Gy in 24–33 fractions of 1.8–2.2 Gy, 5 times a week [67, 68, 87–97]. Table 3 presents the results of published studies using SIB modalities. It should be noted that no prospective trial investigates the regional failure rates associated with less than 1.8 Gy per fraction. A sequential plan is more often used compared to SIB. Indeed, a sequential treatment is preferred as it may be more convenient to plan treatment break in case of severe acute toxicity and to determine the final boost dose based on tumor response on treatment. Finally, SIB modality needs to be validated with larger prospective studies to be considered as a valuable and validate scheme. As shown in Table 4, elective nodal irradiation from the inguinal region with doses ranging from 36 to 39.6 Gy obtained excellent control rates (96–100%) with fairly good tolerance. Further prospective and randomized studies are required to compare 36 Gy versus 45 Gy in terms of local control and toxicity.

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