

Anal cancer treatment: Current status and future perspectives

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There are no indications for induction or maintenance therapies in locally advanced tumors. Many novel strategies, such as targeted therapies, vaccination, immunotherapy and photodynamic therapy are in clinical trials for the treatment of AC, with promising results in some indications.

Key words: Anal cancer; Optimum treatment; Updates; Guidelines; Novel approaches

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Core tip: This paper will be the newest study with the most recent updates in the treatment of anal cancer. After a brief review of different treatment of localized and metastatic anal cancer, the current options as well as novel therapies and approaches in future.

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Abstract

Anal cancers (AC) are relatively rare tumors. Their incidence is increasing, particularly among men who have sex with other men due to widespread infection by human papilloma virus. The majority of anal cancers are squamous cell carcinomas, and they are treated according to stage. In local and locally advanced AC, concomitant chemoradiation therapy based on mitomycin C and 5-Fluorouracil (5-FU) is the current best treatment, while metastatic AC, chemotherapy with 5-FU and cisplatin remains the gold standard.

INTRODUCTION

Anal cancers (AC) are relatively rare malignancies, representing less than 2.5% of all gastrointestinal (GI) cancers^[1]. When localized, they usually have an acceptable prognosis, with a five-year survival of 80%^[2].

The incidence of AC is currently increasing in men and women, particularly in men who have sex with other men, due to infection by human papilloma virus (HPV)^[3]. Anal cancer is typically preceded by high-grade anal intraepithelial neoplasia (AIN grade 2 or 3)^[4].

Factors reflecting a poor prognosis in AC include male sex, positive lymph nodes and a tumor size exceeding 5 cm^[5].

According to the WHO classification, ACs are divided into lesions arising either from the anal canal (predominant squamous epithelium) or the anal margin (lined with skin). Given that the majority of anal cancers have a squamous histology, this paper focuses solely on squamous cell cancers of the anal canal.

The treatment of AC depends on the staging of the tumor and is based on radiation therapy (RT), chemotherapy (CT) and surgery. Local and locally advanced anal canal tumors are managed with a combination of CT and RT, whereas chemotherapy alone is generally used to treat metastatic disease. Surgery remains the standard of care for recurrent and residual disease.

This paper reports the latest updates on AC treatment present in the literature. It summarizes all of the important studies and trials concerning possible treatments in AC, highlights the currently approved treatment options and discusses novel approaches and therapies.

EVOLUTION OF TREATMENT MODALITIES

Local and locally advanced AC

Initially, non-metastatic tumors of the anal canal were treated with abdominoperineal resection (APR) and permanent colostomy, with a five-year survival of 40% to 70% and a perioperative mortality of 3%^[6-13]. In 1974, Nigro *et al.*^[14] achieved complete pathological response in 3 patients using a combination of radiation therapy (30 Gy) and chemotherapy that included mitomycin C (MMC) and 5-fluorouracil (5-FU). Based on the findings of several studies and despite the absence of randomized trials comparing APR with radiation or chemoradiation (CRT), the use of concurrent RT with infusional 5-FU and MMC became the standard of care for patients with squamous cell anal cancer (SCAC), even those with T1-2 N0 disease. This treatment yielded five-year survival rates of 72% to 89%^[15-21]. This combination has had a statistically significant impact on overall survival (OS), colostomy-free survival (CFS) and nodal relapse risk reduction^[22]. Conversely, wide local excision can be a less morbid option for the management of well-differentiated T0 and early T1 tumors, if follow-up can be undertaken reliably^[23-25], with cure rates reaching 60% at 5 years and local recurrences of approximately 40%^[13,25,26].

The United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC) have conducted randomized controlled trials to compare concurrent radiotherapy plus 5-FU and MMC with radiotherapy alone (Table 1). The EORTC trial reported a significantly lower colostomy rate,

and both trials showed a significantly lower rate of locoregional failure in patients who received concurrent chemoradiation therapy. Overall survival was not significantly different between the groups in either trial. Fifteen of the 585 patients included in the UKCCCR trial had metastatic disease, and more patients in the CRT arm had T4 lesions or palpable nodes. CRT is therefore significantly superior to RT alone in terms of disease-free survival (DFS), local relapse, and CFS, but whether these benefits apply to early stage disease (T1-2, N0) remains unclear^[27,28].

In the Radiation Therapy Oncology Group (RTOG) 87-04 trial, which was conducted after the observation of increased hematologic toxicities with the use of MMC, significantly lower colostomy and local failure rates at 4 years were shown in patients who received the combination of radiotherapy with 5-FU plus MMC compared with those who received radiotherapy with 5-FU alone. Although the OS did not significantly differ between the groups, DFS was superior in the 5-FU and MMC group (73% vs 51% at 4 years; $P = 0.0003$)^[29]. For the extremely elderly population with T1N0 tumors or those with significant comorbidities, the administration of 5-FU without MMC during RT may be considered^[27].

In 2009, James *et al.*^[30] suggested that cisplatin might replace MMC in the treatment of non-metastatic anal cancer, with less hematologic toxicities and comparable response rates (RR), progression free survival (PFS), CFS, OS, and non-hematologic toxicities. However, these findings were not supported by the US intergroup RTOG 98-11 phase III trial, which showed significant differences favoring the combination of 5-FU and MMC in five-year DFS (68% vs 58%, $P = 0.006$) and OS (78% vs 71%, $P = 0.026$) after long-term follow-up^[31,32]. Moreover, in 2013, James *et al.*^[33] published the results of a randomized, phase III, open label, 2 × 2 factorial, ACT II trial, which included 940 patients with non-metastatic SCAC and compared MMC and cisplatin CRT with or without maintenance chemotherapy. No evidence of any improvement in the complete response (CR) rate or three-year PFS was observed, and similar acute grade 3 and 4 toxic effects were reported when fluorouracil plus cisplatin CRT was compared with fluorouracil plus mitomycin CRT.

However, James *et al.*^[33] also showed that the three-year PFS, colostomy rate and OS were similar in the groups that did or did not receive maintenance chemotherapy with FU and cisplatin ($P = 0.7$).

Patients with T3/4 primary tumors or N2/3 disease are also managed with RT plus concomitant 5-FU and MMC, reaching cure rates of 50% to 60%^[34]. With radiotherapy alone, approximately 70% of inguinal nodes are controlled, whereas 90% of synchronous inguinal nodes are controlled with the addition of chemotherapy^[26,35]. Other treatment options are listed in Table 2.

In 2005, in a population-based series of 308 patients, Nilsson *et al.*^[36] showed a significant benefit of

Table 1 Results of different treatment modalities in localized squamous cell anal cancer

Protocol	CR	CFS	OS	DFS
A RT	54% ^[29]	32% lower colostomy-free rate than C ^[28]	14% higher death rate than C ^[27]	12.9% higher death and relapse rates at 5 yr than C ^[27]
B RT + 5-FU	NA	71% ^[29]	No significant difference from C	51% ^[29]
C RT + 5-FU + Mitomycin	80% ^[29] 89.6% at 26 wk ^[34]	59% ^[28]	78.3% at 5 yr ^[32,33]	67.8% ^[29,30] to 73% ^[29]
D RT + 5-FU + Cisplatin	90.5% at 26 wk ^[34]	NA	70.7% at 5 yr ^[31,32]	57.8% ^[31,32]

NA: Not available; RT: Radiation therapy; 5-FU: 5-Fluorouracil; CR: Complete response; CFS: Colostomy-free survival; OS: Overall survival; DFS: Disease free survival.

Table 2 Studies evaluating recent treatment options in locally advanced anal cancer

Study	Patients, n	Protocol	RR	OS	DFS	CFS	
Induction chemotherapy in LAAC	Nilsson <i>et al</i> ^[36] , 2005 Population-based series	308 invasive SCAC	- Arm A: Neoadjuvant platinum CT followed by RT alone	CR: 92%	63%	NA	NA
		142 locally advanced	-Arm B: RT with or without Bleomycin	CR: 76% <i>P</i> < 0.01	44% <i>P</i> < 0.05	61% at 4 yr	50%
	Meropol <i>et al</i> ^[37] , 2008 ¹ Phase II	45	Induction: 2 28-d cycles (FU + cisplatin) followed by 2 28-d cycles (FU + mitomycin) with concurrent split-course radiation	CR: 82%	68% at 4 yr	61% at 4 yr	50%
Combination of MMC and cisplatin in LAAC	Peiffert <i>et al</i> ^[38] , 2012 ² Phase III RCT	283	-Arm A: 2 ICT cycles (5-FU + cisplatin) then RCT and standard dose boost (SD: 15 Gy) -Arm B: 2 ICT, RCT and high dose boost (HD: 20-25 Gy) -Arm C: RCT and SD boost -Arm D: RCT and HD boost	NA	NA	NA	69.6% 82.4% 77.1% 72.7%
	Crehan <i>et al</i> ^[39] , 2007 Phase II	21	1 st sequence: RT 36 Gy over 4 wk 2 nd sequence: 23.4 Gy over 2.5 wk, gap 16 d MMC and CDDP	CR: 90.5%	NA	NA	NA
	Matzinger <i>et al</i> ^[40] , 2009 ³ Phase II	80	RT: 36Gy + 2 wk gap + 23.4 Gy -Arm A: MMC + Cisplatin + RT -Arm B: MMC + 5-FU + RT	RR: 91.9% RR: 79.5%	NA	NA	NA
	Targeted therapy in LAAC	Olivatto <i>et al</i> ^[48] , 2013 Phase I Deutsch <i>et al</i> ^[49] , 2013 Phase II	21 16	Cetuximab + RT + 5-FU + cisplatin Cetuximab + RT + 5-FU + cisplatin	pCR: 95%	NA	NA
Cisplatin in LAAC	Eng <i>et al</i> ^[50] , 2013 ⁴ Retrospective single institution analysis	197 (41% stage II, 46% stage III, 24% N2-N3)	Weekly (20 mg/m ²) or daily (4 mg/m ²) cisplatin with 5-FU and RT	CR: 94%	86% at 5 yr	81% at 5 yr	88% at 5 yr

¹After induction, 8 CR and 21 PR. A third cycle of FU and cisplatin with radiation boost was given to patients with persistent primary site disease or bulky N2 or N3 disease at presentation; ²Considering the 2 × 2 factorial analysis, the 5-year CFS was 76.5% vs 75% in groups A and B vs C and D, respectively (ICT effect; *P* = 0.37), and 73.7% vs 77.8% in groups A and C vs B and D, respectively (RT-dose effect; *P* = 0.067); ³In the first arm, 9 patients discontinued treatment, with 9 grade 3 hematologic effects. In the second arm, 2 discontinued treatment, and no grade 3 hematologic effects were reported; ⁴The local recurrence rate was 11% after the median follow-up of 8.6 yr, and 8% of the patients developed distal metastases. LAAC: Locally advanced anal cancer; MMC: Mitomycin C; RR: Response rate; NA: Not available; RT: Radiation therapy; 5-FU: 5-Fluorouracil; CR: Complete response; CFS: Colostomy-free survival; OS: Overall survival; DFS: Disease free survival; RT: Radiation therapy.

platinum-based neoadjuvant chemotherapy in locally advanced anal cancer (LAAC). Induction chemotherapy with FU and cisplatin resulted in 8 CR and 21 partial responses (PR) in a phase II study by Meropol *et al*^[37]. After induction and treatment with FU, MMC and RT, CR was achieved in 37 of the 45 patients (82%). However, neither the ACCORD 03 trial nor the RTOG 98-11 trial showed a benefit from the addition of induction chemotherapy to concurrent CRT^[32,38].

The combination of radiation with MMC and cisplatin in LAAC was feasible, with an overall acceptable toxicity profile, according to 2 studies by Crehan *et al*^[39]

and Matzinger *et al*^[40]. Phase III studies are needed. Epidermal growth factor receptor (EGFR) is expressed in 80% to 90% of cases of SCAC^[41-43]. In addition, KRAS mutations, which confer resistance to anti-EGFR drugs, are almost absent in these tumors^[41-44]. Clinical response to anti-EGFR drugs has been observed in single patients^[45,46] and in small case series of patients^[47], suggesting their potential effectiveness in this type of cancer. A phase I and a phase II studies of cetuximab in combination with 5-FU, cisplatin and RT in locally advanced SCAC were closed early due to serious adverse effects^[48,49]. Further studies

are therefore needed to identify acceptable doses of chemotherapy and radiotherapy in the neoadjuvant setting to reduce the risk of severe side-effects^[49]. Although it has also been hypothesized that cetuximab could benefit patients with recurrent disease after chemoradiotherapy, few studies have been carried out in this area.

Recurrent and residual disease

A salvage APR is required in approximately 30% of cases, due to either primary non-response or the recurrence of anal cancer^[51]. Tumors invading local structures often require multivisceral resection. Although the prognosis is poor overall, APR offers the potential for long-term survival^[52-57]. Mullen *et al.*^[58] reported an overall actuarial survival rate of 64% in 31 patients with either persistent or recurrent SCAC treated with radical salvage surgery after a median follow-up of 29 mo. Important prognostic factors following resection include the presence of lymph node metastasis, treatment with a radiation dose of less than 55 Gy, status of the margins, a tumor size greater than 5 cm, adjacent organ involvement, male gender, and associated comorbidities. The use of intraoperative radiotherapy or brachytherapy may improve the local recurrence rates following radical resection when there is concern regarding an incomplete resection or close resection margins. In a study of 32 patients between 1993 and 2012, Hallemeier *et al.*^[59] showed that multimodality therapy, including salvage surgery and intraoperative radiotherapy, was associated with long-term survival (5-year OS: 23%, DFS: 17%) in heavily pretreated patients with recurrent or residual anal cancer^[57-59]. Flam *et al.*^[29] suggested the use of salvage CRT (9 Gy along with 5-FU and cisplatin) in cases with residual disease following definitive CRT before a radical surgical approach, with an approximate 50% salvage rate in patients with biopsy-proven evidence of residual malignancy 4 to 6 wk after the completion of CRT.

Metastatic disease

Data concerning the treatment of metastatic anal cancer are sparse in the literature due to the rarity of metastatic forms. The liver is the most common site of metastatic disease. The combination of cisplatin and 5-FU is considered the standard of care and the first-line regimen in metastatic disease, with overall response rates (ORR) of approximately 60%, most of which are partial responses, and a median survival of approximately 12 mo^[60-64]. Other single agent or combination regimens used in this setting are listed in Table 3. Most of the data come from case reports using treatment regimens that are effective in other related malignancies, such as head and neck SCC, cervical cancer and GI cancers. Surgery has also been successfully used for extrapelvic metastases of SCAC, such as solitary brain and hepatic metastases^[65,66].

Taxanes have established clinical activity in squamous cell cancer of the head and neck and in cervical cancer, both of which are strongly associated with HPV infection^[67]. The study of their efficacy in SCAC is therefore interesting. In 2011, Golub *et al.*^[67] reported the results of the use of paclitaxel, ifosfamide and platinum in 3 patients with recurrent metastatic anal cancer who were previously treated with FU and cisplatin. They concluded that this regimen is highly active in this setting and, hopefully, in the treatment of selected high-risk patients with localized and potentially curable disease and that further studies should be conducted. Khawandanah *et al.*^[68] treated one metastatic anal cancer patient with paclitaxel, ifosfamide and cisplatin, achieving minimal residual disease. On progression five months after finishing therapy, the patient received mitomycin and cetuximab with mixed response after two cycles. Weekly paclitaxel was also used in 7 patients with metastatic SCAC after progression on FU and cisplatin, resulting in four objective responses and 1 stable disease^[70]. In 2013, Kim *et al.*^[70] obtained 4 CR in 8 patients with recurrent advanced (metastatic) SCAC following the use of docetaxel, cisplatin and FU chemotherapy. Interestingly, all patients in CR had HPV-16-positive SCAC, whereas HPV could only be detected among 50% of the non-responding patients.

Chemotherapy regimens for GI cancers were also used in a few case reports. One patient with liver metastases and wild type KRAS treated with FOLFIRI and cetuximab had a PR after 6 cycles and an OS of 21 mo^[45]. In another case report, the use of the FOLFOX regimen in a single patient, followed by FOLFOX and panitumumab, then by FOLFIRI and panitumumab, markedly reduced the primary tumor with disappearance of the metastasis in the lung^[46].

CURRENT TREATMENT OPTIONS

The standard of care in localized and locally advanced tumors of the anal canal remains concomitant radiotherapy and chemotherapy based on a continuous infusion of 1000 mg/m²/d of 5-FU (day 1 to 4 and 29 to 32), 10 mg/m² of MMC (days 1 and 29) and a total radiation dose of 45 Gy divided into 22 sessions that includes the initial tumor and the inguinal lymph nodes^[31]. There are no indications for induction or for maintenance chemotherapy^[30,32].

Chemotherapy is the gold standard in treating metastatic AC and is based on the association of a continuous infusion of 5-FU (1000 mg/m²/d, day 1 to 4) and cisplatin (100 mg/m², day 2) every 4 wk^[60].

HIV-positive patients should be treated similarly to non-HIV-positive individuals. Ideally, the viral load should be below 10000, and the CD4 count should be above 200^[73-80]. Dosage adjustment and/or the omission of MMC can be considered in patients with active HIV/AIDS-related complications or a history of complications^[81-84].

Table 3 Recent case reports and case series evaluating treatment in metastatic anal cancer

Study	n	Characteristics of patients	Regimen	Response	Survival
Jhawer <i>et al</i> ^[71] , 2006	20		MMC, adriamycin, cisplatin followed by bleomycin-CCNU upon progression of disease	60% PR 0% CR	15 mo
Golub <i>et al</i> ^[67] , 2011	3	Previously treated with 5-FU and cisplatin	Paclitaxel 175 mg/m ² on D1 Ifosfamide 1 g/m ² D1 to D4 Cisplatin 75 mg/m ² on D1 Every 3 wk	CR in 3 patients Response duration	Survival since recurrence
	P1			6 mo	14 mo
	P2			2.5 yr	30 mo
	P3			4 mo	17 mo (patient still alive)
Abbas <i>et al</i> ^[69] , 2011	7	Prior progression on cisplatin and 5-FU	Weekly paclitaxel	1 CR, 3PR, 1 SD	12-14 mo ¹
Kim <i>et al</i> ^[70] , 2013	8	Advanced recurrent	Docetaxel 75 mg/m ² day 1, CDDP 75 mg/m ² day 1 and 5-FU at 750 mg/m(2)/day for 5 d every 3 wk	CR: 50%	OS 62.5% at 12 mo
Khawandanah <i>et al</i> ^[68] , 2014	1	Skin and perianal metastasis	(1) Paclitaxel, ifosfamide, cisplatin (4 cycles) followed by (2) Mitomycin, cetuximab (2 cycles)	(1) Minimal residual disease (2) Mixed response	(1) Progression 5 mo after the end of therapy (2) OS 24 mo; 16 mo after paclitaxel was started
Barmettler <i>et al</i> ^[45] , 2012	1	Liver metastasis, KRAS wild type and EGFR 2 +	FOLFIRI + cetuximab	Partial response after 6 cycles	21 mo
Bamba <i>et al</i> ^[46] , 2012	1	Lung metastasis	3 FOLFOX→3 courses of FOLFOX + panitumumab→5 courses of FOLFIRI + panitumumab	Marked reduction of primary tumor, disappearance of lung metastasis.	The patient underwent low anterior resection. No recurrence after 5 mo
Lukan <i>et al</i> ^[47] , 2009 Case report	7	First or subsequent treatment line	Cetuximab alone or with irinotecan first or subsequent line. KRAS mutated in 2/7	PR 3 MR 1 PD 2 (Mutated kras) SD 1	NA
Nitori <i>et al</i> ^[72] , 2011	1	58-yr-old female	Oral S-1 (120 mg/body; day 1-21) + low dose cisplatin (10 mg/body; day 1-5, 8-12) + RT for 2 cycles then rest for 4 wk	CR of the primary lesion and PR for the metastatic lesions	16 mo

¹Duration of clinical benefit in SD and PR after the initiation of Paclitaxel: 4-6 mo. PD: Progressive disease; PR: Partial response; MR: Minor response; SD: Stable disease; NA: Not available.

The combination of radiotherapy and chemotherapy in SCAC induces significant acute toxicities, with high rates of dermatitis and GI adverse effects. Subsequent effects include sexual dysfunction, lower limb venous thrombosis, proctitis, tenesmus, anal stenosis and bladder dysfunction^[85]. These adverse effects usually require treatment breaks, which decrease the efficacy of radiation. Recent radiation techniques, such as intensity-modulated radiotherapy, minimize such adverse effects by decreasing the dose of radiation received by the normal surrounding structures^[86].

NOVEL APPROACHES AND THERAPIES

In 2008, in a series of 118 HPV-positive patients with AIN or anal cancer, Walker *et al*^[87] confirmed that human epidermal growth factor receptor 2 (HER2) is absent and that 96% of invasive carcinomas simultaneously expressed EGFR, c-Met, VEGFR1 and p16. These results are promising because they introduce potential new agents for the treatment of metastatic anal cancer, such as tyrosine kinase inhibitors (TKIs), anti-EGFR monoclonal antibodies, AMG102 (monoclonal antibody against HGF, sole

ligand of c-Met) and AEE788 (TKI of ErbB and VEGF pathways).

Casadei Gardini *et al*^[44] analyzed the KRAS, BRAF and PIK3CA status in 50 patients with squamous cell anal carcinoma treated with concomitant CRT. Though the KRAS and BRAF genes were wild-type in all cases, the PIK3CA gene was mutated in 11 (22%) cases, suggesting that PIK3CA mutation may be involved in the process of carcinogenesis in some cases of SCAC and that this pathway may be used for targeted therapy against anal carcinoma. In another cohort study of 84 patients affected by SCAC, Martin *et al*^[88] identified PIK3CA gene mutations in 16% of the cases. No mutations were found in the BRAF gene.

Rapamycin, an mTOR pathway inhibitor, was found to significantly slow, if not stop, the growth of anal cancer in two preclinical mouse models. The mTOR pathway is indeed activated in human squamous cell carcinomas, including those arising in the cervix and head/neck region, wherein HPV can be an etiological factor^[89].

HPV causes 90% of squamous cell tumors of the anal canal^[90,91]. In 2011, Palefsky *et al*^[92] showed in a randomized controlled trial of healthy men who had

sex with men between 16 and 26 years of age that a reduction in HPV 16/18 associated premalignant lesions (AIN 2/3) occurred with vaccination, without any vaccine-related serious adverse events. The efficacy of the vaccine at preventing anal dysplasia was higher in the per-protocol population (77.5%), which was HPV and dysplasia free (*i.e.*, prophylactic use) at the time of vaccination, than the intention-to-treat population (50.3%), which had active dysplasia or HPV infection, or had incident disease prior to completing the series. Vaccination might play a role in preventing reinfection if the natural clearance of HPV has occurred. Further studies on this topic are needed^[93,94]. Per the Advisory Committee on Immunization Practices guidelines, the universal HPV vaccination of boys and girls at 11-12 years of age remains the most effective way to prevent future HPV-associated disease. The vaccine should also be offered to HIV-positive patients younger than 27 years of age and to older HIV-positive patients if they can afford it.

Photodynamic therapy (PDT), which consists of an infusion of Photofrin followed 48 h later by red light illumination, was suggested by Allison *et al.*^[95] in 2010 for the treatment of early anal cancer in select patients and of local failures. In their study, all 6 enrolled patients completed PDT without adverse effects and maintained local control of disease in the anal region for the length of follow up (18-48 mo).

Immunotherapy against the viral oncogenes, E6 and E7, of high-risk HPV subtypes, such as HPV-16 and HPV-18, is currently being studied. The use of an agent containing a segment of HPV-16 E7 protein for inducing an immune response against E7 appears to be both clinically feasible and safe^[96]. A recombinant vaccine consisting of vaccinia virus MVA E2 induced a significant regression of high-grade cancer lesions in a phase II clinical trial. Other chimeric vaccines, such as VLP and L2, E7, E6 vaccines, are being also studied, and have yielded promising results^[97].

CONCLUSION

The current treatment options in AC are well defined in locally advanced and metastatic disease with acceptable results. Many new strategies are being studied in these tumors, from targeted therapies to immunotherapy and photodynamic therapy. Vaccination, as a prevention strategy, might be the ideal means to decrease the incidence of anal cancer.

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