



SEOM–GEMCAD–TTD clinical guidelines for anal cancer (2025)

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Abstract

Anal cancer is rare but increasingly common, currently accounting for 2% of all digestive neoplasms. Some 50% of anal cancers are diagnosed at the localized stage, 29% as locoregional disease, and 12% as metastatic disease. When clinical suspicion of anal cancer exists, histological confirmation, correct local staging with MRI and distant staging with thoraco-abdominal CT, and management by a multidisciplinary team are mandatory. Chemoradiotherapy with 5-FU and mitomycin C (MMC) is the standard of care for early and locally advanced disease, while combination chemotherapy with a platinum-containing compound and taxanes is the treatment of choice for metastatic disease.

Keywords Anal cancer · HPV · Treatment · Multidisciplinary · Chemoradiotherapy

Introduction

Although anal cancer is a rare malignancy, the incidence of anal squamous cell carcinoma (ASCC)—its predominant histologic subtype—has shown a sustained rise over the past decade. This trend is closely associated with an increase in

human papillomavirus (HPV) infection, detected in approximately 80%–85% of cases, with immunosuppression also playing a crucial role [1]. Optimal management requires biopsy, histopathologic confirmation, local and distant staging, and assessment by a multidisciplinary team to guide individualized treatment strategies [2].

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Methods

This guideline is based on a systematic review of relevant published studies and with the consensus of ten treatment expert oncologists from GEMCAD (Spanish Multidisciplinary Group on Digestive Cancer), TTD (Digestive Treatment Tumor), and SEOM (Spanish Society of Medical Oncology) and an external review panel of two experts designated by SEOM. The Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines has been used to assign levels of evidence and grades of recommendation (Table 1) [3].

Incidence and epidemiology

Anal cancer is a rare neoplasm. The most common histologic type of anal cancer is anal squamous cell carcinoma (ASCC). Over the last decade, the incidence of ASCC has been rising by approximately 2.7% annually from 2001 to 2015 [4]. According to the latest available data, around 54,306 cases of ASCC were diagnosed in 2022 worldwide for both sexes [5].

ASCC represents 2% of all gastrointestinal neoplasms and incidence rates vary between countries, ranging from 0.7 to 1.7 per 100,000 inhabitants/year across the UK, Netherlands, Australia, and the USA. It is more common among women and increases with age. Despite the relatively low incidence of ASCC compared to the high prevalence of HPV among females, its increase is thought to be due primarily to rising rates of HPV infection [1].

Risk factors for anal squamous cell carcinoma

HPV infection is the primary risk factor for ASCC, comprising 80–85% of all cases, most of which are linked to HPV16. Genotyping is always recommended. The quadrivalent HPV vaccine provides long-lasting protection against anogenital diseases caused by HPV types 6, 11, 16, and 18 [6]. Other important factors contributing to anal cancer risk include immunosuppression and sexual behavior, as anal intercourse and multiple sexual partners are associated with HPV infection. Human immunodeficiency virus (HIV) infection, women with HPV-related gynecological cancers or precancerous lesions, as well as patients with solid organ transplants or autoimmune diseases, are at greater risk for ASCC. Additional factors associated with a higher risk of ASCC include older age, female sex, and smoking [1].

Diagnosis and staging

ASCC originates between the anorectal junction and the anal verge. Physical examination and high-resolution anoscopy (HRA) are indispensable to detect premalignant high-grade squamous intraepithelial lesions (HSIL) in high-risk populations, such as people living with HIV. The recently published Anal Cancer HSIL Outcomes Research (ANCHOR) study demonstrated that the risk of anal cancer is significantly lower when anal HSIL is treated *versus* active surveillance [7].

Common symptoms of ASCC include anorectal bleeding, pain, and the presence of a mass. In light of clinical suspicion, a complete detailed medical history and physical examination

Table 1 Levels of evidence/grades of recommendation

Category, grade	Definition
<i>Grades of recommendation</i>	
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy, but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit; does not outweigh risk or disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended
<i>Levels of evidence</i>	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts' opinion

Adapted from the quality and strength of evidence of the Infectious Diseases Society of America clinical practice guidelines [3]

are required, including digital rectal examination (DRE) and vaginal examination, and palpation of inguinal lymph nodes, especially for low anterior tumors. Any suspicious lesions must be biopsied. Proctoscopy or anoscopy is fundamental to establish a pathological diagnosis.

Local staging should be performed with magnetic resonance imaging (MRI) to assess the initial extent of disease and monitor treatment response after standard chemoradiotherapy (CRT) [8]. MRI reveals tumor size, infiltration into adjacent structures, and pelvic nodal involvement, which are critical to determine T and N status. Diffusion-weighted imaging (DWI) highlights hypercellular tissues and enhances MRI diagnostic accuracy and is now recommended as part of the standard MRI protocol for post-treatment restaging. Additionally, a spiral thoraco-abdominal CT should be carried out to rule out metastatic spread at the time of diagnosis. PET-CT can be used, but should not replace conventional CT for diagnosis. 18F-FDG PET/CT has a role to play in assessing treatment response. A complete metabolic response (CMR) on post-treatment PET/CT correlates with significantly improved recurrence-free survival (RFS), colostomy-free survival (CFS), and overall survival (OS), particularly for locally advanced tumors. Furthermore, FDG-PET/CT should be considered to assist in RT [9] (Fig. 1).

The updated TNM staging system (Table 2) for anal cancer contemplates tumor size, local invasion, and nodal involvement, with changes in the classification of lymph

node involvement [10]. Tables 3 and 4 summarize key diagnostic modalities to appraise ASCC, including purposes and relevant clinical considerations.

Risk assessment

HPV infection, especially p16 overexpression, strongly impacts outcomes in anal squamous cell carcinoma (ASCC). Individuals with HPV-positive/p16-positive ASCC display the best survival rates, and CRT yields better survival rates in cases of HPV-positive/p16-positive tumors compared to other combinations. Prognostic factors include skin ulceration, nodal involvement, tumor size, and sex, with males generally having worse outcomes. Larger tumors and greater lymph node involvement are linked to worse locoregional control and OS [11, 12].

Emerging biomarkers, such as CYP2D6 copy number variants (CNVs) [13] determined in paraffin tumor with whole-exome sequencing, are associated with poor disease-free survival in localized ASCC, while other molecular markers like p53 and p21 also display prognostic significance [14, 15]. Moreover, high levels of *Fusobacterium nucleatum* correlate with better outcomes in patients undergoing abdominoperineal resection [16].

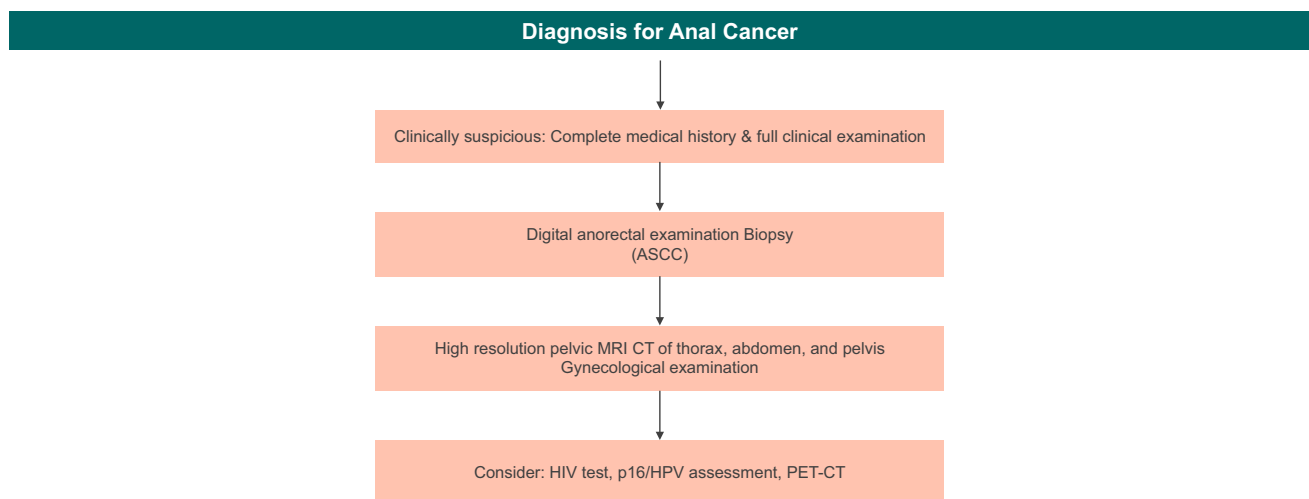


Fig. 1 Diagnostic algorithm for anal cancer. CT, computed tomography; HIV, human immunodeficiency virus; HPV, human papillomavirus; MRI, magnetic resonance imaging; PET, positron emission

tomography; ASCC, anal squamous cell carcinoma. Adapted from the ESMO Clinical Practice Guidelines for anal cancer [2]

Table 2 TNM Staging Classification for Anal Carcinoma (9th ed., 2020) and AJCC anatomic stage/prognostic groups

Category	Definition		
T			
TX	Primary tumor not assessed		
T0	No evidence of primary tumor		
T1	Tumor ≤ 2 cm in greatest dimension		
T2	Tumor > 2 cm, but ≤ 5 cm in greatest dimension		
T3	Tumor > 5 cm in greatest dimension		
T4	Tumor invades adjacent organ(s), such as the vagina, urethra, or bladder		
N			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node involvement		
N1	Involvement of regional lymph node(s)		
N1a	Involvement of inguinal, mesorectal, superior rectal, internal iliac, or obturator nodes		
N1b	Involvement of external iliac nodes		
N1c	Involvement of both N1a and N1b nodes		
M			
cM0	No distant metastasis		
cM1	Distant metastasis		
pM1	Microscopic confirmation of distant metastasis		
AJCC Anatomic stage/prognostic groups			
Stage	T	N	M
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-T2	N1	M0
Stage IIIB	T3	N1	M0
Stage IIIC	T4	N0–N1	M0
Stage IV	Any T	Any N	M1

AJCC American Joint Committee on Cancer

Adapted from the TNM Classification of Malignant Tumours. 9th ed. 2025 [10]

Table 3 Summary of diagnostic modalities for anal squamous cell carcinoma

Modality	Purpose	Comments
Physical examination and digital rectal examination (DRE)	Evaluate tumor size, characteristics, and perirectal nodal involvement	Especially important to detect perirectal node involvement
Proctoscopy/anoscopy	Obtain pathological diagnosis	Necessary to confirm ASCC diagnosis
Chest and abdominal CT	Identify locoregional lymph node involvement and distant metastases	Recommended to stage patients with confirmed diagnosis
Pelvic CT/MRI	Assess locoregional lymph nodes and invasion of adjacent structures	Performed with gadolinium contrast for better imaging clarity
FDG-PET/CT	Assist in staging, but not a replacement for standard CT	FDG-PET/CT may be considered to aid in RT

ASCC anal squamous cell carcinoma, CT computed tomography, DRE digital rectal examination, FDG-PET/CT fluorodeoxyglucose positron emission tomography/computed tomography, MRI magnetic resonance imaging, RT radiotherapy

Table 4 Diagnostic and staging procedures: recommendations and levels of evidence

Procedure	Recommendation	Level of evidence
Physical examination and digital rectal examination (DRE)	Strong	2A
Proctoscopy/anoscopy	Essential	2A
Pelvic MRI	Preferred	2A
Chest, abdominal, and pelvic CT	Standard	2A
FDG-PET/CT	Optional	2B
HIV testing	Important	2A
p16/HPV testing	Context dependent	2B

CT computed tomography, DRE digital rectal examination, FDG-PET/CT fluorodeoxyglucose positron emission tomography/computed tomography, HIV human immunodeficiency virus, HPV human papillomavirus, MRI magnetic resonance imaging

Adapted from the ESMO Clinical Practice Guidelines for anal cancer [2]

Management of local and locoregional disease

Anterior abdominal and perineal resection (APR) was the treatment of choice until the 1970s and includes excising the distal colon, rectum, anal sphincter complex, and anus,

forming a definitive colostomy. APR is associated with a 5-year OS rate of 45–70% [17].

In the 1970s, researchers conducted several studies with CRT consisting of fluoropyrimidine and mitomycin C (MMC) and observed a high complete pathologic response rate (84%), ushering in a new era in the treatment of this disease [18, 19]. Subsequently, some single-arm studies using CRT yielded encouraging results. Thereafter, several Phase III randomized clinical trials established definitive CRT as the best organ-sparing treatment [12, 20–24]. At present, the goal is to achieve a cure while preserving anal function, thus maintaining the best possible quality of life. A multidisciplinary approach is required, involving radiation oncologists, medical oncologists, radiologists, surgeons, and pathologists (Fig. 2). Surgery has a role as salvage therapy and should be contemplated if necessary [III, B]. Evidence-based recommendations for the treatment of anal cancer are summarized in Table 5.

Chemoradiotherapy

Six randomized Phase III trials have evaluated CRT for ASCC. First, Phase III trials demonstrated that synchronous CRT with 5-FU and MMC is superior to RT alone. Later, the Intergroup Phase III study confirmed the superiority of the combination of mitomycin and 5-FU plus RT compared to 5-FU and RT without MMC. No differences were found

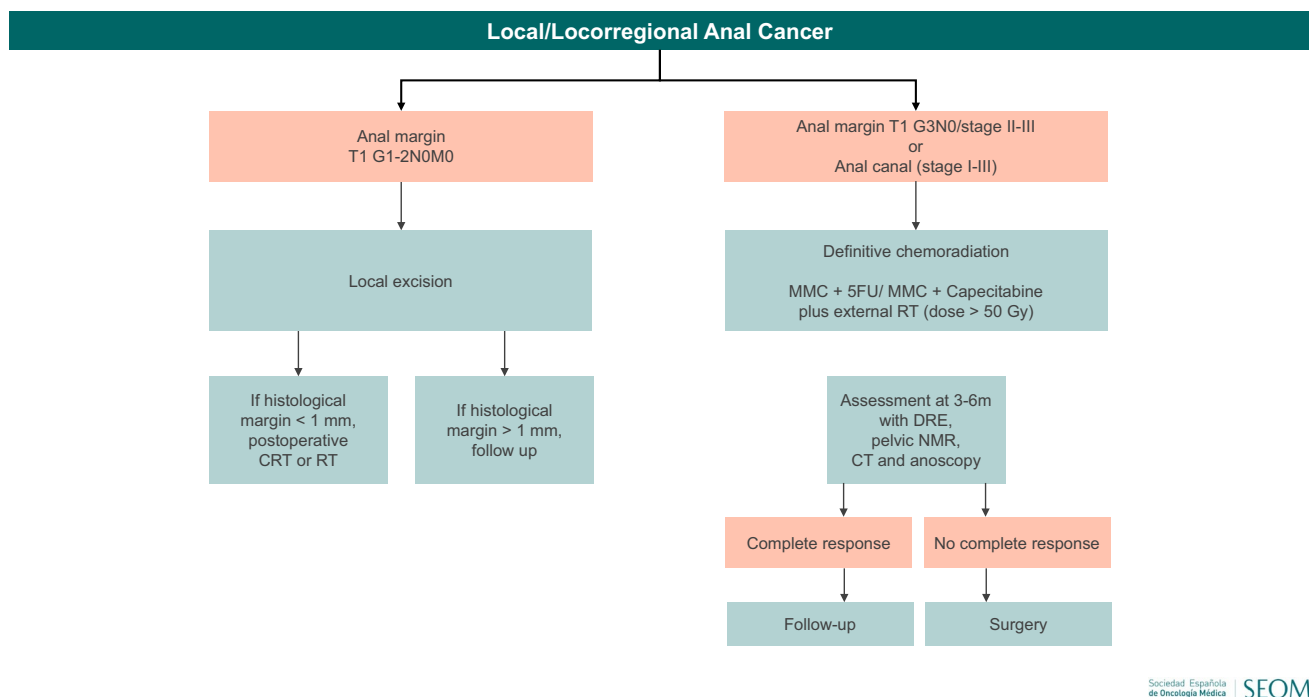


Fig. 2 Algorithm for localized anal cancer. 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; CT, computed tomography; DRE, digital rectal examination; RT, radiotherapy; MMC, mitomycin C; MRI, magnetic resonance imaging

Table 5 SEOM–GEMCAD–TTD recommendations for treatment of anal cancer

	LE, GoR
Management of localized disease	
Chemoradiotherapy with 2 cycles of 5-FU (1000 mg/m ² /days 1–4 and 29–32), MMC (either 12 mg/m ² on day 1, or 10 mg/m ² on days 1 and 29), and radiotherapy at a total dose of 50.4 Gy (55–59 Gy in locally advanced cases) is the best treatment option for ASCC	I, A
Management of advanced and metastatic disease	
Carboplatin–paclitaxel is currently the optimal approved regimen for advanced or metastatic anal carcinoma	I, B
The addition of retifanlimab to carboplatin–paclitaxel is positioned as the treatment of choice in the near future	I, B
Alternative options include modified DCF or platinum-5-FU	III, B
Management of anal cancer in elderly patients	
In elderly patients with anal cancer, a comprehensive geriatric assessment should inform treatment decisions, with radical CRT recommended for fit patients	II, B
Reduced-dose treatments or radiotherapy alone may offer effective options for frail individuals	IV, C
In metastatic anal cancer, standard first-line chemotherapy (paclitaxel plus carboplatin) remains the preferred option for older patients	II, B

5-FU 5-fluorouracil, ASCC anal squamous cell carcinoma, CRT chemoradiotherapy, DCF docetaxel, cisplatin, and 5-fluorouracil, LE level of evidence, MMC mitomycin C, GoR grade of recommendation

Table 6 Phase III trials evaluating CRT as an organ-sparing approach

Trial	N	Trial arms	End inclusion period	Response	Local failure	Survival
UKCCR (17)	585	CRT vs. RT	1991	Good clinical response at 6 weeks: 91% vs. 92%	59% vs. 36% ($p < 0.0001$)	3-y anal cancer mortality 39% vs. 28% ($p = 0.02$) 3y OS 58% vs. 65% ($p = 0.2$)
EORTC (9)	110	CRT vs. RT	1994	Complete remission rate 54% vs. 80%	18% difference in loco-regional failure ($p = 0.02$)	5-y survival 56% for the whole group
Intergroup study (18)	310	MMC-5-FU + RT vs. 5-FU alone + RT	1991	Post-treatment positive biopsies 15% vs. 7% ($p = 0.13$)	Colostomy rates 9% vs. 22% ($p = 0.002$)	DFS 73% vs. 51% ($p = 0.0003$) in favor of MMC
RTOG 98–11 (19)	682	MMC-5-FU vs. induction CT, followed by concurrent 5-FU-CDDP	2005	NR	20% vs. 26% ($p = 0.08$)	5-y CFS 71% vs. 65% ($p = 0.05$) 5-y DFS 67% vs. 57% ($p = 0.006$) 5-y OS 78% vs. 70% ($p = 0.026$)
ACTII (20)	940	2×2 MMC-5-FU vs. CDDP-5-FU and maintenance vs. non-maintenance	2008	90% with MMC vs. 89% with CDDP	NS difference (colostomy rates 11–16%)	3y-PFS 70% vs. 69% with maintenance 3y-PFS with either MMC or CDDP ($p = NS$)
ACCORD (21)	307	2×2 Induction CT vs no induction and High boost vs. standard boost	2005	Complete response: no differences	Colostomy rates: no differences	5-y OS: 71–74%. No differences

CRT chemoradiation therapy, CT chemotherapy, CDDP cisplatin, DFS disease-free survival, MMC mitomycin, CFS colostomy-free survival, NR not reported, NS not significant, OS overall survival, RT radiation therapy, y year

between cisplatin and MMC in terms of efficacy in clinical trials [22, 23] (Table 6). Capecitabine/MMC resulted in similar levels of grade 3/4 toxicity overall compared to 5-FU/MMC, although differences were detected in the patterns of

the toxicities observed, with less hematologic toxicity with capecitabine. Various studies have supported the use of oral capecitabine (825 mg/m² BID on RT days, 5 days per week) as an alternative to 5-FU [25, 26] [III, B].

Radiotherapy

Radiotherapy requires a comprehensive treatment plan, not only because it targets volumes with complex shapes and varying sizes, but also because the anus is situated in close proximity to critical pelvic organs, such as the bladder, rectum, external genitalia, and femoral heads, among others. Doses of at least 45–50 Gy without a treatment gap are recommended for T1–2 N0. Higher doses may be needed for advanced tumors and can be up to 55–60 Gy for T3–4 or node-positive disease [III, B]. Nevertheless, it is not possible to make a definitive recommendation as to the type, dose, or whether to increase beyond 50 Gy, based on inter-trial comparisons of different dose fractionations. Treatment fields should cover the primary tumor and anal canal, nodal regions, and inguinal nodes, while high-dose volumes can include the primary tumor and any sites of probable node involvement [27]. There is evidence that treatment interruptions, either planned or dictated by treatment-related toxicity, can compromise therapeutic effectiveness [28]. Conformal radiotherapy strategies, such as intensity modulated RT (IMRT) or volumetric modulated arc therapy (VMAT), lessen toxicity and may make it possible to administer full radiotherapeutic doses, even within a shorter interval of time and with fewer unplanned delays or interruptions [III, B] [29].

Management of local recurrence/regrowth and the role of surgery

Every effort should be made to treat patients with CRT given its better outcomes compared to historical APR data. APR with colostomy is reserved for salvage therapy in cases of disease recurrence, tumor progression following CRT, or for patients who are not eligible for or refuse definitive CRT [30]. Salvage surgery has a 5-year OS rate of 30–60% [31]. On the other hand, around 10–20% of patients with anal cancer will need a pre-treatment colostomy [III, C]. The most common indications are anorectal pain and fecal incontinence.

Local excision of early-stage cancers in the anal canal is not indicated because surgical clearance generally results in histologically positive margins and the need for subsequent CRT. Furthermore, the combination of surgery with CRT implies higher treatment-related morbidity. A very early-stage anal cancer in the form of superficial invasive ASCC may be the only exception in which local excision is justified [32].

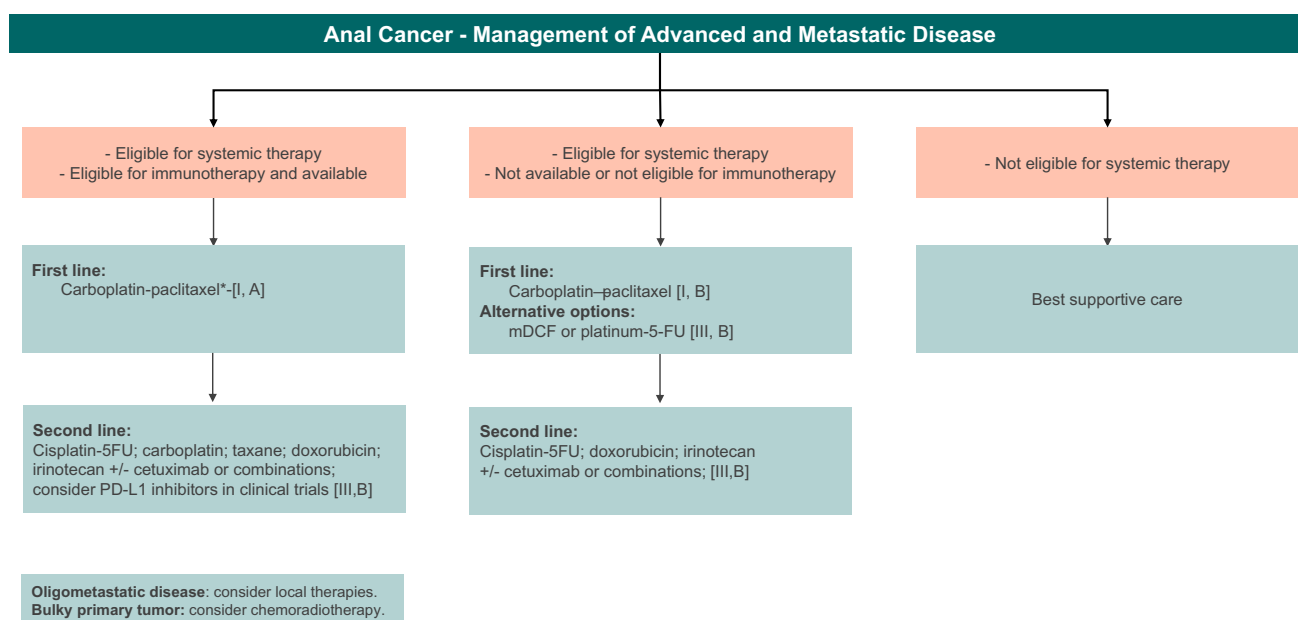
Inguinal node recurrence can be treated with CRT. Patients previously treated with groin radiotherapy should undergo inguinal node dissection.

Management of anal margin cancer

The anal margin is defined as the pigmented skin bordering the anal orifice, extending laterally to a radius of around 5 cm. Local excision of T1 tumors is a treatment option, considering the few patients included in CRT trials, favorable outcomes, and a low risk of complications [IV, C]. The aim of the surgery is to achieve a histological clearance of > 1 mm without damage to the anal sphincter muscle. The available clinical evidence supporting local excision in small T1 anal margin tumors is limited and derives mainly from retrospective analyses. A large retrospective cohort from the National Cancer Database reported comparable outcomes between local excision and definitive CRT, with a 5-year OS of 85.3% for local excision and 86.8% for CRT ($p=0.93$) [1, 33]. In contrast, a systematic review including 23 predominantly retrospective studies showed less favorable results, with a 5-year recurrence rate of 37% and an OS of 69% [34]. Poorly differentiated tumors cannot be treated with local excision. Adjuvant radiotherapy may improve locoregional recurrence rates and survival if the histological margin is < 1 mm [35].

Evaluating treatment response

Given the slow regression of ASCC, an initial evaluation of response to CRT is recommended at 3 and 6 months after starting treatment to assess complete clinical response. This evaluation should include DRE and palpation of inguinal lymph nodes, and pelvic MRI and CT scans. Edema, residual fibrosis, or scar tissue can be difficult to distinguish from persistent active disease. Biopsies of persistent, clinically suspicious lesions 8–12 weeks post-CRT completion are not routinely recommended. Anoscopy or proctoscopy may be performed as additional evaluation procedures [36]. Individuals with persistent disease but without evidence of progression at 3 months can be managed with close surveillance to determine if further regression occurs. This management plan is based on the results of the ACT II study, which demonstrated that 72% of all patients who failed to achieve a complete response at 11 weeks from the start of treatment achieved a complete response by 26 weeks after commencing CRT [37] [II, B]. Persistent disease may continue to regress for up to 6 months from the start of treatment, and APR can be avoided in some cases. In such patients, observation and re-evaluation should be performed at 3-month intervals. The routine use of PET/CT imaging is not recommended given the false positivity associated with local inflammation from RT [III, C]. Residual or recurrent tumors should



*The addition of retifanlimab is pending FDA and EMA approval.

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Fig. 3 Management of advanced and metastatic disease. 5-FU, 5-fluorouracil; DCF, docetaxel, cisplatin, and fluorouracil; mDCF, modified DCF; PD-L1: programmed death-ligand 1

be confirmed histologically prior to considering radical surgery [31, 38].

Management of advanced and metastatic disease

Approximately, 10–20% of patients with anal canal carcinoma present with extrapelvic recurrence, most commonly affecting the liver, lungs, or lymph nodes. Given that advanced-stage anal cancer is extremely rare, evidence supporting treatment in this setting is limited. Nonetheless, several therapeutic options have demonstrated efficacy (Fig. 3).

Chemotherapy

Carboplatin-paclitaxel is regarded as the first-line treatment of choice. A randomized Phase II trial comparing carboplatin plus paclitaxel to cisplatin plus 5-FU found no significant differences in objective response rate (ORR) or progression-free survival (PFS), but demonstrated better OS and a more favorable toxicity profile for the carboplatin-paclitaxel regimen [39]. The schedule consists of carboplatin AUC 5 on day 1, every 28 days, combined with paclitaxel 80 mg/m² on days 1, 8, and 15 [I, B].

Combinations of docetaxel, cisplatin, and 5-FU (DCF) have also exhibited great activity. A Phase II trial demonstrated comparable efficacy between standard and modified DCF regimens [III, B], although the standard DCF schedule was associated with greater toxicity [40]. Platinum-based doublets with fluoropyrimidines were once deemed the treatment of choice, based on small retrospective studies [41]; however, the carboplatin-paclitaxel regimen has since surpassed it in light of better OS and toxicity profiles.

Chemotherapy for refractory disease has not been prospectively studied, limiting the ability to make strong recommendations for this patient population. Carboplatin, doxorubicin, taxanes, and irinotecan ± cetuximab, or combinations of these drugs, have demonstrated some activity [III, B] [41].

Immunotherapy

Combining checkpoint inhibitors with chemotherapy is an emerging strategy, given the activity demonstrated by anti-PD-1 and anti-PD-L1 therapies in refractory cases. Several clinical trials have explored this approach. First, a Phase II trial examining atezolizumab combined with mDCF did not meet its primary end point, with a 12-month PFS of 45%, similar to mDCF alone [42]. Interestingly, patients with a PD-L1 combined positive score (CPS) ≥ 5 may derive some benefit from the combination, although further studies are needed to confirm this finding.

The first results from the Phase III POD1UM-303/InterAACT-2 trial, the largest randomized trial in advanced anal cancer, have recently been published. The study met its primary end point, demonstrating a significantly longer median PFS with retifanlimab plus carboplatin–paclitaxel compared to carboplatin–paclitaxel alone (9.3 months vs. 7.4 months; HR 0.63; 95% CI 0.47–0.84; $p=0.0006$). Moreover, there was a strong trend toward improved OS in favor of the retifanlimab arm (median OS: 29.2 months vs. 23.0 months; HR 0.70; 95% CI 0.49–1.01; $p=0.0273$), although survival data were immature at data cutoff [43]. The ORR was also higher in the experimental arm (55.8% vs 44.2%; $p=0.0129$). Hence, retifanlimab plus carboplatin and paclitaxel may become the new standard of care in recurrent or metastatic ASCC. The results of the ECOG–ACRIN 2176 trial exploring the combination of nivolumab with carboplatin and paclitaxel study are still pending. Table 7 summarizes the most important completed and ongoing studies in advanced or metastatic anal cancer.

In the chemo-refractory setting, checkpoint inhibitors have evinced modest efficacy. Nivolumab yielded a 24% ORR and median OS of 11.5 months in 37 patients [44]. Similarly, pembrolizumab showed an ORR of 11% and a median OS of 12 months in 112 patients, with higher response rates in those expressing PD-L1 (CPS ≥ 1) [45]. Retifanlimab produced similar results with a 14% ORR and median OS of 10.1 months, although PD-L1 expression did not predict response [46] [III, B].

The potential benefit of adding anti-CTLA-4 therapy (ipilimumab) to nivolumab in refractory metastatic anal cancer is currently being studied in a Phase II clinical trial. The CARACAS trial evaluated the efficacy of avelumab

(anti-PD-L1 antibody) in monotherapy and in combination with cetuximab. This non-randomized two-arm study achieved an ORR of 10% and 17% for avelumab alone or in combination with cetuximab, respectively. Median PFS was superior in the combination arm (3.8 months vs. 2.9 months) [47]. Nevertheless, these results must be validated in prospective studies.

Future directions and clinical trials

Other innovative approaches are under investigation. For instance, a Phase II trial is probing the efficacy of a DNA plasmid-encoding interleukin-12/HPV DNA plasmids therapeutic vaccine (INO-3112) in combination with durvalumab [48]. This trial focuses on cases of HPV-associated cancers, including anal cancer that have either recurred or metastasized. This combination of immunotherapy and a therapeutic vaccine represents a promising new avenue in the treatment of HPV-associated cancers.

Another line of research presently underway is the potential role of targeting the immunosuppressive TGF- β pathway in HPV-positive malignancies [49].

Special considerations

Beyond systemic therapies, treating physicians should consider additional factors based on limited retrospective data. In cases of oligometastatic disease, particularly in the liver, resection or ablation could be considered and may lead to long-term survival [50]. The administration of definitive

Table 7 First-line Phase II/III clinical trials in advanced/metastatic anal cancer

Study	Therapy	n	Primary outcome	Key results/status
InterAACT (randomized Phase II study) (36)	Cisplatin + 5-FU vs Carboplatin + paclitaxel (CP)	91	ORR	ORR: 57% vs 59% Median OS: 12.3 vs 20 months (HR 2.0; $p=0.014$) Fewer serious AEs with CP
Epitopes-HPV02 (single-arm, Phase II study) (37)	DCF mDCF	69	PFS at 12 months	PFS: 47% Grade 3–4 AE: 83% for DCF, 53% for mDCF
SCARCE C17-02 (randomized Phase II study) (39)	mDCF $\pm$ atezolizumab	97	PFS at 12 months	PFS: 45% for atezolizumab + mDCF, 43% for mDCF
Phase III POD1UM-303 (randomized Phase III study) (40)	Carboplatin + paclitaxel $\pm$ retifanlimab	308	PFS	Median PFS: 9.3 vs 7.4 months (HR 0.63; $p=0.0006$) Median OS: 29.2 vs 23.0 (HR 0.70; $p=0.0273$)
Phase III ECOG EA2176 (clinical trials.gov)	Carboplatin + paclitaxel $\pm$ nivolumab	Ongoing	PFS	Active; not recruiting

ORR overall response rate, OS overall survival, AE adverse events, DCF docetaxel, cisplatin, and 5-fluorouracil, mDCF modified DCF, PFS progression-free survival

pelvic (chemo)-radiotherapy for local control may be beneficial, typically after initial chemotherapy, especially for bulky disease [51].

Two key factors in managing HIV-positive patients are the increased risk of anal cancer and the need for personalized treatment plans. Due to immune suppression and potential interactions between antiretroviral therapy (ART) and cancer treatments, close collaboration between oncology and infectious disease specialists is crucial. Regular monitoring of CD4 counts is essential, as lower levels are linked to a greater risk of complications and reduced treatment tolerance. Adjustments in cancer treatment doses or regimens may be necessary for patients with low CD4 counts to minimize toxicity, while maintaining effective ART. This balance helps manage both cancer and HIV progression. Although less common, HIV-positive patients are often included in clinical trials for advanced or metastatic anal cancer if HIV infection is well controlled, ensuring therapies are tested on a broader population that contemplates the challenges of immunosuppression and ART interactions [52].

Elderly patients

The incidence of anal cancer has also increased among older people. More than half (54%) of all cases of anal cancer occur in patients ≥ 65 years [53] with 5-year OS of 56%, lower than their younger counterparts (68%). Nevertheless, older people have been traditionally underrepresented in clinical trials defining the current standard of care, including definitive CRT with multiagent chemotherapy.

In older subjects with localized disease, CRT has exhibited high rates of grade ≥ 3 toxicity in some retrospective studies and small series, primarily gastrointestinal (54%) and hematological (57%) [54]. Dose reduction, omission of chemotherapy, or decreased RT have been suggested for elderly and frail patients, but current evidence indicates that these adjustments might negatively impact outcomes. ESMO guidelines [2] advocated for radical CRT for older individuals deemed fit after a comprehensive geriatric assessment (CGA). Regular blood count monitoring is recommended for older people receiving MMC; additionally, a multidisciplinary approach with nutritional support, pain management, and psychological care is advised to optimize outcomes and maintain quality of life.

For patients not deemed fit enough for CRT, radiotherapy alone can offer effective control of local disease. In this context, the DECREASE study is exploring a less toxic option, by randomizing 252 participants to receive either standard CRT with IMRT (28 fractions) vs a reduced dose of IMRT (20 or 23 fractions).

When pondering surgery, risks must be accurately assessed to determine if an older patient is a suitable

candidate. If a colostomy is required, expected outcomes should be carefully discussed, as it can significantly impact both physical performance and social functioning.

In metastatic anal cancer, the standard first-line CT regimen (paclitaxel plus carboplatin) is based on the InterAACT trial [39], with a median age of 61 years, meaning that the elderly are underrepresented, as no subgroup analyses evaluated tolerability in older patients. The same applies to the latest Phase III POD1UM-303/InterAACT-2 trial study [43], in which the median age was 62 years. Second-line treatment with immune checkpoint inhibitors may be equally effective in both younger and older patients, with no additional toxicities. While there is limited prospective evidence of effectiveness and adverse effects in this population, insights can be gleaned from studies in other tumors, where these treatments have shown good tolerability.

Future research in older adults with ASCC should incorporate a geriatric assessment (GA) and ensure that this population is included in Phase III clinical trials to better evaluate new strategies for both localized and metastatic disease.

Follow-up

Patients should be evaluated by clinical examination (DRE, palpation of the inguinal regions) from 8 to 12 weeks after completing CRT.

In cases with a clinical complete response, re-evaluation with clinical examination should be performed every 3–6 months for a period of 2 years and every 6–12 months until completing 5 years after treatment [III, C]. Annual chest, abdominal, and pelvic CT is recommended for the first 3 years to identify disease relapse or metastatic disease [2] for patients who initially present with stage II–III disease [36]. Annual pelvic MRI for the first year is optional [2]. The use of PET/CT is not recommended during follow-up due to false positives caused by RT-induced inflammation, which can lead to unnecessary surgical interventions.

Data from the ACT II [23] study indicate that very few ($< 1\%$) relapses occur after 3 years; therefore, extended imaging surveillance after this time is not recommended.

As anal cancer continues to regress during 26 weeks after therapy, patients with clinical suspicion of persistent disease at the initial post-treatment evaluation can be monitored for up to 26 weeks [23], if there is no progressive disease during this period of follow-up. Progression should prompt a biopsy so that salvage therapy (typically APR) can be offered.

Long-term implications and survivorship

Information regarding treatment-related side effects should be provided, particularly focusing on anorectal and sexual

functioning, to ensure that quality of life is properly balanced with treatment intensity.

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Declarations

Conflict of interest Mónica Guillot Morales: reports speaker fee from Merck, MSD, and Servier; advisory board fee from Roche, and GlaxoSmithKline S.A. Ismael Ghanem Cañete: reports speaker fee from Merck, Amgen, and MSD and advisory board—speaker fee from Servier and AstraZeneca. Jerónimo Jiménez-Castro: reports Speaker from Servier, Merck and Amgen. Joan Maurel Santasusana: reports personal fees from Advance Medical, Amgen, Cancer Expert Now and MSD; advisory board fee from Delcath Systems Inc, GlaxoSmithKline SA (GSK), and Incyte Biosciences International; grant from Amgen, Guardant, Incyte, Merck, and Terumo and non-financial support from GEMCAD. Ana Fernández Montes, Julen Fernández-Plana, M^a Auxiliadora Gómez-España, Mireia Gil Raga, Ignacio Juez Martel, and Eduardo Polo Marqués have nothing to disclose.

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