ANAL CANCER

CHI Formulary Indication Review

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Abbreviations

5-FU	5-Fluorouracil
ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired Immunodeficiency Syndrome
AIN	Anal Intraepithelial Neoplasia
AJCC	American Joint Committee on Cancer
ASCRS	American Society of Colon and Rectal Surgeons
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete Blood Count
CHI	Council of Health Insurance
CrCl	Creatinine Clearance
CT	Computer Tomography
DCF	Docetaxel/Cisplatin/Fluorouracil
DRE	Digital Rectal Examination
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FNA	Fine Needle Aspiration
FOLFCIS	Fluorouracil/Leucovorin/Cisplatin
GFR	Glomerular Filtration Rate
HAS	Haute Autorité de Santé
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hazard Ratio
HTA	Health Technology Assessment
ICI	Immune Checkpoint Inhibitor
IDF	CHI Drug Formulary
IQWIG	Institute for Quality and Efficiency in Healthcare
KSA	Kingdom of Saudi Arabia
mFOLFOX6	Fluorouracil/Leucovorin/Oxaliplatin

MMR	Mismatch Repair
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite Instability High
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Peritoneal Dialysis
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death Ligand-1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
RT	Radiotherapy
SCC	Squamous-Cell Carcinoma
SCCA	Squamous-Cell Carcinoma of the Anus
SFDA	Saudi Food and Drug Authority
SITC	Society for Immunotherapy of Cancer
TMBH	Tumor Mutational Burden High
TNM	Tumor, Node, Metastasis
U.S	United States

Executive Summary

Anal cancer is a rare disease that accounts for less than 1% and less than 3% of all new cancer diagnoses and gastrointestinal tumors, respectively. The most common histological subtype is **squamous-cell carcinoma of the anus (SCCA) with an annual incidence of 0.5-2.0 in 100 000**[1]. However, the incidence of anal cancer in Europe, Australia and the United States is increasing[1]. An analysis of the U.S. Cancer Statistics dataset reported an annual increase of 2.7% between 2001 to 2015 with the greatest increases in age groups ≥50 years[2]. Anal cancer mortality rates (2001–2016) also rose, with an average increase of 3.1% per year[2].

SCCA and its precursor lesion, anal intraepithelial neoplasia (AIN), are mostly attributable to **human papillomavirus (HPV) infection**, which represents the **causative agent in 80%-85% of patients** (especially the HPV16 and HPV18 subtypes)[3]. Factors increasing the risk of HPV infection and/or modulating a host response and the persistence of this infection appear to affect the epidemiology of this tumor. Other important risk factors include **human immunodeficiency virus (HIV) infection**, prior history of anogenital warts, lower genital tract malignancies, immunosuppression in transplant recipients, a history of other HPV-related cancers, autoimmune disorders, and cigarette smoking[3-6]. Cigarette smoking and HIV infection may also affect the modulation and persistence of HPV infection and, hence, treatment outcomes.

HPV Immunization – The Advisory Committee on Immunization Practices (ACIP) recommends **routine use of the 9-valent HPV vaccine in children aged 11 and 12 years, as well as catch-up vaccination for individuals through 26 years of age** who have not been previously vaccinated[7]. The American Academy of Pediatrics concurs with this vaccination schedule. In 2018, the FDA expanded use of the 9-valent vaccine to include individuals aged 27 through 45 years, and the ACIP voted in 2019 to recommend vaccination, based on shared clinical decision-making, for individuals in this age range who are not adequately vaccinated[7].

Pathology – Most primary cancers of the anal canal are of **squamous cell histology**. The term "anal cancer", by common definition, refers to **SCCs arising within the mucosa of the anal canal**. In contrast, **adenocarcinomas** arising from glandular elements within the anal canal are rare but appear to share a **similar natural history to rectal adenocarcinomas**[8]. They are treated in a manner that is similar to rectal carcinoma rather than anal cancer[7]. **Perianal squamous cell carcinomas** are more likely than those of the anal canal to be well-differentiated and keratinizing large-cell types. The presence of skin appendages in perianal tumors can distinguish them from anal canal tumors. However, it is not always possible to distinguish between anal canal and perianal squamous cell carcinoma since tumors can involve both areas[8].

Staging – The TNM staging system for anal canal cancer illustrated in the 8th edition of AJCC Cancer Staging Manual is used and it is based on tumor size/invasion of adjacent structures and the presence or absence of nodal or distant metastases[7]. Pretreatment clinical staging consists of physical examination and biopsy of the primary tumor, palpation of the groin, computed tomography (CT) of the chest, CT or magnetic resonance imaging (MRI) of the abdomen and pelvis, and an integrated positron emission tomography (PET)/CT scan[7].

Clinical findings and Workup– Approximately 45% of patients with anal carcinoma present with **rectal bleeding**, while approximately 30% have either pain or the sensation of a rectal mass[9]. Following confirmation of squamous cell carcinoma by biopsy, a thorough examination and evaluation, including a careful digital rectal examination (DRE), an anoscopic examination, and a palpation of the inguinal lymph nodes are recommended, with fine needle aspiration (FNA) and/or excisional biopsy of nodes found to be enlarged by either clinical or radiologic examination. Evaluation of pelvic lymph nodes with CT or MRI of the pelvis is also recommended. A CT scan of the abdomen is also recommended to assess possible disease dissemination. Since veins of the anal region are part of the venous network associated with systemic circulation, chest CT scan is performed to evaluate for pulmonary metastasis. Gynecologic exam, including cervical cancer screening, is suggested due to the association of anal cancer and HPV. A discussion of infertility risks and counseling on fertility preservation, if appropriate, should be carried out prior to the start of treatment. HIV testing should be performed if the patient's HIV status is unknown. PET/CT scanning, or PET/MRI if available, can be considered to verify staging before treatment[7,10-14].

In the **Kingdom of Saudi Arabia**, in 2010, a total of only 27 cases were diagnosed according to the Saudi Cancer Registry, 18 males and 9 females representing 0.3% of all cases diagnosed in the Saudi population[15].The age standardized rate was 0.3/100,000 for males and 0.2/100,000 for females[15]. According to the Johns Hopkins Aramco Healthcare (JHAH) Tumor Registry Annual Review 2019, 5 cases of cancer of the anal canal were diagnosed between 2017 and 2019 in KSA, which accounted for 0.3% of all diagnosed cancers in that period[16]. Data from the HPV Information Center published in 2023 ranks anal cancer as the second most common HPV-related cancer in KSA (after cervical cancer), with a crude incidence rate of 0.27 and 0.2 cases per 100,000 in males and females respectively[17].

This report compiles all clinical and economic evidence related to anal cancer and associated complications according to the relevant sources. The ultimate objective of issuing anal cancer guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to anal cancer patients in Saudi Arabia.** The main focus of the review was on Saudi, North

American, and European guidelines issued within the last five years in addition to recent systematic reviews and Meta-Analysis.

Treatment strategies for patients with anal cancer are outlined in the below sections[7,10-14]:

- ## Anal canal SCC

A.1. Localized disease

- **Concurrent chemoradiotherapy** (CRT) rather than surgery is the **preferred first-line treatment for patients with localized anal carcinoma** even for T1-2N0M0 tumors (Recommendation Level A, Evidence Level I, II)[7,10-13].
- Local excision may be an option for carefully selected patients with ≤1 cm, superficially invasive tumors that are completely excised and have ≤3 mm of basement membrane invasion and a horizontal spread of ≤7 mm[7].
- During radiation therapy (RT), concurrent use of standard dose of **5-fluorouracil (5-FU)** plus **mitomycin C** is the **preferred chemotherapy regimen** (Recommendation Level A, Evidence Level II). The substitution of **capecitabine** for FU is acceptable (Recommendation Level A, Evidence Level I, II)[7,10-13].
    - Most studies have delivered 5-FU as a protracted **96- to 120-hour infusion** during the first and fifth weeks of RT, and bolus injection of mitomycin is typically given on the first or second day of the 5-FU infusion[7].
- Fluorouracil (5-FU) can be replaced with capecitabine [Recommendation Level A, B, Evidence Level II, III]
    - Capecitabine is given orally, 5 days per week on each day that RT is given, for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiation[7, 12].
- The combination of **5-FU plus cisplatin with RT** is an alternative treatment option (Recommendation Level B, Evidence Level II)[7,10-13].
- Treatment interruptions should be minimized during CRT, and overall treatment time and total dose maintained as much as possible.
- Elderly patients who can tolerate treatment should be treated with curative chemoradiotherapy (CRT) (Recommendation Level C, Evidence Level V). For the extremely aged population with T1N0 tumors, or those with significant comorbidities, reduction of mitomycin and FU doses during CRT may be considered, although this is not a standard approach.

- There has also been interest in the use of **biologic therapies** for the treatment of anal cancer. A phase 3 trial is investigating the use of the programmed cell death protein 1 (PD-1) inhibitor, nivolumab, following combined modality therapy for stage II-IIIB high-risk anal carcinoma. This trial has completed enrollment of 344 participants and results are pending[18].
- Anal SCC in patients living with **HIV** is **treated similarly to those without HIV**. However, patients with active or a prior history of HIV/AIDS-related complications may not tolerate full-dose therapy or require chemotherapy dose adjustment.
- **Treatment response** is **assessed clinically 8 to 12 weeks after completion of CRT**. For patients with a clinical complete response, re-evaluation at **3–6-month intervals** with digital rectal examination and inguinal node palpation is recommended. Anoscopy is recommended at 6-12 months with annual contrast-enhanced CT of the chest, abdomen, and pelvis or MRI for at least three years[7,10-13].
- Patients with clinical suspicion for persistent disease at 8 to 12 weeks can be watched for up to six months following completion of CRT. Biopsy is indicated for overt disease progression or a clinical suspicion for persisting disease ≥6 months after completion of CRT[7,10-13].

A.2. Persistent or locally recurrent disease

- Persistent or locally recurrent anal SCC following CRT can be successfully salvaged with surgery, typically **abdominoperineal resection** (APR), with long-term control in approximately 25 to 40% of cases[7,10-13].
- To avoid surgery, the use of **immunotherapy** with nivolumab or pembrolizumab may be considered prior to APR as some patients may have a good response, however it should be noted that this approach is based on **institutional experience** only and there are currently no published data supporting its use in this setting of otherwise curative intent surgery[7].

A.3. Metastatic anal carcinoma

- **Systemic therapy** is the recommended approach for metastatic anal SCC. **Paclitaxel plus carboplatin** is the **preferred treatment regimen** (Recommendation Level A, B, Evidence Level I, II). Other alternative protocols used in the first line setting are **FOLFCIS** (5-FU/leucovorin/cisplatin); **mFOLFOX6** (5-FU/leucovorin/oxaliplatin) (Recommendation Level A, Evidence Level II); **5-FU + cisplatin**; **Modified DCF** (Docetaxel/cisplatin/5-FU) (Recommendation Level B, Evidence Level II)[7,10-13].
- Several ongoing clinical trials are investigating whether **checkpoint inhibitors** could have a role in the first-line treatment of metastatic anal cancer.

- NCT04444921 is a randomized, phase 3 trial comparing chemotherapy alone (carboplatin and paclitaxel) to chemotherapy plus nivolumab for treatment-naïve metastatic anal cancer[19]. This study is expected to enroll 205 participants and complete in 2023.
- POD1UM-303/InterAACT2 is a similar, phase 3 global study (NCT04472429) investigating the addition of the checkpoint inhibitor, retifanlimab, to carboplatin/paclitaxel chemotherapy and comparing it to chemotherapy alone[20].This trial expects to enroll 300 participants with previously untreated metastatic anal carcinoma and expected completion is in 2024.

- For patients who have progressed on first-line therapy, **immunotherapy** using agents that target the programmed cell death receptor 1 (PD-1) pathway: **pembrolizumab** or **nivolumab** is the **recommended subsequent-line treatment approach** (Recommendation Level A, B, Evidence Level II, III)[7,10-14].
  - **Microsatellite instability (MSI)/mismatch repair (MMR) testing is not required**. MSI is uncommon in anal cancer and responses to PD-1/PD-L1 inhibitors occur in 20% to 24% of patients.
  - A single-arm, multicenter phase 2 trial assessed the safety and efficacy of the anti-PD-1 antibody nivolumab for refractory metastatic anal cancer[21]. Two complete responses and seven partial responses were seen among the 37 enrolled participants who received at least one dose, for a response rate of 24% (95% CI, 15–33)[21].
  - The KEYNOTE-028 trial is a multi-cohort, phase 1b trial of the anti-PD-1 antibody pembrolizumab in 24 patients with programmed cell death ligand 1 (PDL1) – positive advanced squamous cell carcinoma of the anal canal[22]. Four partial responses were seen, for a response rate of 17% (95% CI,5–37), and 10 patients (42%) had stable disease, for a disease control rate of 58%[22].
  - Anal cancers may be responsive to PD-1/PD-L1 inhibitors because they often have high PD-L1 expression and/or a high tumor mutational load despite being microsatellite stable (MSS).
- Combinations of immunotherapy plus cytotoxic chemotherapy are beginning to be studied for first-line therapy; however, until further information is available, this cannot yet be considered a standard approach outside of the context of a clinical trial[7,10-14].
- **Chemoradiotherapy to the primary site for local control** must be addressed on a case-by-case basis. **5-FU+RT** or **capecitabine+RT** are recommended in this setting (Recommendation Level A, Evidence Level II)[7].

Anal adenocarcinoma

For patients with adenocarcinoma of the anal canal, treatment according to a **rectal cancer paradigm** rather than initial FU and mitomycin-containing CRT, as is used for anal SCCs is suggested. For most patients this will include surgery (typically APR) plus fluoropyrimidine-based CRT[7].

Perianal cancer

- For patients with **T1N0 well-differentiated** SCC of the perianal skin forming a discrete skin lesion that is clearly separate from the anal canal, or **select T2,N0 (that does not involve sphincter) wide local excision** alone is recommended if negative margins can be achieved without compromising the sphincter muscles. The American Society of Colon and Rectal Surgeons (ASCRS) defines an adequate margin as 1 cm[7,10-13].
- If the margins are not adequate, re-excision is the preferred treatment option. **Local RT** with or without **continuous infusion 5-FU/mitomycin**, **mitomycin/capecitabine** (Recommendation Level A, Evidence Level II), or 5-FU/cisplatin (Recommendation Level B, Evidence Level II) can be considered as alternative treatment options when surgical margins are inadequate[7,10-13].
- For patients with **T1, N0 Poorly differentiated or T2–T4, N0 or Any T, N+** (± positive para-aortic lymph nodes), **radical concurrent CRT** is recommended, consisting of **local RT** with or without **continuous infusion 5-FU/mitomycin**, **mitomycin/capecitabine** (Recommendation Level A, Evidence Level II), or 5-FU/cisplatin (Recommendation Level B, Evidence Level II)[7].
- For patients with **metastatic perianal cancer**, systemic therapy with **carboplatin/paclitaxel** is the preferred treatment option (Recommendation Level A, B, Evidence Level I, II). Alternative options include FOLFOX (Recommendation Level A, Evidence Level II), FOLFCIS (Recommendation Level A, Evidence Level II), 5-FU/Cisplatin (Recommendation Level B, Evidence Level II), and Modified DCF (Recommendation Level B, Evidence Level II)[7, 12].

Rectal SCC

Primary rectal SCCs, which are very rare, can be difficult to distinguish from anal cancers, and they should be treated according to the same approach as anal SCC[7].

A **summary of drugs used** for the management of anal cancer is illustrated in table 1[7,10-14].

Table 1. Drugs Used in the Management of Anal Cancer

Drugs Used in the Management of Anal Cancer				
Medication	**Indication**	**Line of Therapy**	**Recommendation**	**Evidence**
5-Fluorouracil	First-line treatment of localized anal cancer in combination with mitomycin C or cisplatin with concurrent RT (preferred) First-line treatment of metastatic anal cancer	**1st**	A	I II
Mitomycin C	First-line treatment of localized anal cancer in combination with 5-FU or capecitabine with concurrent RT (preferred) Alternative for surgery in inadequate perianal margins in combination with capecitabine	**1st**	A	II
Capecitabine	First-line treatment of localized anal cancer in combination with mitomycin C with concurrent RT (preferred) Alternative for surgery in inadequate perianal margins in	**1st**	A	II

	combination with mitomycin			
Cisplatin	First-line treatment of localized anal cancer in combination with 5-FU with concurrent RT First-line treatment of metastatic anal cancer Alternative for surgery in inadequate perianal margins in combination with 5-Fluorouracil	**1st**	B	II
Paclitaxel	First-line treatment of metastatic anal and perianal cancer in combination with carboplatin (preferred)	**1st**	A	II
Carboplatin	First-line treatment of metastatic anal and perianal cancer in combination with carboplatin (preferred)	**1st**	A	II
Oxaliplatin	First-line treatment of metastatic anal and perianal cancer (part of the mFOLFOX6 regimen)	**1st**	A	II
Docetaxel	First-line treatment of metastatic anal and perianal cancer	**1st**	B	II

	(part of the modified DCF regimen)			
Nivolumab	Second and subsequent-line treatment of metastatic anal and perianal cancer	**2nd**	A	II
Pembrolizumab	Second and subsequent-line treatment of metastatic anal and perianal cancer	**2nd**	A	II

All the medications in the standard of care therapy are available in the Saudi market; mitomycin C is not SFDA registered but can be imported through healthcare facilities. Section 3 provides a full description of each treatment protocol with a final statement on the place in therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA), reflecting specific drug class role in the anal cancer therapeutic landscape.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in anal cancer were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). A summary of these recommendations is shown in Section 3.

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for drugs used in the management of anal cancer. This is probably because the standard of care for anal cancer, considered a rare tumor, hasn't changed much in the past few years with a proven record of efficacy and safety of the traditional chemotherapy agents. Moreover, these drugs are widely available in international markets with many generics ensuring accessibility and cost effectiveness. However, with the inclusion of new therapies in the international treatment guidelines of anal cancer (although still as off-label use) such as immune checkpoint inhibitors (nivolumab, pembrolizumab), more HTA recommendations are expected and encouraged in the future to support the judicious use of these agents.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

1.1.1 Saudi Oncology Society (2014)

The Saudi Oncology Society released in 2014, their clinical practice guidelines for the management of anal cancer, as part of their clinical management guideline series. The key recommendations of the guideline are outlined below[10].

All cases of anal canal cancer should preferably be seen or discussed in a multidisciplinary form.

a) Pre-treatment evaluation

- History and clinical examination including inguinal lymph node palpation and rigid anoscopy
- Blood count, liver, and renal function levels
- Chest x-ray
- Computed tomography (CT) scan of abdomen and pelvis
- Magnetic resonance imaging (MRI) of pelvis
- Fine needle aspiration of inguinal lymph nodes if clinically palpable
- Human immunodeficiency virus testing in selected cases

b) Staging

The American Joint Commission on Cancer (AJCC)- 2007 pathological staging system is used.

c) Treatment

c.1. Localized disease (clinical stage T1-4, N0-1). Concurrent chemoradiotherapy (EL-2)

- Chemotherapy: 5-fluorouracil and mitomycin C on day one and 29 of radiation therapy5 (EL-1). Alternatively, oral capecitabine at a dose of 825 mg/m^2 twice daily on each day of radiation can be used (EL-3).
- Radiotherapy: 45 Gy administered as 1.80 Gy per fraction in 25 fractions to the pelvis and inguinal node area + 5.4-9.0 Gy boost to the tumor bed.

c.2. Localized disease (clinical stage T_{any} N2-3). Concurrent chemoradiotherapy

- Chemotherapy: 5-fluorouracil and mitomycin C on day one and 29 of radiation therapy (EL-2). Alternatively, oral capecitabine at a dose of 825 mg/m2 twice daily on each day of radiation can be used (EL-3).
- Radiotherapy: 45 Gy administered as 1.80 Gy per fraction in 25 fractions to the pelvis and inguinal node area + 5.4-9.0 Gy boost to the tumor bed and inguinal node area.

c.3. Metastatic disease

- Palliative chemotherapy with 5-fluorouracil and cisplatin (EL-2). Consider palliative radiation to local disease.

c.4. Recurrent disease

- Local recurrence or persistent disease post-chemoradiotherapy[10]:
  - Persistent disease is defined as positive biopsy at 3 months from end of chemoradiotherapy
  - Recurrent disease should be biopsy proven
  - Anal recurrence. Consider abdominoperineal resection (EL-2)
  - Inguinal lymph nodes recurrence. Consider groin lymph node dissection (EL-3) or groin irradiation if not carried out earlier ± chemotherapy: 5-fluorouracil and mitomycin C (EL-3)
- Distant recurrence: (c.f Metastatic disease)

c.5. Follow up.

- Every 4 months in the first year and every 6 months thereafter for 5 years, then annually with digital rectal examination and inguinal palpation (EL-3).
- CT scan of abdomen and pelvis annually for the first 3 years (EL-3).

1.2 North American Guidelines

1.2.1 National Comprehensive Cancer Network (NCCN) (2023)

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of Anal Carcinoma in September 2023, including recommendations for the diagnosis, evaluation, treatment, and follow-up of Anal Cancer[7].

a) Clinical Presentation and Workup

Approximately 45% of patients with anal carcinoma present with rectal bleeding, while approximately 30% have either pain or the sensation of a rectal mass[7].

Following confirmation of squamous cell carcinoma by biopsy, the recommendations of the NCCN Anal Carcinoma Guidelines Panel for the clinical evaluation of patients with anal canal or perianal cancer are very similar. Table 2 summarizes the workup recommendations for patients with squamous cell anal carcinoma as per NCCN guidelines[7].

Table 2. Workup Recommendations for Patients with Squamous Cell Anal Carcinoma (NCCN Guidelines)

Initial Workup (Anal/Perianal Cancer)
▪ Digital rectal examination (DRE) ▪ Inguinal lymph node evaluation ▪ Consider biopsy or fine needle aspiration (FNA) if suspicious nodes ▪ Chest/abdominal CT + pelvic CT or MRI ▪ Consider positron emission tomography (PET)/CTd or PET/MRI (if available) ▪ Anoscopy ▪ HIV testing (if HIV status unknown) ▪ Gynecologic exam, including screening for cervical cancer ▪ Fertility risk discussion/counseling in appropriate patients

b) Staging

- The TNM staging system for anal canal cancer developed by the AJCC is used in the guidelines[7].
- Because current recommendations for the primary treatment of anal canal cancer do not involve a surgical excision, most tumors are staged clinically with an emphasis on the size of the primary tumor as determined by direct examination and microscopic confirmation[7].

c) Primary Treatment of Non-Metastatic Anal Carcinoma

c.1 Primary Treatment of Anal Canal Cancer

- Currently, concurrent **chemoRT** is the recommended primary treatment for patients with non-metastatic anal canal cancer as well as for patients with positive para-aortic lymph nodes that can be included in the radiation field, although only limited retrospective data support use in this setting[7].
- **Mitomycin/5-FU** or **mitomycin/capecitabine** is administered concurrently with **radiation**[7].
- Alternatively, **5-FU/cisplatin** can be given with concurrent radiation (category 2B)[7].

- Most studies have delivered 5-FU as a protracted **96- to 120-hour infusion** during the first and fifth weeks of RT, and bolus injection of mitomycin is typically given on the first or second day of the 5-FU infusion.
- Capecitabine is given orally, 5 days per week on each day that RT is given, for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiation[7].
- The combination of 5-FU, mitomycin C, and cisplatin has also been studied in a phase II trial but was found to be too toxic[7].
- For older patients or those who are unlikely to tolerate mitomycin, the optimal chemotherapy regimen remains uncertain[7].
    - Some NCCN Panel members have used a combination of weekly cisplatin and daily 5-FU on days of radiation for chemoRT in localized anal cancer. Other potential strategies for this patient population may include capecitabine plus RT or RT alone (without chemotherapy).
    - However, due to a lack of data supporting this approach and differing strategies among panel members, there are not yet defined recommendations for patients with anal cancer who are not candidates for intensive therapy.
- RT is associated with significant side effects. Patients should be counseled on infertility risks and given information regarding sperm, oocyte, egg, or ovarian tissue banking prior to treatment. In addition, patients should be considered for vaginal dilators and should be instructed on the symptoms of vaginal stenosis[7].
- The chemoradiotherapy regimens recommended for the first-line treatment of localized anal cancer are outlined in Table 3 below[7].

Table 3. Systemic Therapy for Localized Anal Cancer (NCCN Guidelines)

Chemo/RT for Localized Cancer	
Hormonal Therapy for Recurrent or Metastatic Anal Carcinoma	
Preferred Regimens ▪ 5-FU + mitomycin C + RT ▪ Capecitabine + mitomycin C + RT	**Other Recommended Regimens** ▪ 5-FU + Cisplatin + RT

All recommendations are considered Category 2A unless specified otherwise.

c.2 Primary Treatment of Perianal Cancer

- Perianal lesions can be treated with either **local excision** or **chemoRT** depending on the clinical stage[7].
- Primary treatment for patients with T1,N0 well-differentiated or select smaller T2,N0 perianal (anal margin) cancer that does not involve the sphincter is by local excision with adequate margins.
- The American Society of Colon and Rectal Surgeons (ASCRS) defines an adequate margin as **1 cm**.
- If the margins are not adequate, re-excision is the preferred treatment option.
- **Local RT with or without continuous infusion 5-FU/mitomycin, mitomycin/capecitabine, or 5-FU/cisplatin (category 2B) can be considered as alternative treatment options when surgical margins are inadequate**[7].

d) Treatment of Locally Progressive or Recurrent Anal Carcinoma

- Despite the effectiveness of chemoRT in the primary treatment of anal carcinoma, rates of locoregional failure of 10% to 30% have been reported. Some of the disease characteristics that have been associated with higher recurrence rates following chemoRT include higher T stage and higher N stage.
- Evidence of progression found on DRE should be followed by biopsy as well as restaging with CT and/or PET/CT imaging.
- Patients with biopsy-proven locally progressive disease are candidates for **radical surgery with an APR and colostomy**[7].
- To avoid surgery in local recurrence, the use of **immunotherapy** with nivolumab or pembrolizumab may be considered prior to APR (category 2B) as some patients may have a good response, however it should be noted that this approach is based on **institutional experience** only and there are currently no published data supporting its use in this setting of otherwise curative intent surgery.
- Inguinal node dissection is recommended for recurrence in that area and for patients who require an APR but have already received groin radiation.
- Patients who develop inguinal node metastasis who do not undergo an APR can be considered for palliative RT to the groin with or without 5-FU/mitomycin or mitomycin/capecitabine if no prior RT to the groin was given. Radiation therapy technique and doses are dependent on dosing and technique of prior treatment. If RT was given previously, 5-FU/cisplatin chemotherapy may be given (category 2B)[7].

e) Treatment of Metastatic Anal Cancer

e.1 First-Line Treatment of Metastatic Anal Cancer

- Based on results from the phase II International Multicentre InterAACT study, **carboplatin in combination with paclitaxel has been noted as the preferred regimen** for first-line treatment of metastatic anal cancer by the NCCN Panel[7].
    - In this trial, 91 patients with previously untreated, unresectable, locally recurrent, or metastatic anal squamous cell carcinoma were randomized to either carboplatin plus paclitaxel or cisplatin plus 5-FU.
    - While response rates were similar between carboplatin plus paclitaxel and cisplatin plus 5-FU (59% and 57%, respectively), carboplatin plus paclitaxel showed lower toxicity compared to cisplatin plus 5-FU (71% vs. 76% grade ≥3 toxicity and 36% vs. 62% [P = .016] serious adverse events).
    - Median PFS and OS were 8.1 months and 20 months for carboplatin plus paclitaxel and 5.7 months and 12.3 months for cisplatin plus 5-FU (HR for OS, 2.0; 95% CI, 1.15–3.47; P = .014)[23].
- Other recommended treatment options include 5-FU, leucovorin, and cisplatin (**FOLFCIS**); 5-FU, leucovorin, and oxaliplatin (**FOLFOX**); **5-FU plus cisplatin** (category 2B reflecting its similar efficacy, but higher toxicity, when compared to carboplatin plus paclitaxel in a randomized trial); or modified docetaxel, cisplatin, and 5-FU (**DCF**, category 2B)[7].
- Several ongoing clinical trials are investigating whether **checkpoint inhibitors** could have a role in the first-line treatment of metastatic anal cancer.
    - NCT04444921 is a randomized, phase 3 trial comparing chemotherapy alone (carboplatin and paclitaxel) to chemotherapy plus nivolumab for treatment-naïve metastatic anal cancer[19]. This study is expected to enroll 205 participants and complete in 2023.
    - POD1UM-303/InterAACT2 is a similar, phase 3 global study (NCT04472429) investigating the addition of the checkpoint inhibitor, retifanlimab, to carboplatin/paclitaxel chemotherapy and comparing it to chemotherapy alone[20].This trial expects to enroll 300 participants with previously untreated metastatic anal carcinoma and expected completion is in 2024.

e.2 Second-Line Treatment of Metastatic Anal Cancer

- Although further studies of PD-1/PD-L1 inhibitors are warranted, the panel added **nivolumab and pembrolizumab** as pr**eferred options for patients**

with metastatic anal cancer who have progressed on first-line chemotherapy in the 2018 version of these guidelines[7].

- **MSI)/MMR testing is not required**. MSI is uncommon in anal cancer and responses to PD-1/PD-L1 inhibitors occur in 20% to 24% of patients.
- A single-arm, multicenter phase 2 trial assessed the safety and efficacy of the anti-PD-1 antibody nivolumab for refractory metastatic anal cancer[21]. Two complete responses and seven partial responses were seen among the 37 enrolled participants who received at least one dose, for a response rate of 24% (95% CI, 15–33)[21].
- The KEYNOTE-028 trial is a multi-cohort, phase 1b trial of the anti-PD-1 antibody pembrolizumab in 24 patients with programmed cell death ligand 1 (PDL1)– positive advanced squamous cell carcinoma of the anal canal[22]. Four partial responses were seen, for a response rate of 17% (95% CI,5–37), and 10 patients (42%) had stable disease, for a disease control rate of 58%[22].
- Anal cancers may be responsive to PD-1/PD-L1 inhibitors because they often have high PD-L1 expression and/or a high tumor mutational load despite being microsatellite stable (MSS).
- The panel also notes that platinum-based chemotherapy should not be given in second line if disease progressed on platinum-based therapy in first line[7].
- Systemic therapy regimens for metastatic anal cancer according to NCCN guidelines are outlined in Tables 4 and 5 below[7].

Table 4. Systemic Therapy for Metastatic Anal Cancer (NCCN Guidelines)

Metastatic Anal Cancer		
First-Line Therapy		**Subsequent-Line Therapy**
Preferred Regimens ▪ Carboplatin/ paclitaxel	**Other Recommended Regimens** ▪ 5-FU + cisplatin ▪ FOLFCIS ▪ mFOLFOX6[1] ▪ Modified DCF	**Preferred Regimens** ▪ Nivolumab ▪ Pembrolizumab if neither previously received

[1] Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

All recommendations are considered Category 2A unless specified otherwise.

Table 5. Chemo/RT to the Primary Site for Local Control (NCCN Guidelines)

Chemo/RT to the Primary Site for Local Control
▪ 5-FU + RT ▪ Capecitabine + RT

All recommendations are considered Category 2A unless specified otherwise

f) Follow-up and Surveillance

- Following APR, patients should undergo re-evaluation every 3 to 6 months for 5 years, including clinical evaluation for nodal metastasis (i.e., inguinal node palpation).
- In addition, it is recommended that these patients undergo annual chest, abdominal, and pelvic CT with contrast or chest CT without contrast and abdominal/pelvic MRI with contrast for 3 years.
- Following treatment of inguinal node recurrence, patients should have a DRE and inguinal node palpation every 3 to 6 months for 5 years.
- In addition, anoscopy every 6 to 12 months and annual chest, abdominal, and pelvic CT with contrast or chest CT without contrast and abdominal/pelvic MRI with contrast are recommended for 3 years[7].

1.2.2 American Society of Colon and Rectal Surgeons (ASCRS) (2018)

The American Society of Colon and Rectal Surgeons (ASCRS) published in 2018 clinical practice guidelines for anal squamous cell cancers. The key treatment recommendations relevant for anal cancer are outlined in the following sections[11]:

a) Premalignant neoplasms of the anal canal and perianal region

- Patients at increased risk for anal squamous neoplasms should be identified by history, physical examination, and laboratory testing, noting that the risk is higher in HIV-positive individuals, men who have sex with men (MSM), and women with a history of cervical dysplasia. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.
- Standardized nomenclature with a 2-tiered system should be used. Biomarkers, including p16, should be used selectively to clarify equivocal high-grade lesions. Grade of Recommendation: Strong recommendation based on low- or very-low–quality evidence, 1C.
- Individuals with anal dysplasia should be followed at regular intervals with a history, physical examination, and a discussion of screening options. Grade of

Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

- Screening with anal cytology (or anal Papanicolaou (Pap) tests) may be considered in high-risk populations as part of a comprehensive screening program, but the sensitivity and specificity of the test do not support its use for universal screening. Grade of Recommendation: Weak recommendations based on moderate-quality evidence, 2B.
- HPV testing may be used as an adjunct to screening for anal cancer. Grade of Recommendation: Weak recommendations based on moderate-quality evidence, 2B.
- HRA may be considered as a screening option for patients at high risk for cancer when performed by clinicians with appropriate training in the procedure. Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
- Topical imiquimod, fluorouracil, trichloroacetic acid and cidofovir with close long-term follow-up are each option for the treatment of LSIL or HSIL. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
- Ablative treatments with conventional anoscopy or HRA are appropriate therapies for HSILs. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.
- Vaccination against HPV in men and women under age 26 years for primary prevention is typically recommended. Vaccination of individuals with anal dysplasia for secondary prevention of dysplasia and cancer is not recommended. Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A[11].

b) Malignant neoplasms of the anal canal and perianal region

- A disease-specific history and physical examination should be performed, emphasizing symptoms, risk factors, and signs of advanced disease. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.
- Endoscopic and radiologic evaluation should be performed to help determine tumor extension and assess for metastatic disease. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.
- 2-[18F] Fluoro-2-deoxy-D-glucose positron emission tomography (PET)/CT may be considered as an adjunct radiologic study in the staging of anal SCC,

although it does not replace CT scanning for clinical staging. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

- **The primary treatment for all squamous cell cancers of the anal canal, and for most perianal squamous cell cancers, is chemoradiotherapy (CRT)**. Grade of Recommendation: Strong recommendation based on high-quality evidence, IA[11].
- Multimodal therapy involving chemotherapy combined with radiotherapy provides superior locoregional control compared with treatment with radiotherapy alone. Grade of Recommendation: Strong recommendation based on high-quality evidence, IA.
- **The combination of 5-FU and mitomycin C in conjunction with radiotherapy remains as first-line multimodal therapy for the treatment of squamous cancers of the anus**[11]. Grade of Recommendation: Strong recommendation based on high-quality evidence, IA.
- No oncologic benefit exists for providing radiation doses >59 Gy. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, IB.
- Missed treatments should be avoided, because they are strongly associated with inferior disease control. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, IB.
- Disease surveillance should typically start 8 to 12 weeks from the completion of CRT. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.
- Surveillance involving digital rectal examination, anoscopy, and imaging should be continued for 5 years after completion of CRT. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.
- Abdominoperineal resection is effective salvage therapy for persistent or recurrent disease. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.
- Patients with HIV or AIDS who present with anal cancer as the first manifestation of their immunosuppression, and who are not medically deconditioned, can be safely treated according to the same regimens as immunocompetent patients. Grade of Recommendation: Strong recommendation based on medium-quality evidence, IC.
- Perianal squamous cancers, which are well-differentiated, node-negative, T1 lesions, can be adequately treated with wide-local excision with 1-cm margins

of resection. All other anal margin cancers are preferentially treated with CRT. Grade of Recommendation: Strong recommendation based on low-quality evidence, IC.

- Systemic chemotherapy should be considered for patients with distant metastatic disease. Metastasectomy, radiation, and radiofrequency ablation can be considered in selected cases. Grade of Recommendation: Weak recommendation based on low- or very-low–quality evidence, 2C[11].

1.3 European Guidelines

1.3.1 European Society for Medical Oncology (ESMO) (2021)

The European Society for Medical Oncology (ESMO) released in 2021 clinical practice guidelines for diagnosis, treatment, and follow up of anal cancer. The key recommendations of the guideline are outlined in the following sections[12]:

a) Diagnosis and pathology/Molecular biology

The diagnosis and pathology recommendations for anal cancer according to the ESMO guidelines are shown in table 6[12].

Table 6. Diagnosis and Pathology Recommendations for Anal Cancer (ESMO Guidelines)

Recommendations	Strength
Diagnosis and pathology	
▪ Digital anorectal examination is an essential clinical tool for detection of lesions in the anal area.	I,A
▪ Biopsy is mandatory to confirm SCCA.	I,A
▪ All suspicious anal lesions should be excised or biopsied. Targeted biopsy of anal lesions suspicious for AIN is mandatory in high-risk groups to exclude invasive disease.	I,B
▪ Female patients with AIN should be screened for synchronous cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia. Consider HIV testing.	I,A

b) Staging and Risk assessment

The staging and risk assessment recommendations for anal cancer according to the ESMO guidelines are shown in table 7[12].

Table 7. Staging and Risk Assessment Recommendations for Anal Cancer (ESMO Guidelines)

Recommendations	Strength
Staging and Risk Assessment	
▪ All patients with anal tumors should be referred and discussed in a multidisciplinary team (MDT) meeting with a pre-specified interest in anal cancer.	V,C
▪ Clinical examination including digital rectal exam (DRE) (and vaginal examination in women) and palpation of the inguinal lymph nodes should be carried out for assessment of tumor extent.	V,B
▪ High-resolution T2-weighted MRI is needed for optimal assessment of primary tumor and lymph nodes.	III,A
▪ MRI may also be helpful to note the relationship of tumor/nodes to the sacral segment levels, which would also assist in RT planning.	III,B
▪ Lymph nodes can be difficult to interpret on MRI. Generally, they are more likely to be malignant if they exhibit mixed signal intensity and if breach of the lymph node capsule by tumor signal intensity is observed on high-resolution T2-weighted MRI.	III,A
▪ Contrast-enhanced CT scanning of the thorax, abdomen and pelvis is a requirement for all patients to assess potential metastatic disease sites at diagnosis and follow-up.	III,A
▪ Further characterization of enlarged inguinal nodes by US-guided FNA may be helpful when confirmatory features of malignancy are not evident on either MRI or PET-CT.	V,C
▪ PET-CT may be considered for staging and assisting in RT planning	III,C
▪ HIV testing may be considered in at-risk patients.	III,C
▪ Assessment of HPV or p16 status may be considered as they have treatment response predictive value.	V,C

c) Management of local and regional disease

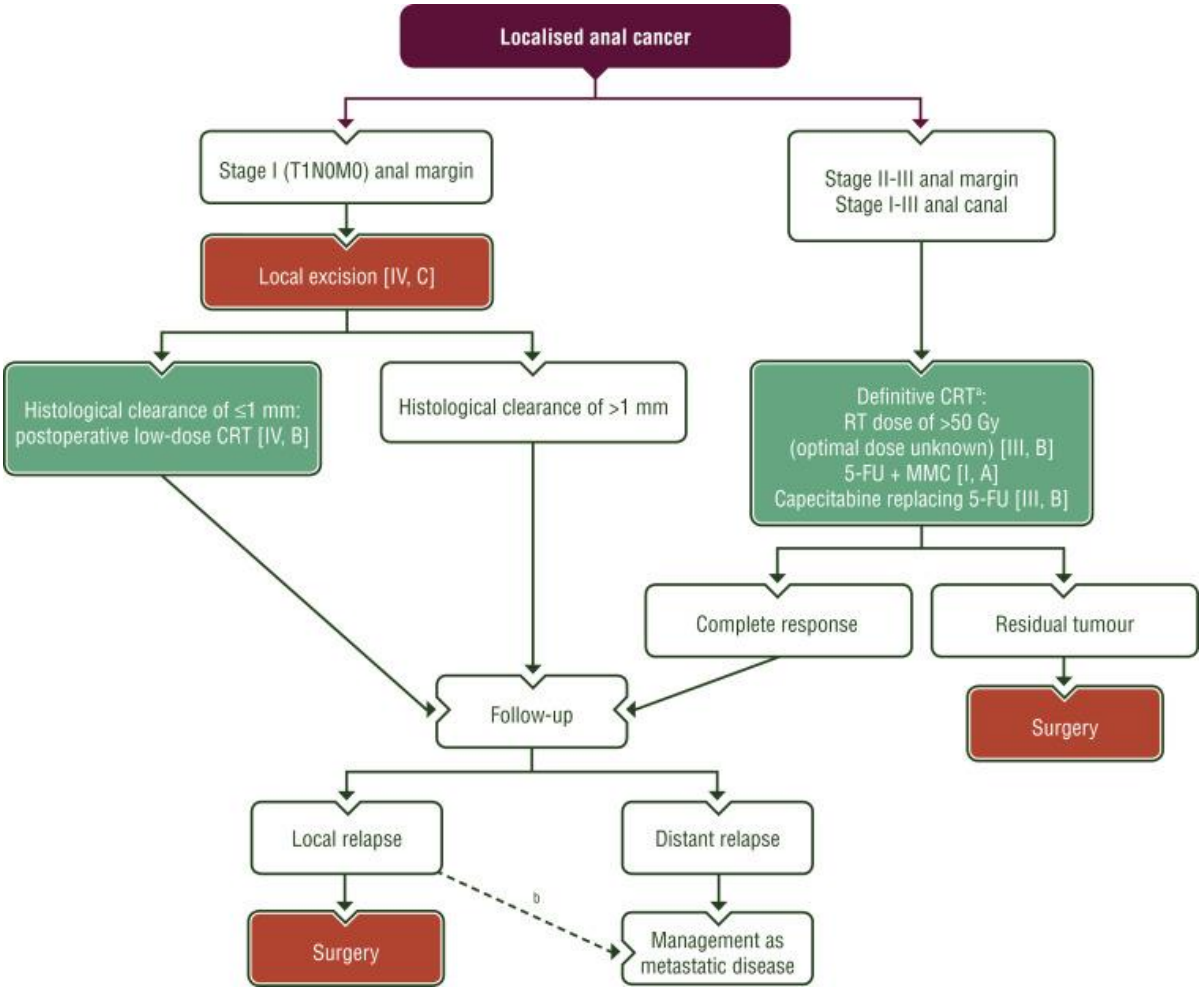
The treatment recommendations for patients with local/locoregional anal cancer according to the ESMO guidelines are shown in table 8[12].

Table 8. Treatment Recommendations for Patients with Local/Locoregional Anal Cancer (ESMO Guidelines)

Recommendations	Strength
Primary Treatment	
▪ All patients with anal tumors should be referred and discussed in an MDT meeting with a pre-specified interest in anal cancer.	V,C
▪ RT with concomitant 5-FU and MMC is recommended as standard of care for patients with localized SCCA.	I,A
▪ CRT for locally advanced anal cancer should be given with an RT dose of >50 Gy; the optimal dose for different tumor stages is not known.	III,B
▪ Capecitabine can be possibly used as an alternative to 5-FU in combination with mitomycin C and RT.	III,B
▪ Neoadjuvant or adjuvant chemotherapy is generally not recommended [I, D].	I,D
▪ Elderly patients who can tolerate treatment should be treated with curative chemoradiotherapy (CRT). Patients who cannot tolerate CRT may benefit from RT for local control.	V,C
▪ The optimal RT dose for primary anal cancer is not known, but doses of at least >45-50 Gy are recommended for T1-2N0 tumors, and doses of 50.4 Gy or higher for T3-4 or N1 tumors.	III,B
▪ Contouring guidelines are helpful for defining treatment volumes.	V,C
▪ Intensity modulated RT (IMRT), volumetric modulated arc therapy (VMAT) or 3D conformal RT are the recommended RT techniques, with RT dose constraints to normal tissue.	III,B
▪ Pre-CRT colostomy should be considered in patients with locally advanced anal cancers with (or anticipated) anorectal pain or fecal incontinence and rectovaginal fistula. Patients should be advised of the likelihood that their colostomy will be permanent.	III,C
▪ There are uncommon scenarios where radical abdomino-perineal excision (APE) may be considered instead of CRT as the primary treatment, e.g., previous pelvic RT.	IV,C
Response assessment	
▪ The optimum time point to assess tumor response after CRT is 26 weeks.	II,B
▪ Clinical assessment must be undertaken pre- and post-treatment.	II,B

▪ A side-by-side comparison of the baseline and post-treatment MRI scans enables an accurate assessment of response.	IV,A
▪ There is insufficient evidence to recommend the routine use of PET-CT in the assessment of treatment response or follow-up.	III,C
Toxicity	
▪ Patients should be assessed for skin and hematological toxicity during CRT treatment.	III,B
▪ Patients should be informed of expected late effects, including changes in anorectal and sexual function, menopause, and risk of infertility.	IV,C
Locally recurrent or residual disease	
▪ Patients with locally residual or recurrent disease after CRT should be considered for salvage surgery.	III,B
▪ Residual or recurrent tumors may be considered for histological confirmation.	II,B
▪ For patients with locally recurrent disease, MRI in conjunction with specialist MDT assessment is important to optimize surgical cure.	III,A
▪ Involvement of the anal sphincter complex requires exenterative surgery, and imaging assessment should include a thorough assessment of the pelvic compartments to enable surgical planning.	III,A
▪ The mainstay of salvage surgery is an APE, but more radical exenterative operations can be considered to achieve an R0 resection.	III,C
▪ APE for relapsed anal cancer is a different operation from that used for rectal cancer. Perineal plastic reconstruction with musculo-cutaneous flaps should be considered in almost all cases.	IV,C
▪ Patients should be warned that long-term morbidity after salvage surgery is high.	IV,C
▪ Many organizations in Europe advocate that this specialized multidisciplinary surgery is centralized.	IV,B
Anal margin cancers	
▪ Early anal margin cancers (cT1N0M0) can be treated definitively by local excision. The aim of this operation is to achieve a histological clearance of >1 mm without damage to the anal sphincter muscle.	IV,C
▪ CRT is recommended for anal margin cancers (T1N0M0) if the margin is 1 mm.	III,B

A proposed algorithm for the management of localized anal cancer is shown in figure 1[12].



5-FU, 5-fluorouracil; CRT, chemoradiotherapy; M, metastasis; N, node; MMC, mitomycin C; RT, radiotherapy; T, tumor. Optimum time point to assess clinical tumor response after CRT is 26 weeks [II, B]. In cases where surgery cannot be carried out.

Figure 1. Treatment algorithm for localized anal cancer. Adapted from Rao S, Guren MG, Khan K, et al. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol. 2021;32(9):1087-1100. doi:10.1016/j.annonc.2021.06.015

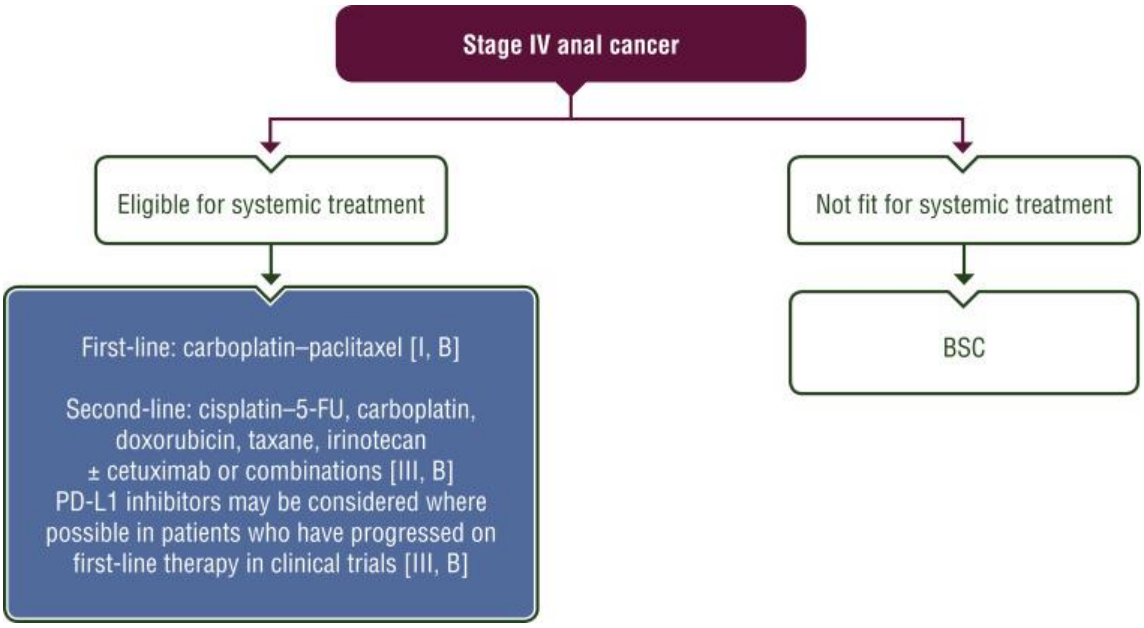
d) Advanced/Metastatic Disease

The advanced/metastatic disease treatment recommendations for patients with anal cancer according to the ESMO guidelines are shown in table 9[12].

Table 9. Treatment Recommendations for Patients with Advanced/Metastatic Anal Cancer (ESMO Guidelines)

Recommendations	Strength
Recurrent/Metastatic EC	
▪ Carboplatin in combination with paclitaxel should be considered a new standard of care in patients with chemotherapy-naive advanced anal cancer.	I,B
▪ Cisplatin in combination with 5-FU/capecitabine, carboplatin or docetaxel-based combinations are alternatives in patients with chemotherapy-naive advanced anal cancer.	III,B
▪ PD-L1 inhibitors may be considered where possible in patients who have progressed on first-line therapy in clinical trials.	III,B

A proposed algorithm for the treatment recommendations for advanced anal cancer is shown in figure 2[12].



FU, 5-fluorouracil; BSC, best supportive care; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Figure 2. Treatment algorithm for advanced anal cancer. Adapted from Rao S, Guren MG, Khan K, et al. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(9):1087-1100. doi:10.1016/j.annonc.2021.06.015

e) Follow-up, Long-Term Implications, and Survivorship

The follow-up, long-term implications, and survivorship recommendations for patients with anal cancer according to the ESMO guidelines are shown in table 10[12].

Table 10. Follow-up, Long-Term Implications, and Survivorship Recommendations (ESMO Guidelines)

Recommendations	Strength
Follow-up, Long-Term Implications, and Survivorship	
▪ Follow-up should be considered in all patients within a protocol-driven program by the anal cancer MDT.	III,B
▪ The primary aim of follow-up is to detect disease which is amenable to salvage therapy; a secondary aim is to manage symptoms related to the cancer and its treatment.	III,C
▪ Patients in complete remission should be evaluated every 3-6 months for a period of 2 years, and every 6- 12 months until 5 years, with clinical examination including DRE and palpation of the inguinal lymph nodes.	II,B
▪ Very few (<1%) relapses occur after 3 years so extended imaging surveillance after this time is not recommended.	II,C
▪ Patients with locally advanced anal cancer may benefit from intensive MRI surveillance in the first 12 months.	III,C
▪ Efforts should be made to document quality of life and late effects.	V,C

1.3.2 German Anal Cancer Guideline Group (2021)

The German Anal Cancer Guideline Group released in 2021, their clinical practice guidelines for the management of patients with anal cancer. The key management recommendations of the guideline are outlined below[13].

a) Treatment of stages I–III anal cancer

- Cancer of the anal margin <2 cm in diameter without regional or distant metastases (stage I) shall be excised locally while ensuring an adequate safety margin (0.5 cm) (grade of recommendation [GR]: A; GRADE: very low).
- Cancer of the anal canal measuring <2 cm in diameter without regional or distant metastases (stage I) should be treated with primary combined chemoradiation (GR: B; GRADE: very low).
- Alternatively, in the case of cancer of the anal canal measuring <2 cm in diameter without regional metastases or distant metastases, R0 excision alone can be considered (stage I) (GR: 0; GRADE: very low).

- For patients with stage II–III disease, combined chemoradiation is the gold standard: Stage II–III anal cancer shall be treated with combined chemoradiation (GR: A; GRADE: low to moderate).
- There are no studies comparing surgical versus radiation oncology treatment for cancer of the anal margin; however, there is consensus among the guideline group that performing excision alone with an adequate safety margin (0.5 cm) can be considered for stage IIA cancer of the anal margin (T2N0M0) (expert consensus [EC]).
- In the context of combined chemoradiation, stage II–III anal cancer shall be treated with a chemotherapy regimen comprising mitomycin and 5-fluorouracil (5-FU) (GR: A; GRADE: moderate to high).
- Alternatively, a chemotherapy regimen comprising cisplatin and 5-FU can be considered in the context of chemoradiation (EC: 0; GRADE: moderate to high [e20–e23]), or 5-FU substituted by capecitabine (GR: 0; GRADE: very low).
- The radiotherapy dose shall not exceed 59.4 Gy (GR: A; GRADE: very low). Radiation therapy shall be performed as IMRT (GR: A; GRADE: very low to moderate).
- In the context of combined chemoradiation, no induction chemotherapy (GR: A; GRADE: moderate) and no maintenance chemotherapy shall be performed (GR: A; GRADE: moderate).
- Further protocols are available for additional studies on a variety of therapeutic regimens, but no results have been published for these regimens as yet[13].

b) Treatment of residual or recurrent anal cancer

- In the case of local residual or recurrent tumor following primary chemoradiation without distant metastasis, surgical resection with curative intent shall be performed (EC).
- Abdominoperineal resection is the standard procedure for local recurrence or residual cancer of the anal canal following primary chemoradiation.
- If R0 resection of residual or recurrent tumor is not possible, an individualized palliative treatment plan shall be offered.
- Patients with locoregional recurrent disease following primary surgical resection shall be treated as treatment-naive patients[13].

c) Treatment of metastatic anal cancer

- For metastatic stage IV anal cancer, platinum-based chemotherapy can be considered (GR: 0).

- Depending on tumor burden and symptoms, additive local treatment can be considered for the primary tumor in the case of synchronous metastatic anal cancer (GR: 0).
- Likewise in oligometastatic anal cancer, local treatment of metastasis can be per - formed as part of a multimodal approach (GR: 0).
- A more recent randomized trial revealed that combination therapy with carboplatin and paclitaxel may be an option for metastatic and/or unresectable anal cancer.
- These results were not available at the time of guideline development. Immunotherapies for the treatment of metastatic anal cancer have only been investigated to date in uncontrolled studies.
- No results have been published as yet for other trials (some of which are randomized) in metastatic and/or unresectable anal cancer.
- All patients shall be offered palliative treatment following the diagnosis of incurable anal cancer, irrespective of whether tumor specific therapy is performed (guideline adaptation, GR: A, evidence level 1)[13].

1.4 International Guidelines

1.4.1 Society for Immunotherapy of Cancer (SITC) (2023)

The Society for Immunotherapy of Cancer (SITC) released in 2023 clinical practice guidelines on immunotherapy for the treatment of gastrointestinal cancers, including colorectal and anal cancer. The key treatment recommendations relevant for anal cancer are outlined below[14]:

- For all patients with CRC and SCCA, PD-L1 expression does not currently inform treatment decisions for ICIs.
- For all patients with SCCA, clinical trial enrollment should be considered at all stages of treatment, when feasible.
- For patients with treatment-naïve, metastatic SCCA with any MSI/MMR status and/or TMB, there is insufficient data to recommend first-line ICI therapy.
- For patients with **previously treated, metastatic SCCA, nivolumab** (LE:3) **or pembrolizumab** (LE:3) are **recommended treatment options regardless of MSI/ MMR, TMB, and PD-L1 status**[14].

1.5 Systematic Reviews/Meta-analysis

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on anal cancer management didn't yield any result more recent than the detailed previous guidelines.

Section 2.0 Drug Therapy

2.1 Alkylating Agents

2.1.1 Carboplatin

Table 11. Carboplatin Drug Information

Scientific Name **Carboplatin[24]**	
Trade Name(s) on Saudi Market	Carboplatin (Ebewe, Hospira), Cartinum
SFDA Classification	Prescription
SFDA approved Indication	Yes, Carboplatin Ebewe, 2001; Cartinum, 2019; Carboplatin Hospira, 2020
FDA approved / off label	Yes, 1989
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Carboplatin Ebewe: 2-355-01 (150mg); 3-355-01 (450mg) Carboplatin Hospira: 15-5287-20 (150mg); 16-5287-20 (450mg) Cartinum: 21-5223-19 (150mg); 22-5223-19 (450mg)
ATC Code	L01XA02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous

Dose (Adult) [DDD]*	**Anal cancer, advanced:** Target AUC 5 on day 1 every 4 weeks (in combination with paclitaxel) for 6 cycles or until disease progression or unacceptable toxicity **or** Target AUC 5 or 6 every 3 weeks (in combination with paclitaxel)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): Dose determination with Calvert formula uses GFR and, therefore, inherently adjusts for kidney dysfunction. In patients with platelet < 50,000 cells/mm^3 or ANC <500 cells/mm^3: dose should be reduced by 25%
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with paclitaxel; To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
ST (Step Therapy)	First-line treatment of metastatic anal cancer in combination with paclitaxel (preferred regimen)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Maximum daily dose (and/or dose per cycle) not to exceed a target AUC 6
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Decreased serum Ca, K, Mg, gastrointestinal pain, nausea and vomiting, anemia, leukopenia, thrombocytopenia, increased liver enzymes, asthenia, pain, decreased creatinine clearance

	- Most serious: Ototoxicity, anemia, leukopenia, thrombocytopenia
Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy. Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Carboplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	History of severe allergic reaction to carboplatin, cisplatin, other platinum-containing formulations, or any component of the formulation; should not be used in patients with severe bone marrow depression or significant bleeding
Monitoring Requirements	CBC (with differential and platelet count), serum electrolytes, serum creatinine and BUN, CrCl, LFTs;; signs/symptoms of hypersensitivity reactions.

Precautions	- Bone marrow suppression - GI toxicity - Hepatic function abnormality - Hypersensitivity - Neurotoxicity - Ototoxicity - Renal toxicity - Vision loss
Black Box Warning	- Experienced physician - Bone marrow suppression - Vomiting - Hypersensitivity reactions
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for carboplatin in anal cancer. This is probably because carboplatin is an established standard of care in metastatic disease management. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Carboplatin

In anal cancer, carboplatin is a preferred first-line agent in the management of metastatic disease in combination with paclitaxel.

There is no data issued by HTA bodies regarding its use.

2.1.2 Cisplatin

Table 12. Cisplatin Drug Information

Scientific Name **Cisplatin**[25]	
Trade Name(s) on Saudi Market	Cisplatin (Ebewe, Hospira), Cipalin, Tinplat
SFDA Classification	Prescription
SFDA approved Indication	Yes, Cisplatin Ebewe, 2001; Cisplatin Jazeera Pharmaceutical Industries (JPI), 2018; Cisplatin Hospira, 2019; Tinplat, 2019

FDA approved / off label	Yes, 1978
EMEA approved / off label	Yes, 1996
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Cisplatin Ebewe: 409222579 (10mg); 0409222580 (50mg) Cipalin: 288-334-18 (10mg); 289-334-18 (25mg); 290-334-18 (50mg) Cisplatin Hospira: 4-5287-19 (50mg) Tinplat: 29-5223-19 (10mg); 30-5223-19 (50mg)
ATC Code	L01XA01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Anal carcinoma, squamous cell, metastatic:** 75 mg/m^2 on day 1 every 4 weeks (in combination with continuous infusion fluorouracil) or 60 mg/m^2 on day 1 every 3 weeks (in combination with continuous infusion fluorouracil)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥60 mL/mine: IV: No adjustment - CrCl 50 to <60 mL/min: IV: 75% of the dose - CrCl 40 to <50 mL/minute: IV: 50% of the dose - CrCl <40 mL/minute: Not recommended - Hemodialysis/PD: Poorly dialyzable due to rapid and high degree of

	protein binding: 50% of the dose after dialysis - CRRT/PIRRT: Use is not recommended - Nephrotoxicity during treatment: Patients that develop AKI (SCr >2 times baseline) may require discontinuation of therapy
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with other chemotherapy agents and/or with RT; To be used with antiemetics, hyperhydration
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Total dose per cycle not to exceed 75 mg/m^2
ST (Step Therapy)	First-line treatment of localized anal cancer in combination with 5-FU and RT. First-line treatment of metastatic anal cancer part of the following protocols: 5-FU + cisplatin; FOLFCIS; Modified DCF.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Total dose per cycle not to exceed 120 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Neurotoxicity, nausea and vomiting, nephrotoxicity, anemia, leukopenia, thrombocytopenia, increased liver enzymes, ototoxicity - Most serious: Neurotoxicity, anemia, leukopenia, thrombocytopenia, hearing loss

Drug Interactions*	- Risk X: Aminoglycosides, Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Taxane Derivatives, Topotecan, Vaccines (Inactivated/Non-Replicating)
Special Population	Renal Impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Cisplatin is present in breast milk. Breastfeeding is not recommended.
Contraindications	Severe hypersensitivity to cisplatin or any component of the formulation
Monitoring Requirements	Blood counts, serum creatinine, BUN, CrCl, and serum electrolytes Neurological examination, consider audiometric and vestibular testing Monitor closely for signs/symptoms of infection, hypersensitivity reactions, neuropathy, ocular toxicity, tumor lysis syndrome, and secondary malignancies
Precautions	- Bone marrow suppression - Extravasation - GI toxicity - Hypersensitivity

	- Nephrotoxicity - Neurotoxicity - Ocular toxicity - Ototoxicity - Secondary malignancies - Tumor lysis syndrome
Black Box Warning	- Myelosuppression - Nausea and vomiting - Nephrotoxicity - Peripheral neuropathy
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for cisplatin in anal cancer. This is probably because cisplatin is an established standard of care in the management of the disease. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Cisplatin

In anal cancer, cisplatin is recommended as a first-line agent in combination with 5-FU and RT for the management of localized disease. It is also a first-line agent in the management of metastatic disease, part of the following regimens: 5-FU + cisplatin; FOLFCIS; and modified DCF.

There is no data issued by HTA bodies regarding its use.

2.1.3 Oxaliplatin

Table 13. Oxaliplatin Drug Information

Scientific Name **Oxaliplatin[26]**	
Trade Name(s) on Saudi Market	Oxaliplatin Medac, Eloxatin, Batipan, Platroxin, Xaltin, Xaltipine, Oxaliplatin AqVida
SFDA Classification	Prescription
SFDA approved Indication	Yes, Oxaliplatin Medac, 2010; Eloxatin, 2017; Batipan, 2019, 2020; Platroxin, 2019; Xaltin, 2019; Xaltipine, 2021; Oxaliplatin AqVida, 2023

FDA approved / off label	Yes, 2002
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating Agent
SFDA Registration Number (New)	Oxaliplatin Medac: 1-463-10 (50mg); 2-463-10 (100mg); 3-463-10 (200mg) Eloxatin: 54-23-17 (50mg); 55-23-17 (100mg) Batipan: 5-5251-19 (100mg); 5-5251-20 (50mg) Platroxin : 25-5035-19 (100mg); 26-5035-19 (50mg) Xaltin : 13-5223-19 (50mg); 14-5223-19 (100mg) Xaltipine: 0703210585 (100mg); 0703210586 (50mg) Oxaliplatin AqVida : 1901233127 (200mg); 1901233128 (100mg); 1901233129 (50mg)
ATC Code	L01XA03
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	85 mg/m^2 on day 1 every 2 weeks (in combination with fluorouracil/leucovorin) until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥30 mL/min: No dosage adjustment - CrCl 20 to <30 mL/min: 75% to 100% of the usual dose - CrCl <20 mL/minute: 75% of the dose

	- Hemodialysis/PD/CRRT/ PIRRT: Avoid use due to the lack of data
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with carboplatin and 5-FU; To be used with antiemetics.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 130 mg/m^2
ST (Step Therapy)	First-line treatment of metastatic anal cancer part of the FOLFCIS, FOLFOX, or DCF treatment protocol.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	130 mg/m^2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Abdominal pain, anorexia, constipation, diarrhea, nausea, stomatitis, vomiting, anemia, leukopenia, thrombocytopenia, increased AST/ALT, increased bilirubin, fatigue, headache, insomnia, pain, peripheral neuropathy, pain, cough, dyspnea, fever - Most serious: Neutropenia, reversible posterior leukoencephalopathy syndrome, pulmonary fibrosis
Drug Interactions*	- Risk X: BCG Products, Brivudine, Cladribine, Dipyrone, Fexinidazole, - Risk D: Deferiprone, Lenograstim, Lipegfilgrastim, Palifermin, Ropeginterferon Alfa-2b, Taxane derivatives, Topotecan
Special Population	Older adults

Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	Oxaliplatin is present in breast milk. Breastfeeding is not recommended during oxaliplatin treatment
Contraindications	Hypersensitivity to oxaliplatin, other platinum-containing compounds, or any component of the formulation
Monitoring Requirements	CBC with differential, blood chemistries, including serum creatinine, ALT, AST, and bilirubin, electrolytes, INR and PT (in patients on oral anticoagulant therapy) ECG monitoring in patients at risk for cardiac toxicities Neurologic evaluation prior to each dose and periodically thereafter. Monitor for signs/symptoms of hypersensitivity, pulmonary toxicity, posterior reversible encephalopathy syndrome, neuropathy, bleeding, and GI toxicity
Precautions	- Bone marrow suppression - Cardiotoxicity - Extravasation - Hemorrhage - Hepatotoxicity - Hypersensitivity - Neuropathy - Posterior reversible encephalopathy syndrome - Pulmonary toxicity - Rhabdomyolysis
Black Box Warning	- Hypersensitivity/Anaphylactic reactions
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for oxaliplatin in anal cancer.

Conclusion Statement – Carboplatin

In anal cancer, oxaliplatin is a first-line agent in the management of metastatic disease, as part of the mFOLFOX6 treatment protocol.

There is no data issued by HTA bodies regarding its use.

2.2 Antimetabolites

2.2.1 5-Fluorouracil (5-FU)

Table 14. 5-Fluorouracil Drug Information

Scientific Name **5-Fluorouracil[27]**	
Trade Name(s) on Saudi Market	Fluorouracil (Hospira); Fluorouracil Ebewe; Floryl
SFDA Classification	Prescription
SFDA approved Indication	Yes, 1997
FDA approved / off label	Yes, 1962
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2004
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Fluorouracil Hospira: 22-237-97 (500mg) Fluorouracil Ebewe: 16-355-01 (500mg); 18-355-01 (1g) 42-355-07 (5g) Floryl: 15-5223-19 (5g); 16-5223-19 (1g); 17-5223-19 (500mg); 18-5223-19 (250mg)
ATC Code	L01BC02
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	

Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Localized disease:** 1,000 mg/m^2/day continuous infusion days 1 to 4 (total dose is 4,000 mg/m^2) and days 29 to 32 (total dose is 4,000 mg/m^2) (in combination with mitomycin and radiation therapy). **Advanced or metastatic disease:** *In combination with cisplatin:* 750 mg/m^2/day continuous infusion days 1 to 5 (total dose/cycle is 3,750 mg/m^2) every 4 weeks (in combination with cisplatin); patients received a median of 4 cycles in the study or 1000 mg/m^2/day continuous infusion days 1 to 4 in combination with cisplatin *FOLFCIS regimen:* 400 mg/m^2 bolus on day 1, followed by 1,000 mg/m^2/day continuous infusion days 1 and 2 (total dose/cycle [bolus and continuous infusion] is 2,400 mg/m^2) every 14 days until disease progression or unacceptable toxicity *DCF regimen:* 400 mg/m^2 bolus on day 1, followed by 1,200 mg/m^2/day continuous infusion days 1 and 2 every 14 days until disease progression or unacceptable toxicity *FOLFOX regimen:* 1,200 mg/m^2/day continuous infusion days 1 and 2 (total dose is 2,400 mg/m^2) every 14 days until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal/Hepatic Impairment (Adult): There are no dosage adjustments provided in the manufacturer's labeling; use with caution.
Prescribing edits*	MD, ST, PE, CU, QL

AGE (Age Edit)	N/A
CU (Concurrent Use)	To be used in combination with RT and/or with other chemotherapy agents and leucovorin; To be used with antiemetics.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Dose per 24h not to exceed 1600 mg/m^2 Dose per cycle not to exceed 4000 mg/m2
ST (Step Therapy)	First-line treatment of localized anal cancer in combination with mitomycin C and RT (preferred) or cisplatin and RT First-line treatment of metastatic anal cancer part of the following protocols: 5-FU + cisplatin; FOLFCIS; mFOLFOX6; Modified DCF Local control of metastatic anal cancer in combination with RT as part of the Chemo/RT approach to the primary site
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Dose per 24h not to exceed 1600 mg/m^2 Dose per cycle not to exceed 4000 mg/m2
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia, neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome

Drug Interactions*	- Risk X: Abrocitinib, Allopurinol, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if fluorouracil is present in breast milk. The manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue fluorouracil, taking into account the importance of treatment to the breastfeeding patient.
Contraindications	N/A
Monitoring Requirements	CBC with differential and platelet count, renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants). Monitor for signs/symptoms of palmar-plantar erythrodysesthesia syndrome,

	cardiotoxicity, CNS toxicity, stomatitis, diarrhea, and hyperammonemic encephalopathy. Promptly evaluate any symptoms suggestive of cardiotoxicity. Consider monitoring ECG in patients on concomitant QT prolonging medications.
Precautions	- Bone marrow suppression - Cardiotoxicity - GI toxicity - Hand-foot syndrome - Hyperammonemic encephalopathy - Neurotoxicity - Dihydropyrimidine dehydrogenase deficiency - Warfarin
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for 5-FU in anal cancer. This is probably because 5-FU is a long-standing drug in the treatment paradigm for anal cancer with a proven record of efficacy and safety. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – 5-FU

In anal cancer, 5-FU is recommended as a first-line agent in combination with mitomycin C and RT (preferred regimen) or cisplatin and RT for the management of localized disease. It is also a first-line agent in the management of metastatic disease, part of the following regimens: 5-FU + cisplatin; FOLFCIS; mFOLFOX6; Modified DCF; or as a single agent in combination with RT as a CRT approach to the primary site for local control.

There is no data issued by HTA bodies regarding its use.

2.2.2 Capecitabine

Table 15. Capecitabine Drug Information

Scientific Name **Capecitabine**[28]	
Trade Name(s) on Saudi Market	Xeloda, Dirogit, Capecitabine SPC, Aceda, Pitacro, Emcap, Xelobine, Catabina
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2004
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, 2001
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2015
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Antimetabolite (Pyrimidine Analog)
SFDA Registration Number (New)	Xeloda: 250-24-04 (150mg); 251-24-04 (500mg) Dirogit: 189-172-18 (500mg) Capecitabine SPC: 1-5171-18 (150mg); 2-5171-18 (500mg) Aceda: 7-5223-18 (500mg); 8-5223-18 (150mg) Pitacro: 2611200294 (500mg); 2611200293 (150mg) Emcap: 1510200212 (500mg) Xelobine: 2202210536 (500mg); 2202210537 (150mg) Catabina: 0706210768 (500mg)
ATC Code	L01BC06
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Tablet
Route of Administration	Oral

Dose (Adult) [DDD]*	**Anal carcinoma: Oral:** 825 mg/m^2 twice daily 5 days/week (in combination with mitomycin [on day 1 only]) during radiation therapy; radiation therapy occurred over 5 to 6 weeks **or** 825 mg/m^2 twice daily on radiation therapy days (in combination with mitomycin [on day 1 only] and radiation therapy)
Dose (Pediatrics)	N/A
Adjustment	Renal/Hepatic Impairment (Adult): In CrCl 30 – 50 mL/minutes: reduce 25% of dose .
Prescribing edits*	MD, ST, PE, QL
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	To be used in combination with RT ± mitomycin C
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose not to exceed 2500 mg/m^2 (to be given in two divided doses)
ST (Step Therapy)	First-line treatment of localized anal cancer (in combination with mitomycin C and RT) (preferred regimen) Local control of metastatic anal cancer in combination with RT as part of the Chemo/RT approach to the primary site
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	Maximum daily dose not to exceed 2500 mg/m^2 (to be given in two divided doses)
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, drowsiness, skin rash, alopecia, nausea and vomiting, diarrhea, stomatitis, proteinuria, hematuria, anemia,

	neutropenia, thrombocytopenia, hemorrhage, increased liver function tests, infection, increased blood urea nitrogen, dyspnea, flu-like symptoms, fever - Most serious: hemolytic-uremic syndrome
Drug Interactions*	- Risk X: Abrocitinib, Allopurinol, Aminolevulinic Acid, Baricitinib, BCG Products, Brivudine, Cedazuridine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Gimeracil, Levoketoconazole, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Pimozide, Ritlecitinib, Ruxolitinib (Topical), Sertindole, Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Domperidone, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, QT-prolonging Agents, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Dihydropyrimidine dehydrogenase deficiency, Older adults
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if capecitabine is present in breast milk. Breastfeeding is not recommended by the manufacturer during treatment and for 1 week after the last capecitabine dose.

Contraindications	Known hypersensitivity to capecitabine, fluorouracil, or any component of the formulation.
Monitoring Requirements	CBC with differential and platelet count, renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants). Pregnancy status Hydration status Monitor for signs/symptoms of diarrhea, dehydration, hand-foot syndrome, new or worsening serious skin reactions, stomatitis, hepatotoxicity, nephrotoxicity, and cardiotoxicity, cardiotoxicity. Consider monitoring ECG in patients on concomitant QT-prolonging medications. Monitor adherence.
Precautions	- Hepatotoxicity - Kidney Impairment - Fluorouracil/leucovorin previous therapy - Proton pump inhibitors - Dihydropyrimidine dehydrogenase deficiency - Older adults
Black Box Warning	Vitamin K antagonist interaction
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for capecitabine in anal cancers.

Conclusion Statement – Capecitabine

In anal cancer, capecitabine is recommended as a first-line agent in combination with mitomycin C and RT (preferred regimen) for the management of localized disease. It is also used in the management of metastatic disease in combination with RT as a CRT approach to the primary site for local control.

There is no data issued by HTA bodies regarding its use.

2.3 Antimicrotubular Agents

2.3.1 Docetaxel

Table 16. Docetaxel Drug Information

Scientific Name **Docetaxel**[29]	
Trade Name(s) on Saudi Market	Docetaxel Ebewe; Docetaxel SPC; Docadex; Taxotere; Docetaxel Accord; Tadoxel; Docetaxel Venus
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Taxane derivative
SFDA Registration Number (New)	Docetaxel Ebewe 10 mg/mL: 56-355-17 (80 mg); 55-355-17 (20 mg) Docetaxel SPC 20 mg/mL: 5-5171-18 (80mg) Docadex 20 mg/mL: 8-5251-20 (80mg); 2-5251-19 (20mg) Taxotere 20 mg/mL: 1-5079-20 (20mg); 2-5079-20 (80mg); 3-5079-20 (160mg) Docetaxel Accord 20 mg/mL: 2-5579-21 (20mg); 3-5579-21 (80mg); 4-5579-21 (160mg) Tadoxel 20 mg/mL: 0206210761 (20mg); 0206210762 (80mg) Docetaxel Venus 20 mg/mL : 2405233720 (20mg); 2405233721 (80mg)
ATC Code	L01CD

Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Anal carcinoma, squamous cell, advanced:** Modified DCF regimen; 40 mg/m^2 every 2 weeks (in combination with cisplatin, fluorouracil, and filgrastim) until disease progression or unacceptable toxicity up to a maximum of 8 cycles
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): - AST/ALT >2.5 to ≤5 times ULN and alkaline phosphatase ≤2.5 times ULN: Administer 80% of dose. - AST/ALT >1.5 to ≤5 times ULN and alkaline phosphatase >2.5 to ≤5 times ULN: Administer 80% of dose. - AST/ALT >5 times ULN and /or alkaline phosphatase >5 times ULN: Discontinue docetaxel.
Prescribing edits*	MD, ST, PE, CU, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	Can be used as a single agent or in combination with cisplatin and 5-FU; To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Daily dose not to exceed 75 mg/m^2
ST (Step Therapy)	First-line treatment of metastatic anal cancer
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol (modified DCF)
Maximum Daily Dose Adults*	75 mg/m^2
Maximum Daily Dose Pediatrics*	N/A

Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Alopecia, dermatological reactions, nails diseases, fluid retention, diarrhea, nausea and vomiting, anemia, leukopenia, neutropenia, thrombocytopenia, increased AST/ALT, hypersensitivity, infection, central nervous system toxicity, asthenia, myalgia, fever, pulmonary disease - Most serious: Febrile neutropenia
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ritlecitinib, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine, CYP3A4 Inhibitors (Strong), Deferiprone, Denosumab, Dronedarone, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if docetaxel is present in breast milk. Breastfeeding is not

	recommended during treatment and for 1 week after the last docetaxel dose.
Contraindications	History of severe hypersensitivity to docetaxel or any component of the formulation; severe hypersensitivity to other medications containing polysorbate 80; neutrophil count <1,500/mm^3.
Monitoring Requirements	- CBC with differential, LFTs (bilirubin, ALT, AST, alkaline phosphatase), renal function. - Pregnancy status - Monitor for hypersensitivity reactions - Monitor for signs/symptoms of neurosensory symptoms, GI toxicity, cutaneous reactions or severe skin toxicity, visual impairment, fluid retention, epiphora, canalicular stenosis, tumor lysis syndrome, and second primary malignancies. - Prompt comprehensive ophthalmic exam if vision impairment occurs.
Precautions	- Bone marrow suppression - Cutaneous reactions - Extravasation - Fluid retention - GI toxicity - Hypersensitivity - Neurosensory symptoms - Ocular adverse effects - Secondary malignancies - Tumor lysis syndrome - Weakness
Black Box Warning	- Increased mortality - Hepatic impairment - Neutropenia - Hypersensitivity - Fluid retention
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for docetaxel in anal cancer.

Conclusion Statement – Docetaxel

In anal cancer, docetaxel is a first-line agent in the management of metastatic disease, part of the modified DCF regimen.

There is no data issued by HTA bodies regarding its use.

2.3.2 Paclitaxel

Table 17. Paclitaxel Drug Information

Scientific Name **Paclitaxel**[30]	
Trade Name(s) on Saudi Market	Anzatax, Ebetaxel, Rotub
SFDA Classification	Prescription
SFDA approved Indication	Yes, Anzatax 1998; Ebetaxel 2006; Rotub 2018
FDA approved / off label	Yes, 1998
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Antimicrotubular, Taxane derivative
SFDA Registration Number (New)	Anzatax: 4-5669-22 (30 mg); 5-5669-22 (150 mg) Ebetaxel: 33-355-06 (300mg); 34-355-06 (150mg); 35-355-06 (100mg); 33-355-06 (30mg) Rotub: 1-5190-18 (30mg); 2-5190-18 (100mg); 3-5190-18 (150mg); 4-5190-18 (300mg)
ATC Code	L01CD01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution

Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Anal cancer, advanced:** 80 mg/m^2 on days 1, 8, and 15 every 4 weeks (in combination with carboplatin) for 6 cycles or until disease progression or unacceptable toxicity **or** 175 mg/m^2 once every 3 weeks (in combination with carboplatin)
Dose (Pediatrics)	N/A
Adjustment	Hepatic Impairment (Adult): 3-hour infusion: - Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m^2 - Transaminases <10 times ULN and bilirubin level 1.26 to 2 times ULN: 135 mg/m^2 - Transaminases <10 times ULN and bilirubin level 2.01 to 5 times ULN: 90 mg/m^2 - Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use
Prescribing edits*	AGE, MD, ST, PE, CU, QL
AGE (Age Edit)	Not used in pediatrics
CU (Concurrent Use)	To be used in combination with carboplatin; To be used with antiemetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Daily dose not to exceed 250 mg/m^2
ST (Step Therapy)	First-line treatment of metastatic anal cancer in combination with carboplatin (preferred regimen)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	250 mg/m^2
Maximum Daily Dose Pediatrics*	N/A

Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: ECG abnormality, edema, hypotension, alopecia, diarrhea, nausea and vomiting, stomatitis, anemia, hemorrhage, leukopenia, neutropenia, thrombocytopenia, increased AST/ALT, hypersensitivity, infection, injection-site reaction, asthenia peripheral neuropathy, arthralgia), myalgia, fever - Most serious: Bradycardia, cardiac arrhythmia, encephalopathy, tonic-clonic seizure, hemorrhage, leukopenia, neutropenia
Drug Interactions*	- Risk X: Abrocitinib, Atazanavir, Baricitinib, BCG Products, Brivudine, Bromperidol, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Fusidic Acid (Systemic), Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: Amifostine, Anthracyclines, Coccidioides immitis Skin Test, COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Lenograstim, Lipegfilgrastim, Obinutuzumab Palifermin, Platinum Derivatives, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults, Hepatic impairment
Pregnancy	Pregnancy Category D: Not used in pregnancy

Lactation	Paclitaxel is present in breast milk. Breastfeeding is not recommended during paclitaxel treatment
Contraindications	Hypersensitivity to paclitaxel, polyoxyl 35/polyoxyethylated castor oil (Cremophor EL), or any component of the formulation Treatment of solid tumors in patients with baseline neutrophil counts <1,500/mm^3; treatment of Kaposi sarcoma in patients with baseline neutrophil counts <1,000/mm^3.
Monitoring Requirements	CBC with differential and platelet count (frequently), liver and kidney function Monitor for hypersensitivity reactions, vital signs (frequently during the first hour of infusion), and continuous cardiac monitoring (patients with conduction abnormalities). Monitor for signs/symptoms of peripheral neuropathy. Monitor infusion site during infusion.
Precautions	- Cardiovascular effects - Extravasation - Hepatic impairment
Black Box Warning	- Experienced physician - Hypersensitivity - Bone marrow suppression
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for paclitaxel in anal cancer. This is probably because carboplatin is an established standard of care in metastatic disease management. Moreover, the drug is widely available in international markets with many generics ensuring accessibility and cost effectiveness.

Conclusion Statement – Paclitaxel

In anal cancer, paclitaxel is a preferred first-line agent in the management of metastatic disease in combination with carboplatin.

There is no data issued by HTA bodies regarding its use.

2.4 Immune Checkpoint Inhibitors (ICIs)

2.4.1 Nivolumab

Table 18. Nivolumab Drug Information

Scientific Name **Nivolumab**[31]	
Trade Name(s) on Saudi Market	Opdivo
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2015
FDA approved / off label	Yes, 2014
EMEA approved / off label	Yes, 2015
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2015
Indication (ICD-10)	C21
Drug Class	Antineoplastic agent
Drug Sub-class	Immune Checkpoint Inhibitor (PD-1 Inhibitor)
SFDA Registration Number (New)	2-960-15 (40 mg); 3-960-15 (100 mg)
ATC Code	L01XC17
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	240 mg once every 2 weeks **or** 480 mg once every 4 weeks until disease progression or unacceptable toxicity.
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:*

	- Grade 2 or grade 3 serum creatinine elevation: Withhold nivolumab; resume nivolumab after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last nivolumab dose. - Grade 4 serum creatinine elevation: Permanently discontinue nivolumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment. *Hepatic impairment **during** treatment initiation* ● Immune-mediated hepatitis without tumor involvement of the liver: - AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold nivolumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper. - AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. ● Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold nivolumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue nivolumab permanently.
Prescribing edits*	MD, ST, PE, QL

AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 480 mg
ST (Step Therapy)	Second and subsequent line treatment of metastatic anal cancer
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	480 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	
Main Adverse Drug Reactions (most common and most serious)	- Most common: Edema, hypertension, pruritus, skin rash, vitiligo, hypercalcemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, increased serum albumin, weight loss, abdominal pain, decreased appetite, diarrhea, increased serum amylase, increased serum lipase, nausea, vomiting, anemia, leukopenia, , neutropenia, hepatitis, antibody development, dizziness, headache, arthralgia, asthenia, increased serum creatinine, cough, dyspnea, fever. - Most serious: Acute coronary syndrome, vasculitis, immune-mediated myocarditis, pericarditis, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypothyroidism, hyperthyroidism, adrenocortical insufficiency, hypophysitis, type 1 diabetes mellitus, Immune-mediated colitis, immune thrombocytopenia,

	autoimmune hemolytic anemia, acquired blood coagulation disorder (hemophilia), disseminated intravascular coagulation, immune-mediated hepatitis and nephritis, uveitis, cerebral hemorrhage, myasthenia gravis, reversible posterior leukoencephalopathy syndrome, pneumonitis
Drug Interactions*	- Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs) - Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Ketoconazole (Enhanced hepatotoxic effect).
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if nivolumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 5 months after the last nivolumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis,

	rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Infusion-related reactions - Auto-immune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for nivolumab in anal cancer.

Conclusion Statement – Nivolumab

In anal cancer, nivolumab is a second and subsequent-line agent in the management of metastatic disease, recommended by all international guidelines, although currently used off-label.

2.4.2 Pembrolizumab

Table 19. Pembrolizumab Drug Information

Scientific Name Pembrolizumab[32]	
Trade Name(s) on Saudi Market	Keytruda
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017
FDA approved / off label	Yes, 2014
EMEA approved / off label	Yes, 2015
MHRA approved / off label	Yes, date not available
PMDA approved / off label	Yes, 2016
Indication (ICD-10)	C21

Drug Class	Antineoplastic agent, monoclonal antibody
Drug Sub-class	Immune Checkpoint Inhibitor (PD-1 Inhibitor)
SFDA Registration Number (New)	2501233168
ATC Code	L01XC
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	200 mg once every 3 weeks **or** 400 mg once every 6 weeks; continue until disease progression, unacceptable toxicity, or (in patients without disease progression) for up to 24 months
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *Kidney impairment **prior** to treatment initiation:* No adjustment necessary *Kidney toxicity **during** treatment:* *Immune-mediated nephritis with kidney dysfunction:* - Grade 2 or grade 3 serum creatinine elevation: Withhold pembrolizumab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue if no complete or partial response within 12 weeks of last dose. - Grade 4 serum creatinine elevation: Permanently discontinue pembrolizumab. Hepatic Impairment (Adult): *Hepatic impairment **prior** to treatment initiation:* No adjustment necessary. Has not been studied in severe hepatic impairment.

	*Hepatic impairment **during** treatment initiation* ● Immune-mediated hepatitis without tumor involvement of the liver: - AST or ALT >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution (to grade 0 or 1) of hepatitis after corticosteroid taper. - AST or ALT >8 × ULN or total bilirubin >3 × ULN: Discontinue permanently. ● Immune-mediated hepatitis with tumor involvement of the liver: - If baseline AST or ALT >1 to ≤3 × ULN and increases to >5 to ≤10 × ULN or baseline AST or ALT >3 to ≤5 × ULN and increases to >8 to ≤10 × ULN: Withhold pembrolizumab. Resume with complete or partial resolution of hepatitis after corticosteroid taper. - AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN: Discontinue pembrolizumab permanently.
Prescribing edits*	MD, ST, PE, QL
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum daily dose 400 mg
ST (Step Therapy)	Second and subsequent line treatment of metastatic anal cancer
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	400 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	

Main Adverse Drug Reactions (most common and most serious)	- Most common: Cardiac arrhythmia, peripheral edema, pruritus, skin rash, vitiligo, decreased serum bicarbonate, hypercalcemia, hypercholesterolemia, hyperglycemia, hyperkalemia, hyperthyroidism, hypertriglyceridemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypothyroidism, decreased serum albumin, hypophosphatemia, hyponatremia, weight loss, abdominal pain, constipation, decreased appetite, diarrhea, nausea, vomiting, dysuria, anemia, leukopenia, neutropenia, hyperbilirubinemia, increased liver enzymes, infection, fatigue, peripheral neuropathy, arthralgia, asthenia, myalgia, increased serum creatinine, cough, dyspnea, fever. - Most serious: Acute myocardial infarction, cardiac tamponade, facial edema, ischemic heart disease, immune-mediated myocarditis, pericarditis, adrenocortical insufficiency, diabetic ketoacidosis, Immune-mediated colitis, immune thrombocytopenia, immune-mediated hepatitis and nephritis, uveitis.
Drug Interactions*	- Risk X: Thalidomide (Enhanced toxicity of thalidomide). - Risk D: Corticosteroids (May diminish the therapeutic effect of ICIs) - Risk C: Acetaminophen, Antibiotics, Efgartigimod, Inhibitors of the Proton Pump, Rozanolixizumab (May diminish the therapeutic effect of ICIs); Desmopressin (Enhanced hyponatremia); Axitinib,

	Ketoconazole (Enhanced hepatotoxic effect).
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy
Lactation	It is not known if pembrolizumab is present in breast milk. The manufacturer recommends discontinuing breastfeeding during treatment and for 4 months after the last pembrolizumab dose.
Contraindications	N/A
Monitoring Requirements	- PD-L1 expression - Hepatic (ALT, AST, and total bilirubin) and kidney function (serum creatinine), thyroid function, blood glucose - Pregnancy status - Monitor closely for signs/symptoms of immune-mediated adverse reactions, including adrenal insufficiency, hypophysitis, thyroid disorders, diabetes mellitus, diarrhea/colitis, pneumonitis, rash/dermatologic toxicity, ocular disorders, encephalitis - Monitor for signs/symptoms of infusion-related reactions
Precautions	- Adverse reactions (immune mediated) - Infusion-related reactions - Auto-immune disorders - Hematopoietic stem cell transplant - Multiple myeloma - Myasthenia gravis
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for pembrolizumab in anal cancer.

Conclusion Statement – Pembrolizumab

In anal cancer, pembrolizumab is a second and subsequent-line agent in the management of metastatic disease, recommended by all international guidelines, although currently used off-label.

Section 3.0 Key Recommendations Synthesis

Most patients with Anal carcinoma have a favorable prognosis. Prognosis is determined primarily by disease stage, grade, histology, and molecular classification (if known)[1,5].

Treatment strategies for patients with bladder cancer are outlined in the below sections[11-16]:

A. Anal canal SCC

A.1. Localized disease

- **Concurrent chemoradiotherapy** (CRT) rather than surgery is the **preferred first-line treatment for patients with localized anal carcinoma** even for T1-2N0M0 tumors (Recommendation Level A, Evidence Level II) [7,10-13].
- Local excision may be an option for carefully selected patients with ≤ 1 cm, superficially invasive tumors that are completely excised and have ≤3 mm of basement membrane invasion and a horizontal spread of ≤7 mm (T1NX)[7].
- During radiation therapy (RT), concurrent use of standard dose of **5-fluorouracil (5-FU)** plus **mitomycin C** is the **preferred chemotherapy regimen** (Recommendation Level A, Evidence Level II). The substitution of **capecitabine** for FU is acceptable (Recommendation Level A, Evidence Level I, II)[7,10-13].
    - Most studies have delivered 5-FU as a protracted **96- to 120-hour infusion** during the first and fifth weeks of RT, and bolus injection of mitomycin is typically given on the first or second day of the 5-FU infusion[7].
- Fluorouracil (5-FU) can be replaced with capecitabine [Recommendation Level A, B, Evidence Level II, III]
    - Capecitabine is given orally, 5 days per week on each day that RT is given, for 4 or 6 weeks, with bolus injection of mitomycin and concurrent radiation[7].
- The combination of **5-FU plus cisplatin with RT** is an alternative treatment option (Recommendation Level B, Evidence Level II)[7,10-13].
- Treatment interruptions should be minimized during CRT, and overall treatment time and total dose maintained as much as possible.
- Elderly patients who can tolerate treatment should be treated with curative chemoradiotherapy (CRT) (Recommendation Level C, Evidence Level V). For the extremely aged population with T1N0 tumors, or those with significant

comorbidities, reduction of mitomycin and FU doses during CRT may be considered, although this is not a standard approach

- There has also been interest in the use of **biologic therapies** for the treatment of anal cancer. A phase 3 trial is investigating the use of the programmed cell death protein 1 (PD-1) inhibitor, nivolumab, following combined modality therapy for stage II-IIIB high-risk anal carcinoma. This trial has completed enrollment of 344 participants and results are pending[18].
- Anal SCC in patients living with **HIV** is **treated similarly to those without HIV**. However, patients with active or a prior history of HIV/AIDS-related complications may not tolerate full-dose therapy or require chemotherapy dose adjustment.
- **Treatment response** is **assessed clinically 8 to 12 weeks after completion of CRT**. For patients with a clinical complete response, re-evaluation at **3–6-month intervals** with digital rectal examination and inguinal node palpation is recommended. Anoscopy is recommended at 6-12 months with annual contrast-enhanced CT of the chest, abdomen, and pelvis or MRI for at least three years[7,10-13].
- Patients with clinical suspicion for persistent disease at 8 to 12 weeks can be watched for up to six months following completion of CRT. Biopsy is indicated for overt disease progression or a clinical suspicion for persisting disease ≥6 months after completion of CRT[7,10-13].

A.2. Persistent or locally recurrent disease

- Persistent or locally recurrent anal SCC following CRT can be successfully salvaged with surgery, typically **abdominoperineal resection** (APR), with long-term control in approximately 25 to 40% of cases[7,10-13].
- To avoid surgery, the use of **immunotherapy** with nivolumab or pembrolizumab may be considered prior to APR as some patients may have a good response, however it should be noted that this approach is based on **institutional experience** only and there are currently no published data supporting its use in this setting of otherwise curative intent surgery[7].

A.3. Metastatic anal carcinoma

- **Systemic therapy** is the recommended approach for metastatic anal SCC. **Paclitaxel plus carboplatin** is the **preferred treatment regimen** (Recommendation Level A, B, Evidence Level I, II). Other alternative protocols used in the first line setting are **FOLFCIS** (5-FU/leucovorin/cisplatin); **mFOLFOX6** (5-FU/leucovorin/oxaliplatin) (Recommendation Level A, Evidence Level II); **5-FU + cisplatin**; **Modified DCF** (Docetaxel/cisplatin/5-FU) (Recommendation Level B, Evidence Level II)[7,10-13].

- Several ongoing clinical trials are investigating whether **checkpoint inhibitors** could have a role in the first-line treatment of metastatic anal cancer.
    - NCT04444921 is a randomized, phase 3 trial comparing chemotherapy alone (carboplatin and paclitaxel) to chemotherapy plus nivolumab for treatment-naïve metastatic anal cancer[19]. This study is expected to enroll 205 participants and complete in 2023.
    - POD1UM-303/InterAACT2 is a similar, phase 3 global study (NCT04472429) investigating the addition of the checkpoint inhibitor, retifanlimab, to carboplatin/paclitaxel chemotherapy and comparing it to chemotherapy alone[20].This trial expects to enroll 300 participants with previously untreated metastatic anal carcinoma and expected completion is in 2024.
- For patients who have progressed on first-line therapy, **immunotherapy** using agents that target the programmed cell death receptor 1 (PD-1) pathway: **pembrolizumab** or **nivolumab** is the **recommended subsequent-line treatment approach** (Recommendation Level A, B, Evidence Level II, III)[7,10-14].
    - **Microsatellite instability (MSI)/mismatch repair (MMR) testing is not required**. MSI is uncommon in anal cancer and responses to PD-1/PD-L1 inhibitors occur in 20% to 24% of patients.
    - A single-arm, multicenter phase 2 trial assessed the safety and efficacy of the anti-PD-1 antibody nivolumab for refractory metastatic anal cancer[21]. Two complete responses and seven partial responses were seen among the 37 enrolled participants who received at least one dose, for a response rate of 24% (95% CI, 15–33)[21].
    - The KEYNOTE-028 trial is a multi-cohort, phase 1b trial of the anti-PD-1 antibody pembrolizumab in 24 patients with programmed cell death ligand 1 (PDL1) – positive advanced squamous cell carcinoma of the anal canal[22]. Four partial responses were seen, for a response rate of 17% (95% CI,5–37), and 10 patients (42%) had stable disease, for a disease control rate of 58%[22].
    - Anal cancers may be responsive to PD-1/PD-L1 inhibitors because they often have high PD-L1 expression and/or a high tumor mutational load despite being microsatellite stable (MSS).
- Combinations of immunotherapy plus cytotoxic chemotherapy are beginning to be studied for first-line therapy; however, until further information is available, this cannot yet be considered a standard approach outside of the context of a clinical trial[7,10-14].

- **Chemoradiotherapy to the primary site for local control** must be addressed on a case-by-case basis. **5-FU+RT** or **capecitabine+RT** are recommended in this setting (Recommendation Level A, Evidence Level II)[7].

Anal adenocarcinoma

For patients with adenocarcinoma of the anal canal, treatment according to a **rectal cancer paradigm** rather than initial FU and mitomycin-containing CRT, as is used for anal SCCs is suggested. For most patients this will include surgery (typically APR) plus fluoropyrimidine-based CRT[7].

Perianal cancer

- For patients with **T1N0 well-differentiated** SCC of the perianal skin forming a discrete skin lesion that is clearly separate from the anal canal, or **select T2,N0 (that does not involve sphincter) wide local excision** alone is recommended if negative margins can be achieved without compromising the sphincter muscles. The American Society of Colon and Rectal Surgeons (ASCRS) defines an adequate margin as 1 cm[7,10-13].
- If the margins are not adequate, re-excision is the preferred treatment option. **Local RT** with or without **continuous infusion 5-FU/mitomycin**, **mitomycin/capecitabine** (Recommendation Level A, Evidence Level II), or 5-FU/cisplatin (Recommendation Level B, Evidence Level II) can be considered as alternative treatment options when surgical margins are inadequate[7,10-13].
- For patients with **T1, N0 Poorly differentiated or T2–T4, N0 or Any T, N+** (± positive para-aortic lymph nodes), **radical concurrent CRT** is recommended, consisting of **local RT** with or without **continuous infusion 5-FU/mitomycin**, **mitomycin/capecitabine** (Recommendation Level A, Evidence Level II), or 5-FU/cisplatin (Recommendation Level B, Evidence Level II)[7].
- For patients with **metastatic perianal cancer**, systemic therapy with **carboplatin/paclitaxel** is the preferred treatment option (Recommendation Level A, B, Evidence Level I, II). Alternative options include FOLFOX (Recommendation Level A, Evidence Level II), FOLFCIS (Recommendation Level A, Evidence Level II), 5-FU/Cisplatin (Recommendation Level B, Evidence Level II), and Modified DCF (Recommendation Level B, Evidence Level II)[7].

B. HTA Recommendations

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for drugs used in the management of anal cancer. This is probably because the standard of care for anal cancer, considered a rare tumor, hasn't changed much in the past few years with a proven record of efficacy and safety of the traditional chemotherapy agents.

Moreover, these drugs are widely available in international markets with many generics ensuring accessibility and cost effectiveness. However, with the inclusion of new therapies in the international treatment guidelines of anal cancer (although still as off-label use) such as immune checkpoint inhibitors (nivolumab, pembrolizumab), more HTA recommendations are expected and encouraged in the future to support the judicious use of these agents.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of anal cancer.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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32. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ 08889: MSD International GmbH; 2020.

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

1. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:

Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.

Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.

Gender Edit: Exemestane in Endometriosis should be used only by Females.

Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

• Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose

Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin

Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.

Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

2. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

3. What information are available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

4. Drug interactions

1. A: No known interaction
2. B: No action needed
3. C: Monitor therapy
4. D: Consider therapy modification
5. X: Avoid combination

5. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

6. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Description

1. **Level of Evidence Adopted:**

Grade of research	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following is the result of the PubMed search conducted for Anal Cancer guideline search:

Query	Filters	Search Details	Results
(((((Anus Neoplasms[MeSH Major Topic]) OR (Anus Neoplasms[Title/Abstract])) OR (Anal Cancer[Title/Abstract])) OR (Anal Cancer[MeSH Major Topic])) OR (Anal Carcinoma[MeSH Major Topic])) OR (Anal Carcinoma[Title/Abstract])	Guideline, in the last 5 years	("anus neoplasms"[MeSH Major Topic] OR "anus neoplasms"[Title/Abstract] OR "anal cancer"[Title/Abstract] OR "anus neoplasms"[MeSH Major Topic] OR "anus neoplasms"[MeSH Major Topic] OR "anal carcinoma"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	8

Appendix D. Treatment Algorithms

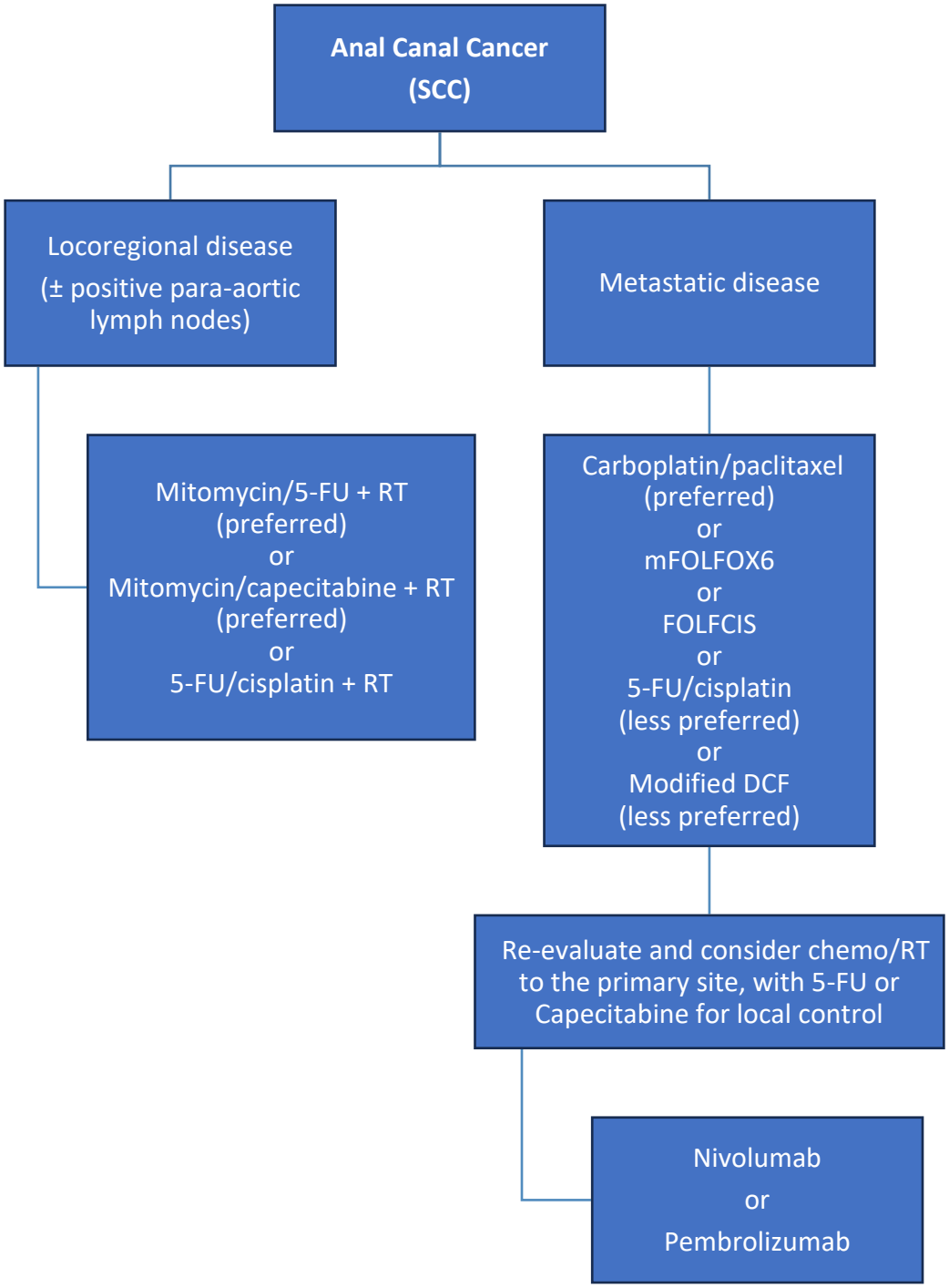

Figure 3. Management of Anal Canal Cancer

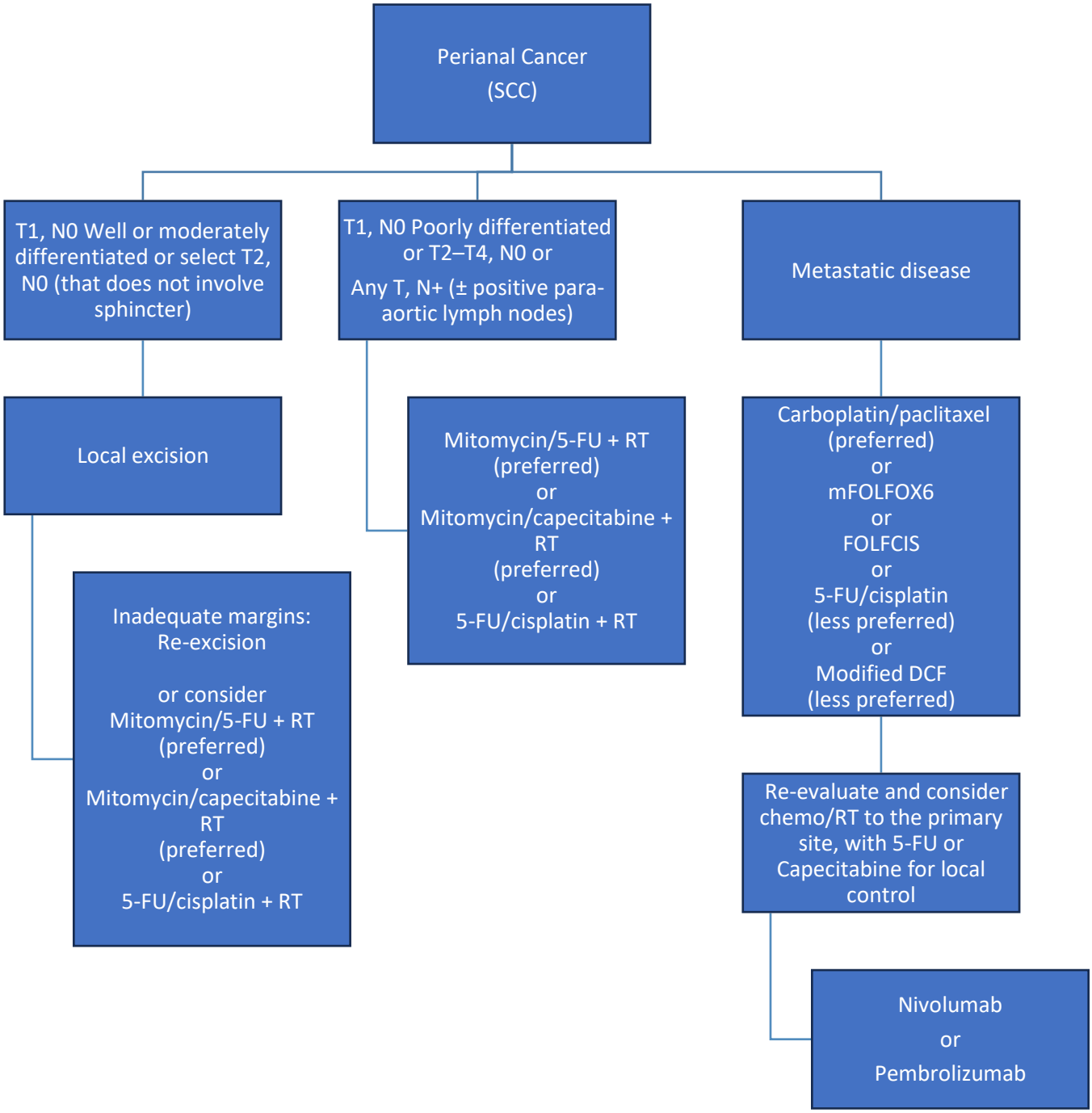

Figure 4. Management of Perianal Cancer