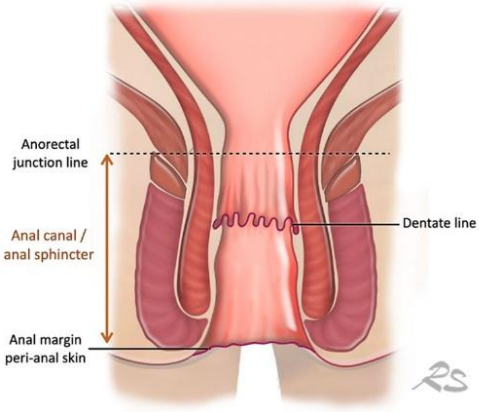
ANAL CANCER

GENERAL OVERVIEW AND STAGING

- **Epidemiology.** Incidence is increasing; squamous cell carcinoma of the anal canal (SCAC) is the dominant histology.
- **Risk factors.** Persistent high-risk HPV infection, smoking, HIV/immunosuppression and a history of other HPV-related anogenital lesions/cancers.
- **Symptoms.** Rectal/anal bleeding, pain, altered bowel habits or a palpable lesion; some patients are asymptomatic.
- **Lymphatic drainage.** Mesorectal/internal iliac drainage predominates above the dentate line; inguinal and external iliac drainage becomes more important distally.
- **Definition.** AJCC version 9 groups anal canal and perianal/anal-margin squamous cancers within the anus staging system; treatment remains site- and anatomy-dependent.



INITIAL WORK-UP

- **Clinical.** DRE, anoscopy/proctoscopy with biopsy, and palpation of inguinal nodes.
- **Imaging.** Pelvic MRI for local staging; CT chest/abdomen/pelvis. FDG-PET/CT is useful for nodal staging and radiotherapy planning when available.
- **Associated conditions.** Document HIV status/immunosuppression. In women, ensure appropriate cervical/vulvar assessment and screening for synchronous HPV-related disease.

AJCC Version 9 — TNM

Primary tumour (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX: cannot be assessed T0: no primary tumour Tis: carcinoma in situ / HSIL T1: ≤2 cm T2: >2 to ≤5 cm T3: >5 cm T4: any size invading adjacent organ(s), e.g. vagina, urethra or bladder. Direct invasion of sphincter, rectal wall, subcutaneous tissue or perianal skin alone is not T4.	NX: cannot be assessed N0: no regional LN N1: regional LN metastasis N1a: inguinal, mesorectal, superior rectal, internal iliac or obturator LN N1b: external iliac LN N1c: N1b plus any N1a LN	M0: no distant metastasis M1: distant metastasis

Anatomic stage grouping — AJCC Version 9

Stage	TNM
I	T1 N0 M0
IIA	T2 N0 M0
IIB	T1–2 N1 M0
IIIA	T3 N0–1 M0
IIIB	T4 N0 M0
IIIC	T4 N1 M0
IV	Any T Any N M1

ANAL CANCER

LOCALIZED DISEASE

CURATIVE TREATMENT

- **Preferred standard.** Definitive chemoradiotherapy (CRT) with IMRT-based pelvic radiotherapy plus mitomycin C and a fluoropyrimidine.
- **Fluoropyrimidine.** 5-FU or capecitabine are acceptable concurrent options; capecitabine is commonly used as the oral alternative.
- **Mitomycin remains preferred.** Cisplatin + 5-FU is a reasonable alternative when mitomycin is unsuitable (for example selected immunosuppressed patients), but routine substitution of mitomycin is not preferred.
- **No induction/adjuvant chemotherapy.** Routine chemotherapy before CRT or additional chemotherapy after CRT is not recommended for localized SCAC.
- **Local excision.** Reserved for carefully selected early anal-margin lesions where adequate margins can be achieved without compromising sphincter function; discuss in MDT.
- **Radiotherapy.** Avoid unnecessary treatment interruptions. Dose and target volumes are individualized by stage and radiotherapy planning.

PRACTICAL UZA RESPONSE ASSESSMENT

- **First assessment.** Clinical examination (DRE + inguinal nodes ± anoscopy) approximately 8–12 weeks after completion of CRT.
- **Do not operate too early.** Tumour regression can continue for months. If there is no clear progression, an incomplete response at the early assessment can be observed up to approximately 26 weeks from start/completion of CRT before declaring persistent disease.
- **Biopsy.** Do not biopsy routinely in an improving lesion. Histological confirmation is required before salvage surgery when residual/persistent tumour is suspected.
- **Complete response.** Continue structured clinical surveillance; cross-sectional imaging is used according to stage/risk and baseline abnormalities.

FOLLOW-UP AFTER COMPLETE CLINICAL RESPONSE

- **Years 0–2.** Clinical examination with DRE and inguinal-node palpation every 3–6 months; anoscopy/endoscopy according to local practice.
- **Years 3–5.** Clinical follow-up every 6–12 months.
- **Imaging.** For initially stage II–III disease, annual CT chest/abdomen/pelvis for approximately 3 years is a pragmatic approach. Pelvic MRI may be added when clinically indicated.
- **PET/CT.** Not routinely recommended for surveillance because post-radiotherapy inflammation can cause false-positive findings.

ANAL CANCER

PERSISTENT / RECURRENT AND METASTATIC DISEASE

LOCAL PERSISTENT OR LOCALLY RECURRENT DISEASE

- **Confirm recurrence.** Biopsy suspicious residual or recurrent disease before radical salvage whenever feasible.
- **Salvage surgery.** Abdominoperineal resection (APR) remains the standard potentially curative salvage strategy for resectable persistent or locally recurrent disease after CRT.
- **MDT.** Discuss complex pelvic recurrence in a specialized multidisciplinary setting, including colorectal surgery and radiation oncology; re-irradiation may be considered in selected cases.

FIRST-LINE ADVANCED SCAC

- **New reference standard.** Retifanlimab + carboplatin/paclitaxel for metastatic or inoperable locally recurrent SCAC (POD1UM-303/InterAACT-2).
- **POD1UM-303 efficacy.** Median PFS 9.3 vs 7.4 months (HR 0.63). Final median OS 32.8 vs 22.2 months (HR 0.75) despite crossover; ORR 56.5% vs 44.8%.
- **Schedule.** Carboplatin AUC 5 day 1 + paclitaxel 80 mg/m² days 1, 8 and 15 every 28 days for up to 6 cycles; retifanlimab 500 mg IV every 4 weeks, continued as monotherapy for up to 1 year according to the EU label.
- **If retifanlimab unavailable.** Carboplatin/paclitaxel remains the preferred chemotherapy backbone based on InterAACT; cisplatin/5-FU is an older alternative.

BELGIAN ACCESS — AUGUST 2026

- **Retifanlimab (Zynyz).** EU-authorised since March 2026 for first-line metastatic or inoperable locally recurrent SCAC in combination with carboplatin/paclitaxel.
- **Belgium.** A FAGG compassionate-use/medical-need programme is currently running for this indication..

SYSTEMIC THERAPY AFTER PROGRESSION

- **No established universal standard.** Choice depends on prior exposure, performance status, disease tempo and trial availability.
- **Chemotherapy options.** FOLFIRI or a taxane-based regimen can be considered in fit patients; evidence is limited and largely non-randomized.
- **Checkpoint inhibition.** Historical phase II data with nivolumab and pembrolizumab demonstrated modest response rates after platinum therapy. In the era of first-line retifanlimab, the value of PD-1 monotherapy after prior PD-1 exposure is uncertain.
- **Cetuximab.** Not a standard option; evidence is sparse and there is no established Belgian reimbursement/label for SCAC.
- **Clinical trial.** Preferred whenever available after progression on standard first-line therapy.

ANAL CANCER

WHAT'S NEW?

WHAT'S NEW — 2025/2026

- **POD1UM-303 / InterAACT-2.** First phase III trial to establish chemo-immunotherapy as the new systemic standard in advanced SCAC. The mature 2026 OS analysis confirms clinically meaningful survival benefit.
- **European approval.** Retifanlimab + carboplatin/paclitaxel received EU approval for advanced SCAC in March 2026.
- **PLATO-ACT4.** Phase II data support the feasibility of reduced-dose CRT (41.4 Gy/23 fractions) in selected early T1–2 (≤4 cm) N0/Nx tumours. The primary 3-year locoregional-failure endpoint remains the key determinant before broad routine de-escalation.
- **Risk-adapted radiotherapy.** The PLATO platform (ACT3/ACT4/ACT5) is refining de-escalation for low-risk and escalation for high-risk disease; this remains practice-informing rather than a blanket UZA standard.
- **Supportive care.** Modern IMRT, minimizing treatment breaks, proactive skin/GI toxicity management and long-term sexual/bowel function surveillance remain important components of cure-oriented treatment.

HISTORICAL PD-1 MONOTHERAPY DATA

- **Nivolumab — NCI9673.** Previously treated metastatic SCAC: ORR ~24%; median PFS ~4.1 months; median OS ~11.5 months.
- **Pembrolizumab — KEYNOTE-028.** PD-L1-positive advanced SCAC: ORR ~17%.
- **Pembrolizumab — KEYNOTE-158.** Previously treated advanced SCAC: ORR ~11%; median OS ~11.9 months.
- **Interpretation in 2026.** These studies established activity of PD-1 blockade but are now mainly historical context because first-line retifanlimab + chemotherapy has changed the treatment sequence.

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