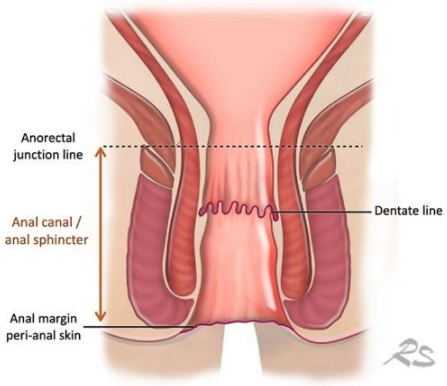
ANAL CANCER

General Overview

- Incidence has increased, particular among women
- Risk factors: Female, HPV infection, smoking, HIV, anal intercourse, multiple sexual partners
- Symptoms: bleeding, rectal mass, asymptomatic
- Lymphatic drainage
    - Above dentate line: mesorectal and internal iliac nodes
    - Below dentate line: superficial inguinal and external iliac nodes
- ! The anal canal extends from rectum to perianal skin. Tumours of anal margin and perianal skin defined as within 5 cm of the anal margin are now classified with carcinoma of the anal canal!

Staging (AJCC Version 9) and Prognosis



- PET-CT, digital rectal examination, anoscopy, palpation regional LN
- For women: screen as well for cervical cancer
- Prognosis:
    - 50% Localized: 80% 5y survival
    - 30% Local involvement: 60% 5y survival
    - 20% distant metastasis: 30% 5y survival

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0**: No evidence of primary tumor **Tis**: carcinoma in situ, Bowen, HSIL, AIN II-III **T1**: Tumor 2cm or less in greatest dimension **T2**: Tumor > 2 cm but no more than 5 cm in greatest dimension **T3**: Tumor > 5 cm in greatest dimension **T4**: Tumor of any size invades adjacent organ(s), eg vagina, urethra, bladder (direct invasion of the rectal wall, perianal skin, SC tissue or the sphincter muscle is not classified as T4)	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: metastasis in regional LN **N1a**: inguinal, mesorectal, superior rectal, internal iliac , obturator lymphnodes **N1b**: external iliac nodes **N1c**: N1b with any N1a node	**M0**: no distant M+ **M1**: distant M+

- Anatomic Stage (https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21780)
    - Stage I: T1N0M0
    - Stage IIA: T2N0M0
    - Stage IIB: T1-2N1M0
    - Stage IIIA: T3N0-1M0
    - Stage IIIB: T4N0M0
    - Stage IIIC: T4N1M0

Update: December 2025

Treatment

- Local excision in carefully selected patients
- Chemoradiotherapy (with mitomycine / 5-FU) for localized disease (1,2)
- Substitution of capecitabine for 5-FU is acceptable
- Replacement of mitomycin by cisplatin: similar pCR, PFS and OS (3)
- Monitor treatment response:
    - Clinically 8 – 12 weeks after completion of chemoradiotherapy
    - In case of clinical complete response (CR): re-evaluate 3 – 6 months with DRE, anuscopy
    - Annual CT thorax/Abdomen for at least 3 years
    - 26 weeks is the optimal time to assess CR if salvage surgery is discussed . Residual tumour should be confirmed histologically (4)
- Treatment of metastatic disease:
    - Cisplatin – 5FU in the past standard first line option (60% RR)
    - Carbo/Taxol (InterAACT trial) (5) currently standard because of similar RR but better survival and tolerability
    - PODIUM-303 study (ESMO 2024): phase 3 (Rao S, et al, INTERAACT 2) (published in Lancet 2025)
        - Retifanlimab (anti-PD1) + carboplatin/paclitaxel superior to chemo alone
        - PFS 9.3 vs 7.4 m. Crossover allowed. OS data immature but trend to better OS
        - New standard of care (**Retifanlimab via compassionate use** since 7/2025)
    - No standard second line. Options:
        - FOLFIRI
        - Paclitaxel
        - Cetuximab (KRAS wild type) (no reimbursement or label)
        - Immunotherapy: nivolumab, pembrolizumab (no reimbursement or label)

References

1) ACT I trial: Lancet 1996 and Northover J *et al* Br J Cancer 2010
2) EORTC trial: JCO 1997;15(5):2040
3) ACT II trial: Lancet Oncology 2013
4) Lancet oncology feb 2017 (Glynne-Jones R *et al*)
5) JCO 2020 Rao S *et al*
6) Lancet 2025 Rao S et al

What's new ?

- Phase II with nivolumab 3mg/kg Q2W (Lancet oncology 2017):
    - 37 patients, 24% RR, PFS 4.1m, mOS 11.5m
- Keynote 028 with pembrolizumab 10 mg/kg Q2W (Annals of oncology 2017):
    - 25 patients, 17% RR,
- Keynote 158 with pembrolizumab 200 mg Q3W (Lancet Gastroenterol Hepatol 2022)
    - 112 patients, 11% RR, mOS 11.9m
- PODIUM-303 study (ESMO 2024): phase 3 (Rao S, et al, INTERAACT 2) (published in Lancet 2025)
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