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Anal Canal Cancer

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Cancer Care Alberta

Clinical Practice Guideline GI-001 – Version 6
www.ahs.ca/guru

Background

The anal canal is delimited superiorly by the proximal extent of the levator-external anal sphincter complex and inferiorly by the anal verge (the junction between the anal mucosa and the hair-bearing skin). Lesions that involve the hair-bearing skin (peri-anal skin within 5 cm of the anal verge) are considered cancers of the anal margin and should also be treated as anal cancers.

This guideline was developed to outline the management recommendations for patients with squamous cell carcinomas that arise within the anal canal. Adenocarcinomas of the anal canal should be treated like rectal cancers (see the Early-Stage Rectal Cancer Clinical Practice Guideline).

Guideline Questions

1. What are the goals of therapy and recommendations for the treatment of adult patients with potentially curable cancer of the anal canal?
2. What are the recommendations for management of adult patients who have undergone curative therapy for cancer of the anal canal?
3. What are the recommendations for management of adult patients with locally recurrent cancer of the anal canal?
4. What are the recommendations for management of adult patients with metastatic cancer of the anal canal?

Search Strategy

Randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team's interpretation of the data.

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with squamous cell carcinomas that arise within the anal canal. Different principles may apply to pediatric patients.

Recommendations

Suggested Diagnostic Work-Up

The incidence of squamous cell carcinomas that arise within the anal canal has increased with the prevalence of Human Papilloma Virus (HPV) infection, Human Immunodeficiency Virus (HIV) infection, and immunosuppression required for organ transplantation. If the use of chemotherapy or radiotherapy is considered and HIV infection is suspected, HIV serology and an evaluation of the CD_4 count are suggested in addition to the complete blood count and both liver and renal function tests.

CT chest abdomen pelvis, MRI of the pelvis are recommended. The addition of a PET/CT scan to the staging workup has a significant impact on therapy planning, particularly identifying those patients who need higher-dose RT to the groin and those with otherwise occult metastatic disease. A meta-analysis of 12 studies concluded that a PET CT changed nodal status in 28% of patients and should be considered[1]. Suspicious lymph nodes should be evaluated with a biopsy by fine-needle aspirate. Female patients should have a gynecological assessment (including a Pap smear) to exclude a synchronous cervical cancer. A colonoscopy should be performed to detect synchronous lesions.

Stage Information

Table 1. American Joint Committee on Cancer Staging Information, Eighth Edition.

Stage	Tumour Stage		Regional Lymph Node Involvement		Metastases	
0	T_{is}	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II-III, high-grade anal intraepithelial neoplasia)	N_0	No regional lymph node metastasis	M_0	Absent
I	T_1	Tumor ≤2 cm	N_0	No regional lymph node metastasis	M_0	Absent
IIA	T_2	Tumor >2 cm but ≤5 cm	N_0	No regional lymph node metastasis	M_0	Absent
IIB	T_3	Tumor >5 cm	N_0	No regional lymph node metastasis	M_0	Absent
IIIA	T_1	Tumor ≤2 cm	N_1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes	M_0	Absent
IIIA	T_2	Tumor >2 cm but ≤5 cm	N_1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes	M_0	Absent
IIIB	T_4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder	N_1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes	M_0	Absent
IIIC	T_3	Tumor >5 cm	N_1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes	M_0	Absent
IIIC	T_4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder	N_1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes	M_0	Absent
IV	T_{any}	See above	N_{any}	See above	M_1	Present

Goals of Therapy and Recommendations for Potentially Curable Cancer of the Anal Canal

1. To render the patient free of disease and to delay or prevent recurrence.
2. To improve the patient's quality of life (to eliminate tumour-related symptoms) and to preserve continence.

Consider treatment on a clinical trial, if available.

Table 2. Recommendations for Potentially Curable Cancer of the Anal Canal.

Stage	Recommendations
Stage 0	• Consider a wide local excision provided that surgical resection can be completed to achieve negative margins and to preserve continence (no involvement of the anal sphincter).
Stage I	• Consider a wide local excision provided that surgical resection can be completed to achieve negative margins and to preserve continence (no involvement of the anal sphincter).

Stage	Recommendations
	• Consider primary chemoradiotherapy (as described for stage II and III_A disease) if sphincter preservation (maintenance of continence) is not possible with a wide local excision. • Consider an abdominoperineal resection for residual or recurrent disease.
Stage II **Stage III_A**	• Primary chemoradiotherapy[2-7] involves the sequential administration of Mitomycin C with a continuous intravenous infusion of 5-Fluorouracil (4,000 mg/m^2 over ninety-six hours) * during week one and week five of a course of radiation (4,500 to 5,400 cGy to the perineum and regional lymph nodes) [I ,A]. Randomized trials have used 2 doses of MitomycinC 10 mg/m2 during weeks 1 and 5 as well as a single dose of Mitomycin C at 12 mg/m^2 during week 1 (cap at 20 mg per dose). This is an evidence based option that is also supported by real world data[8]. This regimen requires placement of a central venous catheter ("CVC") or a peripherally inserted central catheter ("PICC line"). • Consider an abdominoperineal resection for residual or recurrent disease.
Stage $III_{B\&C}$	• Primary chemoradiotherapy: sequential administration of Mitomycin C (10 mg/m^2 IV) followed by a continuous intravenous infusion of 5-Fluorouracil *(4,000 mg/m^2 over ninety-six hours) during week one and week five of a course of radiation. Two doses of mitomycin (cap at 20 mg per dose) is preferred based on real world data demonstrating improved cancer specific survival, reduced distant RFS in stage IIIB and IIIC patients who had 2 doses of mitomycin (10 mg/m2) compared to 1 dose (12 mg/m2)[9]. Consider a boost, if indicated. • Consultation with the multidisciplinary and surgical team should be sought to determine the role of further surgery.

* If a central line is not possible due to logistical reasons, 5FU can be replaced with capecitabine 825 mg/m^2 twice daily, 5 days per week for all days of RT[10] [III, B]

Table 3. Recommended Radiotherapy Dosing[11-13].

Stage	Recommended RT Dosing
Primary Tumour	
T2N0	50.4-54 Gy
T2N1	54 Gy
T3-T4	54-59.4 Gy
Elective Nodes	
T2N0	42-45 Gy
T3-4 or N+	45 Gy
Involved Nodes	
≤3cm	50.4 Gy
≥3cm	54 Gy

Post-Curative Therapy Guidelines

- See Integrating an Early Palliative Approach into Advanced Cancer Care
- Perform a digital rectal examination and consider anoscopy at six to eight weeks after completion of the therapy. Consider biopsy of any suspicious lesions at three months after completion of therapy, but recognize that tumors may continue to respond up to six months after the radiation[14].
- Perform salvage surgery for biopsy-proven persistent, progressive, or recurrent disease.
- After achieving a complete response, repeat digital rectal examination, anoscopy, and examination of the inguinal lymph nodes every four months for two years then every six months for the balance of five years.
- Female patients should have a gynecological assessment (including a Pap smear) due to the

increased risk of cervical cancer. A colonoscopy should be obtained as outlined in the colorectal cancer screening guidelines.

Recommendations for Locally Recurrent Cancer of the Anal Canal

1. For patients whose disease recurs despite prior radical chemoradiotherapy, consider surgical resection, if possible after repeating full staging investigations. Consider palliative therapy (see below) if surgical resection is not possible.
2. For patients whose disease recurs after not having received prior chemoradiotherapy, consider radical chemoradiotherapy (see above) with or without surgery.

Goals of Therapy and Recommendations for Metastatic Cancer of the Anal Canal

1. To maintain or to improve the patient's quality of life (to control or to delay the onset of tumor-related symptoms).
2. To prolong life, if possible.

Metastatic anal canal cancer describes the situation where a cancer that originated within the anal canal has spread beyond the regional lymph nodes to other organs. This represents an incurable situation for which palliative options (e.g.: best supportive care, palliative chemotherapy) may be considered.

Palliative chemotherapy regimens are generally continued as long as tumor shrinkage or stability is confirmed, as long as the side effects remain manageable, as long as the patient wishes to continue, and as long as the treatment remains medically reasonable.
Carboplatin/paclitaxel (Carboplatin AUC 5 on day 1 every 28 days and paclitaxel at 80 mg/m2 on days 1, 8, 15 every 28 days) [I,B]. The InterAACT randomized phase II trial demonstrated the superiority of carboplatin/paclitaxel compared to cisplatin and infusional 5FU in inoperable, locally recurrent or metastatic SCC of the anal canal for overall survival (OS). OS was a secondary endpoint of this trial. Preliminary findings presented at ESMO 2018 demonstrated OS was 12.3 months with cisplatin/5FU versus 20 months with carboplatin and paclitaxel, hazard ratio [HR] 2.0 ($p = 0.014$). There was no difference in response rate, the primary endpoint of this trial (57.1% with cisplatin/5-FU compared to 59.0% with carboplatin/paclitaxel). Median PFS was 5.7 months for cisplatin/5-FU versus 8.1 months for carboplatin/paclitaxel ($p = 0.375$). The incidence of serious adverse events (SAEs) was lower with carboplatin/paclitaxel; SAEs were reported in 62% of cisplatin/5-FU patients compared with 36% of patients receiving carboplatin/paclitaxel ($p = 0.016$). There are no randomized phase III trials in this setting, and patients should be encouraged to participate in clinical trials[15].

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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial GI Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial GI Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2010.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2026. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; CCA, CancerControl Alberta; HPV, Human Papilloma Virus; HIV, Human Immunodeficiency Virus; CT, Computerized Tomography; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging; RT, Radiotherapy; OS, Overall Survival; HR, Hazard Ratio; SAE Serious Adverse Events; SCC Squamous Cell Carcinoma

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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