

## ANAL CANAL CANCER

Date Developed:

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The recommendations contained in this guideline are a consensus of the author's views of currently accepted approaches to treatment, derived from a systematic 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.

## Purpose of Guideline

This guideline was developed to outline the management recommendations for patients with cancer that arises within the anal canal.

## Development Panel

This guideline was developed by the members of the Provincial Gastrointestinal Tumor Team.

## Preamble

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 anal mucosa and hair-bearing skin). Lesions of the anal margin involve the hair-bearing skin (peri-anal skin within 5 cm of the anal verge) and should be treated as a skin cancer.

## 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<sub>4</sub> count are suggested in addition to the complete blood count and both liver and renal function tests.

Because prognosis depends upon the stage of disease, an anatomic assessment with digital rectal examination, anoscopy or sigmoidoscopy (with biopsy), and a CT scan of the abdomen and pelvis (and/or MR or transrectal ultrasound) plus chest x-ray are recommended. Suspicious lymph nodes should be evaluated with a biopsy by fine-needle aspirate.

Whereas lesions under 2 cm in size are rarely associated with invasion into the external anal sphincter or involvement of regional lymph nodes, lesions over 3 cm or with muscular invasion are often associated with nodal involvement. Tumors over 4 cm in size are associated with a high risk of extra-pelvic disease.

## Stage Information

Stage	Depth of Tumor Penetration		Regional Lymph Node Involvement		Metastases	
Stage 0	T <sub>is</sub>	Carcinoma <i>in situ</i>	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage I	T <sub>1</sub>	Tumor ≤ 2 cm in size	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage II	T <sub>2</sub>	Tumor between 2 cm and 5 cm	N <sub>0</sub>	None	M <sub>0</sub>	Absent
	T <sub>3</sub>	Tumor > 5 cm in size	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage III <sub>A</sub>	T <sub>1</sub>	Tumor ≤ 2 cm in size	N <sub>1</sub>	Perirectal lymph nodes	M <sub>0</sub>	Absent
	T <sub>2</sub>	Tumor between 2 cm and 5 cm	N <sub>1</sub>	Perirectal lymph nodes	M <sub>0</sub>	Absent
	T <sub>3</sub>	Tumor > 5 cm in size	N <sub>1</sub>	Perirectal lymph nodes	M <sub>0</sub>	Absent
	T <sub>4</sub>	Invasion into adjacent organs (e.g.: vagina, urethra, bladder)	N <sub>0</sub>	None	M <sub>0</sub>	Absent

Stage	Depth of Tumor Penetration		Regional Lymph Node Involvement		Metastases	
Stage III <sub>B</sub>	T <sub>4</sub>	Invasion into adjacent organs (e.g.: vagina, urethra, bladder)	N <sub>1</sub>	Perirectal lymph nodes	M <sub>0</sub>	Absent
	T <sub>any</sub>	As described above	N <sub>2</sub>	Unilateral internal iliac or inguinal lymph nodes	M <sub>0</sub>	Absent
	T <sub>any</sub>	As described above	N <sub>3</sub>	Perirectal and inguinal lymph nodes Bilateral internal iliac lymph nodes Bilateral inguinal lymph nodes	M <sub>0</sub>	Absent
Stage IV	T <sub>any</sub>	As described above	N <sub>any</sub>	As described above	M <sub>1</sub>	Present

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

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

STAGE	RECOMMENDATION
<u>Stage 0</u> T <sub>is</sub> N <sub>0</sub> M <sub>0</sub>	<ul style="list-style-type: none"> <li>• Provided that surgical resection can be completed to achieve negative margins and to reserve continence (no involvement of the anal sphincter), consider wide local excision.</li> </ul>
<u>Stage I</u> T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	<ul style="list-style-type: none"> <li>• Consider treatment on a clinical trial, if available.</li> <li>• Provided that surgical resection can be completed to achieve negative margins and to reserve continence (no involvement of the anal sphincter), consider wide local excision.</li> <li>• If sphincter preservation (and maintenance of continence) is not possible with wide local excision, consider primary chemoradiotherapy.<sup>1,2</sup> This involves the sequential administration of Mitomycin C (10 mg/m<sup>2</sup> IV) followed by a continuous intravenous infusion of 5-Fluorouracil (1,000 mg/m<sup>2</sup>/24h over nine-six hours) during weeks one and five of a five-week course of radiation (5,000 to 5,400 cGy to the perineum and regional lymph nodes). This regimen requires placement of a central venous catheter ("CVC") or a peripherally inserted central catheter ("PICC line").</li> <li>• Consider an abdominoperineal resection for residual or recurrent disease.</li> </ul>
<u>Stage II</u> T <sub>2,3</sub> N <sub>0</sub> M <sub>0</sub>	<ul style="list-style-type: none"> <li>• Consider treatment on a clinical trial, if available.</li> <li>• Primary chemoradiotherapy<sup>1,2</sup> involves the sequential administration of Mitomycin C (10 mg/m<sup>2</sup> IV) followed by a continuous intravenous infusion of 5-Fluorouracil (1,000 mg/m<sup>2</sup>/24h over nine-six hours) during weeks one and five of a five-week course of radiation (5,000 to 5,400 cGy to the perineum and regional lymph nodes). This regimen requires placement of a central venous catheter ("CVC") or a peripherally inserted central catheter ("PICC line").</li> <li>• Consider an abdominoperineal resection for residual or recurrent disease.</li> </ul>

<p><b>Stage III<sub>A</sub></b>  T<sub>1,2,3</sub>N<sub>1</sub>M<sub>0</sub>  T<sub>4</sub>N<sub>0</sub>M<sub>0</sub></p>	<ul style="list-style-type: none"> <li>• Consider treatment on a clinical trial, if available.</li> <li>• Primary chemoradiotherapy<sup>1,2</sup> involves the sequential administration of Mitomycin C (10 mg/m<sup>2</sup> IV) followed by a continuous intravenous infusion of 5-Fluorouracil (1,000 mg/m<sup>2</sup>/24h over nine-six hours) during weeks one and five of a five-week course of radiation (5,000 to 5,400 cGy to the perineum and regional lymph nodes). This regimen requires placement of a central venous catheter (“CVC”) or a peripherally inserted central catheter (“PICC line”).</li> <li>• Consider an abdominoperineal resection for residual or recurrent disease.</li> </ul>
<p><b>Stage III<sub>B</sub></b>  T<sub>4</sub>N<sub>1</sub>M<sub>0</sub>  T<sub>any</sub>N<sub>2</sub>M<sub>0</sub>  T<sub>any</sub>N<sub>3</sub>M<sub>0</sub></p>	<ul style="list-style-type: none"> <li>• Consider treatment on a clinical trial, if available.</li> <li>• Pre-operative chemoradiotherapy<sup>1,2</sup> involves the sequential administration of Mitomycin C (10 mg/m<sup>2</sup> IV) followed by a continuous intravenous infusion of 5-Fluorouracil (1,000 mg/m<sup>2</sup>/24h over nine-six hours) during weeks one and five of a five-week course of radiation (5,000 to 5,400 cGy to the perineum and regional lymph nodes). This regimen requires placement of a central venous catheter (“CVC”) or a peripherally inserted central catheter (“PICC line”).</li> <li>• Recommend resection of residual disease at primary site and both superficial and deep inguinal lymph nodes.</li> </ul>

<b>Post-Curative Therapy Guidelines</b>	
<ul style="list-style-type: none"> <li>• Perform a digital rectal examination and anoscopy at six to eight weeks after completion of the therapy and biopsy any suspicious abnormalities.</li> <li>• Perform an abdominoperineal resection and regional lymph node dissection for biopsy-proven persistent or recurrent disease.</li> <li>• 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 five years.</li> <li>• Obtain a colonoscopy as outlined in the colorectal cancer screening guidelines.</li> </ul>	

### **Recommendations for Locally Recurrent Cancer of the Anal Canal**

- For patients whose disease recurs despite prior radical chemoradiotherapy, consider surgical resection, if possible. Consider palliative therapy (see below) if surgical resection is not recommended.
- 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**

- To maintain or to improve the patient’s quality of life (to control or to delay the onset of tumor-related symptoms).
- 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. Palliative chemotherapy may involve the sequential

administration of anti-emetics, adequate prehydration, and Cisplatin (75 mg/m<sup>2</sup> in 250 mL of normal saline IV over one hour) followed by a continuous intravenous infusion of 5-Fluorouracil (1,000 mg/m<sup>2</sup>/24h over nine-six hours) every twenty-eight days. This regimen requires placement of a central venous catheter (“CVC”) or a peripherally inserted central catheter (“PICC line”).

## References

1. Bartelink H, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer radiotherapy and gastrointestinal cooperative groups. *J Clin Oncol* 1997;15:2040-2049.  
*Level of evidence: 1b*
2. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet*. 1996 Oct 19;348(9034):1049-54.  
*Level of evidence: 1b*

## Other Useful References

3. Boman BM, Moertel C, O’Connell M, et al. Carcinoma of the anal canal: A Clinicopathologic study of 188 cases. *Cancer* 1984;54:114.  
*Level of evidence: 2b*
4. Nigro ND, et al. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum* 1974;17:354.  
*Level of evidence: 4*
5. Flam M. et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol* 1996;14:2537.  
*Level of evidence: 1b*

Level	Description of Evidence
1a	Systematic reviews of randomized controlled trials
1b	Individual randomized controlled trials
1c	All or none randomized controlled trials
2a	Systematic reviews of cohort studies
2b	Individual cohort study or low quality randomized controlled trial
2c	Outcomes research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles”