

American College of Radiology ACR Appropriateness Criteria®

ANAL CANCER

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Summary of Literature Review

Background

Anal canal cancers are rare, accounting for about 10% of cancers in the anorectal region and approximately 5,200 cases annually in the United States [1]. Beginning in the early 1980s, the traditional management of abdominoperineal resection (APR) for tumors of the anal region was progressively replaced by radiotherapy alone and, eventually, by chemoradiation. The emergence of a successful nonsurgical treatment for anal cancer was a paradigm shift and helped usher in a new era of organ preservation treatment for other cancer disease sites [2]. Although there are no randomized trials comparing APR with radiation or chemoradiation, chemoradiation has supplanted other forms of therapy primarily because of its superior local control and colostomy-free survival rates for most patients with anal cancer. Abdominoperineal resection (and radiotherapy to a lesser degree) results in a permanent colostomy with its associated functional, anatomic, and psychologic complications. The treatment of anal cancer with chemoradiation has served as a prototype for attempts at organ-preserving treatment of esophageal and other cancers [3-7].

Histology

Tumors of the anal region can be keratinizing or nonkeratinizing. Basaloid and cloacogenic cancers arise from the functional zone just above the dentate line and are considered by most investigators to be types of squamous cancer. Primary adenocarcinoma of the anus is

rare. It is an aggressive disease that is associated with a high rate of distant metastases.

The role of routine chemoradiation for adenocarcinoma is not firmly demonstrated in the literature. A report from the M.D. Anderson Cancer Center recommended preoperative chemoradiation followed by surgery [8]. However, in a Rare Cancer Network (RCN) retrospective multicenter study [9] reporting on a group of 82 patients, outcomes did not greatly differ from results reported with squamous cell cancer of the anus [10-12]. Small-cell carcinoma of the anal region is even rarer, and experience in treating it is limited. Other rare histologies include melanoma, lymphoma (including mucosa-associated lymphoid tissue [MALT] lymphomas), and sarcoma.

Distant Metastases

Systemic spread of anal cancer occurs in less than 10% of cases [13]. The most common sites of distant spread are the liver and lungs. The treatment of such patients is varied [14]. The risk for distant metastases in adenocarcinoma of the anus is about 10% [15].

Tumors of the Anal Margin

The anal margin is defined generally as an area within a 5 cm radius outside but not impinging upon the anal verge. Due to their location and consequent proclivity for early diagnosis, these tumors tend to have a better prognosis. Patients with very early stage (T1M0N0) anal margin cancer are very well managed by local wide excision or by radiotherapy alone [16-17], similar to the treatment for a skin cancer. The recommended radiation dose in these cases is between 60 and 65 Gy in 6-7 weeks. More advanced diseases at the anal margin or any lesions that involve the anal verge are managed with treatment options similar to those for anal canal cancers, stage for stage.

Staging Systems

Several clinical staging systems have been proposed and used in the past, including classifications from the Mayo Clinic, Roswell Park, and the Centre Léon Bérard. The recently modified TNM classification system has been used in the treatment guidelines because it is suitable for a disease treated primarily with nonsurgical means and because of its increasing acceptance in the literature (See [Appendices 1 and 2](#)) [18].

Prognostic Factors

The size of the primary and the presence of nodal metastases are determinates of outcome. Recent data suggest that de-novo tumors >5 cm are at significantly increased risk of requiring a colostomy [19] and contribute to inferior disease-free and overall survival rates [20]. Additionally, male gender and positive HIV

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status may portend unfavorable long-term outcomes [20-21].

Treatments

Surgical Management

Radical surgery in the form of APR that resulted in permanent colostomies was the standard treatment of choice for anal cancers until the 1970s, before radiotherapy alone and then chemoradiation supplanted it (See the ACR Appropriateness Criteria® on “[Local Excision in Early Stage Rectal Cancer](#).”) Abdominoperineal resection yielded 5-year survival rates of approximately 50% and local recurrence rates of approximately 30% [22-23]. The role of APR for chemoradiation failures is discussed below under “Salvage Treatment.”

Local excision with wide margins may be an alternative to radiotherapy in the treatment of selected patients with T1N0M0 anal canal cancers as long as sphincter function can be preserved. The cure rates are markedly lower, however: approximately 60% at 5 years, with local recurrences at about 40% [22-24]. The reciprocal figures for radiotherapy alone are 90%-100% 5-year survival rate and 10%-20% local failure rate. Local excision alone should be reserved for special clinical circumstances such as a patient with a poor performance status and/or significant comorbidities.

Biopsies for initial diagnosis and for establishing local residual or recurrent disease should also be done with caution in the interest of sphincter function.

Radiation Alone—External Beam

The efficacy of radiation alone in patients with anal cancer has been well studied. Touboul et al [25] reported on 270 patients with T1-T4 carcinoma of the anal canal treated with radiation alone. Local control for tumors smaller than 4 cm was 90% at 10 years, whereas for tumors larger than 4 cm it was 65% at 10 years. Overall, 57% of patients maintained normal anal function [25]. Newman et al [26] reported similar results with radiation alone. Local control was related to T stage. They reported 100% local control for T1 tumors, 86% for T2, 92% for T3, and 63% for T4. Overall, 74% of patients maintained a functional anus [26]. Despite encouraging results of radiation alone, chemoradiation has been shown to be superior to radiation in patients with anal canal cancer, as will be discussed below.

Radiation techniques have evolved over the past decade with the advent of intensity-modulated radiation therapy (IMRT). The goal of this form of inverse planning and delivery of external beam radiotherapy is to increase the therapeutic ratio [27]. Until the publication of Radiation Therapy Oncology Group® (RTOG®) 0529 a phase II study examining the role of IMRT in anal cancer in order to reduce morbidity, the ACR Appropriateness Committee cautiously recommends the use of IMRT as “may be appropriate” if performed outside of a protocol setting. Even for patients enrolled on RTOG® 0529, quality control and technical issues with IMRT were thought to be challenging. For T1N0 patients, high-energy

photon fields that cover the pelvis in an AP/PA or 4-field box are most often used. For more advanced lesions (eg, \geq T2 or N+), the pelvis and inguinal lymph nodes are treated with photons, and then electron fields are used to treat the inguinal lymph nodes to dose above the threshold of the femoral heads.

Radiation Alone—Interstitial Radiation (Brachytherapy)

Few studies have reported on the efficacy of brachytherapy alone. James et al [28] reported that brachytherapy was relatively effective for patients with small node-negative anal canal cancer. Local control for tumors $<$ 5 cm was 64% and diminished to 23% for tumors $>$ 5 cm. Survival was also related to tumor size. The long-term survival rate was 60% for tumors $<$ 5 cm and only 30% for tumors $>$ 5 cm. Eighty-two percent of patients who had no evidence of recurrent cancer retained normal anal function [28]. No direct comparison of brachytherapy versus chemoradiation has been made; however, these results are clearly inferior to those of combined-modality treatment.

Radiation Alone Versus Chemoradiation

Concurrent chemotherapy and radiation yield results superior to those of radiation alone or radical surgical resection. Consequently, chemoradiation is now the standard of care. Cummings et al [29] reported the results of one of the largest experiences with the use of chemoradiation for anal canal cancer. They described 192 patients treated with either radiation alone, radiation with 5-fluorouracil (5FU), or radiation with 5FU and mitomycin (MMC). Treatment with radiation with concurrent 5FU and mitomycin resulted in the highest degree of local control and the best 5-year survival rate (86% and 78%, respectively); however, mitomycin was associated with increased frequency and severity of toxicity, particularly hematological toxicity [29].

Two major randomized studies have compared the use of radiation alone versus combined chemoradiation. Bartelink et al [30] reported the results of a study by the European Organization for Research and Treatment of Cancer Radiotherapy (EORTC) that compared radiation alone to radiation plus concurrent chemotherapy for patients with T3, T4, and N0-N3 and patients with T1, T2, and N1-3. In that study, local control was increased from 55% with radiation alone to 73% with combined chemoradiation. Similarly, the colostomy-free rate increased from 45% with radiation alone to 77% with combined-modality therapy. The 5 year survival rate was the same at 56%, and there was no difference in late toxicity between the two arms [30]. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Anal Cancer Working Party reported the results of radiation alone versus chemoradiation for patients with T1-T4, N +/- . Its findings indicated that local control with radiation alone was inferior to that of chemoradiation, 41% vs 64%. They concluded that chemoradiation with surgical salvage for failure was superior to radiation alone [31]. (See [Variant 1](#) and [Variant 2](#).)

Use of Mitomycin

In a large intergroup study by Flam et al [4], the use of mitomycin (MMC) combined with 5FU and radiation was shown to be superior to 5FU and radiation alone. The disease-free survival rate increased from 51% with 5FU and radiation to 73% with radiation combined with 5FU and mitomycin [4]. The colostomy rate decreased from 22% with radiation and 5FU to 9% with radiation, 5FU, and mitomycin. (See [Variant 3](#) and [Variant 4](#).)

Use of Cisplatin

Several single-institution and phase II studies have examined the use of radiation given concurrently with 5FU and cisplatin (CDDP) rather than with 5FU alone or 5FU and mitomycin. Rich et al [32] reported promising results in 39 patients treated with concurrent infusional 5FU, cisplatin, and radiation. Local control at 5 years with both 5FU and CDDP administered by infusion along with radiation to 54-55 Gy was 85% compared with 73% for patients treated with 5FU and radiation to similar doses [32]. Toxicities, especially hematologic toxicity, were limited [32]. Martenson et al [33] combined bolus CDDP with infusional 5FU and radiation therapy in a phase 2 trial of the Eastern Cooperative Oncology Group (ECOG). The regimen resulted in an overall response rate of 95%; however, significant toxicity occurred, indicating that this regimen was near the maximal tolerated dose [33]. The difference in the toxicities in these two studies may be based on several variables such as the schedule of CDDP administration, the agents, or the use of induction therapy. Hung et al [34] and Gerard et al [35] showed comparable overall survival, local control, and colostomy-free survival rates in two studies with 92 and 95 patients, respectively, with CDDP replacing mitomycin. Less hematologic and other toxicities may be evident with infusional cisplatin, similar to the difference noted in the toxicity profile between bolus and infusional 5FU during postoperative chemoradiation for locally advanced rectal cancer [36].

Recently, the results of a phase III intergroup trial of 644 patients comparing 5FU, mitomycin, and radiation to 5FU, CDDP, and radiation were reported [37]. The substitution of CDDP for mitomycin did not improve disease-free survival. Moreover, the colostomy rate was significantly higher for the group randomized to CDDP instead of mitomycin. Mitomycin did, however, have greater toxicity than CDDP. The authors concluded that CDDP should not be used en lieu of mitomycin. Given the results of this phase III trial, the question of whether CDDP is superior to mitomycin seems to be closer to an answer, albeit the follow-up of 2.51 years was short.

The EORTC has published phase II data comparing mitomycin, continuous 5FU, and radiation to mitomycin, weekly CDDP, and radiation [38]. More patients in the CDDP arm discontinued treatment than in the 5FU arm, and there were more grade 3 hematological toxicities with CDDP and none with 5FU. The rates of other toxicities were the same. The authors concluded, however, that since the CDDP arm had more activity it warranted

further study, while the 5FU arm did not. They also found the greater toxicity to be acceptable.

Dose of Radiation

The appropriate radiation dose for anal cancer has not been fully elucidated. A minimum dose of at least 45 Gy has been established for even the earliest stages of anal cancer, T1N0 [5]. Several studies suggest that doses in excess of 55.8 Gy result in higher local control rates than lower doses [32,39]. However, increased radiation dose did not increase local control when given in a split-course fashion in a phase 2 RTOG[®] study, and a maximum dose of 59 Gy is standard for even the most advanced cases. A split course resulted in less grade 3 or higher toxicity; however, the colostomy rate was also noted to be higher [40]. Therefore, a preplanned split-course of radiation is not recommended. If there are significant skin breakdown issues, a treatment break of no more than 10 days is currently allowed by the most recent RTOG[®] protocol [37]. Conventionally for early-stage disease, radiation doses of 50.4 to 55.8 Gy are often sufficient, whereas for later, bulkier stage disease, doses of 55.8 Gy to 59.4 are generally prescribed.

Nodal Metastasis

Anal cancers spread to the perirectal, inguinal, and internal and external iliac groups of lymph nodes. This occurs in about 30% of patients in surgical series [41]. Consequently, all four groups of lymph nodes are included in radiotherapy fields described in chemoradiation series [3-4]. (See [Variant 5](#).)

The presence of synchronous lymph nodes in anal cancer has a marked negative influence on survival and colostomy rates [4,23]. In the prospective randomized RTOG[®] study (87-04) the addition of mitomycin to 5FU and radiotherapy showed a significant benefit in reducing colostomy rates.

With radiotherapy alone, about 70% of inguinal nodes are controlled, whereas 90% of synchronous inguinal nodes are controlled with chemoradiation [23,41].

Suitability for Definitive Treatment

Most patients with anal cancer, and even those with locally advanced disease, have good or acceptable general performance status ($\geq 50\%$). Known human immunodeficiency virus (HIV) infection is not necessarily a contraindication to the use of standard recommended treatments. However, patients with cytopenias or with frank manifestations of acquired immunodeficiency syndrome (AIDS) may have a decreased ability to tolerate treatment. A patient's overall performance status, complete blood count (CBC), and T cell counts (CD3/CD4 status) should be considered in selecting therapy [42]. Ideally, the viral load should be below 10,000 and the CD4 count above 200. Modern HIV therapies have made the treatment of anal cancer with standard chemoradiation much more feasible, although cases should be individualized pending the results of large randomized trials.

Other relative reasons that might preclude definitive treatment include previous pelvic radiotherapy or surgery and underlying medical, psychiatric, and/or social reasons.

Salvage Treatment

The committee consensus was that progressive or recurrent disease after chemoradiation requires APR for salvage. With a median follow-up of 29 months after radical salvage surgery, Mullen et al reported that the overall actuarial survival rate was 64% in 31 patients with either persistent or recurrent squamous cell cancer of the anal canal [43]. Flam et al [4] have shown that the use of 9 Gy along with 5FU and cisplatin can result in an approximate 50% salvage rate for patients with biopsy-proven evidence of residual malignancy 4-6 weeks following completion of chemoradiation [4]; however others argue that a complete response would be achieved with further follow-up, and therefore they do not recommend a biopsy or salvage chemoradiation. (See [Variant 6.](#))

Treatment of Adenocarcinoma

The RCN study [9] concluded that combined treatment with chemotherapy and radiotherapy is the treatment of choice, giving the best survival rates, and that APR should be reserved for salvage treatment of persistent or recurrent disease.

Summary

- Chemoradiation with 5FU and mitomycin remains the standard of care.
- Doses of radiation between 50.4 and 59.4 Gy are most commonly used.
- The use of IMRT and cisplatin is still undergoing study.
- Routine biopsy after chemoradiation is discouraged, and abdominal-perineal resection is reserved for salvage in most cases.

Supporting Document(s)

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Appendix 1. AJCC 2010 Staging Classification for Cancer of the Anus [18]

Primary tumor (T)

Stage	Definition
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i>
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder*

*Note: Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

Regional lymph nodes (N)

Stage	Definition
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Distant metastasis (M)

Stage	Definition
M0	No distant metastasis
M1	Distant metastasis

Appendix 2. Stage Grouping

Stage	Definition
Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
	T3, N0, M0
Stage IIIA	T1, N1, M0
	T2, N1, M0
	T3, N1, M0
	T4, N0, M0
Stage IIIB	T4, N1, M0
	Any T, N2, M0
	Any T, N3, M0
Stage IV	Any T, Any N, M1

Clinical Condition:

Anal Cancer

Variant 1:

45-year-old patient, T3N0M0. KPS 80.

Treatment	Rating	Comments
RT + 5FU + MMC	9	For CDDP, see text.
RT alone	2	
RT + 5FU	2	
External beam + brachytherapy	2	
APR	1	
If RT + Chemo: RT Dose to Primary		
40 Gy/2.0 Gy	1	
45 Gy/1.8 Gy	2	
50.4 Gy/1.8 Gy	5	
59.4 Gy/1.8 Gy	9	
Technique: RT		
IMRT	6	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4 field box	3	
If RT + Chemo: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	8	
Pelvis + primary + lateral inguinal LNs	7	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:

Anal Cancer

Variant 2:

50-year-old patient, T1N2M0 right inguinal 2-cm node + M0. KPS 90.

Treatment	Rating	Comments
Pre-RT Induction Chemotherapy		
5FU + MMC	1	
5FU + CDDP	1	
Primary Treatment		
RT + 5FU + MMC	9	For CDDP, see text.
RT alone	2	
APR	1	
Groin dissection + RT + chemo	1	
Dose to Primary + Right Inguinal Node with RT + Chemo		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	4	
50.4 Gy/1.8 Gy	7	
59.4 Gy/1.8 Gy	7	
Technique: RT		
IMRT	6	
AP/PA photons	6	
PA + laterals + electron boost to inguinal LNs	8	
4 field box	5	
If RT + Chemo: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	2	
Pelvis + primary + lateral inguinal LNs	9	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:

Anal Cancer

Variant 3:

73-year-old patient, T1N0M0. KPS 80.

Treatment	Rating	Comments
Local Excision, Negative Margins		
RT + 5FU + MMC	9	For CDDP, see text.
RT alone	4	
APR	1	
Brachytherapy alone	1	
Local Excision, Positive Margins		
RT + 5FU + MMC	9	For CDDP, see text.
RT alone	4	
Re-excision	1	
APR	1	
If RT + Chemo: RT Dose to Primary		
40 Gy/2.0 Gy	1	
45 Gy/1.8 Gy	6	
50.4 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	4	
Technique: RT		
IMRT	6	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4 field box	3	
If RT + Chemo: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	8	
Pelvis + primary + lateral inguinal LNs	4	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:

Anal Cancer

Variant 4:

65-year-old patient, T2N0M0. KPS 80.

Treatment	Rating	Comments
RT + 5FU + MMC	9	For CDDP, see text.
RT + 5FU	6	
RT alone	4	
External beam + brachytherapy	2	
APR	1	
If RT + Chemo: RT Dose to Primary		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	4	
50.4 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	6	
Technique: RT		
IMRT	6	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4 field box	3	
If RT + Chemo: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	8	
Pelvis + primary + lateral inguinal LNs	6	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:

Anal Cancer

Variant 5:

45-year-old patient, T4N3M0. KPS 80.

Treatment	Rating	Comments
Pre-RT Induction Chemotherapy		
5FU + MMC	1	
5FU + CDDP	1	
Primary Treatment		
RT + 5FU + MMC	9	For CDDP, see text.
RT alone	2	
APR + node dissection	1	
APR + node dissection + chemo RT	1	
If RT + Chemo: RT Dose to Primary		
50.4 Gy/1.8 Gy	3	
55.8 Gy/1.8 Gy	7	
59.4 Gy/1.8 Gy	9	
70.2 Gy/1.8 Gy	2	
Technique: RT		
IMRT	6	
AP/PA photons	6	
PA + laterals + electron boost to inguinal LNs	8	
4 field box	3	
If RT + Chemo: RT Volume Needed		
Pelvis + primary + medial inguinal LNs	2	
Pelvis + primary + lateral inguinal LNs	9	
Primary alone	1	
Routine Post-treatment Biopsy		
If progressive disease observed	9	
If clinical regression observed	1	
If stable disease observed	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:

Anal Cancer

Variant 6:

56-year-old patient, T3N0M0, dose 50.4 Gy with 5FU + MMC with initial CR, now with biopsy of primary at 7 months = positive (recurrent).

Treatment	Rating	Comments
APR	9	
Postoperative chemo + APR	3	
Additional RT + chemo	2	
Brachytherapy alone	1	
Local excision	1	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		