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ANAL CANCER

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Summary of Literature Review

Background

Anal canal cancers are rare, accounting for approximately 10% of cancers in the anorectal region and approximately 6,230 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-preserving 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. APR (and radiotherapy to a lesser degree) results in a permanent colostomy with its associated functional, anatomic, and psychological complications. The treatment of anal cancer with chemoradiation has served as a prototype for organ-preserving treatment attempts of esophageal and other cancers [3-7].

Histology

Tumors of the anal region are most frequently keratinizing or nonkeratinizing squamous cell carcinoma. Basaloid cancers arise from the functional zone just above the dentate line and are considered by most investigators to be types of squamous cancer. These and other subtypes of squamous cell carcinoma are treated like squamous cell carcinomas, as there is no prognostic significance. 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 MD Anderson Cancer Center recommended preoperative chemoradiation followed by surgery [8]. However, in a Rare Cancer Network 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 lymphomas), and sarcoma.

Because squamous histology is by far the most common, it should be noted that the evidence cited in this review is primarily applicable to squamous cell carcinoma of the anal canal; treatment of other histologies is not as well defined in the literature.

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Distant Metastases

Systemic spread of squamous cell anal cancer occurs in less than 10% of cases [13]. The liver and lungs are the most common sites of distant spread. Treatment of such metastases in patients is varied [14]. The risk for distant metastases in adenocarcinoma of the anus is 28% higher [15].

Tumors of the Anal Margin

The anal margin is defined generally as a 5-cm radius outside but not impinging upon the anal verge. Due to tumor location and consequent proclivity for early diagnosis, patients with these tumors tend to have a better prognosis. Patients with very early stage (T1N0M0) anal margin cancer are very well managed by local wide excision or by radiotherapy alone [16,17], similar to 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 lesions that involve the anal verge are managed stage-for-stage with treatment options similar to those for anal canal cancers.

Staging

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 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 [18].

Because anal cancer is now typically treated nonsurgically, optimal treatment and outcomes are dependent on adequate pretreatment staging. The combination of positron emission tomography (PET) and/or computed tomography (CT) for identifying the primary tumor and involved nodes should be used [19,20]. These modalities, although quite good, are not perfect, and pathologic staging with a sentinel lymph node biopsy may be considered [21].

Prevention

Anal cancer is preceded by high-grade anal intraepithelial neoplasia (AIN). AIN can be caused by infection with human papillomavirus (HPV), primarily types 16 and 18. The quadrivalent HPV vaccine, when given prior to HPV exposure, has been shown to reduce the rates of AIN and should be considered in populations at high risk for anal cancer, which includes men who have sex with men, women with cervical or vulvar cancer, or individuals who are immunosuppressed [22].

Prognostic Factors

The size of the primary tumor and the presence of nodal or distant metastases are determinates of outcome. Patients with de novo tumors >5 cm are at significantly increased risk of requiring a colostomy [23], and such tumors contribute to inferior disease-free and overall survival rates [24]. Additionally, male gender and positive HIV status may portend unfavorable long-term outcomes [24,25].

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. Then, chemoradiation supplanted APR. APR yielded 5-year survival rates of approximately 50% and local recurrence rates of approximately 30% [26,27]. The role of APR for chemoradiation failures is discussed 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 approximately 40% [26-28]. Reciprocal figures for radiotherapy alone note a 5-year survival rate of 90%–100% and a local failure rate of 10%–20%. Local excision alone should be reserved for special clinical circumstances such as a patient with a poor performance status and/or significant comorbidities. (See the ACR Appropriateness Criteria® topic on "Local Excision in Rectal Cancer," although note that some of the presented data refers to excision of adenocarcinoma, a relatively rare histology in the anal canal.)

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 [29] reported on 270 patients with T1-T4 carcinoma of the anal canal treated with radiation alone. Local control for tumors <4 cm was 90% at 10 years, whereas it was 65% at 10 years for tumors > 4 cm. Overall, 57% of patients maintained normal anal function [29]. Newman et al [30] reported similar results with radiation alone in a study for which 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 [30]. Despite encouraging results of radiation alone, chemoradiation has been shown to be superior to radiation in patients with anal canal cancer.

Radiation Alone—Interstitial Radiation (Brachytherapy)

Few studies have reported on the efficacy of brachytherapy alone. James et al [31] 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 [31]. No direct comparison of brachytherapy to 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 [32] reported the results of one of the largest experiences with chemoradiation for anal canal cancer. They described 192 patients treated with either radiation alone, radiation with 5-fluorouracil (5-FU), or radiation with 5-FU and mitomycin (MMC). Radiation treatment with concurrent 5-FU and MMC resulted in the highest degree of local control and the best 5-year survival rate (86% and 78%, respectively); however, MMC was associated with increased frequency and severity of toxicity, particularly hematological toxicity [32].

Two major randomized studies have compared the use of radiation alone to combined chemoradiation. Bartelink et al [33] 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 tumors and patients with T1, T2, and N1-3 tumors. In that study, local control increased from 55% with radiation alone to 73% when combined with chemoradiation. Similarly, the colostomy-free rate increased from 45% with radiation alone to 77% with combined-modality therapy. The 5-year survival rate was 56%, and there was no difference in late toxicity between the 2 arms [33]. The United Kingdom Coordinating Committee on Cancer Research Anal Cancer Working Party reported the results of radiation alone versus chemoradiation for patients with T1-T4, N positive/negative tumors. Its findings indicated that local control with radiation alone was inferior to that of chemoradiation, 41% versus 64%, respectively. The party concluded that chemoradiation with surgical salvage for failure was superior to radiation alone [34]. (See Variant 1 and Variant 2.)

Use of Mitomycin

In a large intergroup study by Flam et al [4], the use of MMC combined with 5-FU and radiation was shown to be superior to 5-FU and radiation alone. The disease-free survival rate increased from 51% with 5-FU and radiation to 73% with radiation combined with 5-FU and MMC [4]. The colostomy rate decreased from 22% with 5-FU and radiation to 9% with radiation combined with 5-FU and MMC. (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 5-FU and cisplatin (CDDP) rather than with 5-FU alone or 5-FU and MMC. Rich et al [35] reported promising results in 39 patients treated with concurrent infusional 5-FU, CDDP, and radiation. Local control was 85% at 5 years with both 5-FU and CDDP administered by infusion along with 54–55 Gy of radiation compared with 73% local control for patients treated with 5-FU and radiation to similar doses [35]. Toxicities, especially hematologic toxicity, were limited [35]. Martenson et al [36] combined bolus CDDP with infusional 5-FU and radiation therapy in a phase II trial of the Eastern Cooperative Oncology Group. The regimen resulted in an overall response rate of 95%; however, significant toxicity occurred, indicating that this regimen was near the maximal tolerated dose [36]. The difference in the toxicities in these 2 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 [37] and Gerard et al [38] showed comparable overall survival, local control, and colostomy-free survival rates in 2 studies with 92 and

95 patients, respectively, with CDDP replacing MMC. Less hematologic and other toxicities may be evident with infusional CDDP, similar to the difference noted in the toxicity profile between bolus and infusional 5-FU during postoperative chemoradiation for locally advanced rectal cancer [39].

The EORTC published phase II data comparing MMC, continuous 5-FU, and radiation to MMC, weekly CDDP, and radiation [40]. More patients in the CDDP arm discontinued treatment than in the 5-FU arm, and there were more grade 3 hematological toxicities with CDDP and no hematological toxicities with 5-FU. The rates of other toxicities were the same. The authors concluded, however, that since the CDDP arm had more activity it warranted further study, and the 5-FU arm did not. They also found acceptable the greater toxicity.

Most recently, a long-term update of The Radiation Therapy Oncology Group® (RTOG®) 9811 was published. This phase III trial randomized 649 patients and compared 5-FU, MMC, and radiation to induction 5-FU and CDDP followed by 5-FU, CDDP, and radiation. In the initial analysis [41] there was a significant decrease in colostomy failures with the use of MMC, but trial researchers also reported that MMC was associated with greater grade 3-4 acute hematologic toxicity than CDDP (late toxicity was the same). At that time, with only 2.51 years of follow-up, there was no statistical difference in disease-free survival or overall survival. However, in the recent update of RTOG 9811 [42], the use of MMC was associated with better disease-free survival (67.8% versus 57.8% at 5 years, P=.006) and better overall survival (78.3% versus 70.7% at 5 years, P=.026) when compared to the CDDP arm. There was a trend toward statistical significance in terms of locoregional relapse, colostomy-free survival, and decreased colostomy failure favoring the MMC arm.

RTOG 9811 confirmed that induction chemotherapy with CDDP and concurrent chemoradiation was inferior to upfront concurrent chemoradiation with MMC. The use of induction in the CDDP arm, however, is a potential confounder. The ACT II trial in the United Kingdom attempted to address this issue with a direct comparison of CDDP to MMC in the concurrent chemoradiation alone setting. Preliminary data with a median follow-up of 5 years presented at the 2012 American Society of Clinical Oncology meeting suggest an equivalence between radiation with 5-FU and MMC and radiation with 5-FU and CDDP [43]. Based on the current evidence, it has been concluded that concurrent chemoradiation with 5-FU and MMC remains the standard of care [44].

Radiation Dose and Technique

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 [45]. Dosimetrically IMRT use can reduce dose to normal structures [46] and clinically is associated with decreased acute toxicity compared to historic outcomes, with less than 25% of patients experiencing grade 3+ gastrointestinal and dermatologic toxicity [47-49]. A retrospective review by Bazan et al [50] compared treatment of anal cancer with IMRT with conventional radiation therapy. Patients treated with conventional radiation required more treatment breaks and longer treatment duration. They reported better overall survival at 3 years, locoregional control, and progression-free survival with IMRT compared to conventional radiation (88%, 92%, and 84%, respectively for IMRT versus 52%, 57%, and 57%, respectively for conventional radiation). RTOG 0529 is a phase II study examining the ability of IMRT to reduce acute morbidity in anal cancer. Reducing acute toxicity enables patients to complete treatment with few breaks, which overall could lead to better outcomes [51]. Since preliminary results are encouraging [49,52], the expert panel now recommends the use of IMRT as "usually appropriate" if performed outside of a protocol setting. However, it is important to note that even for patients enrolled in RTOG 0529, quality control and technical issues with IMRT were thought to be challenging, in particular with regard to target volume contouring. For T1N0 patients, high-energy photon fields that cover the pelvis in an anteroposterior (AP)/posteroanterior (PA) or 4-field box are used most often. For more advanced lesions (eg, ≥T2 or N+), typically 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.

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 stage 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 [35,53]. If the use of IMRT in RTOG 0529 yields expected tumor control rates while minimizing toxicity, it would provide a way to safely explore dose escalation. However, increased radiation dose did not increase local control when given in a split-course fashion in a phase II RTOG study, and currently 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 higher [51]. 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 [41]. Conventionally, doses of radiation between 50.4 Gy and 59.4 Gy are appropriate.

Nodal Metastasis

Anal cancers spread to the perirectal, inguinal, and internal and external iliac groups of lymph nodes. This occurs in approximately 30% of patients in surgical series [54]. Consequently, all 4 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 [4,27]. With radiotherapy alone, approximately 70% of inguinal nodes are controlled, whereas 90% of synchronous inguinal nodes are controlled with chemoradiation [27,54].

Suitability for Definitive Treatment

Most patients with anal cancer, even locally advanced disease, have good or acceptable general performance status (≥ 50%). Poor performance status may preclude adherence to a standard course of chemoradiation. Known human immunodeficiency virus (HIV) infection is not necessarily a contraindication to standard recommended treatments, and these patients should continue on antiretroviral therapy throughout chemoradiation. However, patients with cytopenias or with frank manifestations of acquired immunodeficiency syndrome may have a decreased ability to tolerate treatment. A patient's overall performance status, complete blood count, and T cell counts (CD3/CD4 status) should be considered in selecting therapy [55]. Ideally, the viral load should be below 10,000, and the CD4 count should be above 200 [25]. Modern HIV therapies have made the treatment of anal cancer with standard chemoradiation much more feasible, although cases should be individualized pending large randomized trials results.

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 determined by consensus 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 [56] reported that the overall actuarial survival rate was 64% in 31 patients with either persistent or recurrent squamous cell cancer of the anal canal. Flam et al [4] have shown that the use of 9 Gy along with 5-FU and CDDP 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, 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, which produces the best survival rates, and that APR should be reserved for salvage treatment of persistent or recurrent disease.

Summary

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

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Anal Cancer**

Variant 1: **45-year-old patient, T3N0M0. Karnofsky performance score (KPS) 80.**

Treatment	Rating	Comments
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	2	
RT + 5-FU	2	
External beam + brachytherapy	2	
APR	1	
If RT + Chemotherapy: RT Dose to Primary		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	3	
50.4 Gy/1.8 Gy	5	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	8	
Technique: RT		
IMRT	8	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: 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		
5-FU + MMC	1	
5-FU + CDDP	1	
Primary Treatment		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	2	
APR	1	
Groin dissection + RT + chemotherapy	1	
Dose to Primary + Right Inguinal Node with RT + Chemotherapy		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	3	
50.4 Gy/1.8 Gy	7	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	6	
Technique: RT		
IMRT	8	
AP/PA photons	6	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	5	
If RT + Chemotherapy: 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 + 5-FU + MMC	9	For CDDP, see text.
RT alone	4	
APR	1	
Brachytherapy alone	1	
Local Excision, Positive Margins		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	4	
Re-excision	1	
APR	1	
If RT + Chemotherapy: RT Dose to Primary		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	7	
50.4 Gy/1.8 Gy	7	
54 Gy/1.8 Gy	5	
59.4 Gy/1.8 Gy	2	
Technique: RT		
IMRT	7	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: 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 + 5-FU + MMC	9	For CDDP, see text.
RT + 5-FU	6	
RT alone	4	
External beam + brachytherapy	2	
APR	1	
If RT + Chemotherapy: RT Dose to Primary		
40 Gy/2.0 Gy	2	
45 Gy/1.8 Gy	4	
50.4 Gy/1.8 Gy	8	
54 Gy/1.8 Gy	8	
59.4 Gy/1.8 Gy	3	
Technique: RT		
IMRT	8	
AP/PA photons	8	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: 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		
5-FU + MMC	1	
5-FU + CDDP	1	
Primary Treatment		
RT + 5-FU + MMC	9	For CDDP, see text.
RT alone	2	
APR + node dissection	1	
APR + node dissection + chemoradiation	1	
If RT + Chemotherapy: RT Dose to Primary		
50.4 Gy/1.8 Gy	2	
54 Gy/1.8 Gy	7	
55.8 Gy/1.8 Gy	7	
59.4 Gy/1.8 Gy	8	
70.2 Gy/1.8 Gy	3	
Technique: RT		
IMRT	8	
AP/PA photons	6	
PA + laterals + electron boost to inguinal LNs	8	
4-field box	3	
If RT + Chemotherapy: 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, 50.4 Gy dose with 5-FU + MMC with initial complete response, now with biopsy of primary at 7 months = positive (recurrent).**

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