Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. National Cancer Institute. *Comprehensive Cancer Information*. http://www.cancer.gov/cancertopics/types/anal/. Accessed 22 October 2012.	Review/Other-Tx	N/A	Definition of anal cancer and treatment.	N/A	4
2. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med* 2000; 342(11):792-800.	Review/Other-Tx	N/A	Review of the current state of knowledge about the causes, treatment and outcomes of anal cancer.	Concomitant treatment with EBRT and chemotherapy with 5-FU and MMC represents the standard approach to combination treatment. Appropriate cytologic screening of high-risk populations and the integration of platinum compounds into treatment regimens will most likely reduce mortality from this disorder even further.	4
3. Cummings B, Keane T, Thomas G, Harwood A, Rider W. Results and toxicity of the treatment of anal canal carcinoma by radiation therapy or radiation therapy and chemotherapy. *Cancer* 1984; 54(10):2062-2068.	Observational-Tx	55 total patients: 25 RT; 30 FUMIR	To compare the results of treating anal canal carcinoma by radical EBRT or by combined FUMIR, in nonrandomized groups of patients treated in a single center.	The uncorrected 5-year survival rate in each group was approximately 70%, but primary tumor control was achieved in 93% (28/30) with FUMIR compared to 60% (15/25) treated with RT. Acute hematologic and enterocolic toxicity with uninterrupted EBRT courses of 5000 cGy in 4 weeks plus chemotherapy led to the adoption of split-course treatment. Colostomies were needed as part of treatment for residual carcinoma or for the management of treatment-related toxicity in 11/25 treated by RT and have been required to date in 4 /30 treated by FUMIR. The improvement in the primary tumor control rate and the reduction in the number of patients requiring colostomy when compared with the results of RT favor combined chemotherapy and radiation as the initial treatment for anal canal carcinoma.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
4. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of 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(9):2527-2539.	Experimental-Tx	310 total patients (291 assessable): 145 received 45-50.4 Gy of pelvic RT plus 5-FU at 1,000 mg/m2/d for 4 days; 146 received RT, 5-FU, and MMC	Phase III randomized trial to determine the importance of MMC in the standard chemoradiation regimen and to assess the role of salvage chemoradiation in patients who have residual tumor following chemoradiation.	Post-treatment biopsies were positive in 15% of patients in the 5-FU arm vs 7.7% in the MMC arm (P=.135). At 4 years, colostomy rates were lower (9% vs 22%; P=.002), colostomy-free survival higher (71% vs 59%; P= .014), and DFS higher (73% v 51%; P=.0003) in the MMC arm. A significant difference in OS has not been observed at 4 years. Toxicity was greater in the MMC arm (23% vs 7% grade 4 and 5 toxicity; P≤.001). Of 24 assessable patients who underwent salvage chemoradiation, 12 (50%) were rendered disease-free. Despite greater toxicity, the use of MMC in a definitive chemoradiation regimen for anal cancer is justified, particularly in patients with large primary tumors. Salvage chemoradiation should be attempted in patients with residual disease following definitive chemoradiation before resorting to radical surgery.	1
5. Flam MS, John M, Lovalvo LJ, et al. Definitive nonsurgical therapy of epithelial malignancies of the anal canal. A report of 12 cases. *Cancer* 1983; 51(8):1378-1387.	Review/Other-Tx	12 patients	To describe cases of definitive nonsurgical therapy of epithelial malignancies of the anal canal.	Complete regression of the anal mass occurred in all patients. Biopsies of the anal region performed after completion of therapy revealed no evidence of residual cancer. 10/12 patients are alive without evidence of disease 4-24 months (median, 14 months) after completion of treatment. All patients developed proctitis, diarrhea, and moist perineal desquamation which resolved by 4 weeks post-treatment. The described chemoradiation/RT protocol offers a definitive alternative to surgery of epidermoid cancer of the anal region.	4
6. Sischy B, Doggett RL, Krall JM, et al. Definitive irradiation and chemotherapy for radiosensitization in management of anal carcinoma: interim report on Radiation Therapy Oncology Group study no. 8314. *J Natl Cancer Inst* 1989; 81(11):850-856.	Observational-Tx	79 patients	To describe the long-term effectiveness of combined therapy at the anal canal disease site and examine the feasibility of a RTOG study involving concomitant RT and chemotherapy.	The OS rates are 97% at 1 year and 73% at 3 years. Patients with lesions <3 cm in diameter and those treated strictly according to the protocol did significantly better than those with larger lesions and those whose treatment did not comply with the protocol. The interim outcome of the study demonstrates that this combined therapy is effective for patients with anal cancer and allows preservation of the sphincter and of sexual function.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Tiver KW, Langlands AO. Synchronous chemotherapy and radiotherapy for carcinoma of the anal canal--an alternative to abdominoperineal resection. *Aust N Z J Surg* 1984; 54(2):101-108.	Review/Other-Tx	5 patients	Case reports to describe patients with squamous or basaloid carcinoma of the anal canal treated with synchronous chemotherapy and EBRT.	All patients remain disease free with a median follow-up of 14 months. Eradication of tumor at the primary site has been confirmed histologically in the 3 operable cases. A growing volume of data from the medical literature suggests that patients with operable carcinoma of the anal canal treated with this regimen have a probability of cure at least equal to that of APR and have the advantage of retaining normal anal function and avoiding permanent colostomy.	4
8. Chang GJ, Gonzalez RJ, Skibber JM, Eng C, Das P, Rodriguez-Bigas MA. A twenty-year experience with adenocarcinoma of the anal canal. *Dis Colon Rectum* 2009; 52(8):1375-1380.	Observational-Tx	34 consecutive patients	A retrospective cohort study to evaluate disease control and survival outcomes in patients with adenocarcinoma of the anal canal in patients treated between 1983 and 2004.	Median DFS was 13 months after local excision and 32 months after radical surgery (P=0.055). OS at 5 years was 43% for patients treated with local excision and 63% for patients treated with radical surgery (P=0.3). Tumor grade was predictive of OS (P=0.04) and recurrence (P=0.046). On multivariate analysis, the type of surgical treatment was an important predictor of OS (P=0.045) and DFS (P=0.004). Combined modality treatment with radical surgical resection improves survival among patients with adenocarcinoma of the anal canal, but a high risk for distant failure emphasizes the need for effective adjuvant therapeutic regimens.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. Belkacemi Y, Berger C, Poortmans P, et al. Management of primary anal canal adenocarcinoma: a large retrospective study from the Rare Cancer Network. *Int J Radiat Oncol Biol Phys* 2003; 56(5):1274-1283.	Observational-Tx	82 patients: 45 RT/surgery; 31 combined RT/chemotherapy; 6 APR alone	To evaluate the prognostic factors and outcome after the three most commonly used treatment approaches for primary adenocarcinoma of the anus.	The actuarial locoregional relapse rate at 5 years were 37%, 36%, and 20%, respectively, in the RT/surgery, RT/chemotherapy, and APR groups (RT/surgery vs RT/chemotherapy, P=0.93; RT/chemotherapy vs APR, P=0.78). The 3-, 5-, and 10-year OS rate were: 47%, 29%, and 23% in the RT/surgery group, 75%, 58%, and 39% in the RT/chemotherapy group, 42%, 21%, and 21% in the APR group, (RT/chemotherapy vs RT/surgery, P=0.027). The 5- and 10-year DFS rate were: 25% and 18% in the RT/surgery group, 54% and 20% in the RT/chemotherapy group, 22% and 22% in the APR group, (RT/chemotherapy vs RT/surgery, P=0.038). Multivariate analysis revealed four independent prognostic factors for survival: T stage, N stage, histologic grade, and treatment modality. Primary adenocarcinoma of the anal canal requires rigorous management. Multivariate analysis showed that T and N stage, histologic grade, and treatment modality are independent prognostic factors for survival.	2
10. Billingsley KG, Stern LE, Lowy AM, Kahlenberg MS, Thomas CR, Jr. Uncommon anal neoplasms. *Surg Oncol Clin N Am* 2004; 13(2):375-388.	Review/Other-Tx	N/A	Review of the neoplasms of the anus.	Since anal neoplasms are uncommon, they lack a consistent diagnostic and treatment algorithm derived from prospective clinical trial datasets.	4
11. Dujovny N, Quiros RM, Saclarides TJ. Anorectal anatomy and embryology. *Surg Oncol Clin N Am* 2004; 13(2):277-293.	Review/Other-Tx	N/A	Review of the histology and treatment of anal cancer.	The anal canal is complex in its anatomy and embryologic origin. The various types of anal cancer can be explained by the intricate and changing histology of the anal canal. An understanding of the venous and lymphatic drainage of the anal canal aids in explaining its methods of dissemination. The basis for the treatment of anal cancer is derived from the cancer's anatomic origins.	4
12. Pineda CE, Welton ML. Management of anal dysplasia. In: Ben-Josef E, Koong A, ed. *Radiation Medical Rounds: Lower Gastrointestinal Malignancies.* Vol 1, Issue 2. New York, NY: Demos Medical Publishing; 2010:399-408.	Review/Other-Tx	N/A	Book chapter.	N/A	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Kuehn PG, Beckett R, Eisenberg H, Reed JF. Hematogenous Metastases from Epidermoid Carcinoma of the Anal Canal. *Am J Surg* 1965; 109:445-449.	Review/Other-Tx	10 cases	To provide documentation of cases of primary epidermoid carcinoma of the anal canal with proved microscopic involvement of the liver and lungs.	It has been known and suggested for many years that lymphatic metastases are most important when discussing proper treatment for epidermoid carcinoma of the perianal skin and anal canal. Methods to control local infiltration have been devised because of frequent involvement of contiguous structures, such as the vagina, rectum, and bladder. Hematogenous metastases in the past were thought to be unimportant and therefore, attempts to control this route of spread were ignored. Since hematogenous metastases occurred after APRs for anal cancer (9 cases), the possibility of dissemination at surgery is considered; it is recommended that high ligation of the inferior mesenteric vein be carried out early in the operative procedure.	4
14. Flam MS. Chemotherapy of persistent recurrent or metastatic cancer. In: Cohen AM, Winawer SJ, eds. *Cancer of the Colon, Rectum, and Anus.* New York, NY: McGraw-Hill; 1995:1051-1060.	Review/Other-Tx	N/A	Book chapter.	N/A	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Myerson RJ, Karnell LH, Menck HR. The National Cancer Data Base report on carcinoma of the anus. *Cancer* 1997; 80(4):805-815.	Review/Other-Tx	2,339 total patients: 1,050 patients from 1988: 1,289 patients from 1993	To review the patterns of presentation, care, and outcome reflected in data from the National Cancer Data Base representing a broad range of medical centers.	There was an increase in the use of chemotherapy between 1988 and 1993 (from 61.6% to 67.2%), and substantial differences were observed in the management of epidermoid carcinomas and adenocarcinomas. The majority of epidermoid carcinomas were managed nonsurgically, principally with combined chemotherapy and RT, whereas three-fourths of patients with adenocarcinoma underwent surgery. The most important factors for favorable 5-year survival were early stage (ranging from 71.3% for stage I to 23.1% for stage IV), epidermoid carcinoma histology (57.6%, compared with 41.3% for adenocarcinoma), and female gender (56.2%, compared with 49.6% for males). For stage I-II epidermoid carcinomas, the 5-year survival for patients who received nonsurgical treatment with radiochemotherapy was equivalent to that of patients who received surgical treatment (64.0% and 65.4%, respectively). This study confirms a trend in patterns of care favoring nonsurgical management with radiochemotherapy for epidermoid carcinomas of the anus. For adenocarcinomas, there has been a trend toward increasing use of multimodality therapy with surgery and adjuvant radiochemotherapy. Survival data from the 1988 cases confirmed the efficacy of conservative treatment with radiation plus chemotherapy for epidermoid carcinomas.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
16. Frost DB, Richards PC, Montague ED, Giacco GG, Martin RG. Epidermoid cancer of the anorectum. *Cancer* 1984; 53(6):1285-1293.	Observational-Tx	192 patients	To retrospectively review records to determine which patients are candidates for each type of treatment and which would benefit from combined treatment.	Prognostic variables significant at P=0.05 or better were sex, size, nodal status, and level of invasion. A new staging system is proposed that utilizes tumor size, invasion, grade, and nodal status. Actuarial 10-year survival was 100%, 76%, 29%, and 0% for stages A, B, C and D, respectively (P values 0.22, 0.0007, and 0.01, respectively). 12 patients undergoing APR received postoperative RT; when compared by stage with APR alone no survival difference can be shown, although there is a trend towards fewer local recurrences.	2
17. Morson BC. The pathology and results of treatment of squamous cell carcinoma of the anal canal and anal margin. *Proc R Soc Med* 1960; 53:416-420.	Review/Other-Tx	157 cases of anal cancer	To discuss the differences in the pathology of SCC of the anal canal and SCC of the anal margin together with some comments on their diagnosis, treatment and prognosis from the point of view of a pathologist.	Anal canal cancer is about two and a half times as common as anal margin cancer. Most anal canal cancers arise from the unstable transitional zone of epithelium above the anal valves. Anal margin carcinoma arises from the lower part of the anal canal lined by simple squamous mucous membrane and from the perianal skin. The prognosis of anal margin disease is more favorable than in anal canal cancer, the crude five-year survival rate for anal margin cancer being 51.4% and for anal canal cancer 42.4%.	4
18. Anus. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010:207-217.	Review/Other-Tx	N/A	Book chapter.	N/A	4
19. Cotter SE, Grigsby PW, Siegel BA, et al. FDG-PET/CT in the evaluation of anal carcinoma. *Int J Radiat Oncol Biol Phys* 2006; 65(3):720-725.	Observational-Dx	41 consecutive patients	To compare CT and physical examination to FDG-PET/CT in the staging of carcinoma of the anal canal, with special emphasis on determination of spread to inguinal lymph nodes.	FDG-PET/CT detected 91% of nonexcised primary tumors, whereas CT visualized 59%. FDG-PET/CT detected abnormal uptake in pelvic nodes of 5 patients with normal pelvic CT scans. FDG-PET/CT detected abnormal nodes in 20% of groins that were normal by CT, and in 23% without abnormality on physical examination. Furthermore, 17% of groins negative by both CT and physical examination showed abnormal uptake on FDG-PET/CT. HIV-positive patients had an increased frequency of PET-positive lymph nodes.	3

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20. Engledow AH, Skipworth JR, Blackman G, et al. The role of (1)(8)fluoro-deoxy glucose combined position emission and computed tomography in the clinical management of anal squamous cell carcinoma. *Colorectal Dis* 2011; 13(5):532-537.	Review/Other-Dx	40 patients	To evaluate the role of FDG-PET/CT in the management of anal SCC.	All primary tumors were FDG avid. PETCT did not alter the T stage but did result in disease upstaging (N and M stages). Management was altered in 5 (12.5%) patients: 1 patient was identified to have an isolated distant metastasis, and 4 patients had FDG-avid lymph nodes not otherwise detected, all of which were tumor-positive on fine needle aspiration cytology/biopsy.	4
21. Mistrangelo M, Pelosi E, Bello M, et al. Role of positron emission tomography-computed tomography in the management of anal cancer. *Int J Radiat Oncol Biol Phys* 2012; 84(1):66-72.	Observational-Dx	53 patients	To compare PET/CT with CT scan, sentinel node biopsy results of inguinal lymph nodes, and anal biopsy results in staging and in follow-up of anal cancer.	At pretreatment assessment, anal cancer was identified by PET/CT in 47 patients (88.7%) and by CT in 30 patients (75%). The detection rates rose to 97.9% with PET/CT and to 82.9% with CT (P=.042) when the 5 patients who had undergone surgery prior to this assessment and whose margins were positive at histological examination were censored. Perirectal and/or pelvic nodes were considered metastatic by PET/CT in 14/53 patients (26.4%) and by CT in 7/40 patients (17.5%). Sentinel node biopsy was superior to both PET/CT and CT in detecting inguinal lymph nodes. PET/CT upstaged 37.5% of patients and downstaged 25% of patients. Radiation fields were changed in 12.6% of patients. PET/CT at 3 months was more accurate than PET/CT at 1 month in evaluating outcomes after chemoradiation therapy treatment: sensitivity was 100% vs 66.6%, and specificity was 97.4% vs 92.5%, respectively. Median follow-up was 20.3 months.	3

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22. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011; 365(17):1576-1585.	Experimental-Tx	602 men	To evaluate the safety and efficacy of quadrivalent HPV vaccine against anal intraepithelial neoplasia associated with HPV-6, 11, 16, or 18 infection in men who have sex with men.	Efficacy of the quadrivalent HPV vaccine against anal intraepithelial neoplasia associated with HPV-6, 11, 16, or 18 was 50.3% (95% CI, 25.7 to 67.2) in the intention-to-treat population and 77.5% (95% CI, 39.6 to 93.3) in the per-protocol efficacy population; the corresponding efficacies against anal intraepithelial neoplasia associated with HPV of any type were 25.7% (95% CI, -1.1 to 45.6) and 54.9% (95% CI, 8.4 to 79.1), respectively. Rates of anal intraepithelial neoplasia per 100 person-years were 17.5 in the placebo group and 13.0 in the vaccine group in the intention-to-treat population and 8.9 in the placebo group and 4.0 in the vaccine group in the per-protocol efficacy population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, 11, 16, or 18 was reduced by 54.2% (95% CI, 18.0 to 75.3) in the intention-to-treat population and by 74.9% (95% CI, 8.8 to 95.4) in the per-protocol efficacy population. The corresponding risks of persistent anal infection with HPV-6, 11, 16, or 18 were reduced by 59.4% (95% CI, 43.0 to 71.4) and 94.9% (95% CI, 80.4 to 99.4), respectively. No vaccine-related serious adverse events were reported.	1

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23. Ajani JA, Winter KA, Gunderson LL, et al. US intergroup anal carcinoma trial: tumor diameter predicts for colostomy. *J Clin Oncol* 2009; 27(7):1116-1121.	Experimental-Tx	644 total patients	To evaluate whether new predictive and prognostic variables would emerge by combining patients in the two treatment arms of RTOG 98-11.	In the multivariate analysis, tumor-related prognosticators for poorer OS included node-positive cancer (P≤.0001), large (>5 cm) tumor diameter (P=.01), and male sex (P=.016). In the treatment-related categories, cisplatin-based therapy was statistically significantly associated with a higher rate of colostomy (P=.03) than was MMC-based therapy. In the pretreatment variables category, only large tumor diameter independently predicted for time to colostomy (P=.008). Similarly, the cumulative 5-year colostomy rate was statistically significantly higher for large tumor diameter than for small tumor diameter (Gray's test; P=.0074). Clinical nodal status and sex were not predictive of time to colostomy. The combined analysis of the two arms of RTOG 98-11, representing the largest prospective database, reveals that tumor diameter (irrespective of the nodal status) is the only independent pretreatment variable that predicts time to colostomy and 5-year colostomy rate in patients with anal carcinoma.	1
24. Ajani JA, Winter KA, Gunderson LL, et al. Prognostic factors derived from a prospective database dictate clinical biology of anal cancer: the intergroup trial (RTOG 98-11). *Cancer* 2010; 116(17):4007-4013.	Experimental-Tx	644 total patients	To confirm and uncover new prognostic factors by analyzing the prospective database of intergroup RTOG 98-11.	Tumor diameter >5 cm was associated with poorer 5-year DFS (P=.0003) and poorer 5-year OS (P=.0031), and N(+) was associated with poorer 5-year DFS (P≤.0001) and poorer 5-year OS (P≤.0001) in the multivariate analysis. In stratified analyses, N(+) had more adverse influence on DFS and OS than did tumor diameter. This prospective prognostic factor analysis establishes tumor diameter as an independent prognosticator of poorer 5-year DFS and OS and confirms N(+) and male sex as poor prognostic factors. This analysis also uncovers novel subgroups (derived from combining prognostic factors) with incremental worsening of DFS and OS.	1

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25. Kauh J, Koshy M, Gunthel C, Joyner MM, Landry J, Thomas CR, Jr. Management of anal cancer in the HIV-positive population. *Oncology (Williston Park)* 2005; 19(12):1634-1638; discussion 1638-1640, 1645 passim.	Review/Other-Tx	N/A	To review the management of anal cancer in the HIV-positive population.	Continued studies and phase III trials will be needed to test new treatment strategies in HIV-infected patients with SCC of the anus to determine which treatment protocols provide the greatest benefits.	4
26. Greenall MJ, Quan SH, Urmacher C, DeCosse JJ. Treatment of epidermoid carcinoma of the anal canal. *Surg Gynecol Obstet* 1985; 161(6):509-517.	Review/Other-Tx	N/A	To review the treatment of epidermoid carcinoma of the anal canal.	The traditional treatment for carcinoma of the canal, APR, produced a 55% absolute 5 year survival rate but at the expense of permanent colostomy. Initial treatment with 5-FU and MMC combined with EBRT reduced the size of the tumor in 72% of the patients and, with subsequent local excision or APR, resulted in a 78% survival rate in 5 years. The long-term results from combined treatment are better than APR alone with preservation of anal function in 45% of the patients.	4
27. Hardcastle JD, Bussey HJ. Results of surgical treatment of squamous cell carcinoma of the anal canal and anal margin seen at St. Mark's Hospital 1928-66. *Proc R Soc Med* 1968; 61(6):629-630.	Review/Other-Tx	179 total patients: 127 patients with cancer of anal canal; 52 patients with cancer of anal margin	To review results of surgical treatment of SCC of the anal canal and anal margin seen at St Mark's Hospital 1928-1966.	SCC of the anal canal has been defined as a tumor arising on or above the dentate line (Morson 1960). The results of treatment of this type of tumor have improved considerably over the last 20 years. Wide removal of the growth in the perineum is necessary to reduce the incidence of local recurrence, which in a recent series accounted for 50% of the failures. In carcinoma of the anal margin, wide local excision is the treatment of choice.	4
28. Greenall MJ, Quan SH, Stearns MW, Urmacher C, DeCosse JJ. Epidermoid cancer of the anal margin. Pathologic features, treatment, and clinical results. *Am J Surg* 1985; 149(1):95-101.	Observational-Tx	48 patients	To evaluate pathologic features, treatment, and clinical results of epidermoid cancer of the anal margin.	5 year survival was 88%, although locoregional recurrence developed in 46% of these patients during follow-up. A second local excision or inguinal lymphadenectomy provided good results in the patients with recurrence. APR did not provide better OS figures.	3

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29. Touboul E, Schlienger M, Buffat L, et al. Epidermoid carcinoma of the anal canal. Results of curative-intent radiation therapy in a series of 270 patients. *Cancer* 1994; 73(6):1569-1579.	Observational-Tx	270 patients	To evaluate the efficacy of RT alone in T1-4N0N1 patients.	At 5 and 10 years, determinate survival rates were: T1: 86% and 86%; T2: 86.2% and 82.5%; T3: 60.1% and 56.8%; T4: 45% and 45%, respectively. The overall local control rate was 80%. The overall anal conservation rate was 67%. After RT, recognizing the distinction between tumor sizes of ≤4 cm in length and >4 cm in length (which is not considered in TNM Classification criteria [International Union Against Cancer, 1987]) could help to improve treatment strategies. For tumors >4 cm in length and/or with clinically involved lymph nodes, the treatment should be more extensive with combined chemotherapy and RT, but the increased local control with the addition of cytotoxic chemotherapy to irradiation has not been proven.	2
30. Newman G, Calverley DC, Acker BD, Manji M, Hay J, Flores AD. The management of carcinoma of the anal canal by external beam radiotherapy, experience in Vancouver 1971-1988. *Radiother Oncol* 1992; 25(3):196-202.	Observational-Tx	72 patients	To evaluate efficacy of RT alone in T1-4N0-1 patients.	The actuarial survival at 5 years was 66% and the disease specific survival was 78%. 9 patients had inguinal node metastases at diagnosis; their 5-year disease specific survival was 75%. 63 patients were inguinal node negative at presentation; their 5-year disease specific survival was 78%, by UICC 1987 staging: T1 71%, T2 88%, T3 41%, T4 42%. 17 patients developed local recurrence.	3
31. James RD, Pointon RS, Martin S. Local radiotherapy in the management of squamous carcinoma of the anus. *Br J Surg* 1985; 72(4):282-285.	Observational-Tx	74 patients	To evaluate the efficacy of interstitial RT alone.	Interstitial RT is effective for small node negative patients. Local control: T <5 cm, 64%. Local control: T >5 cm, 23%, 5 year survival T <5 cm, 60%, T >5 cm, 30%. 82% of cured patients retained normal anal function. Local treatment using interstitial RT is suggested as useful primary treatment for small, node-negative carcinomas, with surgery held in reserve for failures.	2

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32. Cummings BJ, Keane TJ, O'Sullivan B, Wong CS, Catton CN. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. *Int J Radiat Oncol Biol Phys* 1991; 21(5):1115-1125.	Observational-Tx	192 patients	To prospectively compare RT alone, RT and 5-FU, and RT and 5-FU and MMC.	5-year cause-specific survival rates were 69% overall, 68% RT, 76% 5-FU+MMC, 64% 5-FU only. (Local control%/-5 year survival%): RT alone/56%–68%; RT + 5-FU/60%– 64%; RT + 5-FU + MTC /86%–78%. The most effective treatment protocols as measured by survival rates, primary anal tumor control rates, and the likelihood of conservation of anorectal function included the administration of both MMC C and 5-FU concurrently with RT.	1
33. Bartelink H, Roelofsen F, Eschwege F, 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(5):2040-2049.	Experimental-Tx	110 patients	A randomized phase III trial to investigate the potential gain of the concomitant use of RT and chemotherapy in improving local control and reducing the need for colostomy in patients with locally advanced anal cancer.	Event-free survival, defined as free of locoregional progression, no colostomy, and no severe side effects or death, showed significant improvement (P=.03) in favor of the combined-treatment modality. The 5-year survival rate was 56% for the whole patient group. (RT alone%/chemotherapy%) Local control–55%/73%; Colostomy free rate–45%/77%; 5-year survival–56%/56%. The concomitant use of RT and chemotherapy resulted in a significantly improved LRC rate and a reduction of the need for colostomy in patients with locally advanced anal cancer without a significant increase in late side effects.	1
34. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *Br J Cancer* 2010; 102(7):1123-1128.	Experimental-Tx	577 patients	To follow-up on the patients treated in the UKCCCR Anal Cancer Trial (1996), demonstrating the benefit of chemoradiation over RT alone for treating epidermoid anal cancer.	There are an expected 25.3 fewer patients with locoregional relapse (95% CI, 17.5-32.0 fewer) and 12.5 fewer anal cancer deaths (95% CI, 4.3-19.7 fewer), compared with 100 patients given RT alone. There was a 9.1% increase in non-anal cancer deaths in the first 5 years of chemoradiation (95% CI, +3.6 to +14.6), which disappeared by 10 years. The clear benefit of chemoradiation outweighs an early excess risk of non-anal cancer deaths, and can still be seen 12 years after treatment. Only 11 patients suffered a locoregional relapse as a first event after 5 years, which may influence the choice of end points in future studies.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Rich TA, Ajani JA, Morrison WH, Ota D, Levin B. Chemoradiation therapy for anal cancer: radiation plus continuous infusion of 5-fluorouracil with or without cisplatin. *Radiother Oncol* 1993; 27(3):209-215.	Observational-Tx	58 total patients; 39 patients received 5-FU chemotherapy/RT	To compare the outcomes of patients receiving RT and 5-FU vs RT and 5-FU and cisplatin.	The actuarial survival at 5 years was 81% for the 5-FU chemotherapy/RT group and 94% at 2 years for the 5-FU plus cisplatin chemotherapy/RT group; median follow-up was 54 and 20 months, respectively. Serious late radiation complications have not been observed and may be related to RT fractionation and the use of protracted chemotherapy infusion. 39 patients RT and 5-FU: Local control at 5 years. 50% <45 Gy, 73% 50-54 Gy, 83% >60 Gy. 18 patients XRT and 5-FU and plat: Local control at 2 years, 85% 54-55 Gy. The absence of late morbidity coupled with the high local control rate by the use of this chemotherapy/RT program is an area to investigate for improving the therapeutic ratio for the treatment of anal cancers.	2
36. Martenson JA, Lipsitz SR, Lefkopoulou M, et al. Results of combined modality therapy for patients with anal cancer (E7283). An Eastern Cooperative Oncology Group study. *Cancer* 1995; 76(10):1731-1736.	Observational-Tx	50 total patients	A prospective study to assess the combined modality therapy of patients with International Union Against Cancer classification T1-4 N0 M0 anal cancer.	Survival at 7 years was 58%. White patients and those with favorable performance status had significantly better survival. Of the 46 patients evaluable for response, 34 had a complete response, 11 had a partial response, and 1 had no response. 7-year survival for partial responders was 53%. Freedom from locoregional progression was 80% at 7 years. Treatment with a combination of chemotherapy and RT is effective for patients with anal cancer. The investigation of methods of improving therapy is warranted.	2
37. Hung A, Crane C, Delclos M, et al. Cisplatin-based combined modality therapy for anal carcinoma: a wider therapeutic index. *Cancer* 2003; 97(5):1195-1202.	Observational-Tx	92 patients	To retrospectively evaluate the efficacy of combined modality therapy replacing MMC with cisplatin.	Median follow-up duration of 44 months, the actuarial 5-year OS rate was 85%, the DFS rate was 77%, and the colostomy-free survival rate was 82%. Cisplatin and 5-FU are well tolerated and offer high rates of local control, OS and sphincter preservation that are comparable to the results of MMC and 5-FU.	2

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Gerard JP, Ayzac L, Hun D, et al. Treatment of anal canal carcinoma with high dose radiation therapy and concomitant fluorouracil-cisplatinum. Long-term results in 95 patients. *Radiother Oncol* 1998; 46(3):249-256.	Observational-Tx	95 patients	To evaluate the results of anal cancer treated with 5-FU and cisplatin with high dose radiation including an Ir192 boost.	The median follow-up time was 64 months. At 5 and 8 years the OS was 84% and 77%, the cancer specific survival was 90% and 86% and the colostomy-free survival was 71% and 67%, respectively. The stage and the response of the tumor after EBRT were of prognostic significance. Patients with pararectal lymph nodes had an overall 5-year survival of 76% (vs 88% for non-N1). Among 78 patients who preserved their anus, the anal sphincter function was excellent or good in 72 (92%). Combined concomitant radiochemotherapy appears as the standard treatment of anal cancer. Radical surgery should be reserved for local recurrence or persisting disease after RT. High dose RT in a small volume with concomitant 5 FU- cisplatin appears to give a high rate of long-term local control and survival. Careful evaluation of pararectal nodes is essential for a good staging of the disease.	2
39. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994; 331(8):502-507.	Experimental-Tx	660 patients	To determine whether the efficacy of chemotherapy could be improved by administering 5-FU by protracted infusion throughout the duration of RT and whether the omission of semustine would reduce the toxicity and delayed complications of chemotherapy without decreasing its antitumor efficacy.	Median follow-up was 46 months among surviving patients. Patients who received a protracted infusion of 5-FU had a significantly increased time to relapse (P=0.01) and improved survival (P=0.005). There was no evidence of a beneficial effect in the patients who received semustine plus 5-FU. A protracted infusion of 5-FU during pelvic RT improved the effect of combined-treatment postoperative adjuvant therapy in patients with high-risk rectal cancer. Semustine plus 5-FU was not more effective than a higher dose of systemic 5-FU given alone.	1

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Matzinger O, Roelofsen F, Mineur L, et al. Mitomycin C with continuous fluorouracil or with cisplatin in combination with radiotherapy for locally advanced anal cancer (European Organisation for Research and Treatment of Cancer phase II study 22011-40014). *Eur J Cancer* 2009; 45(16):2782-2791.	Experimental-Tx	80 total patients: 40 patients; MMC/cisplatin; 40 MMC/5-FU	A phase II study to assess the feasibility and activity of radio-chemotherapy with MMC and cisplatin in locally advanced anal SCC with reference to RT combined with MMC and 5-FU.	The objective response rate was 79.5% (31/39) (lower bound CI: 68.8%) with MMC/5-FU vs 91.9% (34/ 37) (lower bound CI: 82.8%) with MMC/cisplatin. Radiochemotherapy with MMC/cisplatin seems promising as only MMC/cisplatin demonstrated enough activity (RECIST objective response rate >75%) to be tested further in phase III trials; MMC/5-FU did not. MMC/cisplatin also had an overall acceptable toxicity profile.	1
41. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008; 299(16):1914-1921.	Experimental-Tx	644 patients	To compare the efficacy of cisplatin-based (experimental) therapy vs MMC-based (standard) therapy in treatment of anal canal carcinoma.	Median follow-up for all patients was 2.51 years. 5-year DFS rate was 60% (95% CI, 53%-67%) in the MMC-based group and 54% (95% CI, 46%-60%) in the cisplatin-based group (P=.17). The 5-year OS rate was 75% (95% CI, 67%-81%) in the MMC-based group and 70% (95% CI, 63%-76%) in the cisplatin-based group (P=.10). The 5-year local-regional recurrence and distant metastasis rates were 25% (95% CI, 20%-30%) and 15% (95% CI, 10%-20%), respectively, for MMC-based treatment and 33% (95% CI, 27%-40%) and 19% (95% CI, 14%-24%), respectively, for cisplatin-based treatment. The cumulative rate of colostomy was significantly better for MMC-based than cisplatin-based treatment (10% vs 19%; P=.02). Severe hematologic toxicity was worse with MMC-based treatment (P<.001). Cisplatin-based therapy failed to improve DFS compared with MMC-based therapy, but cisplatin-based therapy resulted in a significantly worse colostomy rate. These findings do not support the use of cisplatin in place of MMC in combination with 5-FU and RT in the treatment of anal canal carcinoma.	1

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. *J Clin Oncol* 2012; 30(35):4344-4351.	Experimental-Tx	649 patients	To determine the long-term impact of treatment on survival (DFS, OS, colostomy-free survival), colostomy-free, and relapse (locoregional failure, distant metastasis) in this patient group.	Of 682 patients accrued, 649 were analyzable for outcomes. DFS and OS were statistically better for RT + 5-FU/MMC vs RT + 5-FU/concurrent 5-FU plus cisplatin (5-year DFS, 67.8% vs 57.8%; P=.006; 5-year OS, 78.3% vs 70.7%; P=.026). There was a trend toward statistical significance for colostomy-free survival (P=.05), locoregional failure (P=.087), and colostomy-free (P=.074). Multivariate analysis was statistically significant for treatment and clinical node status for both DFS and OS, for tumor diameter for DFS, and for sex for OS.	1
43. Glynne-Jones R, James R, Meadows H, et al. Optimum time to assess complete clinical response (CR) following chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance CisP/5FU in squamous cell carcinoma of the anus: Results of ACT II. *J Clin Oncol* 2012; 30(15_suppl):4004.	Observational-Tx	940 patients	To investigate the association between observation of clinical response at 3 different time-points and progression-free and OS, to determine the optimal time to assess this early endpoint.	Patient characteristics (all 940) median age 58 years; tumor site – canal (84%), margin (14%); stage T1-T2 (52%), T3-T4 (46%); N+ (32%), N0 (62%). Cisplatin did not improve OS (hazard ratio: 0.96, P=0.89) or progression-free survival (hazard ratio: 0.85, P=0.43) compared to MMC. This is consistent with the lack of an absolute difference at 18 and 26 weeks, but not at 11 weeks (where a difference was found). Clinical response patients (compared to not-clinical response) had a significantly lower risk of progression/death. The association between these outcomes and response was strongest at 26 weeks. 202/695 (29%) patients not in clinical response at 11 weeks were clinical response at 26 weeks.	1
44. Chin JY, Hong TS, Ryan DP. Mitomycin in anal cancer: still the standard of care. *J Clin Oncol* 2012; 30(35):4297-4301.	Review/Other-Tx	N/A	To review mitomycin in anal cancer.	No results stated in abstract.	4
45. Goodman KA, Disgupta T, Kachnic LA. Management of anal canal cancer: Current chemoradiation strategies and investigations into intensity-modulated radiation therapy. In: Ben-Josef E, Koong A, ed. *Radiation Medical Rounds: Lower Gastrointestinal Malignancies.* Vol 1, Issue 2. New York, NY: Demos Medical Publishing; 2010:367-390.	Review/Other-Tx	N/A	Book chapter.	N/A	4

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Tsai HK, Hong TS, Willins J, et al. Dosimetric comparison of dose-painted intensity modulated radiation therapy versus conventional radiation therapy for anal cancer. *J Clin Oncol* 2006; 24(18_suppl):388.	Review/Other-Tx	2 patients	To present a dosimetric comparison of dose-painted-IMRT with conventional RT.	The percentage of the primary clinical target volume receiving the prescription dose was 99% in both the dose-painted-IMRT and conventional RT plans for the T2N0 patient and 95% and 90%, respectively, for the T2N3 patient. Dose-painted-IMRT provided better tissue sparing of most normal structures as shown in the table below.	4
47. Kachnic LA, Tsai HK, Coen JJ, et al. Dose-painted intensity-modulated radiation therapy for anal cancer: a multi-institutional report of acute toxicity and response to therapy. *Int J Radiat Oncol Biol Phys* 2012; 82(1):153-158.	Observational-Tx	43 patients	To analyze acute toxicity and treatment response in a cohort of patients receiving dose-painted-IMRT and concurrent chemotherapy for anal canal cancer.	Median age was 58 years; 67% female; 16% stage I, 37% II; 42% III; 5% IV. 14 patients were immunocompromised: 21% HIV-positive and 12% on chronic immunosuppression. Median follow-up was 24 months (range, 0.6-43.5 months). 60% completed chemoradiation without treatment interruption; median duration of treatment interruption was 2 days (range, 2-24 days). Acute Grade 3+ toxicity included: hematologic 51%, dermatologic 10%, gastrointestinal 7%, and genitourinary 7%. 2-year local control, OS, colostomy-free survival, and metastasis-free survival were 95%, 94%, 90%, and 92%, respectively.	2
48. Pepek JM, Willett CG, Wu QJ, Yoo S, Clough RW, Czito BG. Intensity-modulated radiation therapy for anal malignancies: a preliminary toxicity and disease outcomes analysis. *Int J Radiat Oncol Biol Phys* 2010; 78(5):1413-1419.	Observational-Tx	47 patients	To report the results of using IMRT in the treatment of anal cancer.	47 patients with anal malignancy (89% canal, 11% perianal skin) were treated with IMRT between August 2006 and September 2008. Median follow-up was 14 months (19 months for SCC patients). Median radiation dose was 54 Gy. 8 patients (18%) required treatment breaks lasting a median of 5 days (range, 2-7 days). Toxicity rates were as follows: Grade 4: leukopenia (7%), thrombocytopenia (2%); Grade 3: leukopenia (18%), diarrhea (9%), and anemia (4%); Grade 2: skin (93%), diarrhea (24%), and leukopenia (24%). The 2-year actuarial OS, metastases-free survival, LRC, and colostomy-free survival rates were 85%, 78%, 90% and 82%, respectively. For SCC patients, the 2-year OS, metastases-free survival, LRC, and colostomy-free survival rates were 100%, 100%, 95%, and 91%, respectively.	2

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal. *Int J Radiat Oncol Biol Phys* 2013; 86(1):27-33.	Observational-Tx	52 patients	To present acute toxicity and radiation planning compliance for patients receiving dose painted-IMRT with concurrent 5-FU and MMC chemotherapy as definitive treatment for anal canal cancer.	Of 63 accrued patients, 52 were evaluable. Tumor stage included 54% II, 25% IIIA, and 21% IIIB. In primary endpoint analysis, 77% experienced grade 2+ gastrointestinal/genitourinary acute adverse events (9811 77%). There was, however, a significant reduction in acute grade 2+ hematologic, 73% (9811 85%, P=.032), grade 3+ gastrointestinal, 21% (9811 36%, P=.0082), and grade 3+ dermatologic adverse events 23% (9811 49%, P<.0001) with dose-painted-IMRT. On initial pretreatment review, 81% required dose-painted-IMRT replanning, and final review revealed only 3 cases with normal tissue major deviations.	1
50. Bazan JG, Hara W, Hsu A, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. *Cancer* 2011; 117(15):3342-3351.	Observational-Tx	46 patients	To compare outcomes in patients with anal canal SCC who were treated with definitive chemoradiotherapy by either IMRT or conventional radiotherapy.	The conventional radiotherapy group required longer treatment duration (57 days vs 40 days, P<.0001), more treatment breaks (88% vs 34.5%, P=.001), and longer breaks (12 days vs 1.5 days, P<.0001) than patients treated with IMRT. 11 (65%) patients in the conventional radiotherapy group experienced grade >2 nonhematologic toxicity compared with 6 (21%) patients in the IMRT group (P=.003). The 3-year OS, LRC, and progression-free survival were 87.8%, 91.9%, and 84.2%, respectively, for the IMRT groups and 51.8%, 56.7%, and 56.7%, respectively, for the conventional radiotherapy group (all P<.01). On multivariate analysis, T stage, use of IMRT, and treatment duration were associated with OS, and T stage and use of IMRT were associated with LRC.	2

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Konski A, Garcia M, Jr., John M, et al. Evaluation of planned treatment breaks during radiation therapy for anal cancer: update of RTOG 92-08. *Int J Radiat Oncol Biol Phys* 2008; 72(1):114-118.	Observational-Tx	67 patients	To evaluate the long-term efficacy and toxicity of RTOG 92-08 with over 10 years of follow-up.	47 patients entered in the mandatory treatment break cohort. The study was reopened in 1995 to the no mandatory treatment break cohort completing accrual with 20 patients in 1996. Of 67 total patients, 1 patient in the mandatory treatment break portion of the study did not receive any protocol treatment and is excluded from analyses. After adjusting for tumor size, neither cohort showed a statistically significant difference in OS or local-regional failure compared with the RTOG 87-04 mitomycin-C arm. No patient in either cohort experienced a Grade 3 or higher late toxicity.	1
52. Kachnic LA, Winter KA, Myerson RJ, et al. Two-year outcomes of RTOG 0529: A phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *ASCO Meeting Abstracts* 2011; 29(4_suppl):368.	Observational-Tx	52 patients	To report on the 2-year outcomes of how dose-painted IMRT reduces grade 3 + gastrointestinal and dermatologic acute toxicity, as compared to the RTOG 9811 5-FU/MMC arm.	Of 63 accrued patients, 52 were analyzable. Median age was 58 years; 81% female; 54% stage II; 25% IIIA; 21% IIIB. Median follow-up was 23.2 months (0.2-33). 2-year local-regional failure, colostomy failures, DFS and 95% CIs are 20% (9%, 31%), 8% (0.4%, 15%) and 77% (62%, 86%), respectively. The causes of death for the 7 patients that died are: anal cancer in 5, morbidity in one and second primary outside the radiation field in one.	2
53. Fung CY, Willett CG, Efird J, Kaufman DS, Shellito PC. Improved outcome with escalated radiation dosing for anal carcinoma. *International Journal of Radiation Oncology*Biology*Physics* 1993; 27, Supplement 1(0):278.	Observational-Tx	27 patients	An analysis of the effect of RT dose on local control and OS in a series of patients treated with RT and concurrent 5-FU and MMC.	3-year actuarial local control rates were 56% for the low dose group and 100% for the high dose group (P=0.0185). 3-year actuarial OS and cancer-specific survival rates were 79% and 86% respectively for the low dose group, while both were 100% for the high dose group. In patients treated with RT concurrent with 5-FU and MMC for localized anal cancer, RT doses of 5400 cGy were associated with a significantly lower rate of local control, compared to doses of >5400 cGy. By shrinking field and electron beam techniques, total doses of 5400-5600 cGy can be given safely to the anus and distal rectum with excellent local control, functional results, and OS.	2

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. Cohen AM, Wong WD. Anal squamous cell cancer nodal metastases: prognostic significance and therapeutic considerations. *Surg Oncol Clin N Am* 1996; 5(1):203-210.	Review/Other-Tx	N/A	To review prognostic significance and therapeutic considerations for anal SCC.	Anal SCC have regional lymph node spread to three sites: rectal mesentery, hypogastric, and inguinal. All such regional sites should be included in the initial radiation treatment fields and monitored for recurrence after the initial therapy.	4
55. Seo Y, Kinsella MT, Reynolds HL, Chipman G, Remick SC, Kinsella TJ. Outcomes of chemoradiotherapy with 5-Fluorouracil and mitomycin C for anal cancer in immunocompetent versus immunodeficient patients. *Int J Radiat Oncol Biol Phys* 2009; 75(1):143-149.	Observational-Tx	36 consecutive patients	To compare treatment outcomes in immunocompetent vs immunodeficient patients with invasive anal SCC treated similarly with combined modality therapy.	Median follow-up was 3.1 years. 3-year OS was 83.6% (95% CI, 68.2-100) and 91.7% (95% CI, 77.3-100) in the immunocompetent and immunodeficient groups, respectively. In addition, there were no differences in acute and late toxicity profiles between the two groups. In the HIV-positive patients, Cox modeling showed no difference in OS by pretreatment CD4 counts (hazard ratio = 0.994, 95% CI, 0.98-1.01). No correlation was found between CD4 counts and the degree of acute toxicities. Data suggests that standard combined modality therapy with 3D conformal RT and 5-FU plus MMC is as safe and effective for immunodeficient patients as for immunocompetent patients.	2

Anal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Mullen JT, Rodriguez-Bigas MA, Chang GJ, et al. Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. *Ann Surg Oncol* 2007; 14(2):478-483.	Observational-Tx	31 patients	To retrospectively review experience with salvage surgery in this group of patients.	Median follow-up time was 29 months. Patients who received an initial radiation dose of <55 Gy had a significantly worse survival than those who received at least 55 Gy as part of their initial treatment (5-year OS 37.5% vs 75%; age-adjusted hazard ratio 8.2 [95% CI, 1.1-59.8], P=.037). The presence of positive lymph nodes at presentation also adversely affected survival (P<.05). Factors that were not found to have an impact on survival included the presence of persistent vs recurrent disease, tumor (T) stage, and margin status of resection. Long-term survival following salvage surgery for persistent or locally recurrent epidermoid carcinoma of the anal canal can be achieved in the majority of patients. However, patients who initially present with node-positive disease and patients who receive a radiation dose of <55 Gy as part of their initial chemoradiation therapy regimen have a worse prognosis after radical salvage surgery.	2

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

5-FU = Fluorouracil

APR = Abdominoperineal resection

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

EBRT = External-beam radiation therapy

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

FUMIR = Fluorouracil, mitomycin C and radiation

HIV = Human immunodeficiency virus

HPV = Human papilloma virus

IMRT = Intensity-modulated radiotherapy

LRC = Locoregional control

MMC = Mitomycin C

OS = Overall survival

RT = Radiation therapy

SCC = Squamous cell carcinoma