Epidermoid Cancers of the Anal Canal: Current Treatment

Jennifer Blumetti, M.D.¹ and Amir L. Bastawrous, M.D.^{1,2}

ABSTRACT

Epidermoid carcinoma of the anal canal is an uncommon disease, but has increased in incidence with the HIV epidemic. Prior to the 1970s, treatment consisted of radical surgery with abdominoperineal resection. With the pioneering work of Dr. Norman Nigro, this has shifted to a nonsurgical approach, with primary treatment consisting of multimodality therapy with radiation and chemotherapy. This review provides an overview of the historical, current, and future treatments of epidermoid anal canal malignancies.

KEYWORDS: Anal canal malignancy, epidermoid carcinoma, chemoradiation, Nigro protocol

Objectives: On completion of this article the reader should be able to summarize the historical and current treatment of epidermoid cancers of the anal canal.

BACKGROUND

Anal malignancies are relatively uncommon, encompassing 1.5% of all digestive system malignancies¹ and 1 to 8% of all anorectal malignancies.²⁻⁵ It is 20 to 30 times less common than colon cancer with ~3400 to 4000 cases diagnosed annually in the United States.^{1,2,6} Historically, this had been a disease of older women, with onset in the 7th decade of life, and a female to male predominance of up to 5 to 1.^{2,7,8} However, with the onset of the HIV epidemic, there has been an increase in the number of younger men afflicted with anal squamous cell carcinoma. These patients have a 120-fold higher risk of developing anal canal cancers than those who are HIV negative.⁹

Anal malignancies are classified according to anatomical landmarks. Anal canal tumors arise from the anorectal ring proximally to the anal verge distally,

and include the anal transition zone and the nonhair or gland-bearing squamous tissue comprising the anoderm. The anal margin is defined as the hair and gland-bearing skin lateral and up to 5 cm away from the anal verge.¹⁻³ This distinction between anal canal and anal margin malignancies is important as anal canal lesions are more aggressive and are treated differently (see Fig. 1).³ The incidence of anal canal lesions is significantly higher than that of anal margin lesions, with anal canal lesions being up to 5 times more common.¹⁰ Staging of anal canal lesions can be seen in Table 1.

Epidermoid carcinoma is the most common type of anal canal malignancy, seen in up to 80 to 85% of all lesions.^{2,4} This includes squamous cell carcinoma and its variants, including cloacogenic, basaloid, and transitional carcinomas. Keratinizing and nonkeratinizing histology may be seen, depending on the origin of the

¹Division of Colon and Rectal Surgery, Department of Surgery, University of Illinois at Chicago, Chicago, Illinois; ²Stroger Hospital of Cook County, Chicago, Illinois.

Address for correspondence and reprint requests: Amir L. Bastawrous, M.D., Stroger Hospital of Cook County, Cook County Admin. Bldg., 1900 W. Polk St., #401, Chicago, IL 60612-3736 (e-mail: bastawro@uic.edu).

Anal Cancer and Retrorectal Tumors; Guest Editor, Jan Rakinic, M.D.

Clin Colon Rectal Surg 2009;22:77-83. Copyright © 2009 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-0029-1223838. ISSN 1531-0043.

Figure 1 Anal canal carcinoma involving the anal margin.

tumor at or distal to the anal transition zone. Treatment and outcomes of these histologic variants are similar, and will be considered together. Figure 2 demonstrates invasive squamous cell carcinoma of the anal canal.

HISTORICAL TREATMENT

Prior to the mid-1970s, surgery with abdominoperineal resection was the treatment of choice for anal canal epidermoid malignancies.^{2,5,7,11} Despite the radical nature of this resection, survival with primary surgery ranged from only 27 to 58%.^{5,11} In patients with small lesions, local excision was performed in an attempt to spare the anal sphincter; however, the results were poor in patients with anal canal lesions and only seemed to

Figure 2 Squamous cell carcinoma of the anal canal. Blue ink (splotches) marks edges of invasion. Color not shown.

benefit those with anal margin lesions less than 2 cm in size.¹¹

Radiotherapy for primary treatment of anal canal malignancies became widely utilized in the 1970s. With primary radiotherapy, treatment doses were typically in the range of 60 to 70 Gy, with a 3-year survival rate at 50%.^{7,8} In one series, 38% of patients developed complications due to the radiation therapy. Eight percent of patients developed severe necrosis, fibrosis, or incontinence, which required surgery; the majority of these patients had received at least 65 Gy of radiation.⁷

In the mid-1970s, Dr. Norman Nigro developed a combined chemotherapy and radiation therapy treatment protocol. This consisted of 3000 cGy radiation given over 3 weeks, combined with 1000 mg/m²/day 5-FU given as a continuous infusion over 4 days and repeated on days 29 to 32. A single dose of mitomycin C (MMC) of 15 mg/m² was also given on day 1.¹² Although this was originally developed as a neoadjuvant protocol, the findings of complete tumor regression in the majority of patients led to its use as a primary treatment.^{13,14} Since Dr. Nigro's initial groundbreaking studies, the treatment paradigm for anal canal epidermoid malignancies has shifted away from operative treatment to chemoradiation (see Fig. 3).

Table 1 TNM Staging for Anal Canal Malignancy

Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor <2.0 cm in greatest dimension
T2	Tumor >2.0 cm but not >5.0 cm
T3	Tumor >5.0 cm
T4	Tumor of any size that invades adjacent organ(s)
Lymph nodes (N)	
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
Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Adapted from Greene FL, Page DL, Fleming ID, et al, eds. AJCC Cancer Staging Manual. 6th ed. New York: Springer-Verlag: 2002.

CURRENT TREATMENT

Several large randomized control trials have explored the use of concomitant chemoradiation: the United Kingdom Coordinating Committee on Cancer Research (UKCCR),¹⁵ the European Organization for the Research and Treatment of Cancer (EORTC)¹⁶ Trial, and the Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Trial (RTOG/ECOG).¹⁷ The UKCCR evaluated 585 patients and randomized them to radiation alone versus radiation plus chemotherapy. The radiation therapy in the 2 arms was

Figure 3 Squamous cell cancer of the anal canal. (A) Pretreatment. (B) Postchemoradiation.

identical, with 45 Gy given over 4 to 5 weeks. The chemotherapy arm received continuous 1000 mg/m² of 5-FU on days 1 to 4 or 750 mg/m² during days 1 to 5, with a second dose given during the last week of radiotherapy. MMC was also given at 12 mg/m² on day 1. At 3-year follow-up, there was a significantly lower local failure rate with chemoradiation compared with radiation alone (39% versus 61%). Despite the difference in local control, overall survival was similar between the two groups.¹⁵

The EORTC performed a phase III trial, which randomized patients to 45 Gy radiation over 5 weeks with a boost of 15 to 20 Gy 6 weeks later or 750 mg/m² infusional 5-FU on days 1 to 5 and 29 to 33 and 15 mg/m² MMC on day one plus radiation. Radiation therapy alone resulted in a 54% complete remission, which was significantly inferior to the 80% complete remission seen in the combined treatment arm.¹⁶

The final large randomized trial evaluated the benefit of MMC to infusional 5-FU and radiation. The RTOG/ECOG phase III trial randomized 310 patients to one arm consisting of 45 to 50.4 Gy radiation plus 4 days of 5-FU at 1000 mg/m². The second arm added MMC at 10 mg/m² for 2 doses. The addition of the MMC did contribute to increased toxicity in this group; however, disease-free and colostomy-free survival were significantly higher with the addition of MMC.¹⁷

Current treatment regimens typically utilize a variation of the above protocols. At this institution 45 Gy of radiation is given initially, with a boost to bring the total dose to 50.4. Inguinal node basins are typically included in the radiation field. Concurrent chemotherapy if given using a continuous infusion of 1000 mg/m² 5-FU on days 1 to 4 and 29 to 32 and a single dose of 10 mg/m² MMC on day 1.

COMPLICATIONS OF TREATMENT AND NEWER PROTOCOLS

Despite the success of chemoradiotherapy, significant side effects have been reported.^{3,4,18,19} Dermatitis, diarrhea, leukopenia, anemia, and thrombocytopenia are common complaints.¹⁸ The use of MMC has been associated with a higher risk of acute hematologic toxicity, typically manifesting as neutropenia.⁴ In the RTOG trial, there were four deaths in the MMC arm, all due to neutropenic sepsis, compared with one death in the 5-FU alone arm.¹⁷ Radiation therapy, especially at total dose higher than 60 Gy or fractions greater than 200 cGy, can lead to significant proctitis, dermatitis, ulceration, or even anorectal fibrosis and stenosis requiring colostomy.^{4,18} The inclusion of inguinal radiation fields is associated with epidermolysis, leg edema, and vascular damage.¹⁹

Complications with chemoradiation can be significant for many patients, leading to decreases in treatment doses of both chemotherapeutic agents as well as radiation therapy. This, in turn, leads to decreased treatment efficacy, with significantly worse survival in those patients receiving less than the prescribed doses of chemotherapy.¹⁸

Advances in computed tomography (CT) scan simulation have led to increased accuracy in planning the radiation field, leading to less damage to normal structures such as the small bowel and bladder.²⁰ Limiting the fractions to 200 cGy per day have been shown to decrease the toxicity of treatment.^{4,18} Intensity-modulated radiation therapy is a newer technique, which alters the intensity of the radiation dose over the radiation field. The radiation is conformed to the tumor and high-risk areas while sparing normal tissues. A recent study has demonstrated decreased dermatologic and gastrointestinal toxicity with this technique.²⁰

Chemotherapeutic regimens with drugs other than MMC have been studied in an effort to reduce toxicity. A recent randomized control trial evaluated the use of cisplatin in place of MMC.²¹ The study found worse toxicity in the MMC group, and no difference in disease-free survival between the cisplatin group and the MMC group; however, there were more study-related deaths in the cisplatin group. In addition, the cisplatin treatment arm utilized an induction "neoadjuvant" chemotherapy regimen prior to chemoradiation, making direct comparison between MMC and cisplatin difficult.

Alternatives to 5-FU are also being evaluated. Capecitabine is an oral chemotherapeutic agent, which is converted to 5-FU at the tumor site and is currently being utilized in clinical trials for colorectal cancer.²² The use of capecitabine would potentially eliminate the need for infusion therapy and resultant cost and complications of long-term indwelling intravenous catheters. A phase II trial in the United Kingdom demonstrated the safety and efficacy of oral capecitabine with a 77% 4-week local control rate and 68% compliance rate to full treatment.

Further studies to evaluate both cisplatin and capecitabine are currently under way.^{22,23} Until these studies demonstrate improved local control and survival, the standard of care for anal cancer is chemoradiation with 5-FU and MMC.^{21,22,24}

FOLLOW-UP AND ASSESSMENT FOR TREATMENT FAILURE

Surveillance regimens after combined chemoradiation therapies are not standardized, and controversies exist regarding evaluation for recurrent disease.²⁵ It is well known that anal cancers continue to regress well after treatment with chemoradiotherapy (CRT) has concluded, but the exact timing of maximal tumor regression is unclear.^{1,25} Studies have demonstrated that up to 12 weeks are needed to see complete clinical response in the majority of patients,^{18,26} and it is this initial response that has been shown to be an independent factor in overall survival.²⁶ Most clinicians recommend routine follow-up to include history and physical exam, including digital rectal exam, anoscopy, and inguinal exam, every 3 to 6 months. CT scans are commonly performed as well; however, no consensus exists for timing of these follow-up studies. Routine biopsy is controversial, with some clinicians advocating multiple random biopsies every 3 months, whereas others biopsy only clinically suspicious lesions.^{1,18,25-28} Whichever technique is used, it is imperative to take multiple biopsies to avoid missing a recurrence due to a sampling error. Biopsy of any new or persistent inguinal lymphadenopathy is also essential.

Endorectal ultrasound (ERUS) has emerged as a surveillance tool, with some centers including this modality in their routine treatment follow-up.^{1,18} The

benefit of ERUS is that it will allow visualization and biopsy guidance for perirectal lymphadenopathy in addition to evaluation of the primary lesion; however, some may not be amenable to ultrasound due to ulceration, pain, or location of tumor outside the anal canal.

Anal cancer is a locoregional disease, with only a small percentage of patients presenting with metastatic disease.^{2,15,26,28} Failure of treatment is primarily locoregional as well. Risk factors for failure include inability to tolerate complete treatment, which occurs more in certain populations such as the elderly and immunocompromised patients. Gaps in treatment due to toxicity lead to decreased effective radiation dose distribution, with resultant worse local control and worse overall survival.^{9,18,29} The reduction or elimination of a chemotherapeutic agent has also been associated with treatment failure.^{17,18} Tumor size at time of presentation has also been associated with locoregional failure.^{26,28,30}

SURGICAL TREATMENTS

Up to 30 to 40% of patients will have local treatment failure, defined as persistent (within 6 months of treatment) or recurrent (greater than 6 months posttreatment) disease. Approximately half of treatment failures will be persistent and half recurrent.^{6,27,31} Surgical salvage with radical resection, which prior to Nigro was the primary treatment for anal cancer, is now the standard of care for locoregional failure after CRT.^{1,6,27,30,31} Outcomes for surgical salvage with abdominoperineal resection vary widely, with the 5-year survival rate ranging anywhere from 24 to 58%.^{1,27,30-32} Proper patient selection for surgical salvage is imperative, and only half of patients who have locoregional failure will be candidates for abdominoperineal resection (APR).²⁸ Extensive preoperative evaluation should be performed including CT or magnetic resonance imaging (MRI) to rule out metastatic disease or pelvic sidewall invasion. Sidewall invasion precluding complete resection is a contraindication to surgical salvage. In the largest series to date, Akbari et al found that no patients who had positive margins after APR survived past 2 years, a result that was similar to those not undergoing surgery.³⁰ Adjacent organ involvement is not a contraindication to surgery provided that a negative margin can be obtained; however, these patients had a worse 5-year survival rate than those with smaller and less-invasive tumors.³⁰ Patients who are considered to have curable disease at the time of surgery had a 40% 5-year survival rate in that study. Other risk factors for failure of surgical salvage include the presence of persistent rather than recurrent disease,^{30,31} inguinal adenopathy at presentation,²⁷ and less than 55 Gy of radiation administered.²⁷

The major complication after salvage surgery is perineal wound breakdown, which occurs in 35 to 80% of patients, with up to 66% demonstrating delayed

Figure 4 Local recurrence in the perineum of a woman who had undergone rectus abdominis myocutaneous flap reconstruction of her perineal wound.

healing of greater than 3 months.^{1,27,29–31} All of these patients have undergone prior radiation therapy, which is a known risk factor for wound complication. In addition, a wide resection of any remaining gross perineal disease is necessary to ensure a negative margin. The use of gracilis or rectus abdominis myocutaneous flaps has been advocated for perineal reconstruction. Rates of wound complications with these techniques range from 0 to 100%.^{6,27,31} In a study by Papaconstantinou et al, all patients undergoing flap reconstruction developed a wound complication; however, all of these occurred in patients with an extensive perineal resection, and all were able to be managed nonoperatively.³¹ Figure 4 demonstrates a local recurrence of squamous cell carcinoma in a patient who had undergone rectus abdominis flap reconstruction of her perineal wound.

TREATMENT OF INGUINAL LYMPH NODE METASTASES

Inguinal lymph node metastases occur in 10 to 25% of patients and are typically unilateral.^{2,19,33} The rate of synchronous metastasis is ~13%.³³ Prior to the introduction of primary chemoradiotherapy, treatment of involved inguinal nodes consisted of radical inguinal node dissection, which included both the deep and superficial inguinal nodes, as well as the iliac and obturator nodes.³⁴ Complications associated with groin lymph node dissection included lymphocele, seroma, hematoma, wound infection or dehiscence, and lymphedema.³⁴ Poor outcomes, high morbidity, and the advent of chemoradiation for the primary tumor have led to a similar shift in treatment for lymph node disease. Many centers, including our own, will now prophylactically include the bilateral inguinal regions in the radiation field.^{1,2,19,33} The use of sentinel inguinal lymph node biopsy and selective inguinal radiation has been studied

in epidermoid anal cancers, but has not been widely adopted.¹⁹ The use of inguinal lymph node dissection is currently reserved to reduce complications of large, growing tumors or to treat clinically evident disease after radiation treatment.^{1,34} One author suggests that the poor outcomes of patients with epidermoid anal cancer and lymph node metastases should lead clinicians to enroll them in clinical trials whenever possible to determine optimal treatment.³⁴

CHEMOTHERAPY FOR SALVAGE AND METASTASES

Surgical treatment has been advocated by most studies for the treatment of locoregional failure; however, a few studies have evaluated the use of salvage chemoradiation. A phase III trial evaluated the role of cisplatin and 5-FU based chemotherapy plus an additional 9 Gy of radiation and found that 50% of patients were able to be salvaged with this regimen.¹⁷ Despite the encouraging results of this trial, most clinicians do not advocate additional chemoradiation in those patients who are candidates for surgical salvage.

Metastatic disease is seen in 6 to 10% of patients at presentation.^{2,26} The risk for subsequent development of metastatic disease is independently associated with the ability to maintain locoregional control.²⁶ Combined chemotherapeutic regimens have been advocated in the treatment of metastatic disease; however, these treatments have not been standardized.²⁵ Cisplatin-based treatments are commonly utilized in these patients.

SPECIAL POPULATIONS

Two important subgroups merit discussion: the elderly and HIV patients. Elderly patients (>70 years) are commonly excluded from clinical trials. In retrospective reviews, elderly patients tend to have a high rate of locoregional failure. This may be due to decreases in treatment doses of chemotherapy or radiation, either secondary to toxicity or prophylactically to prevent toxicity. The elimination of MMC is common in elderly patients to reduce hematologic toxicity; however, studies have clearly demonstrated poorer outcomes with single agent chemotherapy.¹⁷ There have been studies demonstrating that elderly patients may be able to tolerate standard CRT doses,⁴ which suggests that treatment should be tailored toward the individual patient's status. Surgery as primary treatment may be considered for those who are unable to tolerate or complete CRT, provided their medical comorbidities can be optimized.²⁹

Patients with HIV are at increased risk of developing anal epidermoid cancer, with up to 120 times the risk of the HIV-negative population. Human papillomavirus (HPV) coinfection and immunosuppression have

been implicated in this increased risk.^{35,36} HIV-positive patients have a 7-fold increased risk of persistent HPV infection, and high-risk HPV has been clearly demonstrated in up to 100% of anal cancers.³⁵ The development of highly active antiretroviral therapy (HAART) has not decreased the incidence of anal cancer; on the contrary, HAART has been shown to have no effect on HPV diseases. With patients living longer, the risk of anal cancer is actually increasing in this population.^{9,35,36} Preventive and screening measures, such as the HPV vaccine, anal pap smear, and high-resolution anoscopy are currently being evaluated to prevent and treat early HPV disease. Diagnosis of anal cancer occurs an average of 6 to 12 years after initial HIV diagnosis.^{9,35} The demographics of the HIV-positive population are distinctly different from those of the HIV-negative population. Whereas the HIV-negative patients with anal cancer tend to be older women, the HIV-positive patients are younger men.^{9,35,36}

Prior to the introduction of HAART in 1996, HIV-positive patients fared poorly with treatment for anal cancer. Recent studies now demonstrate that HIV patients on HAART have similar tolerance to treatment and survival.^{4,9,35-38} Patients on HAART tend to have higher CD 4 counts and tolerate treatment better than those not on HAART, leading some to recommend initiation of HAART prior to anal cancer treatment.³⁸

Initial locoregional control rates in patients with HIV are comparable to rates in patients without HIV, provided the full treatment of CRT is completed.⁹ However, many patients get less than full treatment due to increased toxicity. Up to 69% of patients have treatment breaks due to skin or hematologic toxicity.^{9,35,36} The use of cisplatin-based treatment reduces these complications in some studies.⁹ The development of a new chemotherapeutic regimen with less toxicity may be of benefit to these patients.

CONCLUSION

Anal epidermoid cancer remains a relatively uncommon disease, but is increasing in incidence. Treatment today consists of combined modality chemotherapy and radiation, which was originally developed over 30 years ago. Surgical salvage is an option for those who initially fail chemoradiation or who develop locoregional recurrence. Treatment for unresectable or metastatic disease has not been standardized, and further study is necessary to find optimal regimens for these patients.

REFERENCES

1. Mahmoud NN, Madoff RD. Investigation and management of malignant anal-canal tumours. In: Beynon J, Carr ND, eds. *Progress in Colorectal Surgery*. New York: Springer-Verlag; 2005:115-134
2. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 1999;85(8):1686-1693
3. Whiteford MH, Stevens KR Jr, Oh S, Deveney KE. The evolving treatment of anal cancer: how are we doing? *Arch Surg* 2001;136(8):886-891
4. Wong S, Gibbs P, Chao M, et al. Carcinoma of the anal canal: a local experience and review of the literature. *ANZ J Surg* 2004;74(7):541-546
5. Lopez MJ, Myerson RJ, Shapiro SJ, et al. Squamous cell carcinoma of the anal canal. *Am J Surg* 1991;162(6):580-584
6. Skibber JM, Eng C. Colon, rectal and anal cancer management. In: Chang AS, Ganz PA, Hayes DF, et al, eds. *Oncology, An Evidence Based Approach*. New York: Springer-Verlag; 2006:704-732
7. Salmon RJ, Fenton J, Asselain B, et al. Treatment of epidermoid anal canal cancer. *Am J Surg* 1984;147(1):43-48
8. Mendenhall WM, Sombeck MD, Speer TW, Marsh RD, Carroll RR, Copeland EM III. Current management of squamous cell carcinoma of the anal canal. *Surg Oncol* 1994; 3(3):135-146
9. Oehler-Jänne C, Huguet F, Provencher S, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. *J Clin Oncol* 2008;26(15):2550-2557
10. Welton ML, Varma MG. Anal cancer. In: Wolff BG, Fleshman JW, Beck DE, et al, eds. *The ASCRS Textbook of Colon and Rectal Surgery*. New York: Springer-Verlag; 2007:482-500
11. Golden GT, Horsley JS III. Surgical management of epidermoid carcinoma of the anus. *Am J Surg* 1976;131(3): 275-280
12. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report 1974. *Dis Colon Rectum* 1993;36:709-711
13. Nigro ND, Vaitkevicius VK, Buroker T, Bradley GT, Considine B. Combined therapy for cancer of the anal canal. *Dis Colon Rectum* 1981;24(2):73-75
14. Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer* 1983;51(10):1826-1829
15. UKCCCR Anal Cancer Trial Working Party. UK Coordinating Committee on Cancer Research. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet* 1996;348(9034):1049-1054
16. Bartelink H, Roelofs 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
17. 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

18. Grabenbauer GG, Kessler H, Matzel KE, Sauer R, Hohenberger W, Schneider IHF. Tumor site predicts outcome after radiochemotherapy in squamous-cell carcinoma of the anal region: long-term results of 101 patients. *Dis Colon Rectum* 2005;48(9):1742-1751
19. Gretscher S, Warnick P, Bembenek A, et al. Lymphatic mapping and sentinel lymph node biopsy in epidermoid carcinoma of the anal canal. *Eur J Surg Oncol* 2008;34(8): 890-894
20. Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. *J Clin Oncol* 2007;25(29):4581-4586
21. 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
22. Glynne-Jones R, Meadows H, Wan S, et al; National Cancer Research Institute Anal Sub Group and Colorectal Clinical Oncology Group. EXTRA—a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. *Int J Radiat Oncol Biol Phys* 2008;72(1):119-126
23. James R, Meadows H, Wan S. ACT II: the second UK phase III anal cancer trial. *Clin Oncol (Royal College of Radiologists) Editorial* 2005;17:364-366
24. Glynne-Jones R, Mawdsley S. Anal cancer: the end of the road for neoadjuvant chemoradiotherapy? *J Clin Oncol* 2008; 26(22):3669-3671
25. Fleshner PR, Chalasani S, Chang GJ, Levien DH, Hyman NH, Buie W; DStandards Practice Task Force, American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. *Dis Colon Rectum* 2008;51(1): 2-9
26. Deniaud-Alexandre E, Touboul E, Tiet E, et al. Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. *Int J Radiat Oncol Biol Phys* 2003;56(5): 1259-1273
27. 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
28. Roohipour R, Patil S, Goodman KA, et al. Squamous-cell carcinoma of the anal canal: predictors of treatment outcome. *Dis Colon Rectum* 2008;51(2):147-153
29. Renehan AG, Saunders MP, Schofield PF, O'Dwyer ST. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. *Br J Surg* 2005;92(5): 605-614
30. Akbari RP, Paty PB, Guillem JG, et al. Oncologic outcomes of salvage surgery for epidermoid carcinoma of the anus initially managed with combined modality therapy. *Dis Colon Rectum* 2004;47(7):1136-1144
31. Papaconstantinou HT, Bullard KM, Rothenberger DA, Madoff RD. Salvage abdominoperineal resection after failed Nigro protocol: modest success, major morbidity. *Colorectal Dis* 2006;8(2):124-129
32. Nilsson PJ, Svensson C, Goldman S, Ljungqvist O, Glimelius B. Epidermoid anal cancer: a review of a population-based series of 308 consecutive patients treated according to prospective protocols. *Int J Radiat Oncol Biol Phys* 2005; 61(1):92-102
33. Gerard JP, Chapet O, Samiei F, et al. Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. *Cancer* 2001; 92(1):77-84
34. Swan MC, Furniss D, Cassell OCS. Surgical management of metastatic inguinal lymphadenopathy. *BMJ* 2004;329(7477): 1272-1276
35. Wexler A, Berson AM, Goldstone SE, et al. Invasive anal squamous-cell carcinoma in the HIV-positive patient: outcome in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2008;51(1):73-81
36. Blazy A, Hennequin C, Gornet JM, et al. Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2005;48(6):1176-1181
37. Place RJ, Gregorcyk SG, Huber PJ, Simmang CL. Outcome analysis of HIV-positive patients with anal squamous cell carcinoma. *Dis Colon Rectum* 2001;44(4): 506-512
38. Stadler RF, Gregorcyk SG, Euhus DM, Place RJ, Huber PJ, Simmang CL. Outcome of HIV-infected patients with invasive squamous-cell carcinoma of the anal canal in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2004;47(8):1305-1309