

## Anal Carcinoma

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**Abstract:** Anal carcinoma accounts for less than 2% of all gastrointestinal malignancies. The incidence of anal cancer is increasing and may be associated with an increase in anal receptive intercourse or higher number of sexual partners. Such behaviors have also increased the risk of infection with both HIV and human papilloma virus (HPV). HPV appears to induce dysplasia in the anal mucosa, which is readily detectable and treatable.

The strong association of HPV has even spurred research into primary prevention in high-risk patients. Models suggest that screening in the highest risk patients would not only confer a survival benefit but also be cost effective. While the overall prognosis is only a 55% survival at 5 years, survival for localized disease remains near 80%. Traditional staging by cross-sectional imaging may be giving way to endorectal ultrasound and sentinel node biopsy. The standard of care for anal canal carcinoma is now combined modality therapy (CMT) with chemoradiation therapy obtaining excellent oncologic results as well as organ preservation. Advances in intensity modulated radiation therapy (IMRT) and brachytherapy have significantly decreased toxicity. Surgery improves survival in patients with persistent or residual disease. Within the next decade, anal cancer may emerge as a preventable form of cancer.

### INTRODUCTION

According to National Cancer Institute estimates, 5070 new cases of anal carcinoma will be diagnosed in 2008 with 640 deaths [1]. Although malignancies of the anus are a histologically varied group including squamous cell (epidermoid) cancers as well as adenocarcinomas and melanomas, this article will limit discussion to the most common histotype, squamous cell neoplasia.

These neoplasms should be classified into either anal margin or anal canal tumors. The pathogenesis of squamous cell cancer in both locations appears related to chronic inflammation secondary to HPV, analogous to cervical carcinoma. The important distinction, though not perfectly dichotomous, addresses differences in biology, natural history and treatment.

Much as colon cancer can be detected at dysplastic stages, anal carcinoma may become a preventable disease. Well-established risk factor control and vaccines may prove effective primary prevention against dysplasia. Secondary prevention, or the treatment at the dysplastic level, would require an annual anoscopy and an anal pap smear for high-risk patients. Sadly, only half of anal cancers are diagnosed with localized disease [2]. Treatment of advanced disease is less successful and imposes greater cost on both the patient and society, despite significant advances in the last few decades.

Combined modality therapy to include chemoradiation as well as surgery for salvage has greatly improved rates of organ preservation, patient quality of life and survival. Initially pioneered by Nigro *et al.* [3], induction chemotherapy with concurrent radiation has reduced colostomy rates to between 20% and 30%. Patients can be treated using chemoradiation with curative intent, while those requiring subsequent surgery may find available the option of sphincter-sparing surgery.

### ANATOMY

Differentiating anal canal and anal margin cancer remains a simple matter of physical exam. The border separating these is the junction of the fully keratinized, potentially hair-bearing perianal skin with the glabrous mucosa internally known as the anal verge. The change can be both felt and seen, though large tumors may arise near the border or grow across the anal verge, making clear distinctions difficult.

The proximal boundary of the anal canal may be defined in two ways. Histologically, the mucosa of the anal canal distal and proximal to the dentate line differs significantly. The predominantly squamous epithelium distal to the dentate line transitions to the glandular intestinal epithelium proximally. The innervation and lymphatic drainage of these two areas differ as well. Functionally and surgically however, the boundary of the anal canal is the pelvic floor musculature. Below the levator ani muscles lay the anal sphincters and tumor at this location compromises sphincter function. Conversely, adenocarcinomas of the anus, regardless of location, behave as rectal cancers and should be treated as such [4]. While squamous epithelium and hence squamous tumors may be found proximal to the dentate line, tumor behavior is similar to those distal to the dentate line. The dentate line

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being a histological transition zone may be 10-15mm in length, thus adding variation to what may be classified as anal or rectal tumors.

The superficial and deep inguinal nodes drain tumors distal to the dentate line, while the iliac, para-aortic and paravertebral basins drain more proximal tumors. Tumors of the anal margin tend to invade directly, more so than canal tumors that may present with lymphatic spread in 15-25% of patients. In addition to involving sphincter muscles, anal canal cancers are more likely to involve pelvic organs, including the bladder, than tumors at the margin. Again sufficient variation exists in both the definitions of these zones and tumor behavior. All nodal regions should be fully assessed for both anal margin and anal canal carcinomas.

## EPIDEMIOLOGY

In the general population, anal carcinoma is an uncommon neoplasm. Recent SEER data from 2001 to 2005, shows a broader peak in incidence at a younger age of 45-64 than previously reported 58-64 [3]. Whether this is from a true shift in the population affected or merely earlier diagnosis due to increased awareness and screening is unknown. This may also reflect the rapid increase in the absolute numbers of this disease. While the incidence in the general population has remained steady at approximately 1 case per 100,000, the incidence in homosexual men has more than doubled from 8.6 cases per 100,000 in 1984 to 1990 to 20.6 cases per 100,000 in 1996 to 1999 [5, 6]. The lag between HIV & HPV infections and tumorigenesis is unknown and we may only now be seeing the effects of the initial surge of HIV infections in the 1980's. Conversely, antiretroviral therapies controlling HIV disease may be increasing the latency of disease presentation and the prevalence of this disease may continue to soar.

## HPV

There exists a strong causative role of HPV infection in the pathogenesis of anal carcinoma. Similar to carcinoma of the cervix, viral DNA is found in 60-80% of specimens of anal tumors. More oncogenic strains such as HPV 16 are more prevalent in anal cancer than HPV 18 & 33, which are more common among cervical malignancies. In anal cancer, these variants are frequently found as co-infections. Chronic inflammation resulting from chronic infection remains the putative mechanism for tumorigenesis. The development of HPV-related benign disease does not influence rates of malignancy. Condyloma acuminatum are common in patients with HPV infection, however, these cannot be considered pre-malignant lesions. When looking at all patients treated for condyloma, only 0.75 - 9% of specimens contained dysplasia or carcinoma [7, 8]. These lesions serve as a marker of HPV disease in the perianal skin and anal mucosa.

## IMMUNE DYSFUNCTION

The population with compromised immunity suffers a disproportionately high rate of anal malignancy. The incidence of anal carcinoma is much higher in the AIDS and organ transplant populations. The mechanism may include impaired innate cancer surveillance or alternatively an inability

to adequately suppress HPV-related disease and the accompanying chronic inflammation.

For patients infected with HIV, highly-active or combination anti-retroviral therapy (HAART / cART) does not appear to decrease the rates of malignancy. In a study tracking patients before and after HAART initiation, equal numbers developed new dysplastic anal lesions (7 of 38 patients) as regressed (8 of 38 patients) [9]. An even smaller number with existing dysplasia progressed to high-grade dysplasia or carcinoma in situ. Both these groups experience higher rates of other malignancies, and indeed squamous cell skin cancers are the most common malignancy in kidney transplant recipients.

## SMOKING TOBACCO

The carcinogenic effects of inhaled tobacco on distant organs are less well recognized than in aerodigestive malignancies but are certainly important. These remote effects have been seen in colon and renal cell carcinoma, among others. Population-based studies have helped elucidate the relation between cigarette smoking and anal carcinoma. Not only did a study show an odds ratio of 3.0 for women and 5.0 for men but this risk was attenuated by smoking cessation [10]. A more recent study by the same group further supported this risk for both genders [11]. Tobacco cessation counseling should become an important part of treating high-risk populations for anal malignancy.

## Pathophysiology & Genetics

Unlike colon cancer, a stepwise progression of genetic mutational events has not been discovered to explain anal carcinoma. The mutagenic activity of HPV likely includes a variety of mechanisms. DNA methylation and subsequent loss of function in tumor suppressor genes has been observed [12]. A cell adhesion molecule, IGSF4, and a positive mediator of gamma-interferon induced programmed cell death, DAPK1, are only a few of the gene products affected by HPV induced methylation. Clinically, these hypermethylated gene sequences were present in 75% of SCCa of the anus and 60-70% of High-grade Squamous Intra-epithelial Lesions (HSIL), while being absent in low-grade lesions and benign biopsies. Increased expression of oncogenes found in dysplastic specimens includes p53 messenger RNA, a transformation commonly found in most human malignancies. p53 expression was inversely correlated with disease free survival at 5 years in a multivariate analysis controlling for tumor size and stage ( $p=0.01$ ) [13]. Genetic studies will continue to provide additional information on the tumorigenesis and prognosis.

## Pathology

The definitive diagnosis of cancer always rests on histology, but the least invasive way of diagnosis is by anal cytology. Both techniques are important in the diagnosis of anal malignancy. Similar to a cervical exam, an exam of the anal mucosa with swabs and cytological brushings can obtain atypical or frankly neoplastic cells for diagnosis. Pathologists use the 2001 Bethesda Criteria to define adequate samples and their findings [14]. Originally applied to cervical cytology, this system has been accepted for use in anal

squamous dysplasia. Possible cytology results are 1) inadequate sample, 2) Atypical Squamous Cells of Unknown Significance (ASCUS), 3) Low-Grade Intraepithelial Lesion (LGSIL), 4) Hi-Grade Intraepithelial Lesion (HGSIL). Histology was previously graded as Anal Intraepithelial Neoplasia (AIN) I-III, but updated terminology classifies dysplasia as Low-grade AIN (AIN I) and High Grade AIN (AIN II & III).

Squamous cell carcinomas of the anus have many subtypes. Transitional cell carcinoma, large cell carcinoma, mucocoidermod carcinoma, and cloacogenic carcinoma have a similar natural history and patterns of spread as well as prognosis [15]. Basaloid cancers comprise nearly 10% of squamous malignancies. These tumors have a mixed squamous and adenomatous appearance but are more aggressive, much like small cell carcinoma of the lung [16]. However, the inter-observer reliability in diagnosing these subtypes is low [17] Staging and therapeutic decisions do not rely on these histologic subtypes.

### Prevention

Primary prevention refers to control of risk factors prior to the presentation of disease. The single greatest risk factor for anal carcinoma is HPV infection, which is not curable but is preventable. While safe, protected sexual contact is the best way to prevent HPV transmission, the development of Gardasil (Merck) offers a vaccine for the most oncogenic strains of HPV 6, 11, 16, and 18. The vaccine must be given prior to infection and as a result requires significant screening and counseling of high-risk patients. HPV vaccines are projected to reduce the incidence of cervical cancer by up to 70% among vaccinated women by preventing HPV infection [18]. Gardasil has not been studied and is not approved for HPV prevention in males. However, Merck is currently studying their vaccine in homosexual men. Phase I trials to establish safety of the vaccine in homosexual men are in progress through the National Cancer Institute. The current study is enrolling homosexual men regardless of current HPV status, looking at post-vaccination virus-like particle (VLP) serology and anal pap smear HPV DNA as primary end points. There is also a larger trial looking at HPV negative homosexual men.

In addition to primary prevention using vaccines, secondary prevention involves the early detection of disease. For secondary screening to be effective, the disease must be prevalent, and have an easily performed and sensitive diagnostic test. Furthermore, screening has little value unless treatment is both available and effective. In the HIV population, HPV prevalence runs 54-98%, and HPV-related lesions are easily treated either by local excision or fulguration [19, 20]. There are currently no guidelines for screening, however HIV positive patients or those with anal warts or HPV-related lesions would likely benefit from such screening. Screening using cytology is less invasive in asymptomatic patients without lesions while formal tissue biopsy of visible lesions proves more accurate.

Cytology has the advantage of causing the least trauma, most easily collectible, even by non-physician health care providers, and technologically inexpensive. While the quality of the cytology specimen can be variable, an adequate

specimen is procured greater than 95% of the time [21, 22]. In a randomized study looking at the quality of specimens collected by patients themselves against those collected by physicians, 83% of self collected anal cytology specimens were adequate compared to 92% of physician swabs [23]. Though there was a statistically significant difference, patient collected specimens were useful and would likely facilitate repeat collections.

In a study using cytology positive patients for biopsy, the positive predictive value of any abnormality was 95.7% but was only 55.9% for high grade dysplasia [24]. Studies with comparison to histology have shown sensitivity to range from 69-98% [25]. The largest study of nearly 3000 specimens noted a sensitivity of 69% in HIV positive men. Sensitivity improved to 81% with repeat brushings [26]. Internal anal canal mucosal lesions may be more amenable to detection by brush cytology than external lesions, raising the sensitivity for non-keratinized lesions [27]. The use of cytology to rule-out disease is limited by the inconsistent specificity ranging from 50-100% in these same studies. Studies that show high sensitivity conclude that anal cytology greatly underestimated the severity of disease. Several studies all found that nearly 50% of cytology specimens, which were reported as LGSIL, actually were high-grade lesions on histology [24-26].

While cytology is an inexpensive means of diagnosing a suspicious lesion, it is not sufficient to clear patients from suspicion of cancer. Negative cytology results for suspicious lesions should be followed by a formal tissue biopsy. Patients without lesions and normal cytology need to be followed and cytology repeated over time.

Two studies have used modeling to compare societal cost and benefit. The study by Goldie *et al.* found annual screening with cytology to be cost-effective in American homosexual and bisexual men [28]. Another similarly done study from the UK found contrary results [29]. The primary differences between the studies include the higher estimated incidence for the US, and the significantly higher estimated individual value to additional years of life saved. The UK study also estimated a low rate of progression from high grade AIN to invasive carcinoma and a shorter life-expectancy of the patient. The contrary results arise from different populations and different projections of the course of disease. When comparing the use of annual anal cytology screening for homosexual or HIV positive men to cervical cancer screening, the former would seem at least as cost-effective as the latter. Sensitivity and specificity of anal cytology for malignancy is similar to cervical pap smears, 60-80% [30]. In HIV positive homosexual men, the prevalence of anal cancer exceeds the prevalence of cervical cancer [31]. Given the population data and similarities to cervical cancer, intuitively anal cancer screening by cytology should be cost-effective.

High-Resolution Anoscopy (HRA) provides a more thorough exam of the anal canal than the naked eye [32]. Acetic acid aides in visualizing mucosal lesions for directed biopsies. Lesions suspicious on HRA correlate well with pathologic findings of dysplasia [30, 33, 34]. This technique has excellent sensitivity but a high number of false positive re-

sults. Many of the aceto-whitening lesions seen on HRA are benign [22, 35]. This technique requires special training and a learning curve [31, 36, 37]. Even with significant training while sensitivity for abnormal mucosa remains high, the ability to distinguish high and low grade lesions on HRA is poor [22]. HRA can be used effectively for office-based directed therapy at HPV related lesions or dysplastic lesions.

### Diagnosis

The most common presenting complaints for patients with anal malignancy mirror those of benign disease. Pain, bleeding and pruritis drive patients to seek medical attention. Twenty percent of patients are asymptomatic at presentation and bleeding is the most common presenting symptom. These statements, however, are based on review articles from 1976 and the early 1980's [38-42]. Given the dramatic differences in patient demographics and delivery of health care, new data are necessary to facilitate clinical diagnosis. Physical exam of the perianal skin and gentle anoscopy should readily reveal a clinical diagnosis. Because anal cancer presents as local / regional disease in 80% of cases, lesions may not be subtle but may be mistaken for hemorrhoids or other benign pathology. Malignancy may present with complications suggestive of benign disease, resulting in a higher risk of cancer diagnosis within one year of a benign diagnosis. Benign perianal and anal disease is much more common and therefore a high index of suspicion is required to make the diagnosis of cancer.

### Staging

Patients will most often present with symptoms from their primary tumor and accurate staging is vital. Fig. (1) shows the stage distribution at presentation with accompanying 5 yr survival. Notable is the stark drop off between regional / nodal disease and metastatic disease survival. The American Joint Committee on Cancer (AJCC) system relies on clinical observation. The primary tumor is staged based on its greatest dimension. Invasion into adjacent organs, not including the anal sphincters defines a T4 lesion. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) provide reliable information about local extent of disease, nodal involvement, and distant metastasis [43, 44]. Endoscopic Ultrasound (EUS) correlates well with clinical tumor staging before and after chemoradiation therapy and also to delineate recurrence [45]. Software to create multiplanar 3D images from 2D EUS may increase the accuracy of staging. A 2004 study in 30 patients found 3D EUS images were better able to characterize the lateral margins of the primary tumor [46]. Histologic type and differentiation do not significantly impact survival [47, 48].

Fig. (1). 5 Year Survival by Stage at Presentation

Stage	5 Year Survival
Local	80.6%
Regional	61.1%
Distant Metastasis	20.9
Unstaged	56.6%

Ries LAG. SEER Cancer Statistics Review, 1975-2005.

Tumors greater than 5 cm or invading into surrounding structures (T3/4) are nearly three-times as likely to have nodal disease (16% v. 6%) [49, 50]. Nodal staging may be based on clinically palpable superficial inguinal nodes or imaging. Approximately 15-25% of nodal disease is superficial inguinal lymph nodes [51]. Palpable nodes provide not only prognostic information but also change treatment. By contrast, mesenteric and iliac nodes discovered by imaging are automatically included in the radiation field and do not change treatment. The presence of deep nodal involvement alters prognosis. Nodal staging should be assessed by imaging studies. The flaw in imaging is that 44% of nodal metastasis is smaller than 5mm and difficult to detect with the most sophisticated imaging modalities, including MRI [52]. External sonography of the groins has not been shown to be more accurate than clinical exam [53]. Current World Health Organization (WHO) guidelines recommend the use of EUS in nodal staging [54]. EUS is excellent for the detection of deep nodal metastasis. 3-dimensional and multiplanar EUS further enhances diagnostic accuracy [55]. Positron Emission Tomography combined with CT (PET-CT) detects tumor through hypermetabolism of radiolabeled glucose and localizes to structures on cross-sectional imaging. PET-CT is highly sensitive for distant disease, resulting in upstaging and changes in the course of therapy [55]. In a recent study of anal margin and canal cancers, PET-CT revealed 29% of patients to have metastasis to the groins while conventional CT only detected 16% of positive inguinal nodes [56]. Despite best efforts, nodal staging by imaging is inherently imperfect because tissue, if retrieved at all, is only obtained after chemoradiation therapy.

While tissue diagnosis of palpable nodes is easily obtained by fine-needle aspiration or biopsy, sentinel lymph node mapping and biopsy for anal carcinoma has demonstrated a minimally invasive means of obtaining tissue confirmation of nodal status prior to initiation of therapy. The combined use of radioisotope and blue dye results in consistent yields of 90-100% [57, 58]. When only one modality is employed, sentinel node yield may drop to 76%. With the ability to detect non-palpable disease too small to detect by imaging raises the question of treatment and prognostic significance of the histologically positive sentinel lymph node and basin.

### Treatment of Dysplasia

Anal canal dysplasia can be detected in the office. Studies attempting office-based management have confirmed good results. In immunocompetent, HIV negative patients, needle-tip fulguration and close follow up was successful in the office, with no LSIL lesions found at 10 years after treatment [59]. While 45% of HSIL patients required planned repeat procedures because of circumferential extent of disease, only 1 of 33 patients progressed to in situ carcinoma, which was diagnosed during surveillance. Low rates of progression and recurrence in HIV negative patients with office therapy have been duplicated in prospective studies [60]. In HIV negative patients, one-time treatment with infrared coagulation resulted in cure at median follow up of 516 days. For those not cured with initial treatment, two-thirds required a second treatment for cure while the remaining one-third required a third session. All patients were even-

tually cured and none progressed to invasive cancer [61]. This same study noted HIV positive patients to have a 2 fold rate of persistence and 1.7 fold rate of developing a recurrent lesion. The largest series of 246 patients followed over 10 years showed a low 1.2% rate of progression to invasive cancer. Only 36 (14.6%) required surgery, either initially or after failure of in-office therapy. Seventy eight percent of patients had no HSIL on follow up HRA and only 7 patients suffered surgical complications including bleeding requiring reoperation in one, anal stenosis in two, anal fissures in four [62]. Office-based fulguration or infrared coagulation therapy of dysplasia is not only safe but effective for treating anal dysplasia. Progression to invasive cancer is infrequent and both persistent/recurrent disease, more common in immunocompromised patients, can be effectively treated with repeat procedures in the office. An indication for treatment in the operating room may be extensive, circumferential disease.

### Treatment of Invasive Anal Canal Cancer

Historically, primary surgery for anal canal cancers by abdominoperineal resection (APR) achieved only 40-70% survival rates at 5 years, with local failures from 27-47% [63-65]. Survival greater than 50% was usually only seen with early disease amenable to local excision. Even with current technical advances in surgery, there is a significant 32% morbidity rate including an 18% rate of perineal wound infection [66]. Quality of life for these patients is also permanently altered following APR. The role of primary surgery is now limited to palliation addressing bleeding or fecal obstruction, as primary chemoradiation or Combined Modality Therapy (CMT) is now the standard of care.

External beam radiation therapy (EBRT) has been used for anal cancer since 1920's. Improved technology with Cobalt-based machines allowed for higher dosages necessary for better outcomes [67]. With modern technology EBRT alone showed some modest improvement in survival over surgery alone with 70-90% complete response but much smaller cure rates. Even when able to attain 76% disease specific survival rates, only 54% of patients retained a functional anus [68]. This may have been related to the significantly higher dosages being used. These protocols used EBRT for initial doses of 45-50 Gy with a 15-20 Gy local boost after a 2 week recovery period, often followed by 30 Gy of implantable brachytherapy. The dose-response curve was established early, with 50-55 Gy emerging as a therapeutic minimum [69-71]. These early studies from the 1990's are confirmed by a more recent study which revealed higher locoregional failure rates in patients receiving less than 50 Gy [72]. Chemotherapy in combination with EBRT was discovered to have a radio-sensitizing effect, allowing the use of lower doses of radiation with superior outcomes. Surgery for anal canal cancer was used only in the salvage setting. Soon after, Nigro *et al.* published a protocol for curative chemoradiation using 5-fluorouracil, mitomycin C and concurrent EBRT [73, 74]. Radiation therapy for anal cancer delivered 30Gy by external beam to the lower pelvis.

No randomized studies have directly compared the results of primary surgery to chemoradiation therapy. Randomized studies of radiation alone when compared to chemora-

diation therapy in the treatment of this disease favor combined modality therapy. The impressive results of the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study and European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy and Gastrointestinal Cooperative Groups show improved rates of local and regional control as well as colostomy-free survival. The UKCCCR reported nearly 1.5 times the number of treatment failures in the radiation arm compared to the CMT arm (59% v. 36%) [75]. A similar improvement of 18% in locoregional control and 32% increase in colostomy-free survival achieved with CMT compared to radiation alone emerged from a smaller randomized study by the EORTC. When compared to historical outcomes of primary surgery, these patients experienced not only better outcomes, but less morbidity and were able to avoid a permanent colostomy. In these studies 20-40% of CMT patients experience category 3-4 toxicity most commonly hematologic and dermatologic and less frequently gastrointestinal and renal. Current standards based on the Nigro protocol and subsequent studies have established a minimum overall survival at 5 years of 65% to which all newer regimens are compared.

### Innovation and Variation

A recent study looking at induction chemotherapy with cisplatin and then continued cisplatin against mitomycin C with both arms receiving EBRT and 5-FU showed no benefit in overall or disease specific survival at 5 years. While the cisplatin group did have a lower rate of significant hematologic toxicity, patients in this arm required nearly double the rate of colostomies, 19% v 10% [76]. For patients who cannot tolerate mitomycin C therapy, cisplatin may be a good 2<sup>nd</sup> line, accepting the need for more salvage surgery. Preliminary results from an ongoing European trial of combined EBRT, 5-FU, mitomycin C with and without cisplatin show good tolerance but efficacy data is forthcoming [77].

Intensity Modulated Radiation Therapy (IMRT) uses differentially dosed columns of radiation to maximize tumor exposure while minimizing lateral spread to normal tissue. The conformal technology requires sophisticated imaging to mold the radiation patterns to the shape of the tumor. While relatively new to anal carcinoma, IMRT has been well validated for head and neck tumors and gynecologic tumors where vital pelvic structures need to be preserved [78, 79]. In the head and neck, IMRT has shown decreased rates of xerostomia. Uncontrolled trials in anal cancer have shown good oncologic outcomes with favorable toxicity profiles. Without resulting in any breaks in therapy, IMRT was well tolerated resulting in only 38% dermatologic toxicity compared to historic controls (34-78%) [80]. In addition to decreased immediate toxicity to the patient, narrowing the focus of radiation onto the tumor may decrease complications after surgery in patients requiring salvage therapy by limiting the damage to surrounding tissues.

Compared to IMRT, Iridium-192 based brachytherapy has been used in anal cancer longer and is less technology-intensive. Used as an adjunct to EBRT to boost radiation dosage to the tumor without affecting surrounding tissue, brachytherapy limits spread to surrounding tissue and is not used to treat nodal disease [67]. Early studies used 5-20 Gy

implanted seeds after a full 45-50 Gy of EBRT. Five-year overall survival and sphincter preservation was comparable to previous studies, 65% and 61% respectively. Ninety percent of these patients retained normal anal function and only 20% had some degree of tissue necrosis [81, 82]. A study of combination chemoradiation using both EBRT and brachytherapy, reported a 90% complete response for T1 disease and 78% for T2 disease [83]. Despite an overall higher initial response, there was a 22% local failure rate. Forty-eight percent of these patients required salvage surgery. In a report from 2006, local boost by brachytherapy provided excellent local control, 90%, at 5 years. Remarkably, only 3 of 50 patients (6%) suffered complications such as incontinence or sphincter necrosis [84]. Although traditionally brachytherapy catheters have been placed using CT or ultrasound guidance, 3D ultrasound has been used and may provide a more precise disbursement of radiation [85]. As an adjunctive radiation modality, brachytherapy provides excellent results for local tumor control and sphincter sparing with limited toxicity.

### Treatment of Invasive Margin Cancers

Much less common than anal canal tumors, tumors of the anal margin parallel skin cancers in natural history. The current standard of care includes excision with 1 cm margins. Surgery remains the primary therapeutic modality in this neoplasm but radiation may serve as an important adjunct. In one of the larger studies, primary local excision was followed by EBRT in 29 of 45 patients, while only a minority of these patients received chemotherapy. Despite a high 22 of 29 patients with positive margins on resection, they reported 78% 5-year locoregional control [86]. With only 8 patients having failed, there were no statistically significant predictors found, though all patients had local failure and some followed with inguinal nodal disease. While these results are objectively good, local failure in the face of positive margins raises the question of whether these outcomes could be further improved with margin-negative resections. Controversy exists about the prognosis of anal canal compared to anal margin tumors. While Grabenbauer reported less favorable outcomes for anal margin cancers in terms of 5-year OS (75% versus 54%) and cancer-specific colostomy specific survival rates (87% versus 69%), Peiffert asserted that higher rates of failure in anal margin were due to technical failure based on analysis of patterns of recurrence. [86-88]

### Treatment of Nodal Disease

The treatment of nodal disease for both anal margin and canal carcinomas is controversial and institution-dependent. There is a consensus that the 15% major medical and surgical morbidity that accompanies an elective lymph node dissection is unacceptably high [57]. Injuries to soft tissue and the risk of neurogenic bladder are only a few of the major morbidities. Treatment of clinically positive groins continues to be irradiation. In a groin without palpable adenopathy, PET-CT or other imaging may reveal subclinical metastasis eligible for therapy. In the absence of any clinical or imaging evidence of inguinal nodal involvement, some advocate routine prophylactic inguinal irradiation. In canal carcinomas, only 7.4-7.8% of patients with clinically negative nodes will go on to develop inguinal metastases if not radiated [57,72].

Sentinel lymph node biopsy (SLNB) has been used to target radiation therapy. After 18 months of followup, Bobin *et al.* reported that none of the 44 patients who had benign inguinal SLNBs developed inguinal metastasis despite withholding prophylactic radiation [58]. A more recent study showed that inguinal nodes were the sentinel nodes for anal canal neoplasms in only 50% of patients while the remainder had lymphatic drainage map to deeper pelvic nodes. Patients with lymphatic spread to these basins would not likely benefit from inguinal irradiation. Only 6 of 20 nodes were positive for malignancy resulting in 4 of 7 patients with T1 tumors receiving treatment that otherwise would not have. By contrast 6 of 10 patients with T2 tumors that would have received radiation were spared because of negative SLNB. None of the patients in whom biopsy changed management experienced a recurrence. In patients where sentinel node mapping was negative, inguinal disease arose in 1 of 16 patients [89]. SLNB may help target low-risk anal canal tumors that will benefit from radiation while sparing others unnecessary morbidity.

Less controversial in anal margin tumors, prophylactic groin irradiation may be of more value because of higher rates of locoregional failure. Six of 9 recurrences occurred in patients who did not receive prophylactic radiation. In another study the only patient to progress with inguinal disease had not received radiotherapy [90, 91]. The higher prevalence of inguinal nodal metastasis in anal margin cancers highlights the anatomical differences and the higher likelihood of deep pelvic metastasis in anal canal neoplasms.

### Salvage Therapy

Salvage therapy is the use of either surgery to eliminate residual disease. Continued response to chemoradiation has been seen up to 9-12 months after initial treatment. Disease presenting more than 6 months from the completion of primary curative therapy is defined as recurrent, while less than 6 months is considered persistent. According to Das *et al.*, T stage and nodal status predict locoregional failure. Node status and basaloid histology predict distant metastasis. HIV status also effects overall survival [92]. Although locoregional failure increases when radiation takes longer than 54 days, there is conflicting data regarding planned breaks in therapy [93, 94].

While very effective, chemoradiotherapy fails in 20-30% of patients. Sixty-75% of these patients are eligible for surgical salvage [92, 95]. Only small studies of this population are available with survival rates varying in the literature between 30-60% at 5 years. Preoperative nodal disease seems to be the strongest predictor of recurrence after salvage [96]. While the main role of surgery is as salvage therapy, it is effective in improving survival for this group of patients.

Patients who are surgically unresectable may have technically unresectable local disease, distant metastasis, or extensive comorbidities preventing salvage surgery. These patients should be considered for salvage chemotherapy.

### CONCLUSION

Anal cancer remains one of the most challenging cancers to treat. A multidisciplinary team including surgical, radia-

tion, and medical oncologists should manage patients with anal cancer. The use of organ-sparing combination of radiotherapy and chemotherapy has significantly improved quality of life and survival in patients.

Combined modality therapy is the treatment of choice in anal cancer, with surgery reserved for persistent or recurrent tumors.

IMRT, which helps to reduce treatment-related toxicity, is currently being investigated with early promising results.

Appropriate cytologic screening of high-risk individuals may decrease the risk of anal cancer.

Under investigation is the development of a vaccine (such as the one for patients at risk with cervical cancer) to help prevent anal cancer.

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