Anal Squamous Cell Carcinoma
A Curable Disease

Squamous cell carcinoma of the anus is the most well known member of an uncommon group of GI neoplasms. The incidence of this tumor has been increasing slowly, with 3,500 cases reported in the United States in 2001, and 5,260 cases reported in 2009.

THE ANAL CANAL
The anus is the most distal end of the colon. The surgical anal canal begins at the anorectal ring, which is the upper end of the puborectalis muscle and internal anal sphincter. It continues to the anal verge. The perianal region, marked by skin with hair bearing appendages, extends 5 cm outward from the anal verge. The proximal anal canal is lined by a columnar epithelium. At the dentate line, located one to two centimeters proximal to the anal verge, the mucosa transitions to a squamous epithelium.

Anal canal malignancies comprise eighty five per cent of all anal cancers. In anal canal cancers, there is a marked female to male preponderance of 5:1. However, in locales with large numbers of high-risk males, the ratio approaches 1:1. Perianal cancers are found almost equally in men and women. Homosexual males have a 10 to 30% higher incidence of cancer in all anal locations when compared with heterosexual males. HIV-positive men are at particularly higher risk.

SIZE MATTERS
Treatment is influenced by the size of the tumor, the depth of invasion, and by nodal involvement. Generally, the area above the dentate line has a lymphatic basin which drains into the superior rectal lymphatics and then to the inferior mesenteric nodes. Additionally, lateral drainage occurs through the middle and inferior lymphatics and the ischioanal fossa into the internal iliac nodes. Distal to the dentate line, drainage is primarily to the inguinal nodes.

Knowledge of the lymphatic drainage is important in guiding therapy of anal cancers to ensure that the nodal basins are included in the treatment. The TNM system used in the staging of squamous cell cancer of the anus places primary importance on tumor size, with T1 tumors measuring less than 2cm in diameter, T2 tumors measuring 2 to 5 cm in diameter, T3 tumors measuring greater than 5 cm in diameter and T4 tumors of any size demonstrating invasion of adjacent structures. Survival statistics and local control are inversely related to tumor size. In patients with synchronous or metachronous nodal involvement, or, in those with distant metastases, five year survival rates diminish dramatically.

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While there exists many associations between anal cancer and a variety of possible causes such as smoking, anoreceptive intercourse and various environmental factors, data points to the human papilloma virus (HPV) as the causative agent, similar to its causation in cervical cancer. Both sexual and non-sexual modes of HPV transmission may occur.

Those at higher risk should be screened. Men with a history of homosexual or bisexual activity and/or anoreceptive intercourse, HIV-positive men and women, and women with cervical or vulvar lesions or carcinoma should be evaluated with physical exams and anal Papanicolaou smears. With 95% accuracy, abnormal Pap smears should prompt a closer evaluation using anoscopy and biopsies of areas targeted by acetic acid staining. Biopsies demonstrating benign anal intraepithelial neoplasia (AIN) are graded as AIN I, II or III, with AIN III requiring treatment.

**PERIANAL DISEASE**

Squamous cell carcinoma of the perianal area does not differ from other skin based squamous cell cancers. The tumor appears as a central ulcer with rolled, everted edges. It may be small, less than 1 cm in size, or large, with obstruction of the anal opening. These tumors are slow growing, often presenting with only local invasion. They are five times rarer than their anal canal counterparts. The sphincters are usually spared. When lymphatic spread occurs, it is commonly to the inguinal and femoral nodes. Males and females are equally affected, with an average age at presentation of between sixty and seventy.

These lesions are often diagnosed up to twenty four months after the first appearance of symptoms, even though a mass, bleeding, pain, discharge or pruritus should have alerted the patient or physician to an abnormality at a much earlier time. Misdiagnosis is frequent, and patients may have been erroneously treated for hemorrhoidal disease or other benign conditions. Diagnostic delay does not seem to worsen the prognosis, underscoring the slow growing nature of these tumors. Treatment is similar to that of the more common anal canal cancers.

**ANAL CANAL DISEASE**

The more common anal canal squamous cell carcinoma is a tumor that has been given many names such as cloacogenic carcinoma, basaloid carcinoma or nonkeratinizing carcinoma. Patients may present with a hard, mobile or fixed mass on digital examination. Symptoms of an anal canal cancer may have been present for months to years before a correct diagnosis is suspected. Bleeding is common, as is anal pain, pruritus, discharge and a mass. Advanced tumors may present with incontinence, an anovaginal fistula, a change in bowel habits or pelvic pain. These symptoms may represent a tumor with sphincter involvement and later stage disease.

A confirmatory biopsy performed through an anoscope or proctoscope is diagnostic. However, an open surgical biopsy may be preferable both for enhanced visualization and patient comfort. The tumor location relative to the dentate line is noted. An endorectal ultrasound may be helpful in evaluating possible nodal disease. CT scanning will also be useful when evaluating the inguinal regions or the pelvis. Definitive biopsy should be performed on suspicious inguinal disease to differentiate nodal carcinoma which needs treatment, from reactive hyperplasia.

As many as 20% of patients have nodal involvement at the time of diagnosis and up to 25% may develop disease at a later time. Lymphatic spread seems to correlate with the size of the tumor, the depth of invasion and the histologic grade of the tumor. In tumors less than 2 cm in size, nodal spread is rare when compared to those malignancies larger than 2 cm, in which spread may be encountered in up to 35% of cases. With smooth muscle involvement, affected nodes may be found in 30% of patients and in 60% in those with tumor spread beyond the external sphincter.

**THIS DISEASE IS CURABLE**

Formerly, surgical excision was the mainstay of treatment for all lesions, with wide local excision (WLE) used for smaller, more superficial lesions, and abdominoperineal resection (APR) used for larger, invasive lesions. Through experience, it has been found that WLE is associated with a high recurrence rate unless reserved for carcinoma in situ or T1 lesions. There must be a 1 cm margin of normal tissue at the excision site and the sphincters must be spared. Superficial tumors treated in this fashion have a 5 year survival rate approaching 100%. In properly selected cases, morbidity is minimal. However, for larger, T2, T3 or T4 lesions, WLE and APR have local recurrence rates as high as 60%, with survival rates decreasing dramatically. Distant metastases are common.

Searching for methods to improve the treatment and survival following an abdominoperineal resection, Norman Nigro, in 1974, began giving preoperative radiation therapy to the tumor, pelvis and inguinal nodes over 15 days, combined with 5-FU and Mitomycin C. He found that there was a complete absence of tumor in many of the surgically resected specimens. Further study led to the present practice of treating all but the most superficial and non-invasive lesions with chemoradiation alone. An Abdominoperineal resection, with a possible radiation boost, is reserved for patients with residual or recurrent disease after the initial chemoradiation.

With chemoradiation, complete responses occur in up to 87% of cases, local control in up to 86%, with five year survival rates between 66 and 92%. In T1 and T2 disease, complete response rates are as high as 90%. Tumors larger than 5cm (T3 and T4) are more problematic, with 50% requiring a salvage APR. However, if patients with these larger tumors are disease free at the conclusion of chemoradiation, only 25% will require a salvage APR.

Currently, in HIV-positive patients with invasive anal cancer and CD4 levels greater than 200/cc, treatment is similar to that in uninfected patients. In those with lower CD4 counts, treatment remains individualized.

With radiation doses greater than 40 Gy, the complication rate increases. Complications may be systemic, such as dermatitis, mucositis, diarrhea and incontinence, fatigue or bone marrow depression. Death is rare. Local complications include cystitis, small bowel obstruction and arterial stenosis. Anorectal function is commonly preserved in up to 90% of patients, but there may be associated anorectal irritability with tenesmus, proctitis, diarrhea, bleeding, urgency or incontinence. Most of these can be controlled with medication, but a proximal ostomy may become necessary. Far from causing further disability, an ostomy may be a welcome relief from symptoms caused by disease treatment.

**THE GOOD NEWS**

Squamous cell carcinoma of the anus is a curable disease when diagnosed and treated early in its course.