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Squamous cell carcinoma of the anal margin

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A B S T R A C T

Squamous cell carcinoma of the anal margin is a rare disease. Accurate clinical staging with physical exam and imaging is important and determines the treatment. Evidence-based management is challenging because there is a paucity of randomized controlled trials and existing literature seldom distinguishes between anal canal and margin tumors. In this article, we review the anatomy, presentation, classification, and clinical management of squamous cell carcinoma of the anal margin.

Introduction

Perianal and anal canal cancers are not common. In 2014, an estimated 7210 new cases of anal cancer will be diagnosed and 950 deaths will be attributed to this diagnosis.[1] Anal cancers comprise 0.4% of all newly diagnosed cancers in the United States.[2] The etiology includes human papilloma virus (HPV) infection, most notably HPV types 16 and 18. Risk factors include immunosuppression, long-term steroid therapy, anal intercourse, history of other HPV infections, and HIV.

Perianal cancers frequently are cited to be one-fifth as common as anal canal cancers, making them unusual and difficult to assess even within a multi-institutional study.[2] In addition, the variability of anatomic definitions of anal canal, perianal, and skin cancers through the years has probably led to misclassifications of perianal cancers and affected inclusion criteria in studies evaluating anal canal cancers.

Among perianal cancers, the most common histology is squamous cell carcinoma. Other anal margin pathologies include Buschke–Lowenstein tumors, basal cell carcinoma, Bowen's and Paget's disease, melanoma, lymphoma, and leiomyosarcoma.

This review concentrates on squamous cell carcinoma of the anal margin, focusing on the anatomy, presentation, workup, staging, and management.

Anatomy

Anal margin cancers, also referred to as perianal cancers, are located within a 5-cm radius of the anal opening.[3] The perianal region overlaps with the vulva in women. As shown in Figure 1, these lesions are easily visible on retraction of the buttocks. Anal canal lesions are not visible or partially visualized with retraction. Lesions identified as skin lesions are located beyond the 5-cm radius. Correct anatomic identification is critical for diagnosis and management of these cancers (Figs. 2 and 3).

Squamous cell carcinomas of the anal margin have varied histologies, including well-differentiated, keratinizing tumors and poorly differentiated tumors, but they exclude melanocytic, hematolymphoid, and neuroendocrine histology.[4] Anal margin cancers are predominantly squamous, well-differentiated and produce keratin.[5] Although histologic subtypes of anal SCC are multiple, they bear no prognostic value.[4]

Presentation and diagnosis

Due to the slow progression of squamous cell carcinoma (SCC) of the anal margin, there is a wide range of symptom duration prior to diagnosis, and often SCC is misdiagnosed initially as a benign lesion such as hemorrhoids.[5] The presenting symptoms include pain, bleeding, discharge, weight loss, or a palpable mass. Not surprisingly, there is often a lag time of several months between presentation and correct diagnosis.

Evaluation of the patient should begin with a focused history and physical exam. History should elicit symptoms, predisposing factors, and relevant medical history. Depending on the history, HIV testing and CD4 count is part of the workup. Physical exam should include digital rectal exam, and vaginal exam in females, as the perianal margin can extend beyond the perineum into the vulva. Palpation of inguinal nodes to determine lymphadenopathy should be performed. Anal margin cancers drain to the superficial inguinal lymph nodes, with metastatic disease dependent on tumor size. T1 tumors, <2 cm, infrequently metastasize, while tumors that are 2–5 cm have a 23% chance of metastasizing, and

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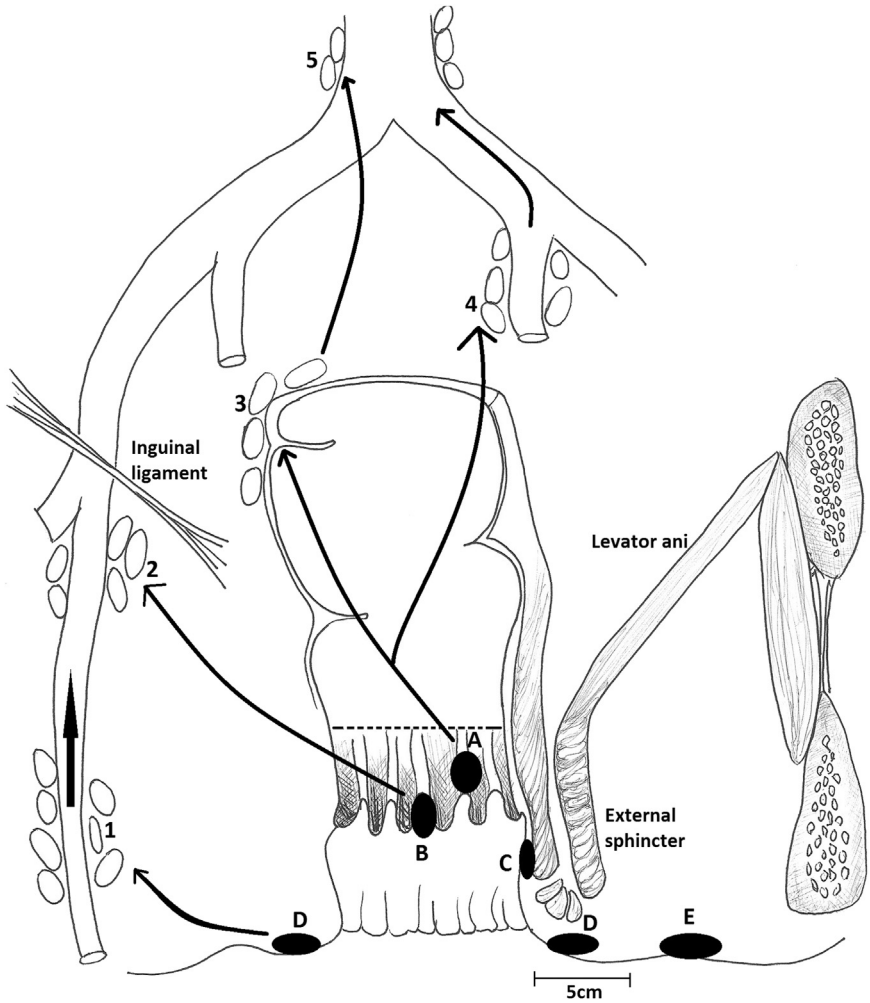

Fig. 1. Squamous cell carcinoma of the anus and corresponding lymphatic drainage. Dashed line denotes the anorectal junction. Anal canal (i.e., intra-anal) is the area that cannot be visualized at all or in entirety when gentle traction is placed on the buttocks (A–C). Anal margin (i.e., perianal) is defined as the region that lies within 5 cm of the anal opening and is visualized with gentle traction on the buttocks (D). Cutaneous skin constitutes the area beyond 5 cm from the anal opening (E). The lymph nodes are superficial inguinal, 1; deep inguinal, 2; perirectal, 3; internal iliac, 4; and para-aortic, 5.

tumors greater than 5 cm have a 67% rate of metastasis.[6] Palpable nodes can be biopsied. Anoscopy and biopsy should be part of the workup, but colonoscopy is not required as synchronous lesions have not been reported.[7]

Metastatic workup should include chest, abdominal, and pelvic contrast-enhanced diagnostic computed tomography (CT) or magnetic resonance imaging (MRI). In a series of 53 patients with anal canal and margin SCC, ^{18}F-labeled fluorodeoxyglucose-positron emission tomography–CT (FDG-PET–CT) was found to be superior to contrast-enhanced CT in detecting the primary tumor (97.9% vs 82.9%, $p = 0.042$). PET can be useful for fine-tuning the extent of the radiation field of the primary and lymph nodes.[8]

Management

Further management is dependent on the clinical stage. It is important to note that in the 7th edition of the American Joint Committee on Cancer staging system, anal margin SCC is classified along with other cutaneous squamous cell cancers.[9] However, the NCCN Clinical Practice Guideline in Oncology (NCCN Guidelines®) for Anal Carcinoma, which acknowledge the distinction of anal margin SCC and cutaneous SCC, apply the AJCC staging for anal canal cancers to perianal cancers.[10] The NCCN Guidelines® advocate for the use of anal canal staging due to the high incidence of concurrent invasion or presence of pre-cancerous lesions in the anal canal.

Due to rarity of the disease, only single-center or small multicenter experiences are available for comparison of treatment algorithms in anal margin cancer. A retrospective review of 26 patients from Lyon demonstrated that SCC of the anal margin, much like cutaneous SCC, is radiosensitive.[11] Radiotherapy (RT) alone compared to RT with surgery offered higher rate of local control in tumors greater than T2 (63.6–100% vs 33%, respectively). In a review of six nonrandomized studies that investigated the results of local excision, abdominoperineal resection, with or without radiotherapy, for superficial T1N0 tumors where adequate margin (>1 cm) could be obtained without sphincter muscle involvement, wide local excision appeared to be a viable option much like the treatment for cutaneous SCC.[12]

Several centers have small series comparing RT with or without chemotherapy. Between 1979 and 2000, 19 patients with T1–T3 anal margin cancer were treated with RT alone (12 patients) or with adjuvant chemotherapy (9 patients) at the University of Florida.[5] Chemotherapy dosing mirrored that for anal canal and included fluorouracil (FU) with mitomycin C (MMC) or cisplatin. Local control was observed in all patients. One patient with T1 disease did not receive elective inguinal node radiation and subsequently developed recurrence in the ipsilateral inguinal node and died with disease. Four patients who received RT only died