Squamous Cell Carcinoma of the Anal Margin

Published on Physicians Practice (http://www.physicianspractice.com)

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Based on our experience and a review of the literature, we conclude that superficial, well- to moderately differentiated T1 cancers of the anal margin may be successfully treated with radiotherapy alone or local.

Introduction

Squamous cell carcinoma of the anal margin or perianal skin is relatively uncommon, and most physicians, even those practicing at large referral centers, encounter very few patients with this entity. The goal of treatment is to cure the patient while preserving anal function, thus avoiding a permanent colostomy. Traditionally, treatment has consisted of either local excision or, in advanced cases, abdominoperineal resection (APR). In recent years, a few centers have reported promising results with radiotherapy alone or combined with concomitant chemotherapy. The purpose of this paper is to review the epidemiology, diagnosis, staging, natural history, and results of treatment for this disease.

Squamous cell carcinoma of the anal margin is defined as a lesion originating between the dentate line and the outer limit of the perianal skin, defined to be 5 cm from the anal verge in any direction.[1-5] These lesions represent only one-fourth to one-third of all squamous cell carcinomas of the anus and should be distinguished from squamous cell carcinoma of the anal canal, which has a different natural history and a less favorable prognosis.[2,4-7]

Diagnosis and Staging

Jensen et al.[6] observed the following symptoms in 76 patients with squamous cell carcinoma of the anal margin treated in Denmark: palpable mass (100%), bleeding (78%), pain (70%), change in bowel habits (29%), discharge (20%), and pruritus ani (20%). The median duration of symptoms was 6 months (range, 2 to 60 months). Associated condylomata and chronic fistulae are observed in approximately 15% of patients.[9] Jensen et al[6] observed that an erroneous diagnosis was made at the first physician visit in 29% of patients with squamous cell carcinoma of the anal margin, as compared with 55% of 125 patients with squamous cell carcinoma of the anal canal. The majority of anal margin tumors tend to be well- or moderately differentiated keratinizing squamous cell carcinomas; less than 10% of lesions are poorly differentiated or cloacogenic carcinomas.[2,9]

Squamous cell carcinoma of the anal margin is staged according to either the American Joint Committee on Cancer (AJCC)[10] or Union Internationale Contre le Cancer (UICC)[11] staging system.[2,12,13] The AJCC staging system for anal margin carcinoma is the same one used for other skin cancers (Table 1) and differs from the staging system used for the anal canal. The AJCC and UICC systems for anal margin carcinoma are virtually identical.[10,11]

Natural History and Spread Patterns

The primary tumor usually starts as a slow-growing nodule that remains localized to the perianal skin until late in the course of the disease, when it may invade the anal canal.[2] The lesion is usually ulcerated and may have a significant palpable subcutaneous component. The sphincter muscle is rarely invaded.[2] The distribution of primary tumor size varies, depending on referral patterns. Pinna Pintor et al[5] found the following UICC[11] T-stage distribution in 83 patients treated at St.
Mark's Hospital for Diseases of the Colon and Rectum in London: stage T1, 14%; stage T2, 50%; stage T3, 32%; and stage T4, 4%.
The medial inguinal nodes are the first-echelon lymph node drainage for the anal margin, whereas the perirectal nodes are the first-echelon drainage for the anal canal. The iliac nodes are also occasionally involved. The incidence of inguinal lymph node involvement is approximately 15% to 25%, and is related to the size and histologic differentiation of the primary tumor.

Cummings et al reported on the relationship between primary tumor diameter and the risk of inguinal lymph node invasion at diagnosis in a series of 29 patients treated at the Princess Margaret Hospital, Toronto. They found inguinal node invasion in 0 of 13 (0%) of patients with tumors less than 5 cm in diameter, as compared with 4 of 16 (25%) of those with tumors 5 cm or more. In 57 patients, Papillon and Chassard documented the following rates of inguinal lymph node involvement, according to primary tumor size: less than 2 cm, 0 of 10 (0%); 2 to 5 cm, 9 of 38 (24%); and 5 cm or more, 6 of 9 (67%).

Distant metastases are rare at presentation.

The pretreatment evaluation of the patient should take into account the spread patterns of the disease and should include a chest roentgenogram and CT scan of the abdomen and pelvis. Computed tomography is obtained to evaluate the presence and extent of lymph node metastases, exclude the unlikely possibility of liver metastases, and complement the physical examination of the primary lesion.

Surgical Management

Early lesions of the anal margin may be successfully treated with local excision; a skin graft may be necessary if the surgical defect cannot be closed primarily or healed by secondary intention. An APR is necessary for resection of more advanced lesions. The inguinal lymph nodes are not dissected unless they are deemed to harbor metastatic disease.

Greenall et al reported on 31 patients treated with local excision alone at Memorial Sloan-Kettering Cancer Center between 1950 and 1978. Local recurrence alone developed in nine patients (29%), one patient had recurrences at both the primary site and the inguinal lymph nodes, and isolated inguinal node metastases developed in three patients. Of the nine patients who experienced a local recurrence alone, eight underwent a second local excision and one required an APR. The 5-year absolute and cause-specific survival rates were 68% and 88%, respectively.

Greenall et al described an additional 11 patients who underwent a primary APR; one patient died postoperatively and two patients died secondary to recurrence. Seven patients (64%) were alive and disease-free 5 years or more after surgery.

At the Cleveland Clinic, 10 patients were treated with local excision between 1951 and 1971, as reported by Al-Jurf et al. Local recurrence developed in 3 patients (30%), 2 of whom were salvaged by a second local excision. Seven patients were alive and disease-free at 5 years or more, one patient died of intercurrent disease at 15 months, one patient was alive with disease at 6 years, and one patient died of disease at 8 years.

Schraut et al reported on 16 patients treated surgically at the University of Chicago. The disease was controlled in 9 of 11 patients after a local excision and in 4 of 5 after an APR. Beahrs and Wilson described 27 patients treated with local excision for in situ or superficial squamous cell carcinoma of the anal margin at the Mayo Clinic between 1950 and 1970. The local control rate was not stated; all patients apparently survived 5 years.

In a series of 49 patients who underwent local excision alone or combined with radiotherapy at St. Mark's Hospital for Diseases of the Colon and Rectum, London, the 5-year absolute and cause-specific survival rates were 65% and 68%, respectively. An additional 16 patients underwent an APR alone or combined with radiotherapy; 5-year absolute and cause-specific survival rates were 38% and 40%, respectively. Local control rates after surgery were not presented.

Radiation Therapy

Superficial, well-differentiated T1 and early T2 lesions may be irradiated through a perineal field alone using either cobalt-60 or an electron beam. The inguinal nodes should be electively irradiated in patients with more advanced and/or poorly differentiated lesions. In patients presenting with inguinal lymph node metastases and/or advanced T3 and T4 primary lesions, the pelvic lymph nodes are also treated.

University of Florida Series
Between 1979 and 1993 at the University of Florida, Gainesville, 10 patients with AJCC T2, N0 (8 patients) and T3, N0 (2 patients) squamous cell carcinoma of the anal margin were treated for curative intent with radiotherapy alone (7 patients) or combined with concomitant chemotherapy (3 patients).[1] Four patients with T2 primary lesions had cloacogenic carcinomas. Minimum follow-up was 2 years in all patients and 5 years in 8 of 10 patients. No patient was lost to follow-up. The dose to the primary lesion ranged from 50 to 69 Gy, at approximately 1.8 Gy per fraction, in a continuous course of radiotherapy. The regional lymph nodes were electively irradiated in all 10 patients. One patient underwent an excisional biopsy, which showed positive margins, before radiotherapy, and a second patient underwent an excisional biopsy, which was pathologically negative, after radiotherapy. Adjuvant chemotherapy consisted of two cycles of fluorouracil and mitomycin (Mutamycin) in one patient, two cycles of fluorouracil and cisplatin (Platinol) in one patient, and three cycles of fluorouracil and cisplatin in one patient.

Local control was observed after radiotherapy in all 10 patients (100%). No patients had inguinal node recurrence or distant metastases. Three patients died of intercurrent disease at 29, 37, and 113 months, respectively, after radiotherapy. The remaining seven patients were alive and disease-free from 24 to 143 months after treatment (Table 2). No patient suffered a severe complication, and all had a functional anal sphincter after treatment.

Other Series

According to a report by Papillon and Chassard,[3] eight patients with T1 and T2 lesions were treated with a radium implant alone (six patients) or combined with external-beam radiotherapy (two patients) at the Centre Léon Bérard (Lyon, France). The disease was locally controlled in all eight patients, although one developed an inguinal lymph node recurrence. Another 36 patients received 40 Gy in 10 fractions over 17 days through a cobalt-60 perineal field combined with an interstitial boost in 4 patients and adjuvant fluorouracil and mitomycin in 11 patients. The cure rates (defined as alive and disease-free or dead of intercurrent disease) according to T-stage were as follows: stage T1, 3 of 3 (100%); stage T2, 21 of 25 (84%); and stage T3, 4 of 8 (50%). Local recurrence alone was noted in seven patients, six of whom were salvaged with local excision. In five patients, synchronous local and inguinal node recurrences developed, and all five died of disease. The overall and cause-specific 5-year survival rates were 59% and 80%, respectively. The majority of patients in this series had squamous cell carcinoma; a small subset of patients had other histologic subtypes, such as mucoepidermoid, basal cell, or undifferentiated carcinoma.

Cummings et al[15] reported on 29 patients treated with external-beam radiotherapy alone (11 patients) or combined with fluorouracil and mitomycin (18 patients) at the Princess Margaret Hospital, Toronto. Follow-up ranged from 1 to 15 years (median, 7 years). Local control rates after radiotherapy were as follows: stage T1 and T2, 13 of 13 (100%); stage T3, 5 to 10 cm in diameter, 7 of 10 (70%); stage T3, more than 10 cm in diameter, 2 of 5 (40%); and overall, 22 of 28 (79%). One patient who was treated with concomitant chemotherapy and radiotherapy died of pneumonia during treatment. In three patients, necrosis developed at the primary site; two healed with conservative treatment and one required a colostomy.

In a series reported by Cutuli et al,[12] 21 patients were treated with radiotherapy alone at the Institut Curie, Paris, between 1962 and 1980. Patients were followed for a minimum of 5 years. Local control rates after radiotherapy were as follows: stage T1, 13 of 13 (100%); stage T2, 5 to 10 cm in diameter, 7 of 10 (70%); stage T3, more than 10 cm in diameter, 2 of 5 (40%); and overall, 13 of 15 (87%). Three patients developed a local recurrence alone, two of whom were salvaged by an operation and one by an interstitial implant. Thus, the ultimate overall local control rate was 14 of 21 (67%). The 5-year absolute and cause-specific survival rates were 52% and 72%, respectively. Necrosis developed in two patients; one healed with conservative treatment and one required an excision and colostomy.

Touboul et al[13] described 17 patients treated with radiotherapy alone between 1973 and 1991 at the Hôpital Tenon, Paris; 2 patients were lost to follow-up at 9 months and 15 months, respectively, after treatment and were excluded from the analysis of end results. Local control rates according to 1987 UICC staging were as follows: stage T1, 9 of 9; stage T2, 3 of 5; stage T3, 1 of 1; and overall, 13 of 15 (87%). Salvage therapy was unsuccessful in both patients in whom a local recurrence developed. The 5-year absolute and cause-specific overall survival rates were both 87%. Necrosis developed in two patients (12%); one was treated conservatively and the other required a colostomy.

Cheung treated 16 patients with radiotherapy alone at the London Regional Cancer Center, London,
Ontario, between 1952 and 1983.[8] Local control was obtained in 12 patients (75%) after treatment. One patient required a colostomy for a radiation necrosis. Svensson et al.[19] reported on 15 patients treated with radiotherapy alone or combined with bleomycin (Blenoxane) at the Södersjukhuset, Stockholm, between 1985 and 1990. Local control was obtained in approximately 70% of patients. The 5-year absolute and cause-specific survival rates were 57% and 71%, respectively. Dalby and Pointon[20] described 26 patients treated, for the most part, with an interstitial radium implant at the Holt Radium Institute, Manchester, England, between 1932 and 1955. The 5-year cause-specific survival rate was 63%; the local control rate was not stated.

**Adjuvant Chemotherapy**

Very limited data are available on the role of adjuvant chemotherapy in squamous cell carcinoma of the anal margin. In addition to these data, one may extrapolate information on anal canal carcinoma, for which the value of chemotherapy is better defined.[7] In a study by Cummings et al.[15] local control was obtained in 7 of 11 patients (64%) treated with radiotherapy alone, as compared with 15 of 17 patients (88%) treated with radiotherapy and concomitant fluorouracil and mitomycin. Adjuvant concomitant chemotherapy is probably indicated for patients with tumors that are poorly differentiated, 5 cm or more, and/or associated with inguinal node metastases. Currently, the optimal chemotherapy regimen consists of two cycles of fluorouracil and mitomycin, although it may be possible to substitute cisplatin for mitomycin to decrease toxicity without sacrificing efficacy.[21]

**Conclusions**

No randomized data are available for the management of squamous cell carcinoma of the anal margin. Because of the relative rarity of this disease, it is unlikely that a randomized trial will be forthcoming. Thus, treatment decisions must be made on the basis of nonrandomized data and personal experience. The literature on anal margin carcinoma is limited, and many of the papers cited do not employ a staging system or provide locoregional control data (Tables 3 and 4). Despite these caveats, it is possible to arrive at some reasonable treatment guidelines:

1. Superficial, well- to moderately differentiated T1 and T2 lesions may be successfully treated by either local excision or radiotherapy alone.
2. Patients with more advanced disease are probably best treated with combined radiotherapy and adjuvant chemotherapy.
3. Abdominoperineal resection should be reserved for patients presenting with fecal incontinence and those with extensive, locally recurrent disease after conservative treatment.
4. Inguinal lymph node dissection is not indicated for patients treated with primary surgery unless the nodes are known to contain metastatic disease.

**References:**


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