Review

Malignant tumors of the anal canal: a comprehensive review

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Malignant tumors of the anal canal are a rare and diverse group of tumors of the gastrointestinal tract. Due to the paucity of this malignancy it has been difficult to establish generally accepted guide-lines for treatment. While for some neoplasms, the treatment of choice is clear cut, for others it is still controversial. This review article makes an attempt to clarify current clinical, pathological and therapeutic options for anal canal tumors in the light of recent information.

ANATOMY AND HISTOPATHOLOGY

Anal canal carcinoma (ACC) has been difficult to study. The rarity of these tumors as well as the multiple treatment options available (e.g., surgery, radiotherapy, chemotherapy, or combination therapy) has led to publication of relatively small series with no randomized control trials. Additional problems include the lack of uniform terminology and staging systems.

One of the difficulties with terminology has been differing definitions of the anal canal. Authors define the anal canal in relation to the internal sphincter muscle.[1,2] Currently, the American Joint Committee for Cancer Staging (AJCC), and the Union Internationale Centre le Cancer (UICC) refers to any lesion proximal to the anal verge as an anal canal tumor, and those distal to the anal verge as anal margin tumors.[3] The natural history and treatment of anal canal tumors differ from those of anal margin tumors, so they are considered separate clinical entities,[4] and not included in this study.

The lining of the anal canal is both endodermal and ectodermal in origin, and in the adult contains several types of epithelium: columnar epithelium at the proximal edge, transitional epithelium above the dentate line (elements of both columnar and squamous), squamous epithelium below the dentate line, and modified squamous epithelium towards the anal verge.[5]

The proximity of the anal mucosa to the anal sphincters, the extensive blood supply and lymphatic drainage in this area, are important oncologic considerations. Lymphatic spread of anal canal lesions occurs in three different directions, superiorly to the mesorectal and superior hemorrhoidal nodes, laterally to the internal iliac nodes, and inferiorly to the inguinal and external iliac nodes.[2,5] However, if obstruction exist, lymph can drain to the superior rectal nodes, or along the inferior rectal lymphatics to the ischioanal fossa.

Different types of cells in anal canal or anal gland lining give rise to the different histologic variations seen with these tumors. A variety of histologic patterns may be found, with several elements occasionally occurring in the same tumor. They include epidermoid carcinoma, adenocarcinoma, melanoma and sarcoma. Epidermoid or squamous cell carcinoma (SCC) is the most common anal canal neoplasm.[1,4] Also included in this clinical entity are lesions with different histologic appearance (e.g., Transitional cell, Cloacogenic, Basaloid, Epitheloid, Basosquamous and Mucoepidermoid). These tumors are considered variants of squamous cell carcinoma, as they exhibit a similar natural history, response to treatment, and prognosis.[2] In a recent study of 192 pathologic specimens, 74% were squamous cell carcinomas, 19% adenocarcinomas and 4% melanomas. The remaining 6 (3%) were sarcomas 3, neuroendocrine tumors 2 and one lymphoma.[4]

INCIDENCE

Whereas malignancies of the lower gastrointestinal tract comprise a large portion of the practice of colorectal surgery, anal canal malignancies are uncommon. Pre-

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viously the incidence of these lesions was one-twentieth that of rectal adenocarcinoma and comprised 1.5 to 4% of large bowel cancers,[6] but recent experience indicates that this incidence is increasing. A seven-fold increase in the annual incidence of ACC was reported in 1985-1987 compared to 1973-1978.[7] Mean age at presentation varies from 58 to 67 years and the age range is wide; the proportion of patients aged 25-44 years, 45-64 years and 65 years or more is 5, 37 and 58% respectively.[8] They show a marked female predominance, the female: male ratio, although variable, is around 5:1. In Sweden the annual age-adjusted incidence per 100.000 population for squamous cell carcinoma is 1.40 for women and 0.68 for men.[8] However in centres with a large proportion of male patients at high risk, the female: male ratio may approach 1:1.[9] ACC occurs thoughout the world but are particularly common in Brazil and India. In these countries the incidence is closely related to that of carcinoma of the cervix, penis and vulva, suggesting a common etiological factor.[10]

RISK FACTORS

The etiology of the disease seems to be multifactorial, representing an interaction between genetic and environmental factors. The genetic factors may be related to changes in chromosome 11 (11q22) or the short arm of chromosome 3 (3p22).[12] Several environmental factors have been implicated. ACC has usually been associated with lack of personal hygiene, chronic irritation, infection and/or immune suppression.[7] ACCs have occurred following radiotherapy for pruritus, or in association with long-standing anal fistula. The latter may e associated with Crohn's disease. In a study,[13] ACC accounted for 14% of large bowel cancer in those with Crohn's disease and 1.4% of those without. Smoking has also be found to be a significant risk factor, but only in male homosexuals.[11] Sexual orientation is another major risk factor. Male homosexuality and especially anoreceptive intercourse is consistently found to be associated with ACC. Relative to heterosexuals or those not employing anal intercourse the risk is 33.1 and 12.4 respectively.[11] Also women practicing anal intercourse are at increased risk. In a study 30% of ACC in women occurred in those practicing anal intercourse.[14,15]

There is also a strong link between viral warts in the anogenital region and ACC. Palefsky and others[16] have presented evidence linking ano-genital cancers with human papilloma virus (HPV) infections. The so-called oncogenic HPV genotypes (HPV 16,18,31) have been detected in 16-80% of squamous or cloacogenic carcinomas.[17] The mechanisms by which HPV contributes to the development of neoplasia are not completely understood. HPV infections are thought to occur in areas of trauma and result in cellular hyperplasia of the basal layer of squamous, transitional and cuboidal epithelial cells. Viral genomes have been cloned from infected tissue.[18] HPV E_6 and E_7 gene products bind and inactivate p53 and Rb protein products of tumor suppressor genes, thought to be cellular growth regulators. Binding of p53 and Rb protein by E_6 and E_7 inactivates their tumor suppressor function, thereby permitting under appropriate circumstances (deficient immune status), subsequent malignant transformation and tumorigenesis.[18]

Anal intraepithelial neoplasia (AIN), like cervical intraepithelial neoplasia (CIN) is also a precursor to SCC of the anus, found more commonly in patients practicing anal receptive intercourse and especially in immunodeficient populations.[18] A number of studies have demonstrated a relationship between HIV-induced immunodeficiency, HPV infection and the development of anal neoplasia, focusing primarily on AIN.[19,20] AIN occurs in 30 to 35% of homosexuals HIV-positive and in 4.7% of homosexuals HIV-negative males.[20] Immunosuppressed organ transplant recipients are also at increased risk of HPV infection and malignancy, occurring an average of 7 years after transplantation.[21] Therefore, current evidence suggests that the etiology of ACC is a multifactorial interaction between environmental factors, HPV infection, immune status and suppressor genes.[11]

DIAGNOSIS

The signs and symptoms of ACC are non-specific with most (70-80%) being initially diagnosed as benign anorectal conditions. It is also important to recognize that in the early stages of the disease, the patient is often symptom-free or does not has sufficient discomfort to seek medical attention.[4] Bright red bleeding, pruritus, pain and discharge each occur in over half of patients. Symptoms such as discharge, incontinence, change of bowel habits, pelvic pain or anovaginal fistula, suggest advanced lesions with malignant infiltration of the sphincters.[11]

Detailed history, including that of previous anal pathology and sexual habits, should precede a meticulous physical examination. The later should identify the lesion, its size and anatomical boundaries.[7] ACCs often begin as small fissures with slightly raised indurated margins. They are characteristically infiltrative, polypoid growths being rare because of the absence of lumen when

the anal canal is in the resting position.

Clinical examination includes: I) Inspection and digital examination of the anus, perineum, vulva, vagina, regional lymphatic basins, anal and cervical Pap smears; II) Evaluation of the extent of penetration and fixation to surrounding structures; III) Anoscopy and proctosigmoidoscopy or colonoscopy with biopsy of the primary tumor and FNA of suspicious lymph nodes; IV) Anal-transrectal ultrasonography with lateral beam probe manually rotated 360° to evaluate recto-anal wall and pelvic nodes; V) Chest x-ray, liver function tests, HIV serology; VI) Pelvic and abdominal CT; and VII) Examination under anesthesia if I, II and III are unsatisfactory.[7]

STAGING

ACC is predominantly a locoregional disease, with fewer than 10% of patients having distant metastases at presentation.[22] Visceral metastases occur in the liver, lung, skin or bones. Cloacogenic tumors may present with secondaries to the brain, perineum or spinal cord.[23] ACC may spread to either the inguinal or the pelvic lymph nodes. The overall incidence of clinically positive inguinal lymph nodes is 10-20%, but this fibure approaches 30-60% for T_3 or larger tumors. Twenty-five percent of lymph node positive patients have bilateral involvement.[4]

Dukes' staging of colorectal carcinoma is not applicable to anal canal tumors. However histological grade and extent of tumor spread are related to prognosis.[6,24] The current AJCC/UICC staging system complies with the new trends in the approach to ACCs and unavailability of pathological staging when induction to chemoradiotherapy is used.

The principles of 1997 AJCC/UICC TNM staging for ACC are[25]: I) All histologic variants in the anal canal tumors have the same staging criteria; II) Anal canal tumors are staged on clinical basis only (inspection, palpation, chest X-ray, transanorectal ultrasound, abdominal and pelvic CT, and FNA for clinically suspicious lymph nodes; III) T_{1-3} is determined by size only; IV) T_4 is determined only by penetration to adjacent organs; V) Grading and depth of penetration can be evaluated but are not included in the staging; and VI) Melanoma is staged like any other melanoma.

Staging criteria and stage grouping of ACCs (AJCC/UICC, 1997)[25] are shown in tables 1 and 2 respectively.

TREATMENT

Epidermoid carcinoma

SCC represents the majority of anal canal tumors.

Table 1. TNM staging criteria for ACC

Primary tumor (T)	
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_1	Tumor 2cm or less in greatest dimension
T_2	Tumor more than 2cm but not more than 5cm in greatest dimension
T_3	Tumor more than 5cm in greatest dimension
T_4	Tumor of any size invading adjacent organ(s) e.g. vagina, urethra, bladder
[involvement of sphincter muscle(s) alone is not classified as T_4]	
Lymph nodes (N)	
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in perirectal lymph node(s)
N_2	Metastasis in unilateral internal iliac and/or inquinal lymph nodes
N_3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
Distant metastasis (M)	
M_x	Presence of distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

Table 2. Stage grouping of ACCs

Stage				
0		T_{is}	N_0	M_0
I		T_1	N_0	M_0
II		T_2	N_0	M_0
		T_3	N_0	M_0
III_A		T_1	N_1	M_0
		T_2	N_1	M_0
		T_3	N_1	M_0
		T_4	N_0	M_0
III_B		T_4	N_1	M_0
	any	T	N_2	M_0
	any	T	N_3	M_0
IV	any	T		M_1
			any N	

Prior to the protocols of Nigro et al,[26,27] abdominoperineal resection (APR) and colostomy were the mainstay of treatment, with 5-year survival rates achieved for 38-71% of patients and recurrence developing is 27-43%.[6,28] The introduction of chemoradiation as the primary treatment resulted in survival and recurrence rates similar to those for surgery, but with preservation of sphincter function in the majority of patients (80%).[4,2] Nowadays epidermoid anal carcinoma lesions are considered a model for tumors responding to chemo-radiotherapy. Complete response rates are in the region of 70-90%, being 85 and 73% respectively for tumors less or greater than 4cm in size.[30,31] Approximately 15% of patients will have persistent disease initially, while a further 15% will develop late locoregional recurrence.[30,32] The 5-year survival figures of 60-80%, along with an 80% preservation of anal function, makes non-surgical management an attractive option for anal canal tumors.[8,31] However toxicity can be expected in around 20% of patients, but severe toxicity is uncommon. Unfortunately sterility is virtually inevitable and young patients must be warned of this.[33]

Based on the work of Nigro et al,[26,27] and on the experience of Cummings[30] and Papillon and Montbarbon,[31] a typical regimen for primary treatment of SCC includes the following: I) 5-FU 750-1000 mg/m^2 over 24h continuous i.v. infusion, days 1-4; II) Mitomycin C 10-15 mg/m^2 i.v. bolus, day 1 (alternatively Bleomycin 15 units once a week, or Cisplatin 4 mg/m^2 with reduced 5-Fu dose to 250-300 mg/m^2); III) XRT at 180-250 cGy/fraction, starting day 1, 5 days/week, whole pelvis, for a total dose of 45-55 Gy. Boosts of up to 60 Gy may be given to both inguinal regions for stages III_B and IV; IV) 5-Fu 750-1000 mg/m^2 identical to first dose, on days 29 through 32; V) Clinical and bioptic evaluation 6-8 weeks after completion of therapy. The response to radiochemotherapy is usually delayed, but complete response is expected in up to 90% of the treated patients.[7]

In addition to the combination of radiotherapy and chemotherapy, the use of interstitial irradiation by Iridium 192 implants has attracted much interest. It seems to offer better local tumor control, especially in patients with high risk of local relapse (T_3), if radiotherapy is used without chemotherapy. However, the need for interstitial irradiation when radiochemotherapy is administered to the patients remains unclear.[34]

Some T_1 lesions may be locally excised with or without adjuvant radiotherapy with acceptable results, but the indications for radical surgery (APR) are limited to salvage procedures for incomplete responses, or for locally recurrent lesions, or for a selected group of severely symptomatic patients i.e. perineal sepsis, intractable urinary of fecal fistula, intorelable incontinence etc.[35]

The morbidity associated with prophylactic inguinal lymph node dissection appears to outweight the expected benefit. Although half of clinically detectable synchronous inguinal lymph nodes are inflammatory, their involvement by tumor is associated with a poor 5-year survival rate of less than 20%.[36] However, if metachronous nodes occur (usually within 18 months), combined groin dissection and boost radiotherapy, together with chemotherapy if the nodes are fixed, confers a better prognosis, with a 5-year survival rate of 40-70%.[37]

Virtually all failures result from locoregional recurrence. Recurrence after APR is associated with a poor prognosis, the median survival time after recurrence being 9 months. Palliative radiotherapy or chemotherapy may prolong mean survival to 14 months, but complete response is very rare.[36-38]

Melanoma

The anal canal is the third most common site of melanoma, exceeded only by the skin and the eyes, representing 0.3 to 1.6% of all melanomas. The mean age of occurrence is in the fifth decade, and females are affected more frequently than males.[2] It arises from epithelium in the region of the dentate line. Symptoms are indistinguishable from other conditions in the region. The lesions are usually elevated, and in 70% of cases are pigmented. Small lesions that are pigmented have been mistaken for thrombosed hemorrhoids.[39]

Surgery provides the only hope for cure, but significance differences in survival between patients treated with local excision and those with APR has not been demonstrated.[39] However APR seems to provide better local control of the disease. Unfortunately, local recurrence in these cases was often accompanied by the appearance of distal or regional metastases as well.[39,40] There is some indication that prognosis is related to the depth or thickness of the tumor as it is for cutaneous melanoma. Some investigators recommend APR for lesions less than 3.0 mm in depth, as they believe these tumors are the only lesions that are potentially curable.[40,41] Prophylactic inguinal lymphadenectomy is not indicated for clinically negative nodes, but is helpful for clinically suspicious nodes. Radio-chemotherapy has demonstrated little benefit in this disease. Patients treated in a curative fashion have a survival of 6 to 20%, while series including all patients have reported 5-year survival rates that range from 0 to 12%.[39,41,42]

Adenocarcinoma

Adenocarcinomas of the anal canal are rare tumors, and are thought to arise in the ducts or the intramuscular anal glands, and in the long-standing fistulas.[13,43] These neoplasm affect older age groups and have no sexual predominance. Most of these lesions are slow growing, locally aggressive and rarely metastasize. The abundant mucin production of these tumors may explain their tendency to dissect soft tissue planes.[2]

A wide local excision may be performed for small and well-differentiated carcinomas that have not invaded sphincter mechanism. Otherwise APR is indicated.[44]

Sarcomas

Anorectal sarcomas are very rare and produce symptoms similar to those related to other anal lesions. Moluar et al[45] reported on nine patients with anorectal sarcomas and reviewed the literature on the subject. They may grow as intraluminal extraluminal, or dumbbell-shaped lesions. Histologic diagnoses include leiomyosarcoma, fibrosarcoma, and anaplastic sarcoma. These tumors are all radioresistant, and APR is the treatment of choice. Despite radical operation no 10-year survival rates were recorded in that study.

FOLLOW-UP

Patients should be followed for detection of local and systemic failures, as well as for the treatment of complications. Local inspection, digital examination, anoscopy and biopsy of any suspicious area are recommended every 3 months for two years, and twice a year thereafter. Early detection of local recurrence may enable less extensive salvage surgical procedures. Distant failures of epidermoid cancer are responsive to radiotherapy and up to 30% of patients respond to second line chemotherapy (Cisplatin containing combination). Therefore, chest x-ray, liver function tests and pelvic CT are recommended every 6-12 months for two to three years after therapy for cure.[7]

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