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Review Article

Cancers of anal canal: A review article

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ABSTRACT

Malignant tumoursof the anal canal are rare and diverse group of tumours of gastrointestinal tract and comprises of 2.5 percent of all digestive system malignancy in United States. Although incidence rates are still low, there has been a significant increase in squamous cell carcinoma over the last 50 years. HIV infected homosexual men appear particularly at risk. HPV DNA is detectable in most anal squamous cell carcinomas. Despite its short length, the anal canal produces a variety of tumour types reflecting its complex anatomic and histological structure.Squamous, glandular, transitional, and melanocytic components occur at this site, either alone, or in combination. Due to the paucity of this malignancy it has been difficult to establish generally accepted guidelines 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.

Keywords: Abdominoperineal Ressection, anal canal carcinoma, squamous cell carcinoma, human papilloma virus

INTRODUCTION

Anal cancer comprises 2.5% of all digestive system malignancies in the United States; 7210 new cases are diagnosed annually.[1] The incidence of anal cancer in the general population has increased over the last 30 years, from 10 to about 20 per million.[2] A higher incidence has been associated with female gender, infection with human papillomavirus (HPV), lifetime number of sexual partners, genital warts, cigarette smoking, receptive anal intercourse, and infection with human immunodeficiency virus (HIV).[3] Thus, from an etiologic standpoint, anal cancer is more similar to genital malignancies than it is to other gastrointestinal tract cancers.

Substantial progress has been made in understanding the pathophysiology and the management of anal cancer.[4] In the 1960s, this malignancy was thought to be due to chronic perianal inflammation and was treated routinely by abdominoperineal resection, necessitating a permanent colostomy.[5] As a result of carefully conducted epidemiologic and clinical studies, it is now known that anal cancer is closely associated with HPV infection and that cure of anal cancer is possible in the majority of patients with preservation of the anal sphincter.

DEFINITION

Tumours that are arise in or around the anal canal. The most frequent neoplams of this region are HPV-associated squamous cell carcinomas (SCC) and adenocarcinomas.

ANATOMY AND HISTOLOGY OF ANAL CANAL

The anal canal is defined as the terminal part of the large intestine, beginning at the upper surface of the anorectal ring and passing through the pelvic floor to end at the anus. The most important macroscopic landmark in the mucosa is the dentate (pectinate) line composed of the anal valves and the bases of the anal columns. Histologically, the mucosa can be divided into three zones. The upper part is covered with colorectal type mucosa. The middle part is the anal transitional zone, which is covered by a specialized epithelium with varying appearances; it extends from the dentate line and on average 0.5-1.0 cm upward. The lower part extends from the dentate line and downward to the anal verge and has formerly been called the pecten. It is covered by squamous epithelium, which may be partly keratinized, particularly

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in case of mucosal prolapse. The perianal skin (the anal margin) is defined by the appearance of skin appendages. There exists no generally accepted definition of its outer limit. The term anus refers to the distal external aperture of the alimentary tract. Anal margin tumors are classified according to the WHO histological typing of skin tumors (Figure 1).

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.[6,7] Currently, the American Joint Committee for Cancer Staging, and the Union Internationale Centre le Cancer 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.[8] The natural history and treatment of anal canal tumors differ from those of anal margin tumors, so they are considered separate clinical entities.[9] 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.[7,10] However, if obstruction exists, lymph can drain to the superior rectal nodes, or along the inferior rectal lymphatics to the ischioanal fossa.

Different types of cells in the 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 SCC is the most common anal canal neoplasm.[6,9] Also included in this clinical entity, are lesions with different histologic appearance (e.g. transitional cell, cloacogenic, basaloid, epithelioid, basosquamous, and mucoepidermoid). These tumors are considered variants of SCC, as they exhibit a similar natural history, response to treatment, and prognosis.[7] In a recent study of 192 pathologic specimens, 74% were SCC, 19% adenocarcinomas, and 4% melanomas. The remaining 6 (3%) were sarcomas 3, neuroendocrine tumors 2, and one lymphoma.[9]

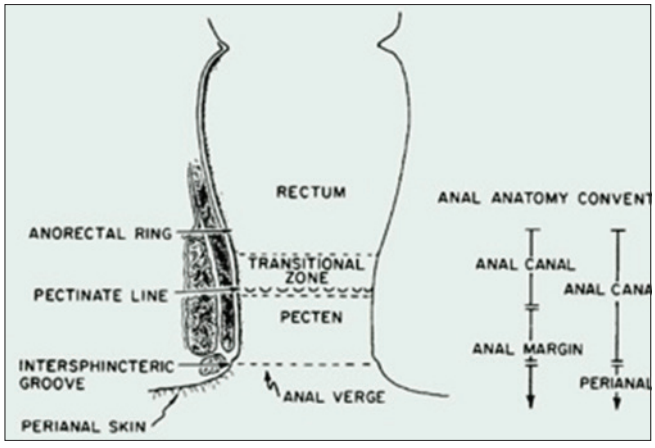

Figure 1: Anal canal anatomy

INCIDENCE

Anal cancer comprises malignancies of the anal canal of principally two morphologic variants: SCC and adenocarcinoma. In most settings, SCC compromises more than 70% of cases. In the general population, anal cancer is uncommon, with age-standardized incidence rates mostly between 1 and 2 per 100000 per year. However, the incidence of anal SCC is increasing by 1-3% per year in developed country settings. High-risk HPV types can be detected in 80-90% of all anal SCC cases, making it second only to cervical cancer in the closeness of its association with this virus. HPV-16 can be detected in ~90% of HPV-positive cases of anal SCC. Case-control studies have demonstrated that sexual risk factors (homosexuality in men and multiple sexual partners in women) are strongly associated with anal cancer risk. Other risk factors include immune deficiency and tobacco exposure. Anal cancer rates are highest in homosexual men, particularly in those who are HIV-positive, in whom anal cancer is among the most common of all cancers. Vaccination against HPV holds great promise for anal cancer prevention for those not already HPV-infected. For the current generation of high-risk adult populations, screening programs to allow early detection and treatment are under investigation. ACC occurs throughout the world but is 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.[11]

RISK FACTORS

HPV: There is a strong link between viral warts in the anogenital region and ACC. Palefsky and others[12] have presented evidence linking anogenital cancers with HPV infections. The so-called oncogenic HPV genotypes (HPV 16, 18, 31) have been detected in 16-80% of squamous or cloacogenic carcinomas.[13] 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 E6 and E7 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 E6 and E7 inactivates their tumor suppressor function, thereby permitting under appropriate circumstances (deficient immune status), subsequent malignant transformation, and tumorigenesis.[14]

HIV: Anal intraepithelial neoplasia (AIN), like cervical intraepithelial neoplasia, is also a precursor to SCC of the anus, found more commonly in patients practicing anal receptive intercourse and, especially in immunodeficient populations.[14] A number of studies have demonstrated a relationship between HIV-induced immunodeficiency, HPV infection, and the development of anal neoplasia, focusing primarily on AIN.[15,16] AIN occurs in 30-35% of homosexuals HIV-positive and in 4.7% of homosexuals HIV-negative males.[16]

Smoking: Cigarette smoking is a well-known risk factor for anal SCC that is independent of sexual practices. The risk

increases 2-5 folds over that of the general population.[17,18] It is speculated based on data demonstrating an increased incidence in premenopausal women of 5.6 with a 6.7% linear increase per pack-year, that smoking may have some anti-estrogenic effect permissive for the disease in the estrogen-sensitive tissues of the anal canal.[19]

Chronic inflammation: At 1 time, benign anorectal conditions such as hemorrhoids, fissures, and fistulas were thought to predispose the development of SCC. The etiology or common mechanism was presumed to be the prolonged exposure of the anal epithelium to chronic inflammatory conditions. Patients with inflammatory bowel disease were believed to be at increased risk, particularly when anal fistula was present.

DIAGNOSIS

Clinical Symptoms and Natural Progression

The most common presenting symptoms of anal cancer include pain, irritation, and bleeding in the anal area. The proper workup for anal cancer should begin with a careful physical examination including digital rectal examination and palpation of the inguinal nodal area. The nature of a suspicious lesion should be confirmed by biopsy. The disease is locally invasive and also spreads via lymphatic channels. Lymphadenopathy is clinically evident in about 20% of cases at presentation.[20] Surgical exploration, however, discloses lymph node metastasis to be present in 30-63% of cases in various series.[21] Tumors originating above the dentate line metastasize via lymph nodes accompanying the lower hemorroidal veins up to the internal iliac nodes and then to the para-aortic chain. Tumors located at a lower level spread predominantly to the femoral and inguinal lymph nodes. Visceral metastasis is present in only about 10% of cases at presentation, with the most common sites of distant metastasis being lung and liver.[4,20,22]

Diagnostic Workup

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 computerized tomography (CT); and (vii) Examination under anesthesia if I, II, and III are unsatisfactory (Figure 2).[23]

CT scans of the chest, abdomen, and pelvis help to define the internal extension of the infiltrating tumors, as well as enlargement of the pelvic nodes and distant metastasis. Endorectal ultrasound is a valuable tool for assessing the extent of tumor infiltration, also, to some degree, peri-anal lymph node involvement.[24] The role of magnetic resonance imaging is undefined for anal cancer evaluation, although from available experience with rectal cancer, this diagnostic method may warrant further investigation.

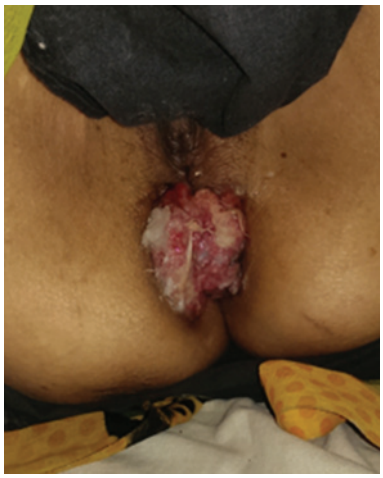

Figure 2: Growth in perianal region

CLASSIFICATION

WHO Histological Classification of Tumors of the Anal Canal

Epithelial tumors

Intraepithelial neoplasia1 (dysplasia):

1. Squamous or transitional epithelium
2. Glandular
3. Paget disease.

Carcinoma:

1. Squamous cell carcinoma
2. Adenocarcinoma
3. Mucinous adenocarcinoma
4. Small cell carcinoma
5. Undifferentiated carcinoma
6. Others
7. Carcinoid tumor
8. Malignant melanoma
9. Non-epithelial tumors
10. Secondary tumors.

STAGING

ACC is predominantly a locoregional disease, with fewer than 10% patients having distant metastases at presentation.[25] Visceral metastases occur in the liver, lung, skin or bones. Cloacogenic tumors may present with secondaries to the brain, perineum or spinal cord.[26] 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 figure approaches 30-60% for T3 or larger tumors. 25% of lymph node positive patients have bilateral involvement.[9]

TNM Staging Criteria for ACC

Primary tumor (T):

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma *in situ*

T1: Tumor 2 cm or less in greatest dimension

T2: Tumor more than 2 cm but not more than 5 cm in greatest dimension

T3: Tumor more than 5 cm in greatest dimension

T4: Tumor of any size invading adjacent organ(s) e.g. vagina, urethra, bladder (involvement of sphincter muscle(s) alone is not classified as T4).

Lymph nodes (N):

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in perirectal lymph node(s)

N2: Metastasis in unilateral internal iliac and/or inguinal lymph nodes

N3: Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

Distant metastasis (M):

Mx: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis.

Stage grouping

Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
	T3 N0 M0
Stage IIIA	T1 N1 M0
	T2 N1 M0
	T3 N1 M0
	T4 N0 M0
Stage IIIB	T4 N1 M0
	Any T N2, N3 M0
Stage IV	Any T Any N M1

TREATMENT

Epidermoid Carcinoma

SCC represents the majority of anal canal tumors. Prior to the protocols of Nigro *et al.*,[27,28] abdominoperineal resection (APR) and colostomy were the mainstay of treatment, with 5 years survival rates achieved for 38-71% of patients and recurrence developing is 27-43%.[6,27] 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%).[7,9] 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 4 cm in size.[29,30] Approximately, 15% of patients will have persistent disease initially while a further 15% will develop late locoregional recurrence.[29,31] The 5 years survival figures of 60-80%, along with an 80% preservation of anal function, makes non-surgical management an attractive option for anal canal tumors.[30,32] 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.*,[27,28] and on the experience of Cummings[29] and Papillon and Montbarbon,[30] a typical regimen for primary treatment of SCC includes the following: (i) 5-FU 750-1000 mg/m^2 over 24 h continuous intravenous (IV) infusion, days 1-4; (ii) Mitomycin C 10-15 mg/m^2 IV 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 IIIB 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 the complete response is expected in up to 90% of the treated patients.[23] The morbidity associated with prophylactic inguinal lymph node dissection appears to outweigh the expected benefit. Although half of clinically detectable synchronous inguinal lymph nodes are inflammatory, their involvement by tumor is associated with a poor 5 years survival rate of <20%.[34] 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 years survival rate of 40-70%.[35]

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 (Figure 3).[34-36]

Melanoma

The anal canal is the third most common site of melanoma, exceeded only by the skin and the eyes, representing 0.3-1.6% of all melanomas. The mean age of occurrence is in the fifth decade, and females are affected more frequently than males.[7] It arises from epithelium in the

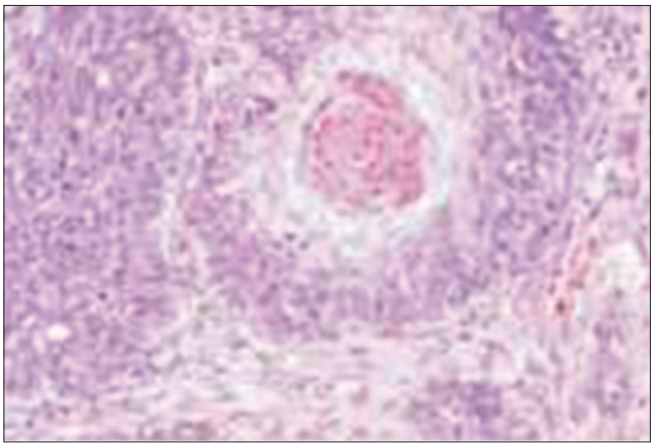

Figure 3: Squamous cell carcinoma showing a combination of basaloid and squamous feature

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.[37]

Surgery provides the only hope for cure, but significance differences in survival between patients treated with local excision and those with APR have 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.[37,38] There is some indication that the prognosis is related to the depth or thickness of the tumor as it is for cutaneous melanoma. Some investigators recommend APR for lesions <3.0 mm in depth, as they believe these tumors are the only lesions that are potentially curable.[38,39] 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 6-20%, while series including all patients have reported 5 years survival rates that range from 0 to 12% (Figure 4).[37,39,40]

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.[41,42] 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. A wide local excision may be performed for small and well-differentiated carcinomas that have not invaded sphincter mechanism. Otherwise, APR is indicated.[43]

Sarcomas

Anorectal sarcomas are very rare and produce symptoms similar to those related to other anal lesions. Molnar *et al.*[44] reported nine patients with anorectal sarcomas and reviewed the literature on the subject. They may grow as intraluminal or extraluminal, or dumbbell shaped lesions. Histologic diagnosis includes leiomyosarcoma, fibrosarcoma, and anaplastic sarcoma. These tumors are all radioresistant, and APR is the treatment of choice. Despite the radical operation, no 10 years survival rates were recorded in that study.

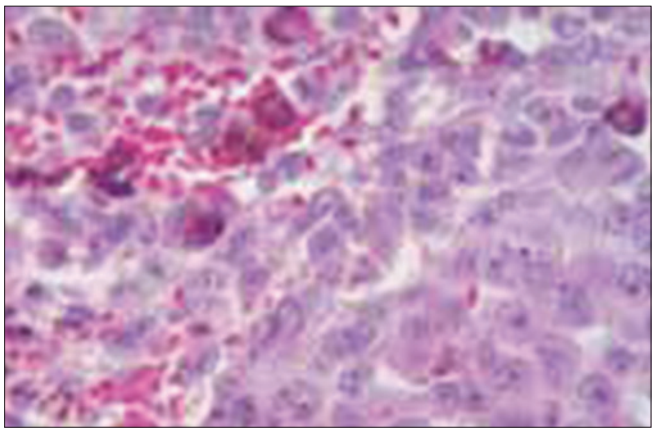

Figure 4: Epithelioid melanoma cells with prominent nucleoli

Evaluation for Treatment Response

The mainstay in tumor response assessment is relatively close clinical follow-up, repeating physical examination of the anal area at approximately 6 weeks intervals. Different researchers recommend different waiting periods after the radiation treatment for the full response of the tumor: Between 6 and 12 and up to 30 weeks. Early biopsy is recommended for clinically apparent tumor progression or failure to respond, however, a biopsy at 6 weeks after completion of treatment may not represent the ultimate true response of a tumor. It is known from the experience at Princess Margaret, and other centers, that anal carcinomas continue to respond up to 9 months after treatment.[45] In an alternate approach, patients were examined every 6 weeks and only those with clinical progression underwent early biopsy. The point in avoiding unnecessary biopsy procedures is to minimize the risk of soft tissue infections, tissue necrosis, and impairment of anal function. There is still controversy regarding the definition and management of the residual disease. Biopsy is recommended earlier for tumor mass progression or unsatisfactory response. RTOG suggested giving an additional 9 Gy of radiation treatment for salvage, rather than resorting to APR immediately. Alternative recommendations include delivering a higher dose of radiation for larger tumors, up to 59.4 Gy, as initial treatment.

Surgical Salvage for Disease Persistence

Patients with residual microscopic foci of the tumor may undergo local resection of tumor. Others with the larger residual disease receive salvage APR. The overall survival data for surgical salvage at 5 years are about 30-60%.[46,47] Some use, as an option, a repeat combined chemoradiation treatment for salvage purposes, with comparable success. There is no randomized study that compares different salvage approaches. In the current RTOG trial, the recommendation is to give an additional combined chemoradiation treatment for persistent disease and to reserve APR for failure of this second-line treatment, as about 50% of patients can still be salvaged with organ preservation.

Treatment of Locally Recurrent and Metastatic Disease with Chemotherapy

Different regimens of salvage chemotherapy may be used for metastatic anal carcinoma, although the most common regimens at present employ cisplatin and 5-FU.[48,49] We may anticipate that as new chemotherapeutic agents are developing, this treatment strategy may undergo changes in the future.

CONCLUSION

Management of carcinomas of the anal canal has progressed from a radical surgical approach to an organ-preserving approach, utilizing combined chemotherapy and radiation treatment, with high rates of success. A good

option for those practicing in a setting in which protocol treatment can be made available is to enter patients on RTOG 98-11; this apparently represents the state-of-the-art treatment. Accrual of larger numbers of patients to the trial will provide greater statistical validity to conclusions, which will shape the treatment of this disease in coming years. If patients are treated outside of a protocol setting, one could consider using a chemoradiation approach in which the chemotherapy consists of 5-FU, 1,000 mg/m^2, delivered by continuous infusion on days 1-4, and 29-32 combined with 10 mg/m^2 mitomycin bolus on days 1 and 29. Treatment with cisplatin-containing regimens is generally considered investigational at this point so that it would be recommended that it be given only under the protocol until results of this latest intergroup trial are known. There is evidence of a radiation dose response available; little more than 30 Gy may be needed to control areas in which there is only a risk of microscopic tumor burden. Gross tumor may require doses >55 Gy to give the optimal probability of disease eradication. As in many other curative treatment situations, continuous-course irradiation apparently confers an advantage over split course radiation treatment. Tumors may continue to regress for several months after treatment. It may be wisest to follow clinically, as long as the tumor is gradually regressing, and not to do biopsy or perform other surgical procedures too quickly, as this could lead to complications, such as infection, fistula, or loss of good sphincter function. Initial local failures may be salvaged by either additional chemoradiation or by abdominal perineal resection. Chemoradiation causes generally tolerable but significant side effects, and efforts continue to retain high disease-free survival rates while mitigating side effects. Anal cancer screening and prevention is gaining more acceptances and warrants further study.[50,51]

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PEER REVIEW

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CONFLICT OF INTEREST

Nil

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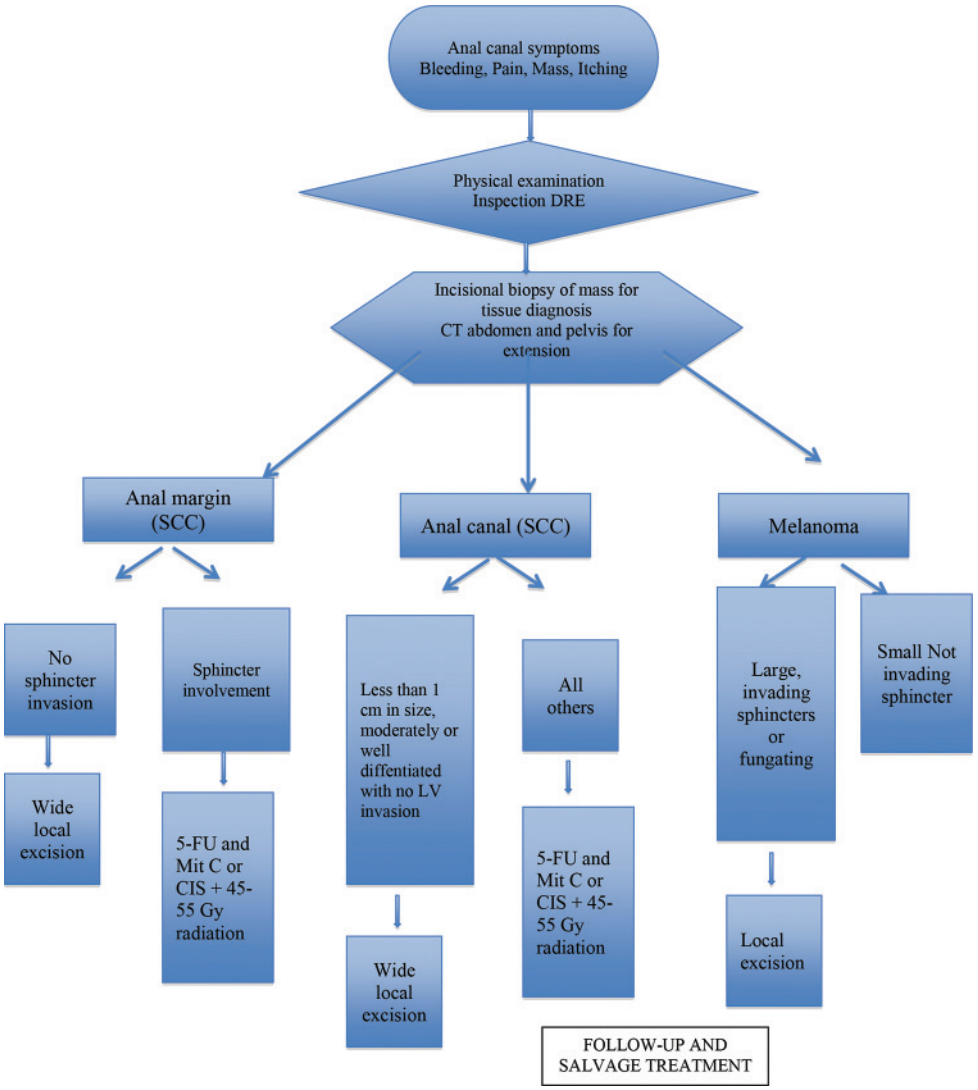

Algorithm for management of CA anal canal