Anal cancer – a review

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Abstract:
Anal cancer accounts for only 1.5% of gastrointestinal malignancies but this disease has shown a steady increase in incidence particularly in HIV positive males. The understanding of pathophysiology and treatment of anal cancer has changed radically over last thirty years . Risk factors have been identified and organ preservation by chemoradiotherapy has become a standard. This article aims to review the clinical presentation, diagnostic evaluation, and treatment options for anal cancer in the light of current literature .

Key words : anal cancer, anal canal, anal margin, chemoradiotherapy, HIV, HPV, salvage, recurrence, imaging.

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Introduction

Cancer of anal canal is uncommonly encountered and it makes upto 4% of all anorectal malignancies and 1.5% of gastrointestinal malignancies. [1, 2] However,in recent decades the incidence of anal cancer has shown an increasing trend globally . But at the same time visibly marked progress has been made in the understanding of pathophysiology of this disease leading to evolution of effective treatment modalities. [3] Cultural changes globally have introduced various identifiable risk factors and the disease is feared to increase in incidence with time. The primary management has undergone radical change from abdominoperineal resection to organ preserving chemoradiation therapy. Concepts of screening for early detection and primary prevention of the disease have also come up in recent times. This article is presented with the aim of reviewing this disease in the light of recent developments.

Anatomy

The anal canal is the caudal segment of large intestine and commences at the level where the rectum enters the puborectalis sling at the apex of the anal sphincter complex. This point is palpable as a thickened ridge on digital rectal examination and termed as an anorectal 'bundle' or 'ring'. The anal canal is approximately 4 cm in length and extends distally to the point referred to as anal verge . The anal verge can be identified visually as the part of the anal canal remaining closed on gentle retraction of the the buttocks. The anal verge roughly coincides with the palpable intersphincteric groove or the outermost boundary of the internal sphincter muscle. Outside of the anal verge lies the anal margin. This is also referred to as the perianal skin and commonly encompasses a radius of 5 cm.

The upper anal canal is lined by columnar tissue that transitions into squamous epithelium at the dentate line. The dentate line, identified by the termination of the anal columns, lies 1 to 2 cm above the anal verge. The squamous epithelium of anal canal is devoid of epidermal appendages such as hair follicles, apocrine glands and sweat glands. The perianal margin bears the true squamous epithelium along with the appendages.

The arterial supply of the anus is derived from branches of the superior rectal artery, the inferior rectal branch of the pudendal artery, and branches of the median sacral artery. The venous drainage of the anal canal is divided into two patterns. Above the dentate line, the venous blood drains through the terminal branches of the superior rectal vein into the inferior mesenteric vein and portal system, and below the dentate line via the inferior rectal vein into the pudendal vein which itself drains into the internal iliac vein. Lymphatic drainage of anal cancers is dependent upon the location of the lesion with respect to the dentate line. Cancers arising proximal to dentate line drain to perirectal and paravertabral lymph nodes in tandem with rectal carcinomas wheras the cancers distal to dentate line drain to inguinal and femoral nodes.

Epidemiology and risk factors

Multiple studies have shown that the incidence of anal carcinoma is increasing. [4 -8] In the US, between 1973 and 1979 the incidence per 100,000 was 1.06 in males and 1.39 in women. In the period 1994 to 2000 this incidence almost doubled with a rate of 2.04 / 100,000 in males and 2,06 / 100,000 in females. Similarly in 2011, there were estmated 6230 new cases and 780 related deaths and in 2008, the number was 5000 new cases and 680 related deaths demonstrating a significant increasing trend from 2003 when approximately 4000 new cases and 500 related deaths were recorded.

In Denmark, simlar trends were documented and age-adjusted incidence rates per 100,000 person-years showed an increase from around 0.2 among both men and women to 0.5 among men and 1.0 among women during the period 1943-1997. [2] A peak in incidence is noted in the seventh decade, with females being more commonly affected than males. [2]

There are multiple recognised risk factors (Table 1) associated with the anal cancer and social and cultural changes globally in last few decades have resulted in increased individual exposure to these risk factors . These risk factors include:

- **Human papilloma virus infection**

Recent data shows that most squamous cell anal cancers are apparently linked to infection by the human papilloma virus (HPV), the virus that causes cervical cancer in females (9-10). In fact, females with a history of cervical cancer /

pre-cancer have an increased risk of anal cancer.

Human papilloma viruses (HPVs) are a large family of double-stranded, small, DNA viruses that cause infection of squamous epithelia. [11] They are called papilloma viruses because some of the subtypes cause papillomas(warts, condyloma acuminatum) . There are about 100 subtypes of the virus but the one strongly associated with anal cancer is called HPV-16. BesidesHPV-16, some other strains are also linked to anal cancer which include HPV 18, HPV 31, HPV 33, and HPV 45. They have also been associated with vulval, vaginal, and cervical carcinomas in females and penile cancer in males.

HPV spreads from one person to another if there is skin-to-skin contact with an infected area of the body. HPV can be passed on during sex which include vaginal intercourse, anal intercourse, and oral sex ,however sex is not mandatory for getting infected with the virus. The single most effective method for complete prevention of HPV infection is absolute avoidance of contact by infected person with anogenital areas.

HPV infection occurs commonly and the body on its own, clears most of these infections but in some cases the infection tends to turn chronic. [11] These chronic infections , particularly with high-risk HPV subtypes , can be the cause of certain cancers which include anal cancer.

Studies have been conducted to study the effects of circumcision on probability of harbouring HPV infection and it has been found that men who have not been circumcised are more likely to be infected with HPV and pass it on to their partners. [12-13] There is no clear explanation for this finding though it is suggested that that the exposed skin on the glans of the circumscribed penis undergoes changes making it more resistant to HPV infection. Another theory is that the surface of the foreskin (which is removed by circumcision) may be more easily volnerable to HPV infection. However circumcision does not afford complete protection against HPV infection - men who are circumcised can still get infected and infect the sexual partners.

On the similar lines, condoms have been found to offer some protection against HPV. Condoms however, cannot protect completely [14-15] because they don't cover every possible HPV-infected area of the body, such as skin of the anal area.

- **HIV Infection**

HIV infection has been found to be an independent risk factor for anal cancer and this cancer has reached epidemic proportions among HIV-infected men who have sex with men (MSM). [16] Effective drug treatment for HIV has decreased the risk for many AIDS related diseases, but same has not been achieved in case of anal cancer. [17-18]

- **Sexual activity**

Promiscuous sexual behaviour increases the risk of HPV and HIV infection , thereby increasing the risk of anal cancer. Receptive anal intercourse also increases the risk of anal cancer in men as well as women, particularly in those younger than 30 years of age inspite of HIV negativity due to sexual exposure to HPV. In USA, the incidence of anal cancer among men who have sex with men (MSM) is higher than the incidence of cervical cancer among women.

- **Smoking**

Smoking has been described in literature as independent factor for increasing the risk of anal cancer. [20] Quitting smoking have been found to reduce this risk . Phillips DH et al in 2004 [21] studied the smoking-related DNA adducts in samples of anal epithelium retrieved from haemorrhoid specimens from active smokers (n = 20) and age-matched life-long non-smokers (n = 16) and concluded that tobacco smoke components inflict genotoxic damage to the anal epithelium of smokers , thereby providing a viable explanation for a causal association between smoking and anal cancer.

- **Chronic immunosuppression not due to HIV**

People with reduced immunity, such as post organ transplant cases on immunosuppressants have higher rates of anal cancer. [22]

- **Gender**

Females are more likely to suffer from anal cancer than males and a ratio of even 5:1 has been mentioned in literature. [2] This is partly due to high prevelance of HPV infection in

females (9-11). For women, certain factors have been linked to an increased risk of genital HPV infection and hence anal cancer, such as:

- Having started sex at an early age
- Having multiple sexual partners
- Having sexual partner who has had many other partners
- Having uncircumcised sexual partner.

- **Race**

Hispanic men had a lower incidence of anal SCC than did non-Hispanic men, but a similar difference was not observed between Hispanic and non-Hispanic women. Cress and Holly also found that Hispanic women had a higher rate of anal cancer than Hispanic men, and that Hispanics overall had a lower incidence of anal cancer than whites and blacks (23). Black men have been reported to have significantly higher incidence of anal SCC than white men, and black women have a significantly lower incidence than the white women. [2,6]

- **Crohn's disease**

Cases with long standing Crohn's disease, particularly the ones with active perianal disease, have a statistically higher risk for the development of anal cancer. [24-27] In cases of Crohn's disease , the relative incidence of anal cancer as a proportion of all colorectal cancers is about 14 % whereas the similar incidence in cases without Crohn's disease is only 1.4%. Different possible reasons have been proposed for this increased incidence of anal cancer in Crohn's disease which include an overall increased propensity of developing malignancies in inflammatory bowel disease and the generally higher incidence of longstanding inflammations in perianal area area due to chronic diseases like fistulae.

Mechanism of tumorigenesis

The mechanism of tumorigenesis have been found to be inactivation of tumor suppression genes via loss of heterozygosity (LOH). In patients who are HIV-negative, mutations in the p53, DCC, and/or APC tumor suppressor genes have been identified as antecedent events. The genomic changes of LOH are most commonly seen at loci 11q23, 17p, 18q, and 5q.7 Much like the development of colorectal adenocarcinoma, a pattern of chromosomal instability is evident in the genesis of the anal cancers. [28] Garvez et al proposed the microsatellite instability rather than chromosomal instability to be the possible pathway for rapid progression towards invasive carcinoma in HIV positive cases. [29]

Anal intraepithelial neoplasia (AIN) – the precursor lesions

Anal intraepithelial neoplasia (AIN) describes the dysplastic changes in the anal canal that are precursors to invasive anal carcinoma. There are three grades of AIN as as shown in Table 2.

Grades 2 and 3 are often grouped together as high-grade squamous intraepithelial lesions (HSIL)/ high-grade anal intraepithelial neoplasia (HGAIN) and are associated with a higher risk of invasive cancer. It has been shown in literature that these lesions are most frequently identified in HIV-positive patients , males who have sex with males (MSM) (30) and in immunosuppressed individuals such as transplanted patients. [22] The natural history of AIN is not entirely known and in particular, the rate of progression of untreated AIN to cancer is not well defined.

AIN has been found to be biologically similar to cervical intraepithelial neoplasia (CIN) . Current treatment for AIN include ablative and topical therapies (31-32). Ablative therapies include surgical excision, infrared coagulation (IRC) and thermal ablation. Topical therapies include immunomodulators such as imiquimod, podophyllin, or 5-FU.

Types of anal cancer

Anal cancers can be broadly classified into anal cancers and anal margin cancers (Table 3).

Anal Canal Cancer

Anal canal cancers arise within the anal canal upto the anal verge and comprise about 85% of anal cancers. Squamous cell cancer of the anal margin is the commonest lesion and the less common variants include cloacogenic cancer and adenocarcinoma. Rest of the malignancies including melanoma, lymophoma and myosarcoma are very rarely reported.

Squamous cell (epidermoid) carcinoma

Squamous cell carcinoma comprises about 75% of all the anal canal cancers and hence in discussed in detail as folowing.

Clinical presentation

Squamous cell cancer of anal canal appears in different forms and may be easily confused with a wide range of benign disorders like fissures, haemorrhoids, dermatitis and anorectal fistulae. [33] It is this similarity with benign anorectal conditions that can result in late presentation and high incidence of early misdiagnosis. [34]

The median age at diagnosis and death for anal/anorectal cancer in US from 2004-2008 was 60 years and 65 years of age respectively. [35] Females are more commonly affected than males. In the US , among the estimated 6230 new cases of anal cancer for the year 2011, 2250 were men and 3,980 were women. In HIV-positive cases, the presentation has been found to be earlier. Place RJ et al in 2001 [36] presented a review based on the tumor registry University of Texas Southwestern Medical Center affiliated hospitals from 1980 through 1999 and found the mean age for squamous cell carcinoma of anus to be 42 years and 36 years for carcinoma in situ.

Patients typically present with a perianal mass with or without pruritus ani, pain or bleeding. Discharge is present in greater than 50% of cases. Bleeding occurs in about 45% of cases. Bleeding from a mass lesion just above anal verge may be ascribed erroneously to haemorrhoids. 30% of patients may suffer from pain or have sensation of ano-rectal mass. 20% of cases may be asymptomatic. A history of anorectal warts may be elicited in about 50% of homosexual males and 20% of females or non-homosexual males. Carcinoma can arise in Crohn's disease in presence of anorectal fistulae and abscesses making the diagnosis very difficult. [37-38] Besides proper examination may be hampered due to discomfort, stricture, or induration of the perineal tissues and at times, even examination under anesthesia can fail to detect the lesion. [37] Anal cancer patients has been reported in literature to present with unusual presentations like isolated inguinal lympadenopathy due to metastasis, multiple abscesses, [39] cerebral metastasis, [40] iris metastasis [41] or disseminated carcinomatosis of bone marrow. [42] The inguinal metastases may be misdiagnosed as an inflammatory node or hernia leading to serious delay in treatment.

Spread of anal cancer

Spread of anal cancer is mainly local and regional. Anal musculature is involved early because the mucosa is very close to the underlying sphincters. Anal canal cancer grows circumferentially and this feature results in narrowing and stenosis of the anal sphincter. When the sphincter is invaded, the tumor spreads into the ischiorectal fossae, the prostatic urethra and bladder in men, and the vagina in women. Anal cancer may spread via the lymphatic vessels (10-15 %) to the perirectal nodes or at a higher level, to nodes at the bifurcation of the superior rectal artery. Hematogenous spread of anal canal cancer develops in fewer than 10% of cases. Liver metastasis is more common than lung or bone metastasis and usually occurs in the case of a tumor arising at the anorectal junction.Cases of metastasis to distant organs like brain and iris are also reported in literature. [41-43]

Anal cancers are staged like other tumors by tumor–node–metastasis (TNM) staging system for anal cancer that has been developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer [44-45] and revised periodically. Currently 7th edition of this staging system is being used and this version was released in 2009 and is depicted in Tables 4-7.

Screening

Since the high-risk groups for anal cancer have been identified , several studies in recent literature have addressed the issue of screening in these high risk groups. Anal swabs for cytological analysis have been proposed as a possible screening method for anal cancer on similar lines to the cervical Papanicolaou (Pap) smear. Sensitivity of anal cytology ranges from 50%–80% and the rates are higher in the HIV positive population. Recent studies have proposed that screening of HIV-positive and HIV-negative homosexual and bisexual men at 2-3 yearly intervals could be cost-effective and have significant benefits on overall life-expectancy. [46-48] Other groups in which there is a potential role for screening include all HIV-positive individuals irrespective of their sexual practices, immunocompromised like post organ transplant cases and women with the past history of cervical dysplasia/cancer.

Possibilities of prevention

Anal cancer has been found to be significantly associated with HPV infection (present in about 80% cases) and this rate is similar to that of HPV-associated cervical cancer and hence it has been suggested that the currently available quadrivalent vaccines have the potential to reduce anal cancer incidence if delivered before initiation of sexual activity. [49-53] Likewise, many workers are advocating programs to educate and encourage sexual safety to minimize transmission of HPV and HIV thereby removing these independently associated and potentially synergistic viral agents as potential contributors toward carcinogenesis. In addition, secondary prevention in the form of evaluation and implementation of screening programs for individuals at increased risk of anal cancer is recommended. [54-55]

Diagnosis of anal cancer

As there are no consistent pathognomonic features of malignancy , physicians need to be cognizant of the possibility of anal canal carcinoma and should have low threshold for subjecting the patient to imaging studies and to biopsy suspected lesions. The imaging modalities used for diagnosis include:

1. Endoanal ultrasound: Endoanal ultrasound has an important role in assessment of anal cancers as it can determine the depth of penetration of anal cancer into the sphincter complex accurately and can be used to gauge accurately the response of these tumors to chemoradiation therapy. [56-59] Otto et al found this modality to be 100 % sensitive in detection of anal cancer and 67% accurate in assessing the depth of tumor as compared to histopathological analysis of serected specimen. However lymph node status cannot be assessed with the endoanal ultrasound.

2. CT Scan: Anal cancer may be directly visualized as a hypoattenuated necrotic mass on a contrast enhanced CT scan. The tumor may however be isoattenuated with respect to the musculature when presence of the lesion can only be suspected from indirect signs like symmetric bulging of the anal sphincters or levator ani muscles in cases of supralevator masses or asymmetry in the thickness of the sphincter and/or levator ani muscles of the two sides or linear stranding and/or asymmetry in the perirectal fat and upper ischiorectal fossa. [60]

3. MRI scan: MRI is a very effective imaging modality for anal cancers and is considered the modality of choice for assessment of loco-regional disease. Roach SC et al [61] found primary and recurrent tumours to be of high signal intensity relative to skeletal muscle on T2-weighted images, and of low to intermediate signal intensity on T1-weighted images . Lymph node metastases were found to be of similar signal intensity to the anal cancer . Goh et al found that MRI features of the tumor or early post treatment imaging are unhelpful in predicting future clinical outcome. [62]

4. PET /CT scan: PET/CT with 18F-fluorodeoxyglucose (FDG-PET/CT) has been found to play an important role in the initial staging and post treatment restaging of patients with anal cancer. [63] PET/CT can help in differentiation between residual viable anal cancer and post-treatment necrosis and fibrosis which is a big challenge with CT imaging and thereby PET/CT helps to determine the need for additional therapy. In particular, PET/CT is sensitive in accurate localization of small anal tumor less than 2 centimeters as compared to other imaging modalities.

Role of sentinal lymph node (SLN) biopsy in anal carcinoma

Inguinal lymph node metastasis is an independent poor prognostic factor for local treatment failure and long term survival. Synchronous inguinal metastasis are found in 10-25 % and metachronous metastasis are reported in 5-25% of patients of anal cancer.Early and accurate evaluation of nodal status is therefore of paramount importance in managing anal cancer. The nodes may be involved even when they are normal sized or minimally enlarged and hence undetectable by other imaging modalities. In a series from Rosswell Park Cancer Institute, 44% of lymph nodes retrieved by clearing technique and documented to have metastasis on histopathological analysis, were less than 5 mm. [64] The failure of detection of metastasis in clinically or radiologically normal looking nodes leads to understaging and adversly affects the outcome of the disease. Conversely

prophylactic inguinal radiotherapy in N0-N1 patients has significant associated complications including inguinal fibrosis,external genitalia edema, lower limb lymphedema and femoral fractures. [65]

The technique of sentinal lymph node biopsy to document nodal involvement in anal cancer was first reported by Kestgar MR et al in 2001 [66] and since than multiple studies [67-69] have proven the safety and reliability of this objective method in detecting micrometastasis in clinically unsuspicious nodes and thereby guiding individual therapeutic decisions in affected cases and avoiding treatment with associated morbidity in unaffected cases. A systematic review of five published series (indexed original articles except case reports) evaluating the outcome of SLN biopsy of clinically normal inguinal nodes in patients with anal cancer has been published by Damin DC et al. In this reviewthe success in identifying the SLN was 90% and 21% of these nodes contained tumor in 83 patients and it was concluded that SLN biopsy can be used effectively and safely in tumor staging. [70] SLN biopsy as a tool for lymphatic assessment in anal cancer has been compared with other imaging modalities in recent studies. Mistrangelo M et al [71] found SLN biopsy superior to dedicated 18F-fluorodeoxyglucose positron emission tomography (PET/CT) .

De Jong J S [72] et al has however advised caution in introduction of this procedure as standard of care in all patients with anal carcinoma. They found SLNs in all 21 patients who underwent a SLNB (100%); 5 patients (24%) had complications after SLNB and 7 patients (33%) who had a positive SLN received inguinal irradiation. However, 2 patients with a tumor-free SLN and no inguinal irradiation developed lymph node metastases after 12 and 24 months, respectively. It is in light of these findings that caution has been advised to avoid undertreatment of patient who otherwise would benefit from inguinal radiotherapy.

Management of anal cancer

The goals of therapy in patients with squamous cell cancers of anal canal are to ablate the neoplasm and to preserve anal sphincter function. The modalities of treatment include:

1. Combined modality therapy (CMT) without surgical intervention: Until few decades ago the standard of practice in managing anal cancer patients was abdominoperineal resection with permanent colostomy. Till only about 30-35 years back, the anal cancer was being managed by abdominoperineal resection, leaving the patient with permanent colostomy. This standard practice was however challenged by Nigro et al in 1974 when they published the results of non surgical treatment of three cases of squamous cell cancer of anal canal and achievement of complete pathological cure after trial of chemo and radiotherapy. Only 30 Gray of external radiation had been administered and chemotherapeutic agents used were mitomycin C and 5 fluoro- uracil (5FU). [73] Ever since that landmark was achieved, workers globally have established the anal preservation with combined chemo radiotherapy (combined modality) as the standard method of managing anal cancer [73-76] and newer techniques and drug combinations are being published in literature to improve the safety profile of this modality and decrease the incidence of side effects. [77-80] With the chemo-radiotherapy regime, complete response is obtained in 70% (64–86%) of patients and overall survival rate at five years is 75% (66–92%). [81] Evaluation of the response to therapy is important and entails careful examination of the anal canal. Since regression of anal canal cancers have been found to continue for up to three or more months after completing the treatment, it is recommended in literature that a biopsy should not be performed sooner than 3 months after the treatment, unless there is evidence of disease progression or other evidence to suggest early recurrence. If pathologic evidence of recurrence is diagnosed, surgical management in form of abdominoperineal resection (APR) is to be contemplated.

Toxicity from combined radiotherapy and chemotherapy for anal carcinoma is significant, with high rates of dermatitis and gastrointestinal toxicity. Later side effects include sexual dysfunction, lower limb venous thrombosis, proctitis, tenesmus, anal stenosis and bladder dysfunction. [81] These early side effects often require treatment breaks decreasing the efficacy of radiation. Recent techniques like intensity-modulated radiotherapy (IMRT) have been found helpful in bringing down the dose of radiation

received by normal surrounding structures, like the bowel, skin, genitalia, and femurs and thereby minimizing adverse effects. [78]

2. Surgical management

a) Salvage operations: A salvage abdominoperineal resection is required in approximately 30% of the cases required due to either primary non-response or recurrence of anal cancer. [82] In majority of such cases, long-term survival can be achieved following salvage surgical operations. [83] In contrast the prognosis have been found to be worse in cases who initially report with lymph nodal metastasis or the ones who receive a radiation dose of less than 55 Gy during initial combined chemo-radiation therapy regimen. [83] The other important prognostic factor of survival following resection is the status of the margin and patients with clear margins (R0) have up to a 75% 5-year overall survival rate. Further predictors of a poor outcome following salvage surgery include tumor size greater than 5 cm, adjacent organ involvement, male gender, and associated comorbidities. Salvage surgery is also reported to be associated with substantial morbidity in up to 72% of patients, due to complications including delayed perineal wound healing, pelvic abscess, perineal wound hernia, urinary retention, and impotence. The poor perineal wound healing is the result preoperative radiation and large size of defects created after complete excision the tumors. Primary closure alone produces poor results and reconstruction by various flaps is the usual requirement. The reconstruction is usually done with tissue flaps including the pedicled omental flap ,gracilis flap, gluteus maximus flap, inferior pedicle rectus abdominis flap and the vertical rectus abdominis myocutaneous flap (VRAM). [84-85] Lefevre JH et al in 2009 presented a series where application of vertical rectus abdominis myocutaneus flap was found to have positive impact on long term survival, recurrence rates, overall morbidity, and wound healing in cases who underwent APR for anal cancer. [84]

b) Local excision: Wide local excision can be less morbid option of management for well differentiated T0 and early T1 tumors if follow up can be undertaken reliably. [86-87]

(c) Miscellaneous surgical interventions:

i) The complete assessment of tumors may require detailed examination and biopsy under general anesthesia.

ii) Temporary stoma formation (loop colostomy or ileostomy) may be required in cases who develop acute toxicity of radiotherapy or are at risk of developing a recto-vaginal fistula. Furthermore, patients with impaired continence due to sphincter invasion need to be defunctioned prior to radiotherapy. Sunesen KG et al in 2011 presented the results of a cohort study (88) and found that after curative-intent radiotherapy or chemo-radiotherapy, 34% of patients had a colostomy, of which 2/3rd were related to tumor and 1/3rd were related to therapy. Large tumor size (> 6 cm) was associated with an increased risk of tumor-related colostomy, whereas history of prior excision was linked to higher incidence of therapy-related colostomy.

Iii) Some surgeons perform inguinal lymphadenectomy for palliative purposes for synchronous groin metastasis and curative inguinal dissection for metachronous metastasis.

iv) Management of extrapelvic metastases.

Inguinal Lymph Nodes Management in anal carcinoma

The current management options for inguinal lymph nodes in patients with squamous cell carcinoma of the anal canal vary according to protocols and preferences of institutions. The conventional approach of prophylactic bilateral inguinal radiation for those with clinically negative nodes and addition of radiation boost for patients with clinically positive nodes is still widely followed in many centers. Surgical lymph node dissection is reserved for primary failure of chemo-radiation (residual disease) and for recurrent disease. In the future, it is possible that a selective approach will be adopted for patients with clinically negative inguinal nodes, particularly in patients with early stage disease. This will likely depend on the wider application of sentinel node sampling and PET scanning to detect nodal disease. Such treatment is desirable, as patients with negative inguinal nodes can avoid potential complications of inguinal node radiation.

Management of recurrent anal cancer

Disease is termed as recurrent when a tumor is discovered after 6 months and as residual tumor if present within 6 months of chemo-radiotherapy. The median time to presentation with features of recurrence is less than 12

months postchemoradiotherapy. Suspicion of recurrence demands comprehensive work up to exclude extra pelvic disease using imaging and biopsy of all lesions. The goal of management is to achieve negative margins around the tumor and therefore most patients will undergo an abdominoperineal excision and permanent colostomy with creation of a large pelvic floor defect. Tumors that have invaded local structures such as the vagina or prostate often require multivisceral resection. The use of intraoperative radiotherapy or brachytherapy may improve local recurrence rates following radical resection where there is concern about an incomplete resection or close resection margins.

Flam et al [89] have however suggested that use of salvage chemoradiation in cases with residual disease following definitive chemoradiation before adapting to radical surgical approach. They also justified the use of mitomycin in a definitive chemoradiation regimen for anal cancer despite greater toxicity, particularly in cases with large primary growths.

Management of metastatic anal cancer

The data about management of metastatic anal cancer is sparse in literature due to rarity of the condition. Even though the outcome of anal cancer has shown marked improvement over last few decades but for patients with extrapelvic metastases, the prognosis continues to be dismal and 2 year survival rate continues to be as low as 10%. One of the important reasons being the biological differences between extrapelvic metastases and the primary anal cancer and its pelvic regional node metastases as reflected by the response to non-surgical treatment. [90] Doses of radiation and concurrent chemotherapy (either 5-FU and mitomycin or 5-FU and cisplatin) which eradicate permanently often quite substantial pelvic tumor masses do not produce more than partial responses in metastases in the liver or other extrapelvic organs. [90] Furthermore the multiplicity of liver metastases and their distribution throughout the liver restricts the doses of radiation that can be used because of the risk of hepatic toxicity. Besides there are no substantial reported attempts at using newer techniques such as focal high dose radiation. There are however recent reports of aggressive surgical approach to management of extrapelvic metastasis. Rogani et al [40] reported a case of 63-year-old female who presented with a solitary right parietal metastasis from a poorly differentiated SCC of the anal canal and was managed with craniectomy and excision. Tokar M [91] successfully repeated aggressive partial hepatectomy in a 54 years old female with recurrent hepatic metastases and suggested that that in selected patients repeated hepatectomy should be part of an aggressive multimodal treatment program with curative intent.

Role of photodynamic therapy in anal cancer

Allison RR et al in 2010 [92] suggested the use of photofrin based photodynamic therapy (PDT) as a new means to salvage local failures or as primary treatment in select patients with early anal cancer. They reported the treatment and outcome of Photodynamic therapy (PDT) in a six patients with anal cancer with failed combined chemo-radiation and two patients with positive margins of resection after excision of small T (1) squamous cell anal cancers. Photodynamic therapy (PDT) was administered on outpatient basis and consisted of infusion of Photofrin at 1.2mg/kg followed 48 h later by red light illumination (630nm). The illumination was delivered by a 5 cm diffusing fiber, treating transphincterally at 300 J/cm followed by microlens illumination at 200 J/cm(2) to the perianal tumor bed with 2 cm margin. All patients completed PDT without adverse effects and maintained local control of disease in the anal region for the length of follow up (18- 48 months).

Role of immunotherapy in management of anal cancer

The viral oncogenes E6 and E7 of high-risk human papilloma virus subtypes such as HPV-16 and HPV-18 are regularly expressed in ano-genital precancerous and cancerous lesions and in recent years thus there have been attempts to develop effective immunotherapy against these gene products. [93] Klencke et al. studied the safety profile and clinical feasibility of using an agent containing a segment of HPV-16 E7 protein for inducing an immune response against E7 and the agent appears to be promising and needs further evaluations. A successful phase II clinical trial has been reported using a vaccinia virus MVA E2 recombinant vaccine, which resulted in significant regression of high-grade cancer

lesions. [94] Similarly Kaufmann et al. undertook a chimeric VLP vaccine trial to study the immunotherapeutic effects of L1 and E7 proteins found the ability of chimeric molecules to induce L1 and E7-specific T lymphocytes and new B cell clones [95] L2E7E6 chimeric vaccines to neutralize HPV infection are also undergoing trials. In the future immunotherapy may emerge as an important modality of management of SCCA.

Prognosis

Tumor size is known to be an important determinant of prognosis . 50-60% percent of patients present with T1–T2 lesions, for which the 5-year survival rate is 80%–90%. A smaller proportion presents with T4 lesions, which have a 5-year survival rate of 50%. The incidence of nodal metastasis is approximately 10% at diagnosis but can increase to as high as 20%–60% for T4 lesions. Mullen et al [83] found that various independent favorable prognostic factors for anal cancer which include recurrence (as compared to persistence) after chemo-radiation (when salvage is potentially curative), absence of lymph node involvement at salvage, and negative resectional margins. Lymph node involvement is an independent poor prognostic factor leading to local treatment failure and long term survival. Salvage inguinal lymph node dissection after failed combined chemo-radiotherapy therapy also has a survival benefit. [83]

Follow-up and surveillance

Patients of anal cancer who have achieved complete remission at 8 weeks should be followed up and thoroughly evaluated 3–6 monthly for initial 2 years and 6–12 monthly from 2- 5 years, with clinical examination including digital rectal examination and palpation of the inguinal lymph nodes. [96] Loco regional relapse is more common than distant metastasis in anal cancer.

Less common anal canal cancers

1. Transitional cloacogenic carcinoma of the anus

Transitional cloacogenic carcinoma of the anus is one of the rare tumors of the alimentary tract. [97] It represents less than two percent of all anorectal cancers and about 1/3rd of anal canal cancers. It arises from the cloacogenic zone of the anal canal proximal to the dentate line. The epithelial lining of this cloacogenic zone is of the transitional variety. This cancer is also named basaloid carcinoma due to the histological appearance of palisade nuclei seen in the periphery of the clumps of cells that are a characteristic feature of this lesion.

Arnold I. Serota et al [98] found the histological pattern of anal cloacogenic carcinoma to be a useful prognostic factor. They found that the glandular variants of these tumors, with an adenocystic or mucoepidermoid pattern, occurred predominantly in men and had a more aggressive course, manifested by early metastases to inguinal and mesenteric lymph nodes, liver, and lung.

Clinical features and risk factors are similar to those of squamous cell cancer of the anal cancer. [98] Mean age of presentation is about 60 years and incidence is higher in females like squamous cell carcinoma of anal canal. Rectal bleeding, a protruding mass, a recent change in bowel habits, perianal pruritis, mucous discharge, recurrent abscesses and rectal pain are the usual presenting symptoms. The onset of symptoms is often abrupt, with the duration of symptoms for cloacogenic carcinoma being generally shorter in comparison to those for squamous cell anal neoplasms. [99] This tumor has been found associated with receptive anal intercourse as early as in 1979 when Cooper HS et al (100) reported this rare lesion in four male homosexuals who had history of engagement in longstanding receptive anal intercourse. Many unusual patterns of presentation have been reported in literature. Krasnoff JB et al [101] reported inflammatory rash over abdomen of poor differentiated cloacogenic tumor. Peppe H et al found [102] that cutaneous metastasis occurs exceptionally in this lesion. Nobusawa S et al [103] reported humoral hyperglycemia in extensive cloacogenic cancer.

The standard treatment is the combined chemoradiotherapy with subsequent repeated local biopsy. Radical surgical excision is reserved for cases with failed chemoradiation. The average life span after diagnosis is about 5 years but there are reports of long term survival even in metastatic tumors. [104] Ohzato H et al [105] documented chemotherapeutic effect of cis-dichlorodiammine-platinum in management of pulmonary and hepatic metastasis. Fayaz S et al [97] reported in 2007 a fifty-two years old

female case of cloacogenic carcinoma of anal canal with extensive liver metastasis who had shown complete remission with 5-Fluorouracil (5FU) and Cis-Dichlorodiammineplatinum(CDDP) chemotherapy only and remained disease free 51/2 years after therapy.

2. Adenocarcinoma of anal canal

Adenocarcinoma of anal canal is one of the rare lesions accounting for only 3 to 9% of all anal canal neoplasms. True anal canal adenocarcinoma need to be differentiated from low rectal adenocarcinoma the distinguishing features include prominent ductal structures, abundance of mucin with organized mucinous pools, and infiltration into the perirectal soft tissue. Anal canal adenocarcinoma mostly originates from anal glands, but cases have been reported where these lesions had developed in chronic fistulae in ano. Multiple risk factors have been identified which include infection with HPV and HIV, history of receptive anal intercourse, smoking, and immunosuppression. As far as the etiology of anal adenocarcinoma is concerned, it is suggested that there occurs a multistep genetic sequence of events which lead to the transformation of normal mucosa to adenoma and finally carcinoma. This concept is similar to etiology of colorectal adenocarcinoma. [106] But due to the submucosal location of the anal glands, the anal adenomas are not easily visible and only become apparent after malignant transformation. Clinical features of anal adenocarcinoma include anal pain, induration of the anal canal, or abscess formation and a palpable lump. The cancer needs to be accurately staged by proper imaging modalities including endoanal ultrasound, MRI or CT scans. Adenocarcinoma arising in fistula-in-ano has been reported to have three characteristic MRI findings which include markedly hyperintense fluid on T2-weighted images, enhancing solid components, and a fistula between the mass and the anus. [107] Management comprises of abdominoperineal resection in combination with neoadjuvant chemoradiation for lesions greater than 2 cm in size (T2), however wide local excision can be performed for small well-differentiated tumors. Makino S et al reported the effective use of preoperative chemoradiation therapy (XELOX/RT) for poorly differentiated anal adenocarcinoma with inguinal node metastasis. [108] Reported disease-free 5-year survival varies from 21 to 58% according to the treatment modality and local recurrences rates range from 20 to 37% at 4 years.

Anal margin cancers

Anal margin cancers account for about 25% of all anal cancers . Squamous cell carcinoma is the commonest lesion. These cancers behave like skin lesions occuring in any other cutaneous site and are staged accordingly.

Perianal squamous cell carcinoma

Squamous cell carcinoma (SCC) is the most frequent tumor of the anal margin of the anal margin but is less common than anal canal SCC, representing one-fourth to one-third of all SCC of the anus. Patients mostly present between 65 to 75 years of age with equal incidence in both genders; however, patients may present early. The presenting features are usually non specific and include pain, itching, burning, bleeding, palpable lump, and discharge. On examination, there is a typical ulcerated lesion with rolled everted edges. There may be a palpable base of the ulcerative lesion within the subcutaneous tissues.The condition is usually misdiagnosed as any other common benign lesion like an anal fissure, fistula, eczema, or hemorrhoids; therefore high degree of suspicion and a biopsy is recommended for any persistent anal margin lesion not responding to conservative therapy. Biopsy reveals majority of these lesions to be well or moderately differentiated keratinizing SCC. When histology is obtained, staging system analogous to cutaneous SCC will allow categorization for treatment recommendations and prognosis. The proper assessment of the extent of locoregional disease is important by visual inspection, digital exam, anoscopy, examination of inguinal lymph nodes and imaging. Distant metastases occur rarely and should be ruled out with imaging including computed tomography (CT) scan of the abdomen, pelvis and a chest. Lymph node involvement has been found to be an important adverse prognostic factor and in one study, the incidence of metastatic lymph nodes is related to tumor size with 0% in tumors less than 2 cm, 23% of tumors 2 to 5 cm and 67% of tumors greater than 5 cm.Other prognostic factors

include the tumor size, differentiation, and invasion of extradermal structures.

Bulky advanced tumors of the anal margin sometimes directly invade the canal making definitive diagnosis of origin difficult even after examination under anesthesia. In these circumstances, treatment is often designed similar to that for tumors of anal canal origin. In contrast, tumors that are limited to the anal margin are treated similar to cutaneous SCC elsewhere on the body.

Favorable lesions include well-differentiated T1 (< 2 cm) or T2 tumors for which a minimal negative margin of 1 cm can be obtained without compromising the anal sphincter. For these tumors, wide local excision (WLE) has been reported as adequate treatment (analogous to resection of cutaneous SCC of other regions of the body) as it preserves continence and obtains adequate local control. These tumors comprise about 60% of all cases. If after local excision,the margins are positive or close, radiotherapy can be administered with good results. If a large skin defect persists after excision, it can be reconstructed by a rotational skin flap or a split skin graft. For early lesions , radiation provides similar control and survival like wide local excision but time spent in treatment and morbidity may be more.

For patients with larger tumors, nodal involvement, or invasion of the sphincter muscle, treatment with chemoradiotherapy, similar to the regimen used for anal canal SCC, is the appropriate treatment providing local disease control ranging from 60 to 100%. Inguinal nodes should always be part of the irradiation field for unfavorable tumors because of the risk of metastasis. Prophylactic inguinal irradiation is well tolerated and omission of groin irradiation can lead to regional or distal recurrence. For persisting tumor following chemoradiation or where disease locally recurs and is not amenable for excision, salvage abdominoperineal resection surgery provides a viable option with a salvage rate of about 50%.

Balamucki CJ et al in 2011 [109] reported that the patients with SCC of the anal margin have a high probability of cure with sphincter preservation after radiation therapy with or without concurrent chemotherapy. Their report was based upon retrospective analysis of 26 cases of anal margin SCC who were cured with RT between 1979 and 2008 at University of Florida. The respective 10-year cause-specific survival, disease-free survival, and overall survival reported were 92%, 88%, and 56%. 24 out of 26 cases had achieved complete tumor regression with local-control rate of 96%. Four patients had developed recurrences (1 local, 2 regional, and 1 local/regional/distant). The two patients had not received elective inguinal lymph-node irradiation and had later on recurred in the inguinal region.

Close follow up for several years is backbone of management proocols due to high risk of local recurrence as well as distant disease. Full anorectal and nodal examination should be performed every 3 months for the initial 2 years after treatment when the risk of recurrece is maximum and then every six monthly for another three years. [110]

Perianal Paget's disease

Perianal Paget's disease was first reported in 1893 by Darier and Coulillaudl and since than about more 200 cases have been reported in literature. [111] This lesion is believed to correspond to an intraepithelial adenocarcinoma arising from dermal apocrine sweat glands.

Patients with this condition tend to present with nonspecific symptoms such as peri anal pruritis, discharge or bleeding. Median age of presentation is around 60 years. Macroscopically the lesion resembles an erythematous plaque which may be ulcerative and crusty or papillary and mimiking benign skin conditions or other perianal diseases such as Bowen's disease, hydradenitis suppurativa, pruritus ani, or Crohn's disease. Microscopically perianal Paget's disease is characterized by large basophilic or vacuolated cells (paget's cells) in the epidermis. With their high mucin content, the Paget cells stain heavily with periodic acid-Schiff. They also contain low-molecular weight cytokeratins and carcinoembryonic antigen; the latter can be seen by immunofluorescence or immunohistochemistry. Expression of c-ErbB-2 oncoprotein may play a role in promoting intraepithelial spread of cancer cells.Perianal Paget's disease may be primary (intraepidermal/intradermal) or secondary disease. The secondary disease is associated with anorectal adenocarcinomas and is thought to be a result of pagetoid phenomenon.

Patients of perianal Paget's disease have been reported to be frequently develop synchronous or metachronous malignancies of

adnexa and viscera. [112] Approximately 50% of patients with anal margin Paget's disease harbor a colorectal neoplasm mandating full colonoscopy for complete evaluation.

When invasive growth is absent wide local excision is recommended. In extensive perianal Paget's disease, a defunctioning colostomy may be required before wide local surgical excision. The surgical defect created may require reconstruction with cutaneous /myocutaneous flaps. Preservation of bowel function is the objective to be achieved. In presence of extensive locally invasive lesions, or a synchronous anorectal adenocarcinoma, abdomino-perineal resection with neoadjuvant chemoradiotherapy is indicated. In an effort to limit radical resection, multiple noninvasive treatments have been tried recently with encouraging results which include photodynamic therapy, radiation therapy, systemic and topical chemotherapy. The recurrence rate can be as high as 30- 60% at 5 years. The frequent association with synchronous/metachronous maligancies and high recurrence rate imposes long term clinical and instrumental follow up.

Bowen's disease

Bowen's disease is a uncommonly reported, slow growing, intraepidermal SCC (carcinoma in-situ) of the peri anal region corresponding to AIN 3. This lesion may serve as a precursor to SCC of the anus and is linked to infection with 16 and 18 HPV genotypes. All the races are affected, with the highest prevalence in patients aged 20 to 45 years and there is almost equal incidence in both genders. [113] They typically present with minor symptoms, such as perianal burning or pruritus. Up to a third of the patients complain of a mass or bleeding lesion. In females ,it is associated with cervical and vulvar intraepithelial neoplasia. On clinical examination, Bowen's disease presents as discrete, erythematous, occasionally brown-red pigmented, noninfiltrating, scaly, or crusted plaques, which sometimes have a moist surface or even nodularity and can be confused with different dermatologic (generally benign) conditions like psoriasis, eczema, tinea corporis, seborrheic keratosis, Paget disease, superficial basal cell carcinoma, actinic keratosis or leukoplakia. A good number of patients report after non-response to local steroidal preparations. The definitive diagnosis may be arrived at only after biopsy of suspected lesions.

The standard treatment is wide surgical excision. The disease needs dedicated followup after surgical excision as very high recurrence rates (up to 30%) have been reported in literature. Wide local excision creates large defects which require reconstruction with skin flaps like rotational v-y skin flap . When surgery is not feasible due to comorbidities or refused, other options are available such as topical chemotherapy (5-FU), laser vaporization (argon or CO2), radiotherapy, immunomodulation (imiquimod) [114-115] and phototherapy.

Basal cell carcinoma (BCC)

Perianal basal cell carcinoma (BCC) is a rare tumor. Even though BCC accounts for about 65-80% of non-melanoma cancers of skin elsewhere, [116] it comprises only 0.2% of BCCs diagnosed in the body and even less than 1% of all cancers in anorectal area.

Men are predominantly affected (60-80%) and presentation age is usually between 65 and 75 years. About 30% of patients have a past history of BCC at other sites. Lesions are generally small with an average size of 1-2 cm. But some cases reports are found in literature where due to lack of suspicion for neoplasm and persistence with management as a benign skin lesion, [117] lesions have grown to bigger dimensions of around 10 cms. [116] This cancer originates from the stratum basale of the epidermis and pilosebaceous follicle units. Certain skin conditions such as basal cell nevus syndrome, xeroderma pigmentosum, and trichoepithelioma [118] may play a role in etiology. Radiation, immunodeficiency, trauma, burns or chronic irritation or infection like chronic perianal fistulae may also play role in perianal BCC development.

Once perianal BCC is diagnosed, whole body needs to be seriously evaluated as there may be multiple associated lesions elsewhere. However perianal BCC seems to be equally aggressive as lesions at other sites. Local examination, BCC is a shallow, mobile, ulcerative lesion with raised edges and minimal potential for metastasis. Histologically perianal BCC is not different from BCCs at other sites of the body. This lesion needs proper differentiation from the similar looking basaloid variant of squamous cell carcinoma as the outcome of the latter condition is worse. Perianal BCC has not been shown to have any association with HPV infection. The management is dependent upon dimension of

the lesion and the extent of its invasion into surrounding tissues. Tumors less than 2 cm are excised along with an adequate margin of at least 1 cm. Lesions larger in size but without extension into the anal canal are excised primarily but require coverage of raw areas with skin grafts or flaps. Mohs microsurgery provides another viable option to excise the tumor with sacrifice of least possible unaffected tissue. Large lesions with extension into the anal canal can be treated with radiation therapy and/or abdominoperineal resection. Five year survival of even 100% has been reported in literature after wide local excision [116] though tumor can recur locally in upto 29% of cases when further treatment is form of re-excision or radiotherapy is needed. In extremely unusual presentations of local recurrences with deep invasion of the anal canal, APR may be mandated.

Malignant melanoma

Malignant melanoma of the anal margin is a rare condition. It accounts for 2 to 4% of all malignant anorectal neoplasmsand is the third most common site after skin and the eye, representing 0.2-0.3%of all melanomas. [119] Symptoms are often nonspecific and include bleeding, pain, and mass. When a lesion is pigmented, melanoma can be confused with with thrombosed hemorrhoids. Amelanotic lesions compromise 30% of the lesions and are more difficult to recognize and their diagnosis depends on demonstration of melanin pigment by immunohistochemistry.

Martinez et al [119] analysed DNA obtained from melanoma arising from chronic perianal fistula by automated direct sequencing and detected V600E (T1799A) mutation in exon 15 of the BRAF gene and concluded that oxidative stress caused by persistent inflammation (like perinal fistulae) plays a significant role in the genesis of BRAF gene mutations.

Wide local excision is the most commonly performed surgical operation for perianal melanoma. Overall prognosis is grave [120] irrespective of the surgical approach and efforts to improve survival with radical resection, including abdominoperineal resection, have not shown benefit.

Overall prognosis is grave and the main determinants are the depth of invasion and stage of disease at presentation. [45, 120] Long-term survival after surgery for anorectal melanoma is a rare occurrence, and the two main surgical options include wide local excision (WLE) and abdominoperineal resection (APR). Wide local excision is the most common approach unless patients have extensive sphincter involvement and are incontinent. [120] The long-term outcome is same for APR and WLE. The response of anorectal melanoma to radiotherapy and chemotherapy is poor. The five year survival reported in literature ranges from 10-26% and the most effective means for improving the dismal prognosis is through earliest possible detection and institution of treatment. [120]

Giant condyloma acuminatum

Giant condyloma acuminatum, also known as Buschke-Löwenstein tumor (BLT) is a very rare sexually transmitted disease that affects the ano-genital region. [121] These tumors are generally large, slow growing cauliflower shaped with tendency to deeply ulcerate and infiltrate into underlying tissues. The causative agent is human pappiloma virus (HPV). The characteristic feature of the disease is the high rate of recurrence (66%) and malignant transformation (40-60%) inspite of histologically benign appearance. [122] But there is no significant metastatic potential. [121,123] The dedicated examination and imaging (MRI) is mandatory to assess the extent and infiltration of the tumor. Wide perineal excision with reconstruction of raw areas is the best surgical choice if the anal canal is not involved. The radical pelvic surgery is indicated only in patients with provable visceral invasion. [121] The incidence of disease can be decreased by mandatory excision of very small condylomas. [121] Radical surgery also plays a significant part in salvage of cases with local recurrences. [45, 123]

Pretreatment counseling and preparation

Before the patient is subjected to chemo radiotherapy, the patient needs to be counseled about the course of disease and treatment. Furthermore, the patient needs:

- Assessment of performance status and optimization of other medical co-morbidity (like renal dysfunction) or active infection.
- Assessment of the cervix, vagina and vulva (in females) and the penis (in males), because of the common role of HPV in these tumors.

- Assessment of HIV status in any patient with a lifestyle that puts them at risk of contracting HIV infections.

Smoking may worsen acute toxicity during treatment and every effort should be made to ensure patients stop smoking before therapy. Sperm banking should be discussed before the commencement of treatment with male patients who wish to preserve fertility. Similarly pre-menopausal women should be informed about loss of fertility and possible requirement of hormone replacement therapy in case of induction of early menopause. The patients with transmural vaginal involvement are at risk of development of an anorectal-vaginal fistula due to radiation therapy and may require a defunctioning colostomy.

Conclusion:

Anal cancers are uncommon lesions but the incidence is showing increasing trend. Early features mimic benign lesions and there is a need to increase awareness so that the patients report early. The physicians should have low threshold for biopsy of all persistant anal lesions. Early diagnosis and appropriate multimodality intervention can improve the prognosis and quality of life of patients.

Acknowledgement

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Table (1). Risk factors of anal cancer

Risk factors for anal cancer
• Human papilloma virus infection • HIV infection • Chronic immunosuppression not due to HIV • Multiple sexual partners • Receptive anal intercourse • Female gender • History of cervical, vulvar, or vaginal carcinoma • Smoking • Crohn's disease

Table (2). Grades of anal intraepithelial neoplasia (AIN).

Anal intraepithelial neoplasia (AIN)	
Grade	**Degree of dysplasia**
1	Low
2	Moderate
3	high

Table (3). Types of anal cancer.

Types of anal cancer	
Anal canal cancers	**Anal margin cancers**
• Squamous cell carcinoma • Transitional cloacogenic carcinoma • Adenocarcinoma • Melanoma • Basaloid carcinoma • Lymphoma	• Squamous cell carcinoma • Basal cell carcinoma • Paget's disease • Bowen's disease • Basal cell carcinoma • Malignant melanoma • Buschke-Lowenstein tumor

Definitions of TNM

The following is a staging system for anal canal cancer that has been described by the AJCC and the International Union Against Cancer. [44]

Table (4). Primary Tumor (T)[a].

[a]*Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.*

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma *in situ* (i.e., Bowen disease, high-grade squamous intraepithelial lesion, and anal intraepithelial neoplasia II–III.)
T1	Tumor ≤2 cm in greatest dimension.
T2	Tumor >2 cm but ≤5 cm in greatest dimension.
T3	Tumor >5 cm in greatest dimension.
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, and bladder.[b]

Table (5). Regional Lymph Nodes (N)[a]

[a]*Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.*

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in perirectal lymph node(s).
N2	Metastases in unilateral internal iliac and/or inguinal lymph node(s).
N3	Metastases in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

Table (6). Distant Metastasis (M)[a].

[a]*Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.*

M0	No distant metastasis.
M1	Distant metastasis.

Table (7). Anatomic Stage/Prognostic Groups[a].

[a]*Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165*

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

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