Società Italiana di Chirurgia ColoRettale
www.siccr.org 2006; 16: 136-145

Cancers of the anus and the perineum - acute manifestations and short note of treatment

Aldo Infantino, Lia Pisegna Cerone

Address for correspondence:
Prof Aldo Infantino
via Paolo Sarpi, 10,
33078 San Vito al Tagl. (PN)
E mail: aldo.infantino@mac.com
Tel 335.6862961
Fax 0434.841592

Abstract

Tumours of the ano-perineal region are infrequent, and often difficult to identify based on their symptoms, especially if these are acute. Objective of this paper is to review the medical literature on ano-perineal tumours with specific attention to their acute symptoms at presentation.
Method: A medline search was carried out including every article published since 1980 that refers to tumours of the anus and the perineum presenting with acute symptoms.
Results: Tumors of the ano-perineal region, when presenting with acute symptoms often simulate more frequent benign inflammatory disease such as anal fistula or abscess. This leads to frequent misdiagnosis and delay in treatment.
Conclusion: Because of their infrequent occurrence tumours of the ano-perineal region are difficult to diagnose, especially when presenting with acute symptoms. A high index of suspicion and liberal use of biopsy and Nuclear Magnetic Resonance (NMR) imaging may lead to earlier diagnosis and improvement in the prognosis.

Keywords: perineal cancer, anal cancer.

Tumours of the anus and of the perineum have variable clinical presentation: acute sepsis is one of the most common, with symptoms such as painful mass, fever and fistulization[1].
The variety and rarity of ano-perineal neoplasms makes gathering and organizing scientific information difficult. Although Medical literature is abundant in case reports, it offered little help in uniformly approaching acute presentation of ano-perineal tumours. Moreover the rarity of these tumours makes the formulation of a unanimously accepted treatment more difficult.[2] Aim of this study is to evaluate the acute symptoms at presentation of ano-perineal cancers.
Method: All medical articles from 1980 in which were present the key words "acute" or "emergency" and "anal cancer" or "perineal cancer" or "perianal cancer" were reviewed. All related articles were also evaluated.
Results: After a review of the selected publications the information was organized according to the histologic tumour type.

Epidermoid carcinomas rarely appear with urgent symptoms: in fact, even at an advanced stage the symptoms are not distinct from chronic benign disorders such as haemorrhoids and fissures; sepsis is usually due to neglected disease. However, some cases presenting with abscesses and fistulas have been described[3]. Carcinomas of the anal canal account for 1-2% of colorectal tumours and for 2-12% of anorectal neoplasia. Eighty-five % of anal cancers are epidermoid tumours and account for 3% of gastrointestinal carcinomas[4]. Tumours of the anal canal affect more frequently older females (M/F 1:3), mainly black single females who live in metropolitan areas and are smokers[5]. Females who have a Human Papilloma Virus (HPV) infection carry a greater risk (3 times more) of anal cancer[6]. The percentage of cancer of the anus among HIV+ patients is relatively high particularly among homosexual men and it is twice in comparison to homosexuals who are not HIV+. HPV infections in the anal canal lead to the formation of flat condylomata that are difficult to visualize but may become evident under high resolution anoscopy after the application of a 3% solution of acetic acid or of Lugol solution[7,8]. The most significative risk factor for the development of invasive anal cancer in HIV+ patients is the length of disease[9]. As a result of the increase of survival, thanks to new retroviral therapies, cancer of the anus has become an increasing problem. Anti-HPV16 (peptideE2 and E7) antibodies have been found in 55% of patients affected by epidermoid anal carcinoma[10]. Recent studies have identified genetic factors such as frequent deletions at chromosomes 3p, 6 and 10 p and epigenic alterations such as inactivation of the TLSC1. The HPV related transformation of the epithelium is a multi-step process, which involves a deregulated transcription of viral oncogenes E6 and E7[11]. The interference of E6 and E7 with the regulators of the cell cycle leads to chromosomal instability. HPV carcinogenesis seems to differ in HIV+ patients since microsatellite rather than chromosomal instability is observed[12]. With the introduction of a highly active retroviral therapy there has been a decrease of HPV related cancer in HIV+ patients[13]. Trans-anal ultrasonography accurately defines local extension of the disease, invasion of sphincter and adjacent organs and the state of mesorectal lymph nodes. Ultrasound T staging was shown to be the only independent factor predicting survival in a multivariate analysis[14]. Synchronous metastasis to groin lymph nodes occur in 10-25% of patients and metachronous metastasis in 5-25% of patients. In a multivariate analysis groin lymph nodes metastasis are among independent prognostic factors for both local recurrence and mortality[15]. The technique of sentinel lymph node (SLN) biopsy is an easy and secure method of evaluating the lymph node status and for obtaining an adequate staging before treatment[16]. In fact negative results make radiotherapy to the groins unnecessary while positive results indicate complete radiation therapy with an extension to the iliac nodes. For SLN biopsy, patients undergo a lymphoscintigraphy after a peritumoural injection of colloidal TC-99[16]. In a review evaluating the efficacy of the procedure 5 studies were analyzed including 84 patients: the SLN was found in 66% to 100% of cases. Of these between 7% and 42% were metastastic[17]. Moreover patients with negative sentinel lymph node did not have groin relapses at a mean follow up time of 18 months. Prophylactic irradiation of the groin is therefore indicated in pN1SN[18] and may not be indicated in pN0SN therefore avoiding treatment related morbidity. The side of groin metastasis is correlated with tumour location. Tumours located on the midline of the anal canal are associated with bilateral lymph nodes in 89% of cases[19]. When the tumour is located on one side of the anal canal synchronous or metachronous metastasis of the groin are ipsilateral in 100% patients[19]. The main treatment of anal cancer is chemotherapy combined with radiotherapy.

Failure to respond to this treatment is a poor prognostic sign[20]. For in situ tumours (< 10 mm) treatment can be local excision only without radiotherapy. For T1 stage tumours local excision is preceded only by external radiotherapy at a medium dose of 45Gy boosted by brachitherapy with a dose of 20Gy[21]. Combined modality treatment with radio and chemotherapy allows good functional results and local control of the disease[22,23]. Standard chemotherapy is 5FU in combination with mitomycin (MMC) but cisplatin (CDDP) is an efficient substitute and is better tolerated than mitomycin. Favourable results have been obtained in terms of toxicity and of local control in phases II/III studies in and in retrospective studies. More recently capecitabine, an oral form of 5FU has been used. Survival after chemotherapy with CDDP seems to be equal or superior to the results of surgery in patients with residual disease at six months from initial non-surgical treatment[24]. In HIV+ patients standard chemotherapeutic regime[25] must be reduced because such individuals develop major toxicity especially when CD4 count is inferior to 200 and therefore require longer intervals between treatment cycles. Conformational radiation therapy reduces the width of the field and therefore the dose to the unaffected small pelvis, bladder and genitals compared to the affected areas. This combines a reduction of acute toxicity with optimal local control of the illness[26]. For local regional relapses, the preferred treatment is abdomino-perineal resection (APR). Radiotherapy prior to salvage surgery increases wound complications[27]. In an article analyzing perineal wound healing after salvage APR, 11 of 18 patients had primary closure of the perineal wound, in 3 patients the wound was left open and in 4 patients it was closed with rectus abdominis myo-cutaneous flap. All dehiscences occurred in patients treated without flap reconstruction[28]. Vaccinations are based on the induction of an immunologic response against infected cells expressing viral antigens E6 and E7 resulting in humoral immunity against viral capsid proteins L1 and L2[29]. The results are encouraging[30].

Perianal Bowen's disease is another rare disease. It is an intraepithelial non-keratinizing carcinoma, that has been historically associated with anal or cervical epidermoid cancer[31,32] The increased rate of HPV-related cancer suggests a causative role[33]. Chronic arsenism is advocated as a possible cause of Bowen's disease[34,35]. The risk of other abdominal malignancy is not higher than in the general population[36] . Bowen disease often appears with pain (4%) and bleeding (24%), and also with signs of mass and itching[37]. Surgical excision is considered the preferred form of treatment[38], but there are controversies on the extent of the surgical margin: in fact local recurrences are in the non -excised perianal skin[39]. If the margins of surgical excision are tumour free, local relapse is unlikely[37,40-42]. Wide resections may require the use of reconstructive flap[33,43]. In case of large lesions a 16 weeks course of 5% topical 5-FU has been successfully used in a study with 6 years follow up[44]. In a recent retrospective study including tumours outside of the perianal region, Bowen's was treated with radiation therapy. Schedules were not uniform in doses and fractions, nevertheless the results were encouraging with a local control rate of 93%[45]. Photodynamic therapy has been successfully used for residual disease but due to the low number of treated patients this technique remains experimental[46]. The same applies to the use of Argon laser[47] and pulsed dye laser[48] both published in case reports. Local treament with imiquimod has been used with success[49] .

Cases of ***adenocarcinoma of the anal canal*** that develops in a longstanding anal fistula are rare[1,50-57] and may present as acute local sepsis[58,59]. Mucinous carcinoma with infiltration of the perineal skin has also been described in Paget's disease[59]. By some authors it is considered a rare variant of anal canal epithelioid tumours [60]. Mucinous adenocarcinoma has been found in rectovaginal fistulas associated with long history of Crohn's disease[61] and has been described as a rare complication of Crohn's disease after proctocolectomy[62]. Also cancer of the rectum may rarely present with a perineal abscess or fistula. The rectal origin can be ruled out with a histochemical test for sialic acid, as no trace of sialic acids can be demonstrated in the anal glands[63,64]. The most common acute symptoms are anal pain, rectal bleeding, discharge and perianal mass. Symptoms are similar to those of benign anal inflammatory conditions, a fact that often contributes to delayed diagnosis[65-67]. Anal glands carcinoma accounts for less than 10% of all carcinomas developing in the anal canal[60]. It seems to be more frequent in males with a long history of perianal disease[68-71], and in the mid-fifty age group[66]. It has been a matter of debate weather the adenocarcinoma origins from the rectal mucosa or from the anal glands[54], but the basis for a correct diagnosis is the histochemical examination that points out the absence of sialic acids which excludes the origin of cancer from the rectum. When

sialic acid is present it is believed that this tumour could have originated from the rectal mucosa, and from there migrated into the anal fistula[72]. Metastasis at presentation are present in 13%[66] to 62%[73] of patients. The most common sites of metastasis are regional lymph nodes, liver, lung, and peritoneum[74]. Surgical resection is the first choice of curative treatment, and additional treatments include chemotherapy, radiotherapy and brachytherapy[75]. Favourable outcome was reported after treatment with external radiotherapy followed by high dose brachytherapy[76,77]. The reported 5-year survival rate ranges between 5% and 40%[66]. The rarity and apparent heterogeneity of this tumour does not allow any comparative study on the treatment. Up to the present day we don't know whether it is possible to differentiate treatment and natural history of anal adenocarcinomas from that of anal squamous or cloacogenic tumours based on histology and anatomic location[78]. Such forms have also been described with a Pagetoid infiltration of the perineal skin[41].

Anal melanoma has been described in literature in little more than 300 cases. The first and most frequent symptom is anal bleeding. The decision whether to carry out local excision with histological free margins or whether, as the majority of authors advocate, to resort to an APR remains controversial[79,80]. Neoadjuvant radiotherapy followed by local excision has been proposed[81]. Nevertheless, as reported in one of the largest published series, anal melanoma has a poor prognosis because of the frequent systemic dissemination: eleven of the 12 patients died with metastasis and only 6/14 patients survived 1 year after treatment. Local excision is followed by high rate local relapse (60%) requiring further surgery[82]. In conclusion, as reported in a review, melanoma continues to be associated with a poor prognosis[83].

Merkel's tumour is a neuroendocrine carcinoma typical of the skin exposed to sunrays. In a case report it was mistaken for a post-partum bleeding haemorrhoid. Excision allowed a correct diagnosis of the disease when it was already metastatic. Local excision is the only course of treatment for this disease, which is usually lethal[84].

Buschke-Lowenstein tumour in its perineal variant is a rare disease secondary to HPV infection. Its pathological characteristics are benign, although it infiltrates and destroys the surrounding tissues. Advanced neglected disease may require urgent treatment for erosions into the rectum and the vagina. At this stage, it is difficult to carry out local excision of the tumour[85].

Lymphomas of the anal and perineal region are infrequent[1,86]. *Leukaemia* of the anoderm, is quite rare. It may appear as perineal ulceration with cutaneous infiltration, but at times, erythema, fistulas or abscesses are absent[87]. Nevertheless, a large perianal mass has been reported as its first sign[88]. The diagnosis is obtained only after the histological exam on biopsies and with appropriate blood tests; it is important to stress that treatment should be conservative (sitz baths, antibiotics, and radiotherapy) and surgery is indicated only when there is a high risk of fulminant sepsis[86]. *Burkitt's lymphoma* is a disease affecting young people and is endemic in tropical Africa. It is frequently localized to the face and the abdomen, but rarely may occur in the perineum. It may appear as a perineal abscess, and only the pathologist is able to offer a correct diagnosis based on biopsies[89]. *Angiocentric T-Cell lymphoma* is a typical subcutaneoaus lymphoma which is mistaken for panniculitis and rarely appears as a lesion of the perineum. The differential diagnosis, once again, is made from the more frequent perianal abscess. In a case report the isolation of a *Staphylococcus Aureus* delayed the diagnosis of neoplasia which was established only after weeks with histological exam of the abscess wall[90].

Paget's extra-mammary disease is rare and may appear in the external genital region, followed by the perineum and the axilla. Cases of triple perineal, genital and axillary localization have also been described. In these cases a higher expression of the CK7 gene is found [91]. The initial symptoms are erythema, pigmentation and cutaneous erosion. When the neoplasia infiltrates the deep tissues, it may require surgery because of severe secretion and pain. Unfortunately there is no specific treatment of the acute symptoms; the treatment of the neoplasia itself is not always well defined; treatment of first choice is extensive surgical excision, but local recurrences are frequent[92,93]. When the area affected is wide and circumferential, staged excision, and coverage with full thickness skin graft, is considered easier to carry out than transpelvic myo-cutaneous flaps, in order to avoid a diverting colostomy[94]. However this approach is followed by a considerable recurrence rate[95]. The role of chemoradiotherapy remains undefined in this disease and the benefit of radiotherapy is controversial. Neoadjuvant or adjuvant chemo-radiotherapy have both been suggested[96,97].

Rhabdomyosarcoma of the perineum may affect organs and soft tissues of the pelvis mainly in young children and adolescents. In the majority of cases, this tumour presents as a perineal mass mimicking an abscess, to the extent that in all the 11 cases presented, initial treatment consisted in antibiotics and incision with drainage before cancer was suspected, diagnosed with biopsy and staged with nuclear magnetic resonance[98]. In adults it is a rare occurence and requires local aggressive surgical treatment; it was suggested that more extensive and radical first intervention leads to a decrease of the disease recurrence[99]. In contrast, in two young patients a conservative approach with local excision and neoadjuvant or adjuvant chemo-radiotherapy, has been described with preservation of anal function and a long term tumour free survival[100]. In the sarcoma group the gastrointestinal stroma tumour (GIST) of the anus belongs to the group of very rare tumours. It presents with rectal haemorrhage and ano -rectal palpable mass. In a case report, transanal excision and long term survival have been described[101].

Kaposi's sarcoma is highly frequent in people with AIDS diagnosis[102], but the anal area is affected very rarely. From an epidemiologic point of view, it has been found that for patients treated with highly active antiretroviral therapy, the AIDS-defining cancers - as Kaposi's sarcoma and non-Hodgkin's lymphoma - may be balanced by the increasing numbers of non AIDS-defining cancers[103]. Unlike anal HIV-associated cancers, the introduction of highly active antiretroviral therapy (HAART) has improved the incidence, clinical features, or overall survival[104]. In addition HAART alone has been successfully used as therapy for early Kaposi's Sarcoma[105].

Perineal necrotizing cellulites has been described in association with ulcerated and suppurated ***rectal cancer***. The infection involves pelvic-perineal layers like in Fournier's syndrome with oedema, fever and perineal pain irradiating to the genitals. The germ more frequently involved is "Pseudomonas aeruginosa". Treatment is carried out urgently, and consists in antibiotic therapy (broad spectrum), surgical debridment and diverting colostomy. Hyperbaric oxygen therapy may help decreasing tissue loss and promote wound healing,. Surgical treatment of cancer of the rectum can be carried out simultaneously or at a later stage, once the conditions of the patient have become stable[106,107].

As we have seen, some of the ano-perineal cancers may appear as an abscess or a mass with a fistula, with more or less rapid growth. It is noteworthy that the same cases may be due to benign neoplasias, which may be locally invasive, such as a pseudotumor caused by ray-fungus disease, leiomyoma, haemangioma, and angiomyxoma. The last two forms will be discussed because of their particular aggressiveness.

Hemangiomas may present with perineal ulcerations. Although the pathology is benign, early diagnosis is preferable in order not to miss a more aggressive malignancy[108].

Aggressive angiomixoma is a mesenchymal tumour that develops from the connective tissue of the perineum or from the pelvis. It is a tumour of great dimensions, and appears as a mass in expansion and/or pain. After an accurate topographic definition with nuclear magnetic resonance (NMR), the surgical procedure chosen is the double access through the abdomen and the perineum. Radical removal of the mass may be difficult due to the widespread sclerosis that involves the pelvic organs[109].

Between tumour metastasizing to or directly invading the anus or perineum, the ***Erysipeloid carcinoma***, from cutaneous metastasis of bladder cancer as well as perineal metastasis of testicular choriocarcinoma, may present as a hard and ulcerated nodule and mistaken for perianal infection[110]. The nodules appeared reddish and painful and only a histological exam is able to offer a precise diagnosis[111].

In all neoplastic diseases presented, the best examination to undergo once tissue is obtained for histological exam is NMR, which provides information on size and boundaries of the mass, anatomy of the fistulous tract, presence of deep abscesses, as well as possible infiltration of rectal wall and the perirectal spaces[112].
In conclusion, every acute anal and perineal manifestation that leads to surgical intervention, must be carefully evaluated. The rare diseases described must be part of the differential diagnosis and excluded, because delayed diagnosis and inadequate treatment may be devastating for the patient, with possible legal controversies.

References

1. Bracey EE, Mathur P, Dooldeniya M, Joshi A, Dawson PM (2003) Unusual perianal tumours masquerading as abscesses. Int J Clin Pract 57:343-6.
2. Cuffy M, Abir F, Longo WE. (2006) Management of less common tumours of the colon, rectum, and anus. Clin Colorectal Cancer. 5:327-37.
3. Nelson RL, Prasad ML, Abcarian H (1985) Anal carcinoma presenting as a perirectal abscess or fistola. Arch Surg 120:632-5.
4. Boman BM, Moertel CG: Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. Cancer 54:114-25, 1984.
5. Maggard MA, Beanes SR, Ko CY: Anal canal cancer: a population-based reappraisal. Dis Colon Rectum. 46(11):1517-23, 2003 Nov.
6. Melbye M, Rabkin C, Frisch M et al: Changing patterns of anal canal incidence in the United States, 1940-1989. Am J Epidemiol 139:772-80, 1994.
7. Hernandez BY, McDuffie K, Zhu X et al: Anal human papillomavirus infection in women and its relationship with cervical infection.Cancer Epidemiol Biomarkers Prev. 14(11 Pt 1):2550-6, 2005 Nov.
8. Ortholan C, Francois E, Gerard JP: Preneoplastic anal lesions and anal canal carcinoma. Bull Cancer. 90(5):405-11, 2003 May.
9. Fagan SP, Bellows CF 3rd, Albo D et al: Length of human immunodeficiency virus disease and not immune status is a risk factor for development of anal carcinoma. Am J Surg. 190(5):732-5, 2005 Nov.
10. Heino P, Eklund C, Fredriksson-Shanazarian V et al: Association of serunm immunogloblin G antibodies against human papillomavirus type 16 capsids with anal epidermoid carcinoma. J Natl Cancer Inst 87: 437-40, 1995.
11. Steenbergen RD, De Wilde J, Wilting SM: HPV-mediated transformation of the anogenital tract. J Clin Virol 32 Suppl 1: s25-33, 2005 Mar.
12. Gervaz P, Hirschel B, Morel P: Molecular biology of squamous cell carcinoma of the anus. Br J Surg. 93(5):531-8, 2006 May.
13. Kim YA, Chung HC, Choi HJ et al: Intermediate dose 5-fluorouracil-induced encephalopathy. : Jpn J Clin Oncol. 36(1):55-9. Epub 2006 Jan 25, 2006 Jan.
14. Giovannini M, Bardou BJ, Barclay R et al: Anal carcinoma: prognostic value of endorectal ultrasound (ERUS). Results of a prospective multicentric study.Endoscopy 33:231-6, 2001.
15. Mistrangelo M, Mobiglia A, Bello M et al: The technique of sentinel lymph nodes in patients with anus neoplasm.Suppl Tumori. 4(3):S32-3, 2005 May - Jun.
16. Damin DC, Rosito MA, Schwartsmann G: Sentinel lymph node in carcinoma of the anal canal: a review. Eur J Surg Oncol. 32(3):247-52, 2006 Apr. Epub 8, 2005 Nov.
17. Fox PA: Human papillomavirus and anal intraepithelial neoplasia.Curr Opin Infect Dis. 19(1):62-6, 2006 Feb.
18. Damin DC, Rosito MA, Gus P et al: Sentinel lymph node procedure in patients with epidermoid carcinoma of the anal canal: early experience. Dis Colon Rectum. 46(8):1032-7, 2003 Aug.
19. Gerard JP, Chalet O, Samiei F et al: Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature.Cancer. 1;92(1):77-84, 2001 Jul. Review.
20. Papaconstantinou HT, Bullard KM, Rothenberger DA et al: Salvage abdominoperineal resection after failed Nigro protocol: modest success, major morbidity. Colorectal Dis.8(2):124-9, 2006 Feb.
21. Ortholan C, Ramaioli A, Peiffert D et al: Anal canal carcinoma: early-stage tumours < or =10 mm (T1 or Tis): therapeutic options and original pattern of local failure after radiotherapy. Int J Radiat Oncol Biol Phys. 1;62(2):479-85, 2005 Jun.
22. Cummings BJ: Current management of anal canal cancer. Semin Oncol. 32(6 Suppl 9):S123-8, 2005 Dec.
23. Ortholan C, Francois E, Gerard JP. Chemoradiotherapy and anal canal

cancer. Bull Cancer. 1;92(12):1039-47, 2005 Dec.

24. Sato H, Koh PK, Bartolo DC: Management of anal canal cancer.Dis Colon Rectum. 48(6):1301-15, 2005 Jun.
25. Kauh J, Koshy M, Gunthel C et al: Management of anal cancer in the HIV-positive population. Oncology (Williston Park). 19(12):1634-8, 2005 Nov.
26. Milano MT, Jani AB, Farrey KJ et al: Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys. 1;63(2):354-61, 2005 Oct.
27. Papaconstantinou HT, Bullard KM, Rothenberger DA et al: Salvage abdominoperineal resection after failed Nigro protocol: modest success, major morbidity. Colorectal Dis. 8(2):124-9, 2006 Feb.
28. Ferenschild FT, Vermaas M, Hofer SO et al: Salvage abdominoperineal resection and perineal wound healing in local recurrent or persistent anal cancer. World J Surg. 29(11):1452-7, 2005 Nov.
29. Sanclemente G: What clinicians should know about human papilloma virus vaccines. Gac Med Mex. 139(2):173-83, 2003 Mar-Apr.
30. Klencke B, Matijevic M, Urban RG et al: Encapsulated plasmid DNA treatment for human papillomavirus 16-associated anal dysplasia: a Phase I study of ZYC101. Clin Cancer Res. 8(5):1028-37, 2002 May.
31. Marfing TE, Abel ME, Gallagher DM. (1987) Perianal Bowen's disease and associated malignancies. Results of a survey. Dis Colon Rectum. 30:782-5.
32. Cleary RK, Schaldenbrand JD, Fowler JJ, Schuler JM, Lampman RM. (1999) Perianal Bowen's disease and anal intraepithelial neoplasia: review of the literature. Dis Colon Rectum. 42:945-51.
33. Sarmiento JM, Wolff BG, Burgart LJ, Frizelle FA, Ilstrup DM. (1997) Perianal Bowen's disease: associated tumours , human papillomavirus, surgery, and other controversies. Dis Colon Rectum. 40:912-8.
34. Chen IS, Kuo HW, Eng HL. Porocarcinoma in a patient with chronic arsenism and multiple Bowen's disease: case report. Dermatol Surg. 31(9 Pt 1):1149-51, 2005 Sep.
35. Kim HJ, Min HG, Lee ES. Bowen's diseases and basal cell carcinomas in a patient. J Dermatol. 26(10):695-7.), 1999 Oct.
36. Chute CG, Chuang TY, Bergstralh EJ, Su WP. The subsequent risk of internal cancer with Bowen's disease. A population-based study. JAMA. 14;266(6):816-9, 1991 Aug.
37. Margenthaler JA, Dietz DW, Mutch MG, Birnbaum EH, Kodner IJ, Fleshman JW. Outcomes, risk of other malignancies, and need for formal mapping procedures in patients with perianal Bowen's disease. Dis Colon Rectum. 47(10):1655-60), 2004 Oct.
38. Kreyden OP, Herzog U, Ackermann C, Schuppisser JP, Spichtin HP, Tondelli P (1996) Eleven cases of anal Bowen's disease. Schweiz Med Wochenschr 126:1536-40
39. Marchesa P, Fazio VW, Oliart S, Goldblum JR, Lavery IC. Perianal Bowen's disease: a clinicopathologic study of 47 patients. Dis Colon Rectum. 40(11):1286-93, 1997 Nov.
40. Alfaro-Rubio A, Nagore E, Serra C et al: Perianal Bowen's disease treated with imiquimod. Actas Dermosifiliogr. 96(7): 468-70, 2005 Sep.
41. Beck DE, Fazio VW, Jagelman DG, Lavery IC. Perianal Bowen's disease. Dis Colon Rectum. 31(6):419-22, 1988 Jun.
42. Ramos R, Salinas H, Tucker L. Conservative approach to the treatment of Bowen's disease of the anus. Dis Colon Rectum. 26(11):712-5, 1983 Nov.
43. Brown SR, Skinner P, Tidy J, Smith JH, Sharp F, Hosie KB. Outcome after surgical resection for high-grade anal intraepithelial neoplasia (Bowen's disease). Br J Surg. 86(8):1063-6, 1999 Aug.
44. Rasmussen OO, Christiansen J. Conservative management of Bowen's disease of the anus. Int J Colorectal Dis. 4(3):164-6, 1989 Aug.
45. Graham BD, Jetmore AB, Foote JE, Arnold LK. Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. ….
46. Lukas VanderSpek LA, Pond GR, Wells W, Tsang RW. Radiation therapy for

Bowen's disease of the skin. Int J Radiat Oncol Biol Phys. 1;63(2):505-10, 2005 Oct.

47. Runfola MA, Weber TK, Rodriguez-Bigas MA, Dougherty TJ, Petrelli NJ. Photodynamic therapy for residual neoplasms of the perianal skin. Dis Colon Rectum. 43(4):499-502, 2000 Apr.
48. Boynton KK, Bjorkman DJ. Argon laser therapy for perianal Bowen's disease: a case report. Lasers Surg Med. 11(4):385-7, 1991.
49. Britton JE, Goulden V, Stables G, Stringer M, Sheehan-Dare R. Investigation of the use of the pulsed dye laser in the treatment of Bowen's disease using 5-aminolaevulinic acid phototherapy. Br J Dermatol. 153(4):780-4, 2005 Oct.
50. Raiss M, Hrora A, Menfaa M, Sabbah F, Ahallat M, al Baroudi S, Hosni K, Benamar A, Oudanane M, Mjahed A, Kettani F, Halhal A, Tounsi A (2001) Adenocarcinoma of the anal glands. Ann Chir 126:452-5.
51. Tsigris C, Pikoulis E, Bramis J, Leppaniemi A, Alexiou D, Bastounis E (2000) Malignant melanoma of the anorectal area. Report of two cases. Dig Surg 17:194-6
52. Marti L, Nussbaumer P, Breitbach T, Hollinger A. Perianal mucinous adenocarcinoma. A further reason for histological study of anal fistula or anorectal abscess. Chirurg. 72(5):573-7, 2001 May.
53. Mates IN, Dinu D, Radulescu G, Iosif C. Infiltrating mucinous carcinoma developed on chronic anal fistula; diagnostic and surgical difficulties. Chirurgia (Bucur). 98(5):459-64, 2003 Sep-Oct.
54. Papapolychroniadis C, Kaimakis D, Giannoulis K, Berovalis P, Karamanlis E, Haritanti A, Leukopoulos A, Kokkonis G, Masoura OM, Dimitriadis A, Giala M, Harlaftis N. A case of mucinous adenocarcinoma arising in long-standing multiple perianal and presacral fistulas. Tech Coloproctol. 8 Suppl 1:s138-40, 2004 Nov
55. Lee SH, Zucker M, Sato T (1981) Primary adenocarcinoma of an anal gland with secondar perianal fistulas. Hum Pathol 12:1034- 7.
56. Navarra G, Ascanelli S, Turini A, Lanza G, Gafa R, Tonini G. Mucinous adenocarcinoma in chronic anorectal fistula. Chir Ital. 51(5):413-6, 1999 Sep-Oct.
57. Schaffzin DM, Stahl TJ, Smith LE (2003) Perianal mucinous adenocarcinoma: unusual case presentations and review of the literature. Am Surg 69:166-9
58. Larghero GC, Scarpettini S, Pavero R, Costanzo A, Cariati A, Berti S, Maritato F, Zoli S (1996) Adenocarcinoma of the anal glands. Description of a clinical case and review of the literature. Minerva Chir 51:573-6
59. Nishimura T, Nozue M, Suzuki K, Imai M, Suzuki S, Sakahara H, Nakamura T, Sugimura H (2000) Perianal mucinous carcinoma successfully treated with a combination of external beam radiotherapy and high dose rate interstitial brachytherapy. Br J Radiol 73:661-4
60. Anthony T, Simmang C, Lee EL, Turnage RH. Perianal mucinous adenocarcinoma. J Surg Oncol. 64(3):218-21, 1997 Mar.
61. Moore-Maxwell CA, Robboy SJ. Mucinous adenocarcinoma arising in rectovaginal fistulas associated with Crohn's disease. Gynecol Oncol. 93(1):266-8, 2004 Apr
62. Keese M, Back W, Dinter D, Gladisch R, Joos A, Palma P. Case report: late perianal mucinous adenocarcinoma after Crohn's disease proctectomy: an oncological rarity. World J Surg Oncol. 2 29;3:42, 005 Jun.
63. Liang MG, Frieden IJ (2002) Perineal ulcerations as the presenting manifestation of hemangioma. Arch Dermatol 138:126-7.
64. Hamada M, Ozaki K, Iwata J, Nishioka Y, Horimi T. A case of rectosigmoid cancer metastasizing to a fistula in ano. Jpn J Clin Oncol. 35(11):676-9, 2005 Nov.
65. Nelson RL, Prasad ML, Abcarian H. Anal carcinoma presenting as a perirectal abscess or fistula. Arch Surg. 120(5):632-5, 1985 May.
66. Abel ME, Chiu YS, Russell TR, Volpe PA. Adenocarcinoma of the anal glands. Results of a survey. Dis Colon Rectum. 36(4):383-7, 1993 Apr.
67. Jones EA, Morson BC. Mucinous adenocarcinoma in anorectal fistulae. Histopathology. 8(2):279-92, 1984 Mar.
68. Tan YS, Nambiar R, Sim CS. Adenocarcinoma associated with chronic

anal fistula. Ann Acad Med Singapore. 18(6):717-20, 1989 Nov.

69. Cirocchi R, Covarelli P, Gulla N, Fabbri B, Bisacci R, Fabbri C, Moggi L. Adenocarcinoma arising from a recurrent fistula-in-ano. Ann Ital Chir. 70(5):771-4, 1999 Sep-Oct.
70. Erhan Y, Sakarya A, Aydede H, Demir A, Seyhan A, Atici E. A case of large mucinous adenocarcinoma arising in a long-standing fistula-in-ano. Dig Surg. 20(1):69-71, 2003.
71. Bronzi R, Puglielli L, Innocenti P, Pizzicannella G, Artese L, Capelli A, Napolitano AM. Mucoid carcinoma of the anus and perianal fistula: a clinical case and review of the literature] G Chir. 10(4):170-2, 1989 Apr.
72. Taniguchi S, Yamanari H, Inada K, Iwamura T, Hokkoku S, Tanaka S, Fukuda M, Setoguchi T (1996) Adenocarcinoma in the anal canal associated with a fistula: report of a case. Surg Today 26:707-10
73. Jensen SL, Shokouh-Amiri MH, Hagen K, Harling H, Nielsen OV. Adenocarcinoma of the anal ducts. A series of 21 cases. Dis Colon Rectum 31:268-272, 1988.
74. Perkowski PE, Sorrells DL, Evans JT, Nopajaroonsri C, Johnson LW. Anal duct carcinoma: case report and review of the literature. Am Surg. 66(12):1149-52, 2000 Dec.
75. Sierra EM, Villanueva Saenz E, Martinez PH, Rocha JR. Mucinous adenocarcinoma associated with fistula in ano: report of a case. Tech Coloproctol. 15, 2006 Mar .
76. Nishimura T, Nozue M, Suzuki K, Imai M, Suzuki S, Sakahara H, Nakamura T, Sugimura H. Perianal mucinous carcinoma successfully treated with a combination of external beam radiotherapy and high dose rate interstitial brachytherapy. Br J Radiol 200; 73:661-4.
77. Wong AY, Rahilly MA, Adams W, Lee CS (1998) Mucinous anal gland carcinoma with perianal Pagetoid spread. Pathology 30:1-3
78. Tarazi R, Nelson RL. Anal adenocarcinoma: a comprehensive review. Semin Surg Oncol. 10(3):235-40, 1994 May-Jun.
79. Weyandt GH, Eggert AO, Houf M, Raulf F, Brocker EB, Becker JC (2003) Anorectal melanoma: surgical management guidelines according to tumour thickness. Br J Cancer 89:2019-22
80. Getz SB jr, Ough YD, Patterson RB, Kovalcik PJ (1981) Mucinous carcinoma developing in chronic anal fistola: report of two cases and review of the literature. Dis Colon Rectum 24:562-6
81. Uner A, Kilic D, Mentes BB, Egehan I, Dursun A. Neoadjuvant radiotherapy in anorectal malignant melanoma. Int J Clin Pract. 57(1):65-7, 2003 Jan-Feb.
82. Moozar KL, Wong CS, Couture J Anorectal malignant melanoma: treatment with surgery or radiation therapy, or both. Can J Surg. 46(5):345-9, 2003 Oct.
83. Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumours of the anal canal: the spectrum of disease, treatment, and outcomes. Cancer. 15;85(8):1686-93, 1999 Apr.
84. Paterson C, Musselman L, Chorneyko K, Reid S, Rawlinson J. Merkel cell (neuroendocrine) carcinoma of the anal canal: report of a case. Dis Colon Rectum 46:676-8, 2003.
85. Dolanc R, Kocher T, Langer I, Marti WR, Pierer G, Harder F (2002) Malignant transformation of perianal Buschke-Lowenstein tumor. Extensive abdominoperineal rectum excision and reconstruction with transpelvic myocutaneous rectus abdominis muscle flap. Chirurg 73:370-4.
86. Porter AJ, Meagher AP, Sweeney JL (1994) Anal lymphoma presenting as perianal abscess. Aust N Z J Surg 64:279-81.
87. Martinez-Hernandez-Magro P, Villanueva-Saenz E, Ramirez-Aceves R (2002) Perianal leukemic infiltration:case report. Rev Gastroenterol Mex 67:199-201.
88. Cresson DH, Siegal GP.Chronic lymphocytic leukemia presenting as an anal mass. J Clin Gastroenterol. 7(1):83-7, 1985 Feb.
89. Rakoto-Ratsimba HN, Razafimahandry HJ, Samison LH, Rakotomalala HS, Ranaivozanany A (2003) A case of Burkitt's lymphoma. Ann Chir. May;128(4):265-7.
90. Dashkovsky I, Cozacov J (2003) Unusual Presentation of Angiocentric T-Cell Lymphoma Mimicking Perianal Abscess. J Cutan Med Surg Apr 30.

91. Van Hamme C, Marot L, Dachelet C, Dumont M, Salamon E, Lachapelle JM (2002) Paget's extramammary disease of the axillae and perineum Ann Dermatol Venereol 129:717-9.

92. McCarter MD, Quan SH, Busam K, Paty PP, Wong D, Guillem JG. Long-term outcome of perianal Paget's disease. Dis Colon Rectum. 46(5):612-6, 2003 May.

93. Beck DE, Fazio VW. Premalignant lesions of the anal margin. South Med J. 82(4):470-4, 1989 Apr.

94. Lam DT, Batista O, Weiss EG, Nogueras JJ, Wexner SD (2001) Staged excision and split-thickness skin graft for circumferential perianal Paget's disease. Dis Colon Rectum 44:868-70.

95. St Peter SD, Pera M, Smith AA, Leslie KO, Heppell J. Wide local excision and split-thickness skin graft for circumferential Paget's disease of the anus. Am J Surg. 187(3):413-6, 2004 Mar.

96. Brown RS, Lankester KJ , McCormack M, Power DA, Spittle MF. Radiotherapy for perianal Paget's disease. Clin Oncol (R Coll Radiol). 14(4):272-84, 2002 Aug.

97. Takahashi A, Yamamoto A (2004) Diagnosis and treatment of extramammary Paget's disease. Gan To Kagaku Ryoho 31356-9

98. Hill DA, Dehner LP, Gow KW, Pappo AS, Crawford D, Pflaumer SM, Furman WL, Hayes-Jordan AA, McDermott MB (2002) Perianal rhabdomyosarcoma presenting as a perirectal abscess: A report of 11 cases. J Pediatr Surg 7:576-81

99. Grobmyer SR, Clary B, Lewis JJ, Delgado R, Woodruff JM, Brennan MF (2001) Adult perineal sarcomas. J Surg Oncol 77:101-4

100. Watanabe Y, Yamaguchi A, Isogai M, Kaneoka Y, Suzuki M, Ando H, Horibe K.Treatment strategies for perianal rhabdomyosarcoma: report of two cases. Surg Today. 2004.

101. Lanteri R, Aliotta I, Racalbuto A, Licata A. Anal GIST in older old patient: a case report. G Chir. 26(4):135-7, 2005 Apr.

102. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, Bordoni A, De Weck D, Franceschi S. Swiss HIV Cohort. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 16;97(6):425-32, 2005 Mar.

103. Bower M, Palmieri C, Dhillon T. AIDS-related malignancies: changing epidemiology and the impact of highly active antiretroviral therapy. Curr Opin Infect Dis. 19(1):14-9, 2006 Feb.

104. Bower M, Powles T, Newsom-Davis T, Thirlwell C, Stebbing J, Mandalia S, Nelson M, Gazzard B. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr. 15;37(5):1563-5, 2004 Dec.

105. Lukawska J, Cottrill C, Bower M. The changing role of radiotherapy in AIDS-related malignancies. Clin Oncol (R Coll Radiol). 15(1):2-6, 2003 Feb.

106. Lamy A, Tissot B, Pigot F (2003) Perineal necrotizing cellulitis disclosing rectal adenocarcinoma. Ann Chir 128:630-2

107. Taniguchi S, Yamanari H, Inada K, Iwamura T, Hokkoku S, Tanaka S, Fukuda M, Setoguchi T. Adenocarcinoma in the anal canal associated with a fistula: report of a case. Surg Today, 26:707-10, 1996.

108. Liang MG, Frieden IJ. Perineal ulcerations as the presenting manifestation of hemangioma. Arch Dermatol 138:126-7, 2002.

109. Amorotti C, Mosca D, Pintaudi U, Maiorana A (2004) Aggressive angiomyxoma of the pelvis and perineum: a case report and review of the literature. Chir Ital 56:717-26

110. Aloi F, Solaroli C, Paradiso M, Formiconi A (1998) Inflammatory type cutaneous metastasis of bladder neoplasm: erysipeloid carcinoma. Minerva Urol Nefrol 50:205-8

111. Ameur A, el Haouri M, Lezrek M, Beddouch A (2002) Cutaneous metastasis revealing a testicular choriocarcinoma. Prog Urol 12:690-1

112. Cuenod CA, de Parades V, Siauve N, Marteau P, Grataloup C, Hernigou A, Berger A, Cugnenc PH, Frija G (2003) Mr-imaging of ano-perineal suppurations. J Radiol 84:516-28.