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Is Primary Surgical Treatment of Anal Carcinoma Safe and Cost-Effective in Low Resource Settings?

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Abstract

The oncological outcome of primary surgical treatment of anal cancer is almost similar to non-surgical treatment with radiotherapy ± chemotherapy for early locally invasive anal cancer. However, the management of anal squamous carcinoma has changed dramatically in the last few years with chemo-irradiation being the treatment of first choice for most lesions. Surgery is the primary treatment modality for small perianal lesions that can be locally excised. Many failures of non-surgical treatment can be salvaged by abdominoperineal excision. Thus, considering the cost, availability, protracted treatment and complications of radiotherapy ± chemotherapy, primary surgical treatment of anal cancer should remain safe and cost effective in low resource settings, provided the patients are pre-operatively well counseled and trained in stoma care management.

Keywords: Anal cancer; Human papillomavirus; Surgery; Chemo-radiotherapy; Stoma

Introduction

Anal cancer is rare, accounting for approximately 4% of large bowel malignancies [1]. However, there is evidence that its incidence is increasing due to the growing endemicity of the Human Papillomavirus (HPV). Areas with a high incidence of anal cancer usually also have a high incidence of cervical, vulva and penile tumors reflecting the common aetiological agent-papillomaviruses [1,2]. The dramatic increase in the incidence of anal cancer in areas where Human Immunodeficiency Virus (HIV) infection is prevalent suggests that the suppression of cell-mediated responses to HPV infection may be important in the pathogenesis of anal cancer [2]. This is also supported by the increased incidence of anal squamous carcinomas in patients receiving systemic immunosuppression following organ transplantation. A history of receptive anal intercourse in males increase the relative risk of developing anal cancer by 33 times compared with controls with colon cancer [3]. A history of genital warts also increased the relative risk (27-fold in men and 22-fold in women) suggesting that a sexually transmissible agent may be an aetiological factor in anal squamous cell carcinoma [3]. Other potential co-carcinogens including other sexually transmissible infective agents such as herpes simplex type II and chlamydia are being investigated. The anal canal and cervix are similar in histology in that each has a squamous-columnar transition zone and has led to the suggestion that anal HPV may progress through grades of dysplasia to carcinoma-*in situ* and thence to squamous cell cancer. This is the basis for screening and treatment strategies aimed at identifying these premalignant changes [4]. Although the natural history of cervical papillomavirus infection and intraepithelial neoplasia is reasonably well understood the same is not true for anal lesions [5]. A quadrivalent HPV vaccine against the high risk (oncogenic) serotypes HPV 6, 11, 16 and 18 is now available but its use is prophylactic. Current recommendations are to vaccinate females before exposure to HPV. The natural history and malignant potential of anal intraepithelial neoplasia are both uncertain [4]. No data are available on the efficacy of this vaccine for preventing anogenital HPV in males [4]. Anal Pap smears are one screening test that has been suggested for homosexual men, especially those that are HIV positive [6]. Over 80% of anal cancers are of squamous origin arising from the squamous epithelium of the anal canal and perianal area; 10% are adenocarcinomas arising from the glandular mucosa of the upper anal canal, the anal glands and ducts. For prognostic purposes most information of clinical value is obtained by distinguishing tumors arising at the anal margin from those in the anal canal and separating them into those greater or less than 5 cm in diameter [6] (Table 1). Tumors <5 cm in diameter and at the anal margin have a more favorable prognosis. Anal melanoma is a very rare with a dismal prognosis, and lymphomas and sarcomas of the anus although increasing in incidence in recent years among patients with HIV infection are even less common [7-10]. However, anal cancers are probably underreported, since some anal tumors are misclassified as rectal tumors and some perianal tumors as squamous carcinoma of skin.

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Early cancers may be confused with papillomas, warts, fissures, and hemorrhoids which may lead to a delay in diagnosis and treatment. The Surveillance, Epidemiology, and End Results Program (SEER) data (2005) quote an incidence of 1.5 per 100000 populations in the USA with similar incidence rates for the UK. Most patients are in their 50s or 60s, and overall, anal cancers are more common in women, although lesions at the anal margin are more common in men [11]. The incidence in HIV negative homosexuals is roughly 35 times that rate and further doubled in HIV-positive males [3]. It appears that in the Highly Active Antiretroviral Therapy (HAART) era this rate has not decreased [12]. Even so, it is generally a rare presenting condition perhaps because the rate of progression is slower than the natural history of the HIV disease [10].

Patterns of Spread and Clinical Presentation

Surgically, the anal region is divided into the anal canal (lying between the anorectal ring and the anal verge), and the anal margin. The natural history, demography and surgical management of anal cancer differ between these areas. Anal cancer spreads locally, mainly in a cephalad direction, so that the tumor may appear to have arisen in the rectum. Advanced tumors may involve the sphincter mechanism causing fecal incontinence and invasion into the rectovaginal septum may cause a fistula. Lymph node metastases occur frequently, initially to the perirectal group of nodes and thereafter to inguinal, hemorrhoidal and lateral pelvic lymph nodes (N0: No Regional Metastasis; N1: spread to perirectal nodes; N2: Unilateral spread to internal iliac and/or inguinal nodes; N3: spread to perirectal and inguinal nodes and/or bilateral internal iliac and/or inguinal nodes). The frequency of nodal involvement is related to the size of the primary together with the depth of penetration. Approximately 14% of patients will present with inguinal lymph node involvement but this rises to 30% when the primary tumor is greater than 5 cm in diameter [7]. Only 50% of patients with enlarged nodes at presentation will subsequently be shown to contain tumor, the rest are due to inflammation or secondary infection [7,13]. These patients with synchronously involved nodes carry a particularly poor prognosis, whereas when metachronous spread develops the salvage rate is much higher. Therefore biopsy or fine-needle aspiration is recommended to confirm involvement of the groin nodes if radical block dissection is contemplated [13]. Distal spread is unusual so hepatomegaly, though it must be looked for is very uncommon. Hematogenous spread tends to occur late and usually associated with advanced local disease. Aggressive tumors metastasize to the liver and occasionally to the bones, abdominal lymph nodes, or even the brain and chemotherapy can often produce a remission of several months. Frequently, other benign perianal conditions will exist in association with anal cancer, such as fistulas, condylomas or leukoplakia. Squamous cell carcinoma may be mistaken for a small benign ulcer and so biopsy is mandatory [3,4,9,10]. The important symptoms of epidermoid anal cancer are pain and bleeding in 50% of cases. The presence of a mass is noted in a minority of patients (25%) and pruritus and discharge occur in a similar proportion. Clinical examination under anesthesia is usually necessary as local tenderness often prevents thorough assessment. This permits optimum assessment of the tumor in terms of size, involvement of adjacent structures and nodal involvement, and also provides the best opportunity to obtain a biopsy. Sigmoidoscopic examination is best performed at this stage. Magnetic Resonance Imaging (MRI) is better than endoanal ultrasound in providing information on spread beyond the anal canal, and serum tumor markers are unhelpful as they do not provide reliable information [13]. No one system of staging has been adopted for anal tumors but the Union International Contre le Cancer (UICC) is the most widely used. To avoid the criticism of the UICC system in requiring assessment of involvement of the external sphincter, the Papillon et al. [7] system of staging has been suggested (Table 1).

Table 1: Staging of anal cancers (anal canal modified (Papillon 1987) [7].

T1	<2 cm
T2	2 cm to 5 cm
T3	>5 cm, mobile
T4a	invading vaginal mucosa
T4b	extending into structures other than skin, rectum or vaginal mucosa
Tx	Insufficient information available
	Anal margin
T1	<2 cm
T2	2.5 cm
T3	>5 cm
T4	extension to muscle, bone, etc

Treatment

Historically and traditionally, anal cancer has been seen as a 'surgical' disease as anal canal tumors were treated by radical abdominoperineal excision and end-colostomy, whereas anal margin tumors were treated by local excision. Over the past decades, non-surgical radical treatments, i.e. radiotherapy with or without chemotherapy, have taken over as primary treatments of choice in most cases. Salvage resection was required only when that fails [13]. Radiotherapists have been treating anal tumors for many years, achieving equivalent survival rates but with advantage of stoma avoidance in the majority of cases which might otherwise have required radical surgery. Ironically, it was a surgeon, Norman Nigro et al. [14], who reported the use of combined chemotherapy and radiotherapy to turn inoperable cases into candidates for surgical salvage, who began to turn surgeons away from operation as first-choice therapy. All patients with anal cancer should now be assessed in an MDT which includes the radiotherapist, surgeon and the clinical oncologist. The patients must be counseled about the local and systemic complications of both radical abdominoperineal excision and chemo-irradiation which include the risk of pelvic autonomic nerve damage with consequent sexual and urinary dysfunction [15].

Arguments against surgery as primary treatment

Ironically, the results of surgery for anal cancer are disappointing for what is essentially a locoregional disease and hence theoretically eradicable by surgery in most cases. The 5-year survival averaged around 55% in most case series [13]. Radical abdominoperineal excision of the rectum and anus is the preferred method which differs little from the procedure used for rectal cancer, but particular care is taken to clear the space (infralevator) below the pelvic floor. Secondly, unfortunately, 20% of cases are incurable surgically at presentation. Thirdly, most postsurgical relapses occurs locoregionally [13]. With the undisturbed pelvis (with well oxygenated tissues with increased tumor radiosensitivity, and less small bowel in the radiation field limiting gastrointestinal toxicity) radiation therapy should reduce local recurrence better than being given after surgery. Postoperatively, there would be the risk of poorer compliance, increased toxicity and a need for higher doses. The development in the 1950s of equipment that

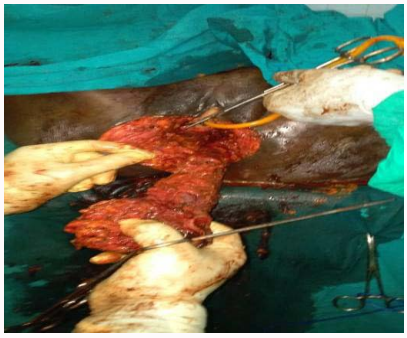

Figure 1: Perineal aspect of abdominoperineal excision of locally invasive anal canal cancer in a 70-year old black African woman (the anorectum containing anal cancer is in the right hand and forceps on posterior vaginal wall). There is adequate clearance of the lateral margin of the tumor with the skin incision at least 2 cm lateral to the tumor taking all the ischiorectal fat. The levator muscles detached from the bony pelvic side walls.

Figure 2: Extraction of specimen (consisting of part of descending colon, sigmoid colon, rectum and anus) *via* the perineum.

could deliver high-energy irradiation by the cobalt source generator or, more recently, by linear accelerators enabled radiotherapist to deliver higher penetrating doses to deeper placed structures with less superficial expenditure of energy. Radiation damage to surrounding tissues was consequently reduced while simultaneously delivering an enhanced tumoricidal effect. Interstitial irradiation alone may produce local tumor control rates of 47%. Improved results have been described using a technique of external beam irradiation, combined with interstitial therapy and two-thirds survived for 5 years, the majority maintaining adequate sphincter function. In the UK high-dose external beam radiotherapy is most commonly used, for which 5-year survival rates of 75% at 3 years have been described [7]. The first experience of using chemoradiation in anal cancer (combined modality therapy) was championed by Norman Nigro [14,16] in 1984 that chose 5-Flurouracil (5-FU) and mitomycin C empirically as a preoperative regimen aimed at improving the results of radical surgery. The radiotherapy then consisted of 30 Gy of external beam irradiation for 3 weeks. After completion of radiotherapy a further infusion of 5-FU was administered and patients later proceeded to abdominoperineal excision. The majority had quite dramatic tumor shrinkage and the tumor was reported to have disappeared completely in his case series. With this success he confined himself to excising the site of the primary tumor after combined modality therapy and later this post treatment 'biopsy' was dropped if the primary tract looked and felt normal after treatment [14,16]. Fourthly, the pre-malignant anal carcinoma in situ lesion may be rapidly progressive in immunocompromised patients (transplant recipients and HIV patients), but as the rate of progression is slower than the natural history of HIV disease there is a need for caution when considering treatment [4]. Radiotherapy may be helpful for symptomatic cases. A less aggressive approach so as to prevent anal stenosis is to excise or biopsy/destroy only gross lesions and submit the remainder to close observation. Chemo-irradiation is the treatment of choice for most invasive anal cancers [13,16]. Salvage abdominal perineal excision can be useful if the CD4 count is >200, otherwise the perineal wound will not heal [9,17-21]. Unfortunately, these modalities of treatment are neither available nor affordable in low resource settings. Finally, stomas are still a taboo in most developing and low resource countries. There are cultural taboos including the Muslim culture. Stoma care is also a major problem in the low resource setting exacerbated by the ensuing management of the excessive fluid loss in the tropical environment. Light clothing, hot climate, high residue diet (vegetables) and poor availability of appliances all make stoma management difficult in the tropics [22]. Although an end colostomy is simple to create as the divided descending/sigmoid colon is brought through the abdominal wall and anastomosis flushed with the skin that allows solid feces falling into the stoma bag, many problems can arise with both the structure and function. Diarrhea and constipation can usually be controlled by drugs, but anatomical defects often need surgical correction. Prolapse of a stoma although looking alarming, unsightly and uncomfortable is rarely dangerous and can be corrected by surgery. Stenosis causing obstruction of the fecal discharge should be treated by refashioning the stoma. Skin rashes are usually the result of failure of an appliance (stoma bag) to fit snugly around the stoma or occasionally from contact dermatitis. Parastomal hernia is a common problem which if troublesome can commonly be controlled by a supporting belt but if severe it can be repaired by surgery [23].

Arguments for surgery as primary treatment

Although the initial treatment for anal cancer for many years was radiotherapy because of the initial unacceptable morbidity and mortality of surgical treatment, it was also recognized since the 1930s that the low-voltage radiotherapy produced severe radionecrosis as a complication [13]. In addition, compared with margin cancer, anal canal cancer is more likely to be locally advanced at presentation and to be associated with subsequent metastases. This would explain the preference by some groups including this author for radical surgery in this setting (Figure 1 and 2) [24]. A randomized multicentre study in 1996 by the UK Coordinating committee on cancer research showed that combined modality therapy gave superior local control of disease compared with radiotherapy alone although there was no overall survival advantage for either treatment regimen [25]. In addition, it is used with caution in elderly people as mitomycin causes much toxicity which includes diarrhea, mucositis, myelosuppression, skin erythema and desquamation. The main risks are thrombocytopenia and agranulocytosis and most oncologists prescribe antibiotic prophylaxis (co-trimoxazole). Late complications include anal stenosis and fistula formation [26]. HIV patients with anal epidermoid cancers are probably best treated with chemoradiation, but have increased toxicity [9,13,26]. 5-Fluorouracil, which has a very short half-life, must be given by slow infusion to ensure synergy with radiation. As surgery became safer, abdominoperineal excision for invading lesions (Figure 1 and 2), and local excision of small lesions, became the standard treatment for the next four decades after 1930. 75% of cancers at the anal margin were treated in the past by local excision based on the perception that margin lesions rarely metastasize. These had disappointing 5-year survival rates of 50% to 70% that might have been better if radical surgery had been applied

more frequently. As anal cancer is relatively uncommon there have been relatively few large follow-up studies after radical surgery, but the 5-year survival rate is about 50% [7,13,14]. The rate of cure for radiotherapy is also at least 50%, but many failures of treatment can be salvaged by abdominoperineal resection. Although radical surgery is now reserved for patients who fail to respond to chemoradiation, patients with obstructive cancers can benefit from a colostomy while they undergo treatment. Surgery is also indicated for small cancers at the anal margin which are less than 2 cm in diameter and have not invaded the anal sphincter. They can be excised locally, but less than 5% of anal cancers fulfill these criteria [13,14]. In addition, there is some evidence that the risk of regional lymph node metastasis is not related to primary tumor size but to the intrinsic biology, which may explain the disappointing results sometimes reported after local excision. Although Nigro's [16] early experience of the dramatic effects of Combined Modality Therapy (CMT) in advanced disease led to wider use of primary nonsurgical approaches, not all groups have been impressed by this approach in more advanced tumors [27,28]. Fifty percent of cases relapsed after complete remission using radiotherapy or combined modality therapy [25]. There are four situations that may require surgery even after primary non-surgical treatment. These are (a) residual tumor, (b) complications of treatment, (c) incontinence or fistula after tumor resolution, (d) subsequent tumor recurrence [13].

Residual tumor

The appearance of the primary site is often misleading after radiotherapy. In most patients complete remission is indicated by the tumor disappearing completely, in some, an ulcer may remain, occasionally looking like an unchanged primary tumor. Only a generous biopsy will reveal if the residual ulcer contains tumor or consists merely of inflammatory tissue [29]. For patients with histologically proven residual disease, a salvage abdominoperineal resection may be the only option as further radiotherapy cannot be given. In fit patients with extensive pelvic disease extending around the vagina or bladder, pelvic exenteration may be considered. This type of surgery carries a high morbidity with impaired wound healing due to the radiotherapy [21,30]. As the salvage rate for radical surgery in disease relapse after CMT may be poor, this may be due to the biologic aggressiveness of this select group of cases and these patients may have fared better if surgery been used as primary treatment [27]. A primary reconstruction of the perineal area using a myocutaneous flap is strongly recommended in these cases.

Complications of treatment

Complications of non-surgical treatment for anal cancer include radionecrosis, fistula and incontinence. Severe anal pain due to radionecrosis of the anal canal lining may necessitate either a colostomy, in the hope that the lesion may heal after fecal diversion, or radical anorectal excision with a flap used to reconstruct the perineum [13,23].

Incontinence or fistula

Occasionally, a tumor is locally extensive that the patient will be rendered incontinent as a consequence of primary tumor shrinkage, due to either breakdown of the rectovaginal septum or sphincter disruption by the tumor. Although rectovaginal fistula may be amenable to repair, sphincter damage is unlikely to improve with local surgery, necessitating abdominoperineal excision of the anorectum in conjunction with a rectus abdominis flap to aid perineal wound healing [31,32].

Recurrent disease

When there is recurrent disease developing after initial resolution, biopsy is mandatory before surgical intervention. These biopsies need to be of reasonable size, number and depth as the histological appearances following radiotherapy can make histopathological interpretation difficult. Careful evaluation of the pattern and extent of recurrence should be undertaken to decide what form of treatment is indicated. If high dose radiotherapy was used for primary treatment, further non-surgical therapy for recurrence is usually contraindicated, making radical surgical removal necessary [33]. Some regard surgical salvage in these circumstances as essentially palliative [27,30].

What about Inguinal metastases?

Inguinal lymph nodes are enlarged in 10% to 25% of patients with anal cancers [1,7,13]. The initial radiotherapy field includes the tumor and the inguinal lymph nodes. The patient is treated over 4-5 weeks and this inevitably gives rise to moist desquamation of the perineum which heals three weeks after the completion of radiotherapy [14,16]. Young women will suffer an artificial menopause and azoospermia in men. A boost requiring a short general anesthetic is generally given to the primary tumor by using a radioisotope. However, although inguinal lymph node involvement may be treated by radiotherapy, some argue in favor of surgery [23,24]. Histological confirmation is advisable before radical groin dissection as up to 50% of cases of inguinal lymphadenopathy may be due to inflammation alone [34]. Enlargement of groin nodes sometime after primary therapy is most likely to be due to recurrent tumour. Radical groin dissection is indicated in this situation with up to 50%, 5-year survival [35].

Patient welfare

Although the surgeon will be the first to suggest that a stoma will be necessary, preoperative explanation and counseling will usually be undertaken by a stoma care nurse. The presence of a stoma is enough of a burden for a patient which is increased enormously if the stoma is badly sited or badly constructed. To avoid the problem of bad sitting the stoma care nurse should examine the patient before the operation to determine the ideal position. Features to be taken into account include the nature of the skin surrounding the proposed stoma which should flat and free from scars and the presence of anatomical irregularities such as the umbilicus and anterior superior iliac spine. Note should also be taken of clothing, such as the position of belts. Most patients cope well with their stomas. However, they may benefit from association with one of the voluntary organizations for the welfare of patients with stomas [36].

Conclusion

The oncological outcome of primary surgical treatment of anal cancer is almost equivalent to non-surgical treatment with radiotherapy ± chemotherapy for early locally invasive anal cancer. Considering the cost, availability, protracted course and complications of radiotherapy ± chemotherapy, primary surgical treatment of anal cancer should remain safe and cost effective in low resource settings. This is provided the patients are pre-operatively well counseled and trained in stoma care management by stoma care nurses.

References

1. Frisch M, Melbye M, Møller H. Trends in incidence of anal cancer in Denmark. BMJ. 1993;306(6875):419-22.

2. Palmer JG, Scholefield JH, Coates PJ, Shepherd NA, Jass JR, Crawford LV, et al. Anal cancer and human papillomaviruses. Dis Colon Rectum. 1989;32(12):1016-22.

3. Daling J, Weiss N, Hislop T, Maden C, Coates RJ, Sherman KJ, et al. Sexual practices, sexually transmitted diseases and the incidence of anal cancer. N Engl J Med. 1987;317(16):973-7.

4. Scholfield J, Hickson W, Smith J, Rogers K, Sharp F. Anal intraepithelial neoplasia: part of a multifocal disease process. Lancet. 1992;340(8830):1271-3.

5. Palefsky J. Humam paillomavirus in HIV-infected patients. Top HIV Med. 2007;15(4):130-3.

6. Scholfield JH, Northover JM, Carr ND. Male homosexuality, HIV infection and colorectal surgery. Br J Surg. 1990;77(5):493-6.

7. Papillon J, Mayer M, Montbarbon JF, Gerard JP, Chassard JL, Bailly C. A new approach to the management of epidermoid carcinoma of the anal canal. Cancer. 1983;51(10):1830-7.

8. Miles AJG, Wastell C. AIDS and the general surgeon. Recent advances in Surg. 1991;14:85-98.

9. Beck DE, Wexner SD. AIDS and the Colorectal Surgeon. Part II; anorectal diseases. Postgrad Adv Colorectal Surg. 1990;0:1-13.

10. Weledji EP. Human immunodeficiency virus and the anorectum. Alex J of Med. 2013;49(2):163-7.

11. Shiels MS, kreimer AR, Coghill AE, Darragh JM, Devesa SS. Anal cancer incidence in the united States 1977-2011: Distinct patterns by histology and behavior. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1548-56.

12. Palefsky JM, Holly EA, Efirde JT, Da Costa M, Jay N, Berry JM, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS. 2005;19(13):1407-14.

13. Uronis HF, Bendell JC. Anal cancer-an overview. Oncologist. 2007;12(5):524-34.

14. Nigro ND, Vaitkevicus VK, Considine B Jr. Combined therapy for cancer of the anal canal. A preliminary report. Dis Colon Rectum. 1974;17(3):354-6.

15. Weledji EP, Eyongeta D. The anatomical basis for autonomic dysfunction in surgical coloproctology. Int J Surgic Res. 2014;3(1):7-14.

16. Nigro N. An evaluation of combined therapy for squamous cell cancer in the anal canal. Dis Colon Rectum. 1984;27(12):763-6.

17. Smit S. Guidelines for surgery in the HIV patients. Continuous Medical Education (CME) 2010;28(8): 356-8.

18. Albaran RG, Webber J, Staffes C. CD4 Cell counts as a prognostic factor of major abdominal surgery in patients infected with the Human immunodeficiency virus. Arch Surg. 1988;133(6):626-31.

19. Horberg AM, Hurley LB, Klein DB, Follansbee SE, Quesenberry C, Flamm JA, et al. Surgical outcomes in HIV-infected patients in the era of highly active antiretroviral therapy. Arch Surg. 2006;141(12):1238-45.

20. Weledji EP, Nsagha D, Chichom AM, Enoworock G. Gastrointestinal surgery and the acquired immune deficiency syndrome. Ann Med Surg (Lond). 2015;4(1):36:40.

21. Weledji EP, Palmer J. Audit of perineal wound healing after primary closure of the perineal wound without parineal drainage in abdominal perineal resection for malignancy. Int J Surg Res. 2016;5(2):21-5.

22. Roy Douglas. Surgery in tropical countries. In: Taylor, O'Higgin, Chisholm, editors. Surgical Management. London: William Heinemann medical books Ltd; 1986.

23. Phillips RKS. A companion to Specialist Surgical practice: Colorectal Surgery: Phillips Robin, editor, 4th edn. Saunders Elsevier 2009.

24. Shepherd NA, Scholefield JH, Love SB, England J, Northover JM. Prognostic factors in anal squamous cell carcinoma: a multivariate analysis of clinical, pathological and flow cytometric parameters in 235 cases. Histopathology. 1990;16(6):545-55.

25. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Coordinating Committee on Cancer Research. Lancet. 1996;348(9034):1049-54.

26. Cummings B, Keane T, O'Sullivan B, Wong CS, Catton CN. Mitomycin in anal canal carcinoma. Oncology. 1993;50(Suppl 1):63-9.

27. Zelnick R, Haas P, Ajlouni M, Szilagyi E, Fox TA Jr. Results of abdominoperineal resections for failure after combination chemotherapy and radiation therapy for anal cancers. Dis Colon Rectum. 1992;35(6):574-7.

28. O'Brien PH, Williams MR, Jenrette JM 3rd, Pitre BR. Combined modality therapy in the treatment of epidermoid carcinoma of of the anus at the Medical University of South Carolina. J S C Med Assoc. 1993;89(7):333-6.

29. Northover J. Place dela chirurgie dans le cancer epidermoide de l'anus. Lyon Chir 1988;87:82-84.

30. Tanum G. Treatment of relapsing anal carcinoma. Acta Oncol. 1993;32(1):33-5.

31. Salat SA, Alkali A. Anal cancer- a review. Int J of Health Sci (Qassim). 2012;6(2):206-30.

32. Nisar PJ, Scott HJ. Myocutaneous flap reconstruction of the pelvis after abdominoperineal excision. Colorectal Dis. 2009;11(8):806-16.

33. Longo WE, Vernava AM 3rd, Wade TP, Coplin MA, Virgo KS, Johnson FE. Recurrent squamous cell carcinoma of the anal canal. Predictors of intial treatment failure and results of salvage therapy. Ann Surg. 1994;220(1):40-9.

34. Pinna Pintor M, Northover JMA, Nichlls RJ. Squamous cell carcinoma of the anus at one hospital from 1948 to 1984. Br J Surg. 1989;76(8):806-10.

35. Boman B, Moertel C, O'Connell M, Scott M, Weiland L, Beart R, et al. Carcinoma of the anal canal. A clinical and pathological study of 188 cases. Cancer. 1984;54(1):114-25.

36. Irving MH, Hulme O. Intestinal stomas. In: Jones DJ, Irving MH, editors, ABC of Colorectal Diseases. 1st edn-BMJ publishing group 1993.