G Chir Vol. 38 - n. 4 - pp. 176-180
July-August 2017

original article

Five year experience of the treatment of squamous cell carcinoma of the anus

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SUMMARY: **Five year experience of the treatment of squamous cell carcinoma of the anus.**

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Objectives. *The best treatment of early stage anal squamous cell carcinoma (SCC) is under debated. Wide local excision (WLE) may be considered adequate for stage 1 anal margin cancer. This study demonstrates our experience in treatment of patients with SCC over 5 years.*

Patients and methods. *We conducted a retrospective study of patients who had undergone anal screening or anal cancer surveillance between October 2010 and 2015 in our department. Each patient underwent anal Pap test, HPV test PCR HPV DNA and cytology by Thin Prep. The examinations were performed by Proctostation THD©. Data were collected and analysed.*

Results. *We included 25 patients, 16 male (64%) and 9 female (36%). Twenty-four patients had SCC and 1 patient had adenocarcinoma. Of this cohort: 10 underwent chemoradiotherapy (CRT) because T3-4 N1-2 M0, 13 underwent only surgery because T1/T2 and 2 patients had CRT and surgery because they already have had anal cancer treated in the past with CRT. Seventeen patients (68%) of this cohort, including 5 with micro-invasive SCCs, had regular follow-up without recurrences. Four patients (17%) died from metastatic disease and 4 patients (17%) had recurrent disease.*

Conclusions. *In this small cohort we demonstrated satisfactory results in treatment of SCCs, underlining the effective role of surgery in early stages of SCC. Screening program and follow up were fundamental to identify early stage and recurrent disease. Also we found the High-resolution video-proctoscopy a valid diagnostic tool.*

KEY WORDS: SCC - Treatment - Early stages - High-resolution video-proctoscopy - HIV - Screening.

Introduction

Anal carcinomas are relatively rare malignancies, representing less than 2.5% of all gastrointestinal carcinomas (1). In Europe, the annual incidence is 1 in 100000. The incidence is higher in women and increasing. Approximately 2000 males and 2300 females are diagnosed with anal cancer every year (2).

The most common malignancy of the anal canal and anal margin is squamous cell carcinoma (SCC). Screening programs using anal cytology and high-resolution anoscopy have been proposed for high-risk populations (MSM and HIV– women with a history of anal intercourse or other HPV-related ano-genital malignancies) based on the achievements obtained in cervical cytology screening. However, no randomised control study has yet demonstrated the advantage of screening in these high-risk populations (3).

Anal carcinoma treatment is based on current NCCN guidelines, recommending 5-FU with mitomycin C and concurrent radiotherapy (CRT, chemoradiotherapy) for all invasive/localized anal canal carcinomas (Nigro protocol) (4). 5-FU with cisplatin is the recommended therapy for widely metastatic disease (5). Anal margin cancers are treated in a slightly different fashion from anal canal tumours. Early stages, such as T1 and early T2 anal margin cancers that do not involve the sphincter muscle might be treated with wide local excision with 1 cm margins (6). Overall, while chemo radiation remains the main treatment for most patients with anal cancer, surgery may still be indicated in early stages, recurrent and palliative disease.

We describe results of a 5-year experience of treatment of SCC in patients with and without HIV.

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Patients and methods

We conducted a retrospective study of patients who underwent anal screening or surveillance between October 2010 and January 2015 at the University of Perugia Medical Centre. The study was approved by a local Institutional Research Board that gave permission to proceed without further patient consent and allowed publication of images as long as they remain anonymous. We included patients with AIDS, immunosuppressed transplanted patients, patients with previous treatment for leukaemia-lymphoma, individuals with a history of sexually transmitted diseases (STD), previous anal neoplasia, women presenting a history of cervical cancer or of cervical, vulvar or vaginal squamous intraepithelial lesions and those patients presenting with anal symptoms who underwent anal examination in the Proctologic Unit. Data were collected for the presence of anal cancer and additional risk factors, including smoking and previous diagnosed anal, vaginal, oral HR HPV. Anal cytology was classified on the basis of the 2001 revised Bethesda System of cervical cytology classification (7). Each patient underwent anal Pap test, HPV test PCR HPV DNA and cytology by Thin Prep, high resolution video-proctoscopy with and without acetic acid 3%.

Surveillance and screening

The examinations were performed by Proctostation THD© device (THD SPA, 2016. Correggio RE, Italy), which consists of a portable touch screen 16-9 connected to a high resolution camera. The camera (Figure 1) is wrapped in a disposable cover to prevent contamination during the examination. The apex of the cover is connected to a disposable self-illuminating anoscope. The anoscope is equipped with side windows in order to perform biopsies and ablative treatments under visual control. The patient management software allows storage of demographic and clinical data in patients' personal folder, which can be updated during the follow-up examinations. Each examination is recorded as a complete video with associated audio; the operator can also take pictures. Electronic software allows adapting several parameters such as contrast, brightness, resolution, zoom, etc. Contrary to what happens when using the colposcope adjusted for anoscopy, VPS with proctostation is performed in the Sims position, as a standard anal examination, therefore patients need no bowel preparation. The operator inserts the anoscope with aid of an introducer, which is then replaced by the camera. The operator then uses the tool with a single hand, observing the examination on the monitor. A pedal allows the operator to turn the recording on/off and to take pictures of areas of interest. Afterwards, acetic acid is introduced. If necessary, biopsies can be performed under direct vision by introducing forceps through the side windows without changing position or switching off the instrument. Once the examination is concluded, VPS is extracted and the disposable part is disposed of en bloc.

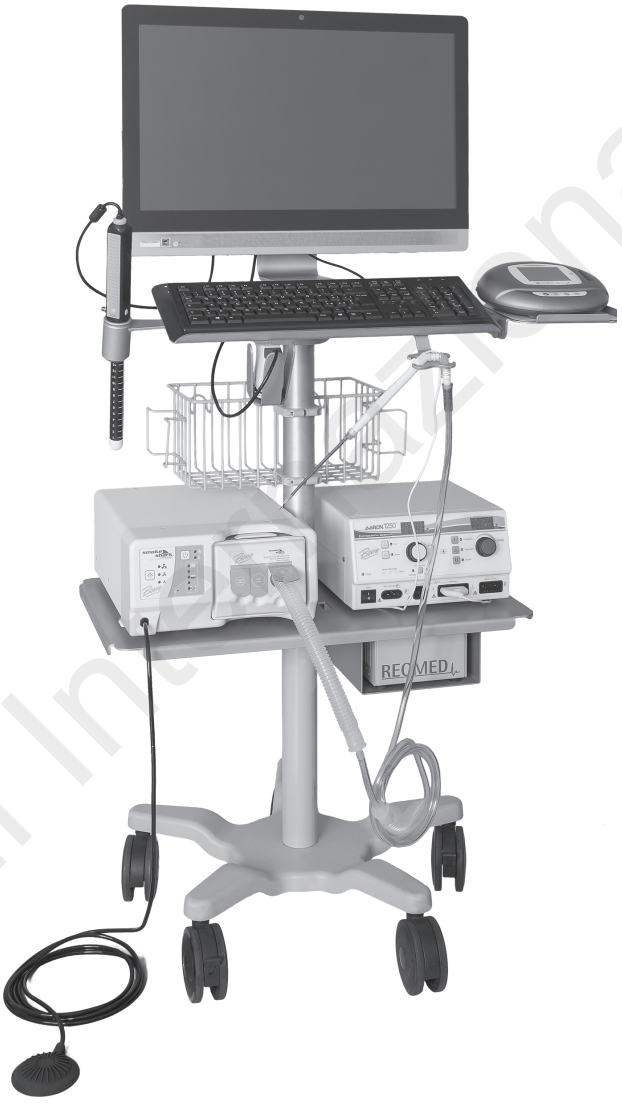

Figure 1 - The THD Proctostation with the HR proctoscopy is a great tool to detect recurrent lesions.

Treatment

Once a diagnosis of SCC was made (Figure 2), the patients were treated on the basis of our local protocol and discussion at our Multidisciplinary Team (MDT) meeting, composed of radiotherapists, oncologists, radiologists and surgeons. Patients affected by cT1 of the anal canal and cT1/T2 of the anal margin underwent WLE without CTR. Subsequently, in cases of micro-invasive SCC with free margins, they underwent observation and biopsy after 6-8 months, and in cases of involved margins they underwent re-excision of the mar-

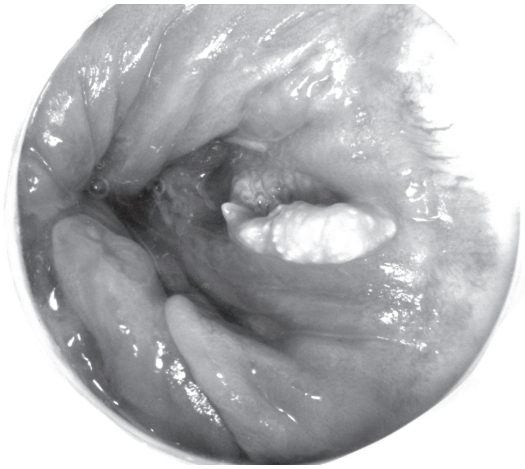

Figure 2 - SCC lesion visualised with the HR proctoscopy.

gins and eventually CRT. For cases of invasive cancer, ultrasound of the inguinal-femoral lymph nodes, thorax and abdomen CT scan and pelvic MRI were performed and Nigro-protocol was recommended, followed by close surveillance with biopsy.

WLE is performed in a standard way. Briefly, the edges of the lesion were defined with indelible pen and dissection was performed with a scalpel. The specimen was then orienting to define the edges with landmarks and finally a picture of the specimen was taken. Particular attention in the dissection of the lesion and in the preparation of the specimen is thought to guarantee better results in terms of staging, treatment and control of the disease.

Results

We identified 24 cases of SCC and one case of adenocarcinoma of the anal canal in a patient with perianal Paget's disease, resulting in a total of 25 patients. The median age was 58 years (range 18-76). We had 16 male (64%) and 9 female (36%). Fourteen patients (58%) had HIV: 11 male (79%) and 3 female (21%). Among the male HIV group, 90% had a history of anal intercourse and 75% were smokers. Among the female HIV group, 2 (67%) of them had previous treatment for CIN.

One patient had previous Hodgkin's lymphoma; another had HIV and HBV infection. Five patients had a diagnosis of micro-invasive SCC. The interval between the HIV diagnosis and SCC diagnosis was a median of 14 years (range 8-19). A diagnosis of AIDS was made in all patients and they were all on anti-retroviral therapy. Median nadir CD4 count was 65 cell/mmc.

Across the whole cohort ten patients were treated with CRT, two by surgery combined with CRT and twelve by surgery alone. The first group, consisting of 10 patients with T3-4, N1-2, M0 of the margin/canal/both, underwent CRT according to Nigro protocol. In one of these patients, with extensive anal and rectal infiltration cancer, and in another, with rectovaginal fistula, a palliative colostomy was necessary in addition to CRT. The second group, 2 patients, affected by recurrence of a previous anal cancer were treated with CRT alone as first treatment and underwent surgery associated with CRT in this study. The third group of 13 patients (52%) with cT1/T2 of the anal margin and cT1 of the anal canal underwent surgery alone. One patient of the group treated by surgery alone, presented advanced disease and underwent abdomino-perineal excision (APE) and follow up.

Most of the SCCs were situated in the anal margin (44%), others in both anal margin/canal (24%) and less in the anal canal (12%).

Within the group of patients with HIV 79% had confirmed SCC, this was more than those without HIV. Also in this HIV positive group, two patients with anal margin SCC developed AIN3 and one with anal canal SCC developed HPV+ lesions after WLE. These were treated by cycles of imiquimod which was efficacious in 2 of the cases.

The median follow-up of the total cohort (25 patients) was 36 months (range 12-60 months). Seventeen patients (68%) had regular follow-up and no evidence of recurrance. Four patients with invasive SCC (17%) died from metastatic spread to the liver (n = 2) and local relapse (n = 2) within 5 years of diagnosis. Four patients (17%), 2 affected by previous anal cancer and then treated by WLE and other 2 treated by CTR alone, had local recurrence of disease; three of them underwent re-excision and 1 died from a separate diagnosis of bronchial cancer.

The pathology reports after WLE demonstrated five cases of micro-invasive SCCs (superficially invasive squamous cell carcinoma anal, SISCCA, based largely on depth, <7 mm in size, and width of invasion, < 3 mm) (14); these patients were treated by surgery alone and did not have any recurrence during the follow up. Most of the patients (92%) had free margins after WLE, while only 8% underwent re-excision because of margin involvement.

Discussion

Treatment of anal cancer is dependent on location and stage. A clear distinction must be also made between anal canal carcinoma and anal margin carcinoma, since the treatment can differ radically between the two (6, 8). Until the mid-1980s, radical surgery was the cornerstone of treatment. However, with the development of combined modality therapy, surgery as the primary

therapeutic option has generally been abandoned. Still today, smaller lesions (<2 cm in diameter), involving the anal margin and not poorly differentiated may be treated by primary surgery in the form of wide local excision provided adequate margins (>5 mm) can be obtained without compromising sphincter function (9). Stage I anal margin SCC is treated by local excision (re-excision or chemoradiation if involved/close margins), while for stage I anal canal SCC surgery (radical or local excision) is generally contra-indicated as primary treatment option (9). A recent study demonstrated the success of local excision alone in cases of T1 of the anal verge in high risk patients, for example, people living with HIV (PLWH) (10). Conversely, extensive surgery is reserved for those with persistent, progressing and recurrent disease after treatment with the Nigro protocol (11). Although aware that our study is limited by a small cohort, our data demonstrated satisfactory results, in terms of recurrences and surveillance, in patients affected by T1 of the anal canal and T1-2 of the anal margin treated by wide local excision without CRT. Moreover, by following a meticulous excisional surgical technique every time we performed a WLE, we achieved specimens with free margins in 92% of the cases. We demonstrate that surgery in the early stages of the anal margin/canal SCC without CRT is an effective treatment and did not observe any cases of recurrent disease. Of the four cases presenting to us with recurrent disease all underwent effective treatment with surgery alone without recurrence. Recurrences were identified during the follow-up period and all patients with invasive disease underwent subsequent CRT. The follow up clearly has a fundamental role in detecting recurrence lesions, thanks especially to the new tool for anal screening (HR-VPS) which has been used in our department. Until recently, anal cancer involved the necessary use of CRT for early and advanced stages and also after surgical excisions of tumours. Nowadays things have changing. After a complete excision of the cancer in the anal margin, confirming the radial and deep margins negativity for residual disease, the use of radiotherapy on the cancer bed would represent an overtreatment since no tumoral tissue would be irradiated. If there is no evidence of lymph node involvement is confirmed at clinical staging, again, the CRT would have no target both in the tumoral primary site than in the nodal region. This approach could not only reduce the morbility related to CRT, but also leaves a full treatment option in case of anal or lymph node recurrence arising during follow up. It is obvious that a more conservative treatment requires a close and precise follow up as a fundamental tool to control the disease over time.

By comparing the results in the HIV- and HIV+ groups, this increases the value of the anal screening for HIV+ patients which allows timely diagnosis of anal cancer and to treat the disease with less discomfort for the patient by offering surgical treatment excluding CRT at early stages. We also used imiquimod therapy in two of the HIV + patients, this because we support this therapy even though further studies are needed to document its utility to prevent high-grade dysplasia and/or anal cancer (12).

The comparison between invasive and minimally invasive SCC (SISCCA) showed the more aggressive behaviour of infiltrating SCC which caused the four cases of relapse and the four deaths we recorded in our data. Patients with histopathological results positive for SISCCA, after biopsy and more often surgical excisions can be treated by surgery alone. According to the literature SISCCA is potentially amenable to conservative sphincter-sparing surgical therapy (13) with lower morbidity. The identification of SISCCA category would have the benefit of clearly identifying patients that might be amenable to surgery alone, excluding the risk for metastasis. Our data demonstrated the satisfactory use of surgery alone without evidence of recurrences in patients with micro-invasive cancer in 5 years follow up.

Among patients with invasive anal cancer, a preventive screening by anal Pap tests has not been always carried out, either because several diagnoses were antecedent the period of study or because of the reluctance of the patients to inform the physician of the presence of symptoms and/or anal lesions. For the rest of the patients, an early diagnosis was made either due to the readiness and timeliness of the patients to communicate signs and symptoms or an efficacious anal screening. A significant difference in disease evolution and prognosis was made by precocious diagnosis mainly based on extensive screening program with digital rectal evaluation (DRE), anal pap-test and high resolution anoscopy.

We have been using the high resolution video-proctoscopy (HR-VPS) which has many objective advantages as convenience, easy to use, low cost and availability of HD images.

Certainly, a meticulous screening tool as HR-VPS allows bettering recognizing suspicious lesions, to particularly define the staging of the disease and to have the best quality of data collection for a functional follow up.

The inclusion of a patient with an adenocarcinoma raised on a Paget's disease highlights the idea of an effective screening program of SCC. Rare conditions of the anal region can be found and these should be treated properly: so, doctors dedicated to the treatment of anal cancer should be aware of the very rare histologic entities as well as the most common SCC related to HPV infection.

It is also important to consider risk factors when we value the increase of the recurrence. It is clear in the literature that HIV infection and increased number of high-grade dysplasia increases the risk of recurrence (13-16). Indeed, most of the patients with recurrences were

HIV+ (75%) and recurrence of HPV+ lesions and AIN3 after WLE were recorded only in HIV+ patients. The cases of death were only in HIV+ patients and one of these patients was affected by a viral co-infection (HIV-HBV).

Conclusion

Anal squamous cell carcinoma is a rare malignancy and its treatment is still debated. While the primary therapy is chemo radiation, surgery has a role in the treatment of persistent or recurrent disease and earlier lesions, involving the anal margin and not poorly differentiated, with good results. A valid screening program is the key aimed to reduce the progression of AIN to SCC and, consequently, the incidence of invasive cancer in high risk population. Our results showed a clear efficacy of surgery in the early stages of the disease in anal margin and anal canal cancer. Anal Pap smear remains fundamental in the screening. We also found the high resolution proctoscopy a great tool to detect recurrent lesions in follow up time.

Declaration of conflicting interests

All the authors declare that there is no conflict of interest regarding the publication of this paper.

Funding acknowledgement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Research ethics

An ethical approval was not necessary for this study being a retrospective service evaluation. An Institutional Research Board approval was anyway gained.

Informed consent

This was a retrospective study and an informed consent was no necessary.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. Cancer J Clin. 2013;63:11-30.
2. Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst. 2013;105:175-201.
3. National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology. Anal Carcinoma (Version I). Fort Washington, National Comprehensive Cancer Network, 2016.
4. Nigro ND, Vaitkevicius VK, Considine B. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum. 1974;17:354-356.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Anal Carcinoma Version 2. 2014. Available from: URL: http://www.nccn.org/professionals/physician_gls/ pdf/anal.pdf. Accessed on Feb 26, 2016 and Oct 11, 2016.
6. Osborne MC, Maykel J, Johnson EK, Steele SR. Anal squamous cell carcinoma: an evolution in disease and management.. World J Gastroenterol. 2014 Sep 28;20(36):13052-9.
7. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287:2114-2119.
8. Young SC, Solomon MJ, Hruby G, Frizelle FA. Review of 120 anal cancer patients. Colorectal Dis. 2009 Nov;11(9):909-14.
9. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, Arnold D; European Society for Medical Oncology (ESMO); European Society of Surgical Oncology (ESSO); European Society of Radiotherapy and Oncology (ESTRO). Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol. 2014 Oct;40(10):1165-76.
10. Alfa-Wali M, Dalla Pria A, Nelson M, Tekkis P, Bower M. Surgical excision alone for stage T1 anal verge cancers in people living with HIV. Eur J Surg Oncol. 2016 Jun;42(6):813-6.
11. Gilshtein H, Khoury W. Surgical management of anal cancer. Minerva Chir. 2015 Apr;70(2):141-5.
12. Sanclemente G, Herrera S, Tyring SK, Rady PL, Zuleta JJ, Correa LA, He Q, Wolff JC. Human papillomavirus (HPV) viral load and HPV type in the clinical outcome of HIV-positive patients treated with imiquimod for anogenital warts and anal intraepithelial neoplasia. J Eur Acad Dermatol Venereol. 2007 Sep;21(8):1054-60.
13. Goldstone SE, Johnstone AA, Moshier EL Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. Dis Colon Rectum. 2014 Mar;57(3):316-23.
14. Gaisa M, Ita-Nagy F, Sigel K, Arens Y, Hennessy MA, Rodriguez-Caprio G, Mullen M, Aberg JA, Cespedes M. High Rates of Anal High-Grade Squamous Intraepithelial Lesions in HIV-Infected Women Who Do Not Meet Screening Guidelines. Clin Infect Dis. 2017 Feb 1;64(3):289-294.
15. Meyer JE, Panico VJ, Marconato HM, Sherr DL, Christos P, Pirog EC. HIV positivity but not HPV/p16 status is associated with higher recurrence rate in anal cancer. J Gastrointest Cancer. 2013 Dec;44(4):450-5.
16. Darragh TM, Colgan TJ, Thomas Cox J, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC; Members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Int J Gynecol Pathol. 2013 Jan;32(1):76-115.