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ANAL CANCER IN HIV-POSITIVE PATIENTS: STATE OF THE ART

F. MARTELLOTTA[1], F. FIORICA[2], A. MALORGIO[2], A. STEFANELLI[2]

[1]Department of Medical Oncology, National Cancer Institute, IRCCS, Aviano (PN), Italy
[2]Radiotherapy Department, Azienda Ospedaliera S. Anna, Ferrara, Italy

Abstract – *The anal carcinoma is substantially a rare neoplasm. Its incidence, however, also due to HPV infection is increased in the past 30 years. For many years, the surgical treatment has been the first therapeutic option, but with a major impact on quality of life (permanent colostomy) and unclear results on the local control. Radiochemotherapy with 5-fluorouracil (5-FU), mitomycin C, and/or cisplatin is currently the standard of conservative therapeutic approach. Current data show that toxicity, particularly myelosuppression and neurotoxicity, is significantly more frequent in the patients treated with the combined therapy compared with patients treated with antineoplastic drugs alone. The introduction of HAART into clinical practice has had a dramatic impact on the natural history of HIV-related disease, including cancer. Chemotherapy plus HAART-treated patients have a better survival than chemotherapy alone, suggesting that the reduction of opportunistic infections (OIs) morbidity by HAART other than the good performance status of these patients, may improve the overall outcome of the combined treatment patients. Also, the new techniques of intensity modulated radiotherapy (IMRT) seem to have an important role on the lower incidence of side effects and improve local control of the disease.*

KEYWORDS: *Anal cancer and HIV, Anal cancer, HIV and cancer, Radiochemotherapy.*

BACKGROUND

The anal carcinoma is substantially a rare cancer. Its incidence, however, also due to HPV infection is increased in the past 30 years. For many years, the surgical treatment has been the first therapeutic option, but with a major impact on quality of life (permanent colostomy) and unclear results on the local control.

Radio-chemotherapy with 5-fluorouracil (5-FU), mitomycin C, and/or cisplatin is currently the standard of conservative therapeutic approach. Current data show that toxicity, particularly myelosuppression and neurotoxicity, is significantly more frequent in the patients treated with the combined therapy compared with patients treated with antineoplastic drugs alone.

The introduction of HAART into clinical practice has had a dramatic impact on the natural history of HIV-related disease, including cancer. Chemotherapy plus HAART-treated patients have a better survival than chemotherapy alone, suggesting that the reduction of opportunistic infections (OIs) morbidity by HAART other than the good performance status of these patients, may improve the overall outcome of the combined treatment for these patients.

Also, the new techniques of intensity modulated radiotherapy (IMRT) may have an important role on the lower incidence of side effects and in improving local control of the disease.

EPIDEMIOLOGY, RISK FACTORS AND PATHOGENESIS

The anal squamous cell carcinoma (ASCC) is uncommon; it represents more than 4% of all anorectal malignancies and 1.5% of gastrointestinal malignancies. Several studies *have demonstrated*

Corresponding Author: Antonio Stefanelli, MD; e-mail: a.stefanelli@ospfe.it

that the incidence of ASCC is increasing. In the US in 2011 there were estimated 6230 new cases and 780 related deaths with a greater incidence in the 70th decade with the females more commonly affected than males (ratio 5:1). This cancer has shown a steady increase in patients with the virus human immunodeficiency acquired (HIV)[1]. The introduction of the highly active antiretroviral therapy (HAART) had a dramatic impact on morbidity and mortality of individuals living with HIV and had contributed to the decline in HIV-related diseases.

However, the incidence of some non-AIDS-defining cancers (NADCs) as Hodgkin's lymphoma, ASCC, hepatocellular carcinoma and lung cancer, did not change and remaining significantly higher in the HAART era. Recent epidemiologic data describe not only a different ASCC incidence rate between HIV-positive and HIV-negative population but also increased incidence rates of anal cancer among HIV-infected patients in the highly active antiretroviral therapy (HAART) era compared to the pre-HAART era. Data on ASCC in HIV-positive patients show a predominance of advanced disease at the time of diagnosis compared to general population where ASCC is predominantly a loco-regional disease and rarely metastatic. Furthermore, the risk of developing ASCC is more common among HIV-infected people with lower CD4+ T cell counts and more advanced clinical stage of HIV disease. This evidence is probably a result of the effect of HIV infection and immune suppression on the natural history of anal HPV infection[2].

ASCC associated multiple risk factors as the sexual activity; Human papilloma virus (HPV) infection; HIV infection and immune suppression. Several epidemiologic studies reported a high incidence receptive anal intercourse, history of genital warts or gonorrhoea in men with anal cancer compared to controls; whereas women with ASCC were more likely to have a history of genital warts, of anal intercourse or to be seropositive for herpes simplex virus or *Chlamydia trachomatis*. HPV is a DNA double-stranded virus that causes infection of squamous epithelia. HPV infection is the most common sexually transmitted infection in the general population and approximately 75% of all sexually active adults acquire a genital HPV subtype during their lifetime[3]. There are over 80 different HPV subtypes, at least 23 of which have been shown to infect the anogenital mucosa. High-risk HPV subtypes (16; 18; 31; 33; 35; 39; 45; 50; 51; 53; 56; 59; 68) are most frequently associated with invasive anal cancer or high-grade dysplasia lesions in population-based studies, whereas low-grade HPV subtypes are more frequently identified in lesions with only low-grade dysplasia. Similarly to cervical cancer, invasive anal cancer has precursors known as anal intraepithelial neoplasia (AIN) 2-3 or high-grade squamous intraepithelial lesions (H-SIL). AIN 1 and low-grade squamous intraepithelial lesions (L-SIL) are not considered direct precursors of invasive anal cancer but may precede the later development of AIN 2-3 or H-SIL. The simultaneous presence of multiple HPV subtypes is common in HIV positive patients with ASCC because HIV infection not only increases susceptibility to HPV persistence but also increases the risk of acquisition of new HPV infections and reactivation of latent infections[4,5].

High-risk HPV-16 and -18 encode for three oncoproteins (E5; E6; and E7) with growth stimulating and transforming properties. The integration of viral HPV-DNA in host genome results in chromosomal instability and favours the progression from AIN towards invasive carcinoma[2]. HIV infection favours the persistence of HPV infection through a gradual loss of control over HPV replication within infected cells during the early stage of carcinogenesis. The role of immune suppression in anal cancer development derives from reports on higher risk for cancer in patients receiving chronic immunosuppressive therapy after solid organ transplant.

ANATOMY, HISTOLOGY AND CLINICAL PRESENTATION

The anus is divided into the mucosa-lined anal canal and the epidermis covered anal margin (anal verge). Most of the anal canal is lined by squamous mucosa, which is present between the anal verge and the dentate line. Tumors arising below the dentate line are more often keratinizing squamous-cell carcinomas whereas tumors arising above the dentate line in the transitional mucosa are frequently non-keratinizing squamous-cell carcinomas. Anyway, both tumors appear to share similar biology and prognosis[2,6]. ASCC spreads via lymphatic system and less commonly by hematogenous spread. Lymphatic drainage of anal cancer depends on the location of the tumor in relation to the dentate line. Tumors below the dentate line drain to the inguinal and femoral nodes while tumors above the dentate line drain to the perirectal and paravertebral nodes. Liver and lung are most common sites of distant metastases[2]. Approximately 50% of patients affected by ASCC presents a perianal mass with or without pain and rectal bleeding as the most common initial symptoms. A history of anorectal warts may

TABLE 1. Randomized trials from 1996-1997.

Trial	*Patients*	*Schedule*	*Complete remission (RC) %*	*Local control (LC) %*	*Overall survival (OS) %*
UKCCCR, 1996	279	RT: 45 Gy	30	39 (3 years)*	58 (3 years)
(T1-T4; N0, N+)	283	CRT: RT + 5-FU (1 g/m2 D1-4, 29-32) + MMC (12 mg/m2 D1)	39	61 (3 years)*	65 (3 years)
Flam et al, 1996 (ECOG/RTOG;	145	CRT: RT 45-50.4 Gy/25-28 fx + 5-FU	85	66 (4 years)*	67 (4 years)*
T1-T4; N0, N+)	146	CRT: RT + 5-FU + MMC (10 mg/m2 d1, 29) + 9 Gy Boost (+ 5-FU/Cis)	92	84 (4 years)*	76 (4 years)*
Bartelink et al, 1997 (EORTC;	52	RT: 45 Gy/25 fr + split course 6 weekly 15-20 GyBoost, if CR/PR	54*	55 (3 years)*	
T1-2; N+ any T3/4)	51	CRT: RT + 5-FU (750 mg/m2 d1-5, 29-33) + MMC (15 mg/m2 D1)	80*	69 (3 years)*	

*$p < 0.05$

be present in about 50% of homosexual males and 20% of females or nonhomosexual males. ASCC arise in Crohn's disease in the presence of anorectal fistulae and abscesses making the diagnosis very difficult[1]. ASCC patients have been reported in the literature to present with an unusual presentation like isolated inguinal metastatic lymphadenopathy, multiple abscesses, cerebral metastasis or disseminated carcinomatosis[7].

A tumor-node-metastasis staging system (TNM) for anal cancer has been development by the American Joint Committee on Cancer (AJCC)

TABLE 2. Randomized trials Phase 3 and a Phase 1 that compared 5-FU and cisplatin and cisplatin MMC.

TRIAL	*ARM 1*	*ARM 2*
RTOG 98-11 +	5-FU + cisplatin concurrent chemotherapy for 2 cycles neoadjuvant and concurrent radiotherapy: √ Radiotherapy (45 Gy/ 25 fr + Boost 10-14 Gy) √ 5 FU 1 g/m² day 1-5, 25-29 day concurrent RT √ Cisplatin 75 mg/m² day 1 e 25 of radiotherapy	Concomitant chemoradiotherapy Mitomycin 5 FU concurrent radiotherapy: √ RT (45 Gy/ 25 fr + Boost 10-14 Gy) √ Mitomycin 10 mg/m² day 1 e 25 of radiotherapy √ 5 FU 1 g/m² day 1-5, 25-29 of RT
ACT II	Concurrent CT/RT cisplatin -5FU √ Radiotherapy (50,4 Gy/28 fr) √ Cisplatin 60 mg/m2 day 1 and 25 RT √ 5 FU 1 g/m² day 1-5, 21-25 RT √ After concurrent CT-RT 2 cycles cisplatin e 5 FU	Concurrent Mitomycin + 5 FU √ Radiotherapy (50,4 Gy/28 fr) √ Mitomycina 12 mg/m² day 1 RT √ 5 FU 1 g/m² day1-5, 21-25 RT no CT maintenance after CTRT
ACCORD 03	CT 5 FU + Cysplatin 2 cycles neoadjuvant e concurrent RT: √ RT (45 Gy 25 fr) √ 5 FU 800 mg/m² day 1-4 and 21- RT √ Cysplatin 80 mg/m² day 1 e 25 RT √ RT with boost	Concorrente CT RT Mitomicina + 5 FU: √ RT (45 Gy 25 fr + Boost 10-14 Gy) √ Mitomycin 10 mg/m² day 1 e 25 RT √ 5 FU 1 g/m² day 1-5, 25-29 RT √ RT with boost 15 Gy
EORTC 22011-40014	Concurrent CT-RT mytomicin 5FU: √ RT (36 Gy / 20 fr) √ Cysplatin 25 mg/m² weekly √ Mitomycin 10 g/m² day 1RT √ *Split course 2-5 weeks* √ RT 23,4 Gy /13 fr √ Cysplatin 25 mg/m² weekly √ Mitomycin 10 g/m² day 1 RT	Concurrent CT/RT Mitomycin + 5 FU: √ RT (36Gy /20 fr) √ 5 FU 200 mg/m² continuous infusion RT √ Mitoyicin 10 mg/m² 1 day RT √ *Split course 2-5 weeks* √ RT 23,4 Gy /13 fr √ 5Fu 200 mg/m2 continuous infusion √ Mitomycin 10 g/m² day 1 RT

(Table 1)[8]. Staging include abdominal and pelvic CT scans and 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)[2]. PET FDG has been found to play an important role in the initial staging and post-treatment restaging of patients with anal cancer and can help in differentiation between residual metabolic anal cancer and post treatment necrosis and fibrosis. Moreover, PET FDG is sensitive in accurate localization of small anal tumor less than 2 centimetres[1,2].

SCREENING

Both anal and cervical cancer share an etiologic link to HPV high-risk subtypes infections and they share a similar cytological grading system for dysplasia. Anal pap test, therefore, should be performed to screen high-risk populations including men have sex with men and HIV positive individuals for anal cancer precursors. Abnormalities detected by anal Pap test are most valued by high-resolution anoscopy (HRA) which is similar to colposcopy. The sensitivity and the specificity of the test, evaluated through a comparison between PAP test results and results of HRA ranged from 69% to 93% and from 32% to 59% respectively and are comparable to those of studies examining data obtained from cervical cytological examination versus colposcopy.

Since 2009 EACS (European AIDS Clinical Society) guidelines proposed the screening with digital rectal exam and anal Pap test with a frequency of 1-3 years in high-risk individuals based on the evidence that screening and treatment of AIN 1 reduce the risk of progression to anal cancer[2].

Concomitant chemo-radiotherapy (CRT) and the role of HAART

Historical approach to invasive anal cancer was surgical: abdominoperineal resection as suggested by Miles et al. with a reported overall 5-year survival rates of 38-71%[1]. The studies of Nigro 1974 have changed the therapeutic approach in the treatment of ASCC. The authors observed a pathological complete remission disease in some patients with ASCC underwent abdominal perineal amputation after neoadjuvant treatment with mitomycin C and 5-FU and concomitant low-dose radiotherapy (30 Gy). These results suggested the hypothesis that ASCC could be treat with a radical conservative therapeutic approach, chemotherapy and radiotherapy with concomitant 5-FU and mitomycin C (MMC)[9]. Two large multicentric randomized trials (EORTC trial and UKCCCR Anal Cancer Trial Working Group) published between 1996 and 1997 have demonstrated a significant increased local control and overall survival with concomitant chemo-radiotherapy (CRT) versus radiotherapy (RT) alone (Table 1).

The EORTC trial included 110 patients with locally advanced disease randomized between RT alone (45 Gy/ 25 fractions) followed by boost after 6 weeks based on the clinical response of the disease (15 Gy if complete remission (CR), 20 Gy if partial remission (PR)) versus the same RT regimen plus chemotherapy with 5-FU and MMC (scheme 5FU 750 mg/m^2 Day1-5 and MMC 15 mg/m^2 Day1).

The UKCCCR (ACT 1) study (any stage of disease) included 585 patients randomized between RT alone (45 Gy) versus RT plus chemotherapy with 5-FU and MMC scheme (5FU 1000 mg/m^2 Day1-4 and MMC 10 mg/m^2 Day1). Patients were assessed after to 6 weeks: those with a good response received a boost RT; conversely, those with poor response were going to salvage surgery. The percentage of complete remission (CR) to the revaluation after 6 weeks was strongly in favour of the combined treatment: EORTC: 54% CR in the arm RT alone *vs.* 80% in the arm CRT; ACT 1 30% CR in the arm RT alone *vs.* 39% in the arm CRT. The lower incidence of local recurrence at 3 years was significantly in favour of the combined treatment: ACT 1 61% in the arm RT alone vs. 39% in the arm CRT ($p < 0.0001$) with a colostomy-free interval of 23% *vs.* 39% of the CRT; EORTC 50% in the arm RT alone *vs.* 32% in the arm CRT ($p = 0.02$), an increase of 32% over the interval free of colostomy[10-12].

Since 2008 they have published the results of three important randomized Phase 3 and a Phase 1 study TAB2 that have compared the combination of 5-FU and cisplatin and cisplatin MMC. The study RTOG 98-11 compared CRT with 5FU and MMC versus 5FU and cisplatin showed a more low disease-free survival at 5 years with cisplatin (54% in the arm 5-FU/cisplatin plus -CRT, 60% in the arm 5-FU/MMC plus CRT) and a higher number of colostomy [19% *vs.* 10% *($p = 0.02$)*]. However, hematologic toxicity was higher in the arm with MMC (61% *vs.* 42% *($p = 0.001$)*), with no significant differences in patient compliance between the two schemes[13]. Chemotherapy produces a significant decrease in CD4 lymphocytes and significantly increases the risk of opportunistic infections (OIs) in patients with HIV-related malignancies. The risk of OIs is a function of the intensity of chemotherapy regimen and the degree immune suppression HIV-related. The introduction of HAART into clinical practice has had a dramatic impact on the natural history of HIV-related disease, including cancer. The mechanism whereby HAART decreases the OI incidence in

HIV-infected patients probably is related to its recovery of immune function as the increase of CD4 cell count and/or resume of functional T-cell activity. Patients who receive the combination chemotherapy plus HAART may achieve better response rates and higher rates of survival than patients who receive antineoplastic therapy alone. The combined treatment is feasible, may reduce the incidence of infectious complications in patients with HIV-related cancer, and allows the possibility of administering standard doses of chemotherapy in HIV-positive patients as well as in the general population. However, careful attention must be directed toward the cross-toxicity and the possible pharmacokinetic and pharmacodynamic interactions of antiretroviral and antineoplastic drugs. Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are substrates and potent inhibitors or inducers of the cytochrome P450 system. Since many antineoplastic drugs are also metabolized by the cytochrome P450 system, co-administration with HAART could result in either drug accumulation and possible toxicity or decreased the efficacy of one or both classes of drugs. Current data show that toxicity, particularly myelosuppression and neurotoxicity, is significantly more frequent in the patients treated with the combined therapy compared with patients treated with antineoplastic drugs alone. On the other hand chemotherapy plus HAART-treated patients have a better survival than chemotherapy alone-treated patients, suggesting that the reduction of OIs morbidity by HAART other than the good performance status of these patients, may improve the overall outcome of the combined treatment patients[5].

RADIOTHERAPY

Radiotherapy plays an important role in the treatment of anal cancer. Also, the brachytherapy is an excellent radiotherapy technique capable of delivering a high-dose on the primary tumor after external radiotherapy treatment especially stages T3/ T4 and when cancer doesn't involve more than 2/3 of the circumference of the anal sphincter and there is not an involvement of the adjacent organ. The first study has been conducted by the French school of Gerard at the end of the seventies. He treated 221 patients with external radiotherapy more overdose with interstitial brachytherapy, getting an overall survival rate at 5 years of 53% and a percentage of conservation of the sphincter function of 92%[14]. Historically, it was used the technique to low dose rate with the implantation of radioactive wires. Subsequently, t remote loading techniques after temporary implant to high dose rate (after loading HDR and PDR) have replaced wires technique with improving both the quality of the treatment that the degree of protection of the operators and the patient (Figure 1).

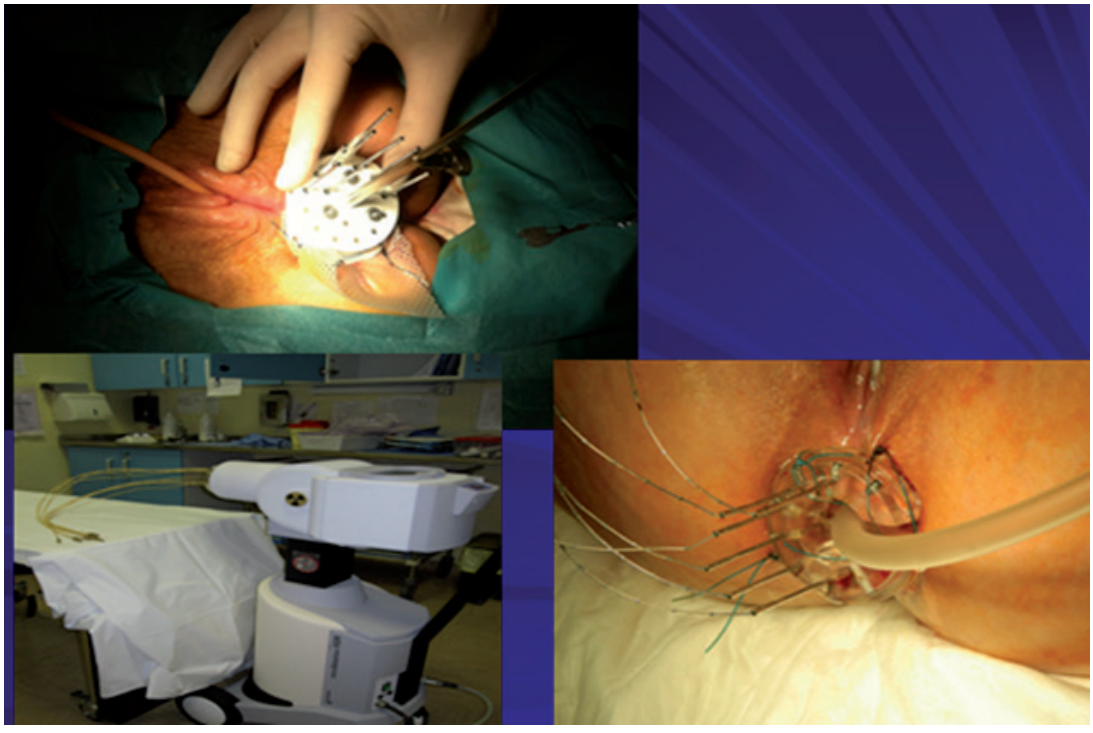

Fig. 1. Implantation of brachytherapy of the anal canal and projector Iridium 192 source (HDR).

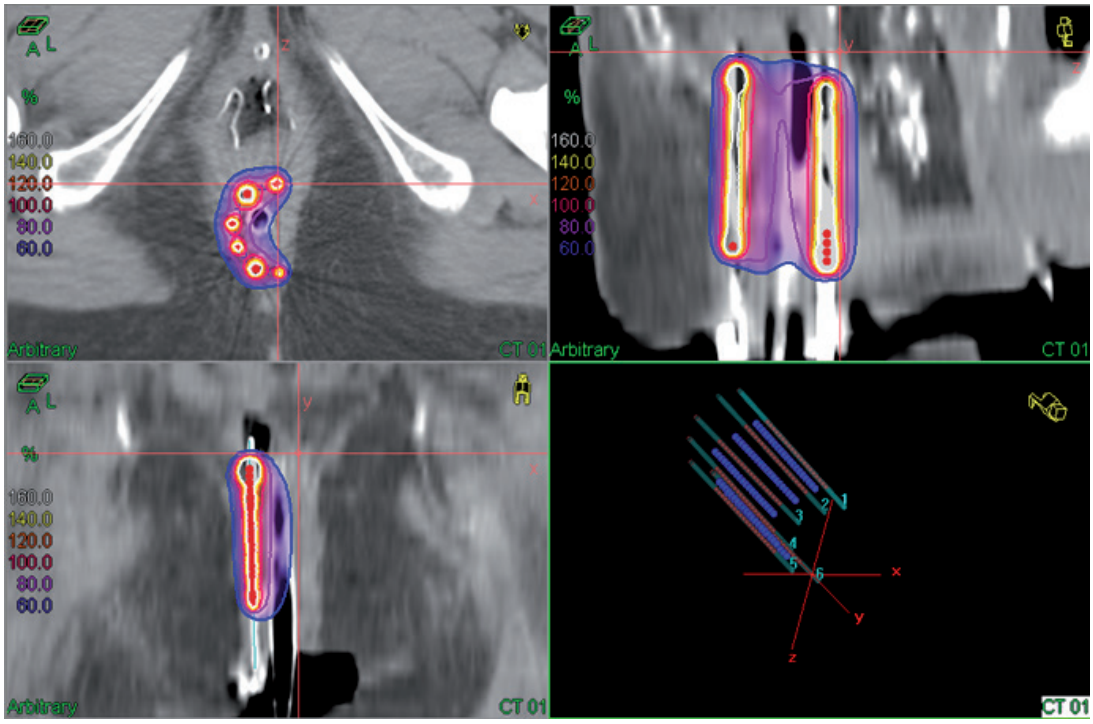

Fig. 2. Brachytherapy, with 3D TC dose calculation algorithms.

Normally, you administer a weekly session of brachytherapy with the delivery of 5 or 6 Gy for one or two fractions[15]. In some studies, the percentage of local complications after a boost with brachytherapy compared to EBRT was decreased from 23% of external beam radiation to the 5% of brachytherapy[16]. Brachytherapy, especially with 3D dose calculation algorithms CT system (Figure 2), delivers high-dose sparing of surrounding healthy tissue and resulting in better control of late effects (proctitis)[17]. The first randomized trials were conducted on case studies of radiotherapy performed with planning techniques 2D fields with anterior-posterior (AP-PA) and planning on orthogonal radiographs. Subsequently, the late 80's, has established the conformal radiotherapy planning with dosimetric CT scans and identifications of the organs at risk even if, however, the use of opposing camps has limited benefit in terms of protection of the same (Figure 3).

The transition to a dosimetric planning CT scans has enabled an important change in the delivery of the dose. 3D RT (three-dimensional radiotherapy) planning remains the radiotherapy technique more widespread.

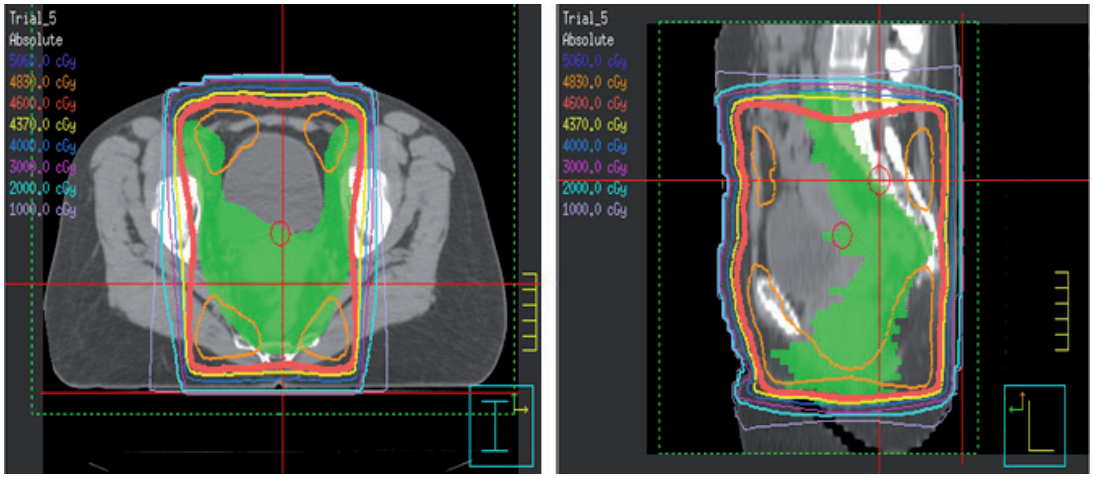

Fig. 3. Conformal Radiotherapy 3 D (3DRT) with computer TC planning dosimetry.

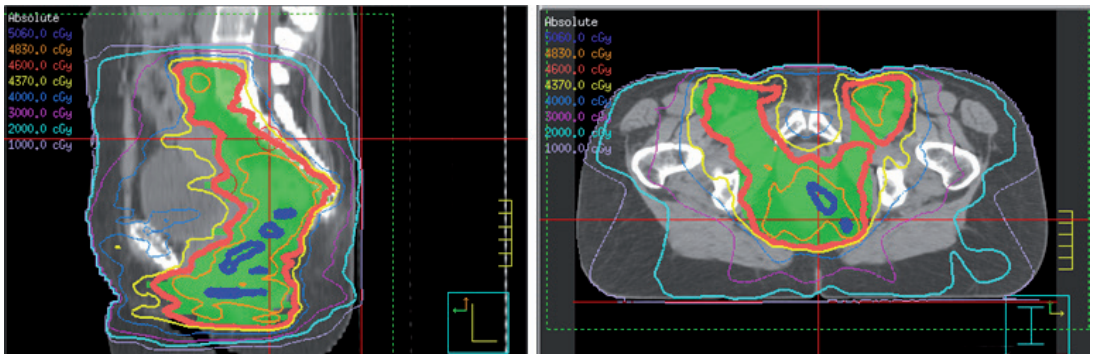

Fig. 4. intensity modulation radiotherapy technique (IMRT).

However, the technique to intensity modulation (IMRT), segmented static, dynamic, volumetric modulated arc therapy and helical tomotherapy allows an extremely precise dose distribution in preserving normal tissues and organs at risk (small intestine, perineum/genitalia, bladder, pelvic bone) with respect to the 3D technology with the ability to modulate the influence of the beam during the delivery of therapy[18,19]. The IMRT also allows a considerable saving of spongy bone tissue pelvic with a favourable impact on hematological toxicity, especially in patients receiving regimens containing mitomycin[20] (Figure 4).

There are any contraindications for the use of IMRT in obese patients where the reproducibility of positioning can be difficult. A recent American multicenter study showed an advantage with IMRT technique compared to 3D without interruption of treatment (patient compliance), the onset grade 3 non-hematological toxicity, the impact on local control and disease-free interval[21].

IMRT with a Simultaneous Integrated Boost of Dose (SIB) could be devised as an innovative intensified strategy to escalate radiation doses to sites of macroscopic disease. This approach has its advantages compared to sequential dosage increment, namely: the possibility to deliver different fraction doses to different volumes, shorten overall treatment time (OTT), and assure better coverage of Gross Tumor Volume (GTV) with non-target tissue sparing. SIB use has also been investigated in diseases other than anal canal cancer, such as head and neck cancer and cervical cancer, and where it has been demonstrated to be feasible and act to reduce acute toxicity[22].

BIOLOGICAL AGENTS

Some studies have indicated that even anal cancer can express the epidermal growth factor receptor (EGFR). Blocking of EGFR could reduce tumor proliferation in squamous cell carcinoma of the anus. A recent phase I study evaluated 10 patients with locally advanced cancer of the anus treated with cetuximab plus 5-FU and cisplatin concurrent RT with complete response in 7 of 10 patients (78%) and without a major impact on toxicity.

It is an ongoing Phase 2 study (ECOG NTC00316888) on cetuximab in combination with 5FU and cisplatin[23,24].

SURGERY

Surgery in ASCC has played an important role up to 70 years since the first radiation treatments for this cancer were burdened with a high rate of complications. However, it was in most cases of radical surgery with removal of rectum-anal segment and colostomy final. Currently, surgery plays a rescue after the failure of concomitant therapy (CT-RT) or in relapse. A study of M.D. Anderson in Houston showed a survival of 64% at five years of 31 patients treated with salvage surgery for persistent or recurrent disease and a major impact on survival in patients who have run salvage surgery after radiotherapy with a lower dose of 55 Gy[25]. A recent American work[26] has retrospectively evaluated the incidence of postoperative complications in 295 patients between 2005 and 2009 surgery for anal cancer (34 patients had received prior chemotherapy treatment radiant conservative) and for the entire group found to be the (46%), for patients undergoing abdominal-perineal resection, the (24%) for local excision and (30%) for those undergoing intestinal deviation. Patients undergoing abdominal-perineal resection had the highest percentage of complications than the local excision and intestinal diversion. However, although highly invasive, the salvage surgery allows a recovery of the disease.

CONCLUSIONS

The strategy of the anal cancer care is multidisciplinary. The radiochemotherapy conservative treatment is the standard approach. To reduce toxicity RT related especially cutaneous and hematological is preferred intensity modulated radiotherapy techniques (IMRT). The introduction of HAART into clinical practice has had a dramatic impact on the natural history of HIV-related cancer. The mechanism whereby HAART decreases the OI incidence in HIV-infected patients probably is related to its recovery of immune function as the increase of CD4 cell count and/or restart of functional T-cell activity. Patients who receive the combination chemotherapy plus HAART may achieve better response rates and higher rates of survival than patients who receive antineoplastic therapy alone. The combined treatment is feasible, may reduce the incidence of infectious complications in patients with HIV-related cancer, and allows the possibility of administering standard doses of chemotherapy in HIV-positive patients as well as in the general population. Currently, surgery plays a rescue after the failure of concomitant therapy (CT-RT) or after relapse disease.

Authors Disclosure

The Authors declare that they have no conflict of interests.

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