DOI: https://doi.org/10.22516/25007440.290

Metastatic anal canal squamous cell carcinoma in a patient with HIV treated with concomitant radiotherapy chemo. Case report and literature review

Handerson Rafael Osma Ch.[1*], Carlos Eduardo Bonilla G.[2], Ricardo Oliveros W.[3], Henry Alexander Vargas D.[4], Julián Alberto Beltrán S.[5], Mario Alexander Melo U.[6]

1. Specialist in internal medicine at the National University of Colombia and the National Cancer Institute in Bogotá, Colombia
2. Specialist in Internal Medicine and Oncology and University Teaching Specialist at the Clinical Oncology Service at the National Cancer Institute in Bogotá, Colombia
3. Specialist in General Surgery and Gastrointestinal Surgery and Coordinator of the Gastroenterology Service at the National Cancer Institute in Bogotá, Colombia
4. Internal Medicine Specialist and Oncology Fellow in the Clinical Oncology Service of the National Cancer Institute in Bogotá, Colombia
5. Specialist in Radiology, Neuroradiology and Interventional Neuroradiology in the Radiology Service of the National Cancer Institute in Bogotá, Colombia
6. Physician and Pathologist in the Pathology Service of the National Cancer Institute in Bogotá, Colombia

*Correspondence: Handerson Rafael Osma, hrosmac@unal.edu.co

Received: 26/08/18
Accepted: 01/11/18

Abstract

Anal canal carcinoma is responsible for up to 4% of all cases of colon, rectum and anus cancer. The most common histological type is squamous cell carcinoma. A non-negligible proportion of patients have metastasized by the time of diagnosis. In these stages the prognosis is poor, and treatment is usually based on palliative chemotherapy with cisplatin and 5-fluorouracil. Five year survival rates do not exceed 30%. Some recent studies have suggested that multidisciplinary chemoradiotherapy (chemotherapy combined with radiation therapy) in earlier stages of the disease could improve survival for a select group of patients.

We present the case of a 54-year-old male patient with squamous cell carcinoma of the anal canal with extensive metastasis who also had HIV. He was treated at an institution specializing in cancer treatment where complete remission of the disease was achieved after treatment with chemoradiotherapy with Mitomycin C and 5-fluorouracil. He remains in remission four years after discontinuation of treatment. We discuss the case and review the literature.

Keywords

Anal canal, neoplasms of the anus, squamous cell carcinoma, HIV, chemoradiotherapy.

INTRODUCTION

Anal canal carcinoma accounts for 2% to 4% of all cases of colon, rectal and anal cancer. (1) Its peak age of presentation is between 58 and 64 years, and its frequency has been increasing. In the United States, incidence rates went from 0.8 cases per 100,000 people/year in 1975 to 1.5 cases per 100,000 per 100,000 people/year in 2011. This could be due to the impact of human immunodeficiency virus infections (HIV). (2) The most common histological type is squamous cell carcinoma which accounts for 85% to 90% of all cases. (2, 3) Half of the patients have localized disease at the time of diagnosis, a third present as regional nodal disease, and 10% to 15% have distant metastases. (4)

There is little information regarding the natural history of metastatic squamous cell carcinoma, especially due to the paucity of prospective studies. (5) The National Comprehensive Cancer Network (NCCN) recommends palliative systemic chemotherapy based on cisplatin and 5-fluorouracil for advanced stages. For some patients, it recommends sequential palliative radiation therapy rather than concomitant radiation therapy. (6) Chemotherapy offers a reasonable response rate but has poor strong outcomes with 5-year survival probability between 15%

and 30%. (7) Recent evidence suggests that for some well-selected patients with metastatic disease, multidisciplinary treatment with concomitant chemoradiation therapy mayd improve survival outcomes. (8)

We present the case of an HIV patient with metastatic anal canal squamous cell carcinoma who was treated at the National Cancer Institute of Colombia. He received concomitant chemoradiation therapy with 5-fluorouracil and mitomycin-C followed by chemotherapy alone with the same protocol for 6 cycles. Sustained complete response over time was achieved, and the patient has been in remission for almost four since discontinuance of treatment. The case is discussed, and the literature is reviewed.

CASE DESCRIPTION

In May 2013, a 54-year-old man came to the institute because of pain and feeling of mass in the rectoanal region. He had a history of HIV infection which had been treated with HAART therapy since December 2012. His CD4 count was 57 cells/μL, and his viral load was 40,612 copies/mL (Log 5.6). Physical examination revealed sarcopenia and multiple lymphadenopathy in left level IV, axillary, and groin area lymph nodes. Examination of the perineal region revealed external edematous hemorrhoids, at least 5 subcutaneous nodules in the gluteal region measuring up to 5 mm in diameter, and a rectal lesion that started above the anal rim on the anterior side of the distal rectoanal canal. The rest of the physical examination was within normal parameters.

A rectosigmoidoscopy found a neoplastic lesion in the rectal ampulla 5 cm from the anal rim. A biopsy reported a moderately differentiated squamous cell carcinoma. An MRI of the pelvis showed neoplastic thickening of the anal canal with an area of anterior focal ulceration in contact with the membranous urethra and apex of the prostate. Magnetic resonance imaging of the abdomen reported metastatic lesions in the right adrenal gland, left paraaortic lymph nodes, and infrarenal, retrocaval, celiac axis and right retrocrural lymph nodes. A CT scan of the chest reported multiple tumor adenopathies in the right axillary, supraclavicular, prevascular, paraesophageal, right retrocrural, and left paraaortic regions. In addition, it showed a cavitating nodular lesion at the base of the left lung and multiple subcentimeter nodules with randomly distributed soft tissue density which led to suspicion of malignancy (Figure 1).

An excisional biopsy of a right axillary node confirmed distant metastatic involvement for squamous cell carcinoma with sarcomatous dedifferentiation of the anal canal. Stage IV T4N2M1 squamous cell carcinoma of the anal canal was diagnosed (American Joint Committee on Cancer, version 7). (9) Despite extensive disease at a distance, given the patient's overall good condition, we decided to provide treatment usually reserved for earlier stages to provide the maximum possible response. We began concomitant chemoradiation therapy with mitomycin C 10 mg/m2 on days 1 and 29 plus continuous infusion of 1,000 mg/m2/day of 5-fluorouracil on days 1 to 4 plus radiation therapy on days 29 to 32. He received this treatment between August 20 and October 5, 2013 without limiting toxicity. A complete clinical response was obtained in the anal canal and a CT scan showed a partial response with more than 30% decrease in the lymph node conglomerate in the left and right axillary IV level, resolution of the mediastinal node component, decreases in the sizes of lung lesions, resolution of some abdominal lymphadenopathy and decreases in the sizes of the right adrenal gland lesions (Figure 2).

Given the good response obtained, it was decided to continue systemic treatment with the same mitomycin C + 5-fluorouracil chemotherapy regimen with close hematological and renal monitoring. The patient completed 6 cycles on October 10, 2014 and has since been followed up. End-of-treatment reevaluation CT scans showed complete pulmonary, axillary nodal, and cervical responses with only a few residual left retrocrural and retroperitoneal adenomegalies remaining and lesion stability in the right adrenal gland. Since then, follow-ups with clinical examinations and imaging have continued. As of the examination of August 2018, the patients lesions are stable and without evidence of disease progression (Figure 2).

DISCUSSION

Most of the literature on the treatment of metastatic anal canal squamous cell carcinoma is limited to case reports and series in which the chemotherapy protocols used for squamous cell carcinomas from other locations such as the lung and cervix have been extrapolated. (10) Although the disease is not yet curable, the most important oncology guidelines advise the use of polychemotherapy with palliative intent while leaving open the option of sequential rather than concomitant pelvic radiation therapy in palliative doses in case of large symptomatic primary tumors. (1, 6) In metastatic stages, median progression-free survival of 5 to 7 months and overall survival of 15 to 22 months has been reported. (7, 8)

Platinum chemotherapy plus 5-fluoruracil (5-FU) has reported partial responses in almost 60% of patients. Median survival time is up to 34.5 months, but there have been no sustained long-term responses. (11, 12) A retrospective series at MD Anderson Cancer Center demonstrated median progression-free survival of 7.2 months and overall survival of 38 months. (13) Other regimens that have been used include the carboplatin/paclitaxel combination which has had overall survival of 12 months. (14) The combination of paclitaxel, carboplatin and 5-FU has been evaluated in a

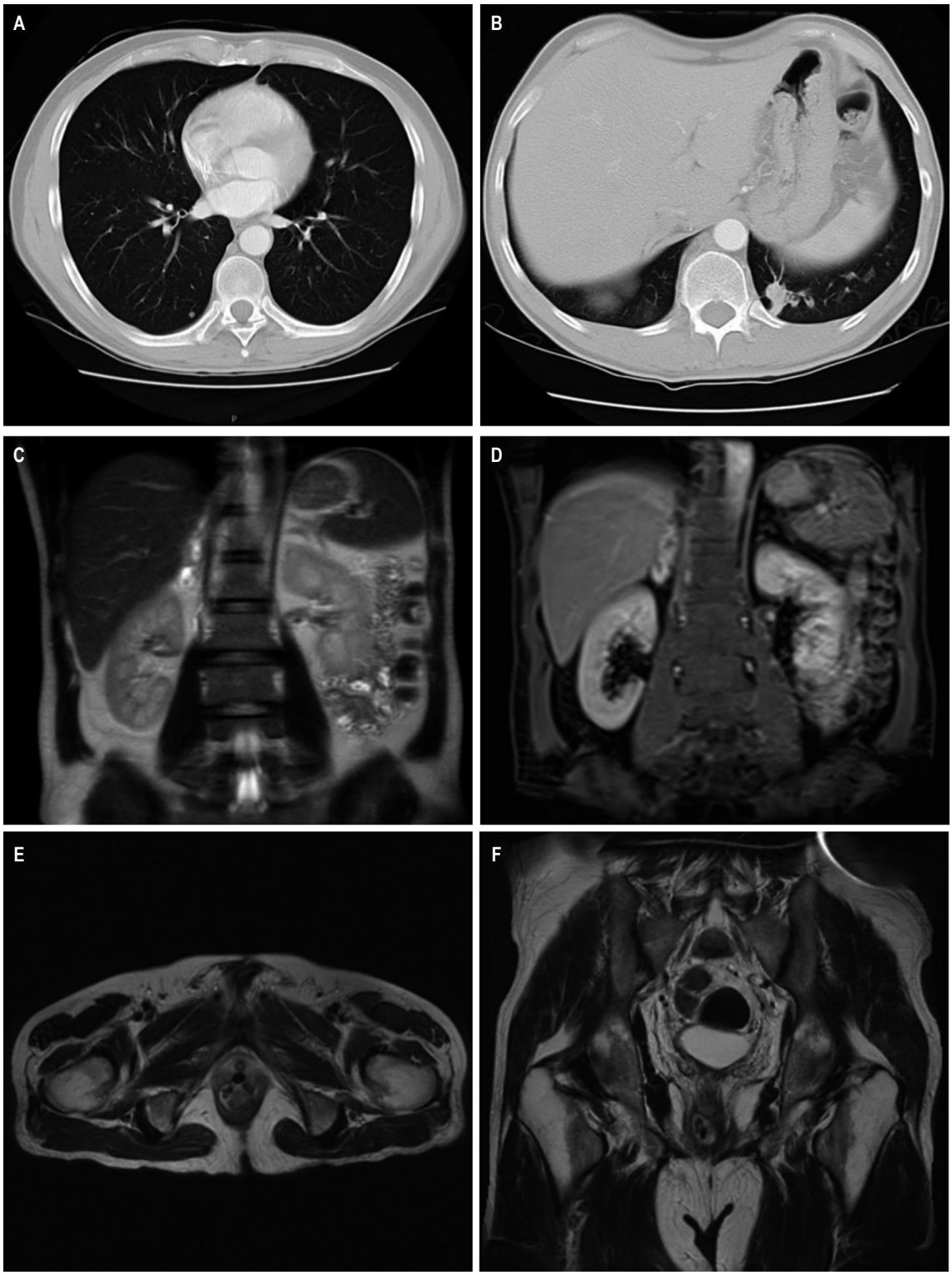

Figure 1. Images of the patient at the time of diagnosis. A and B. Axial projection of CT scan of the chest shows multiple subcentimeter nodules with random soft tissue density and a dominant nodular lesion in the left lung base. C and D. Coronal projection of abdominal MRI shows two focal lesions in the right adrenal gland: one in the 14 x 17 mm medial arm and the other in the body of the 14 x 19 mm gland. The lesion in T2 (C) is hyperintense while the lesion in T1 (D) is hypointense. Neither suppresses signal in out-of-phase sequences, both restrict peripheral diffusion and peripheral enhancement of contrast medium in relation to necrotic metastases (these last two sequences are not illustrated). E and F. Axial and coronal projections in T2 sequence of pelvic MRI shows concentric and neoplastic appearing thickening with an area of anterior ulceration in the anal canal with a thickness of 14 mm. There is moderate enhancement of the contrast medium in contact with the membranous urethra without fistulas to this organ.

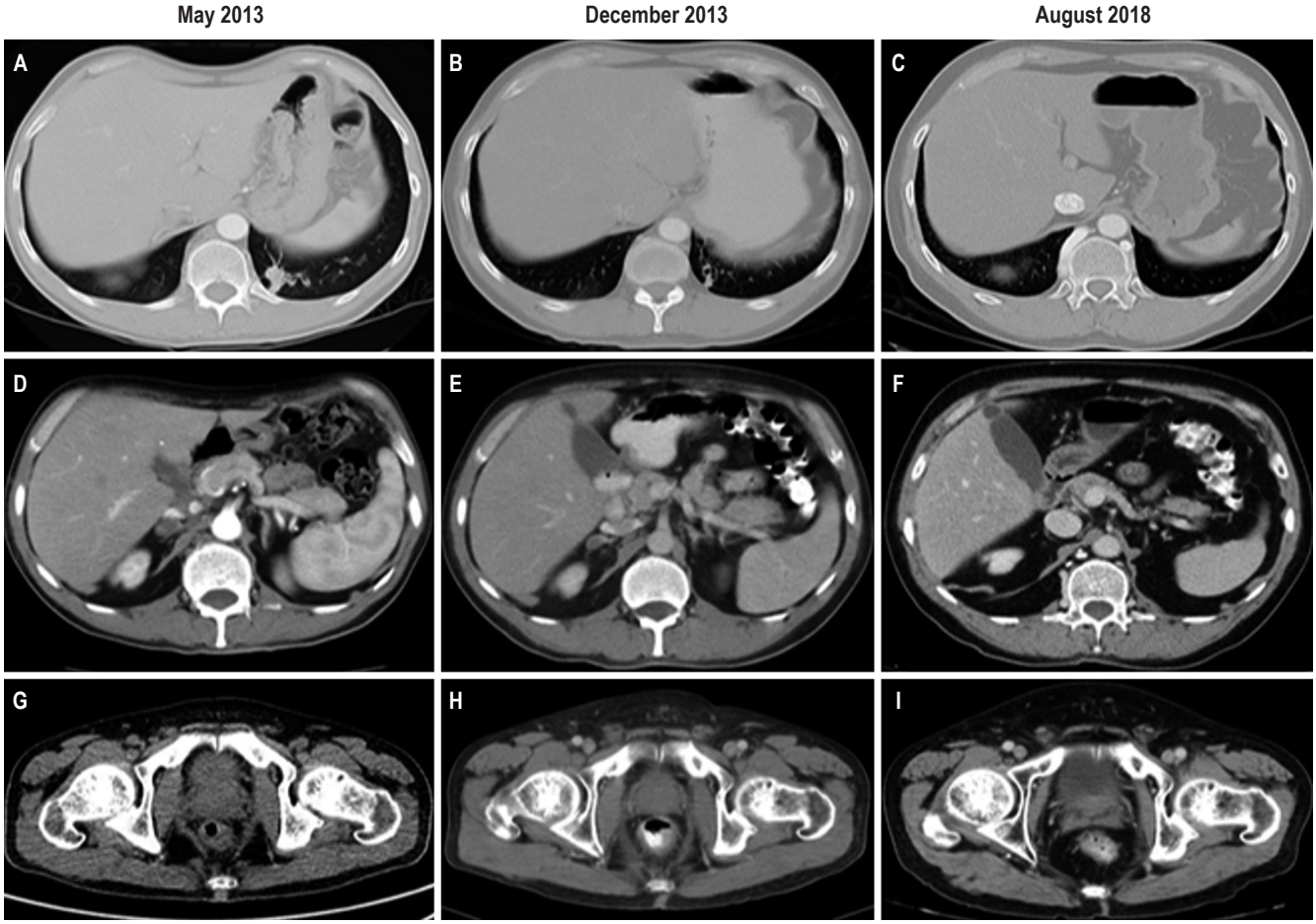

Figure 2. Tomographic monitoring of the patient. A-C. The images show the evolution of the size of the metastatic nodule at the base of the left lung with complete resolution as of the last follow-up. D-F. The evolution of one of the metastatic lesions in the right adrenal gland is evident with complete response in the last study. G-I. The images show partial response in the anal canal with stable disease as of August 2018.

phase II study which tested its efficacy for treating squamous cell carcinoma of several primary sites. It demonstrated overall responses in four of the seven patients with a primary site, but there were considerable side effects including leukopenia (48%), mucositis (28%) and diarrhea (17%). (15) In 2006, Jhawer et al. studied the use of mitomycin C, adriamycin, cisplatin, and bleomycin-CCNU and obtained an overall response rate of 60%, a median progression-free survival of 8 months, and overall survival of 15 months. However, severe toxicity that included leukopenia and thrombocytopenia (10%), vomiting (10%), cramps (5%) and cardiac arrhythmia (5%) developed. (16)

As stated, the prognoses of patients with metastatic disease are very poor. The patient in our case achieved complete local response and partial systemic response with the initial concomitant chemoradiation therapy (standard scheme in non-metastatic disease) and, after 6 cycles of mitomycin C + 5-fluorouracil, the patient achieved complete response which has been maintained for about 4 years.

Sequential chemoradiation therapy in metastatic disease is recommended in international management guidelines, but there is little evidence of the impact that this type of treatment may have nor for the optimal timing for its initiation. Small case series have shown improvement of long-term disease-free survival. (17) Also, optimal duration of therapy for those who achieve adequate responses has not been established although some authors suggest continuing treatment indefinitely to achieve a maximum response in patient who properly tolerated it. (10)

When metastasis is preset, the guidelines suggest using radiation therapy only in combination with 5-FU and a platinum. Here, we present a successful experience using mitomycin C instead of cisplatin, in which an almost complete response and stability of lesions were achieved after four years of

the Nigro scheme. A phase II study comparing the use of cisplatin + 5 FU with weekly administration of carboplatin with paclitaxel for patients with inoperable or locally recurrent metastatic anal canal squamous cell carcinoma is currently underway. The main objective of the study is to evaluate the response rate and secondary outcomes include progression-free survival, overall survival, toxicity, and quality of life. (18)

HIV patients with anal canal carcinoma have worse prognoses than do seronegative patients and may experience greater toxicity with chemotherapy, especially when their CD4 counts are less than 200 cells/μL. They may also require longer rest periods and reduced doses of chemotherapeutic agents. (19, 20) The main toxicities they experience have been hematological, gastrointestinal and dermal. They may also require reduction of the radiation field through intensity modulated radiation therapy (IMRT). (21) Although some authors have found a trend toward improved survival in patents with CD4 counts that are over 200, the evidence is not conclusive and the impact on the immune systems of patients with anal canal squamous cell carcinoma and HIV who undergoing HAART therapy remains to be established. (21, 22) In addition, HIV patients have been excluded from large studies of squamous cell carcinoma of the anal canal such as ACT I, RTOG 98-11 and ACCORD 03. (23) In our case, the patient had an acceptable tolerance of chemoradiation therapy and concomitant antiretroviral therapy, there were no requirements for prolonged rest periods, and all chemotherapy cycles were completed.

In recent years, targeted cancer therapy has become important as demonstrated by the work of doctors Allison and Honjo in cancer immunotherapy for which they were awarded the 2018 Nobel Prize in Physiology or Medicine. (24, 25) The role of human papilloma virus (HPV) in the carcinogenesis of squamous cell carcinoma of the anal canal, especially in immunosuppressed patients, has led to the use of anti-PD-1 antibodies in two recent studies. In 2017, Ott et al. studied the safety and efficacy of pembrolizumab in a cohort of PD-L1 positive patients with locally advanced or metastatic anal canal carcinoma from the phase I KEYNOTE-028 study who had experienced failure of at least one previous attempt with standard therapy. The primary outcomes were safety and overall response rate, and overall outcomes were progression-free survival and duration of response. Twenty-five patients with a median age of 63 years were randomized. Sixty-four percent experienced treatment-related adverse events, with no treatment-related deaths. Four patients had partial responses, the overall survival rate was 17% (95% CI: 5% to 37%), and 42% had stable disease for a median time of 3.6 months. Median progression-free survival was 3 months, and median overall survival time was 9.3 months. The authors concluded that this molecule demonstrated a manageable safety profile and acceptable antitumor activity. (26)

In another phase II study, conducted by Morris et al., the efficacy of nivolumab was assessed in patients who had metastatic anal canal squamous cell carcinoma but had not previously received immunotherapy. A total of 39 patients were randomized. Median age was 56 years. Seven patients (21%) had partial responses, and just over half achieved stable disease, with a disease control rate of 79%. Median progression-free survival time was 4.1 months, and overall survival time was 11.5 months. The most common adverse effects were fatigue, nausea, and rashes. The authors concluded that nivolumab demonstrated potentially significant activity, with adequate tolerance. (27)

Epidermal growth factor receptor (EGFR) inhibitors have also been studied. The use of cetuximab has been described in case reports of patients with wild-type KRAS. Retrospective analyses initially found a possible role for this drug in patients with anal canal squamous cell carcinoma, (28) but safety outcomes found when EGFR inhibitors have been used in patients with locally advanced disease receiving chemoradiation therapy must also be taken into account. Grade 3/4 toxicity rates of up to 90% have been found, and response rates have not been very good. This has led to recommendations that the search for more effective and less toxic therapeutic alternatives continue. Safety and efficacy and safety outcomes for metastatic cases have yet to be verified in randomized clinical trials and prospective studies. (29)

CONCLUSIONS

Our case shows that it is possible to offer concomitant chemoradiation therapy in curative doses, standard for localized disease, in selected patients with distant metastatic disease and to achieve complete and sustained response and control of systemic disease. The MD Anderson Cancer Center case series also supports this approach. This may be the starting point for a change in the oncological paradigm in terms of the prognosis and treatment of this disease. Long-term randomized clinical trials with patient follow-up are required to confirm this hypothesis, and better quality evidence regarding the treatment of stage IV squamous cell carcinoma of the anal canal is still needed.

Funding Sources

The authors' own resources.

Acknowledgements

We would like to thank all of the patients of the National Cancer Institute who are our reasons for the unceasing fight against cancer.

REFERENCES

1. Glynne-Jones R, Nilsson P, Aschele C, Goh V, Peiffert D, Cervantes A, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol. 2014;40:1165-76. doi: https://doi.org/10.1016/j.ejso.2014.07.030.
2. Nelson R, Levine A, Bernstein L, Smith D, Lai L. Changing patterns of anal canal carcinoma in the United States. J Clin Oncol. 2013;31:1569-75. doi: https://doi.org/10.1200/JCO.2012.45.2524.
3. Oliveros R, Rey-León C, Olarte H, Ospina J, Villamizar J, Acosta M, et al. Carcinoma del ano: experiencia con 82 pacientes. Rev Col Cir. 1990;5(3):139-46.
4. Abbas A, Yang G, Fakih M. Management of anal cancer in 2010. Part 1: Overview, screening, and diagnosis. Oncology (Williston Park). 2010;24:364-9.
5. Glynne-Jones R. Chemotherapy, "Lighting the fire" or releasing the brakes" in metastatic anal cancer. Dis Colon Rectum. 2017;60(8):757-8. doi: https://doi.org/10.1097/DCR.0000000000000828.
6. National Comprehensive Cancer Network. Anal carcinoma. V.1.2018. Último acceso:24 de mayo de 2018. Disponible en: https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf (nota del corrector: el link no lleva al documento, revisar).
7. Sclafani F, Morano F, Cunningham D, Baratelli C, Kalaitzaki E, Watkins D, et al. Platinum-fluoropyrimidine and paclitaxel-based chemotherapy in the treatment of advanced anal cancer patients. Oncologist. 2017;22(4):402-8. doi: https://doi.org/10.1634/theoncologist.2016-0241.
8. Eng C, Chang G, You Y, Das P, Bigas M, Xing Y, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. Oncotarget. 2014;5:11133-42. doi: https://doi.org/10.18632/oncotarget.2563.
9. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging manual. New York, NY: Springer. 2009.
10. Shridhar R, Shibata D, Chan E, Thomas C. Anal cancer: current standards in care and recent changes in practice. CA Cancer J Clin. 2015;65(2):139-62. doi: https://doi.org/10.3322/caac.21259.
11. Eng C, Pathak P. Treatment options in metastatic squamous cell carcinoma of the anal canal. Curr Treat Options Oncol. 2008;9(4-6):400-7. doi: https://doi.org/10.1007/s11864-009-0103-7.
12. Faivre C, Rougier P, Ducreux M, Mitry E, Lusinchi A, Lasser P, et al. 5-fluorouracil and cisplatin combination chemotherapy for metastatic squamous-cell anal cancer. Bull Cancer. 1999;86(10):861-5.
13. Pathak P, King BT, Ohinata A, Das P, Crane CH, Chase JL, et al. The treatment of metastatic squamous cell carcinoma (SCCA) of the anal canal: a single institution experience. In ASCO Gastrointestinal Cancers Symposium: Multidisciplinary Approaches to the Prevention, Diagnosis, and Therapy of GI Cancers. 2008.
14. Kim R, Byer J, Fulp W, Mahipal A, Dinwoodie W, Shibata D. Carboplatin and paclitaxel treatment is effective in advanced anal cancer. Oncology. 2014;87:125-32. doi: https://doi.org/10.1159/000361051.
15. Hainsworth J, Burris H 3rd, Meluch A, Baker M, Morrissey L, Greco F. Paclitaxel, carboplatin, and long-term continuous infusion of 5-fluorouracil in the treatment of advanced squamous and other selected carcinomas: results of a Phase II trial. Cancer. 2001;92(3):642-9. doi: https://doi.org/10.1002/1097-0142(20010801)92:3<642::AID-CNCR1365>3.0.CO;2-Z.
16. Jhawer M, Mani S, Lefkopoulou M, Hanh R, Harris J, Catalano P, et al. Phase II study of mitomycin-C, adriamycin, cisplatin (MAP) and bleomycin-CCNU in patients with advanced cancer of the anal canal: an eastern cooperative oncology group study E7282. Investig New Drugs. 2006;24(5):447-54. doi: https://doi.org/10.1007/s10637-006-7667-x.
17. Rogers J, Crane C, Das P, Delclos M, Gould S, Ohinata A, et al. Definitive chemoradiation in oligometastatic squamous cell carcinoma of the anal canal. Gastrointest Cancer Res. 2014;7(2):65-8.
18. Sclafani F, Adams R, Eng C, Benson A, Glynne-Jones R, Sebag-Montefiore D, et al. Inter AACT: an international multicenter open label randomized phase II advanced anal cancer trial comparing cisplatin (CDDP) plus 5-fluorouracil (5-FU) versus carboplatin (CBDCA) plus weekly paclitaxel (PTX) in patients with inoperable locally recurrent (ILR) or metastatic disease. J Clin Oncol. 2015;33(3):TPS792. doi: https://doi.org/10.1200/jco.2015.33.3_suppl.tps792.
19. Bryant A, Huynh-Le M, Simpson D, Gupta S, Sharabi A, Murphy J. Association of HIV status with outcomes of anal squamous cell carcinoma in the era of highly active antiretroviral therapy. JAMA Oncol. 2018;4(1):120-2. doi: https://doi.org/10.1001/jamaoncol.2017.2844.
20. Hoffman R, Welton M, Klencke B, Weinberg V, Krieg R. The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Radiat Oncol Biol Phys. 1999;44(1):127-31. doi: https://doi.org/10.1016/S0360-3016(98)00528-8.
21. Kauh J, Koshy M, Gunthel C, Joyner M, Landry J, Thomas C Jr. Management of anal cancer in the HIV-positive population. Oncology (Williston Park). 2005;19(12):1634-938.
22. Stadler R, Greorcyk S, Euhus D, Place R, Huber P, Simmang C. Outcome of HIV-infected patients with invasive squamous-cell carcinoma of the anal canal in the era of highly active antiretroviral therapy. Dis Colon Rectum.

2004;47:1305-9. doi: https://doi.org/10.1007/s10350-004-0584-1.
23. Wang C, Sparano J, Palefsky J. Human immunodeficiency virus/AIDS, human papillomavirus, and anal cancer. Surg Oncol Clin N Am. 2017;26:17-31. doi: https://doi.org/10.1016/j.soc.2016.07.010.
24. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 1992;11:3887-95. doi: https://doi.org/10.1002/j.1460-2075.1992.tb05481.x.
25. Leach D, Krummel M, Allison J. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 1996;271:1734-6. doi: https://doi.org/10.1126/science.271.5256.1734.
26. Ott P, Piha-Paul S, Munster P, Pishvaian M, van Brummelen E, Cohen R, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol. 2017;28(5):1036-41. doi: https://doi.org/10.1093/annonc/mdx029.
27. Morris V, Salem M, Nimeiri H, Igbal S, Singh P, Ciombor K, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicenter, single-arm, phase 2 study. Lancet Oncol. 2017;18(4):446-53. doi: https://doi.org/10.1016/S1470-2045(17)30104-3.
28. Kim D, Byer J, Kothari N, Mahipal A, Chang Y, Kim R. EGFR inhibitors in patients with advanced squamous cell anal carcinomas: a single-institution experience. Oncology. 2017;92(4):190-6. doi: https://doi.org/10.1159/000452766.
29. Casadei A, Passardi A, Fornaro L, Rosetti P, Valgiusti M, Ruscelli S, et al. Treatment of squamous cell carcinoma of the anal canal: A new strategies with anti-EGFR therapy and immunotherapy. Crit Rev Oncol Hematol. 2018;123:52-6. doi: https://doi.org/10.1016/j.critrevonc.2018.01.007.