Gastrointestinal Cancer: Research & Therapy

Open Access

Austin Publishing Group

Review Article

Carcinoma of the Anus: A Concise Review of Loco-Regional Therapy

Howell KJ[1]*, Lee YS[1] and Kumar R[2]

[1]Department of Radiation Oncology, Banner-University Medical Center, Tucson, Arizona, USA

[2]Department of Radiation Oncology, Banner MD Anderson Cancer Center, Gilbert, Arizona, USA

***Corresponding author:** Howell KJ, Department of Radiation Oncology, Banner-University Medical Center, 1501 N. Campbell Ave., Tucson, AZ 85724, USA

Received: August 11, 2016; **Accepted:** September 02, 2016; **Published:** September 06, 2016

Abstract

Carcinoma of the anus comprises a small portion of patients afflicted with gastrointestinal malignancies. Due to its anatomical location, patients tend to present with signs and symptoms localized to the anal canal or perianal skin. Typically presenting in advanced ages, carcinoma of the anus has been identified as a typical site of squamous cell carcinoma (SCC). While aggressive, cancer, carcinoma of the anus is one of the first anatomical sites successfully treated with organ preservation. Since the 1980's therapy for anal cancer has evolved to continuous radiation management with concurrent chemo radiotherapy (CRT) excluding routine induction chemotherapy, maintenance chemotherapy or radiation boost therapy. Intensity-modulated radiation therapy (IMRT) has demonstrated improvement in the radiation toxicity profile and advances in technology have enabled larger variations in patient set-up and dose-fraction delivery. 5-Fluorouracil (5-FU) and mitomycin (MMC) have been established as the standard systemic therapies, but pro-drugs of these agents have been tested in the treatment of pelvic malignancies. Biomarkers of human papillomavirus (HPV) status and imaging biomarkers select patients at higher risk of relapse or residual disease after conventional therapy, potentiating personally modified therapies in the future.

Keywords: Carcinoma of the anus; Review of anal cancer therapy

Abbreviations

SCC: Squamous Cell Carcinoma; CRT: Chemoradiotherapy; APR: Abdominal-perineal Resection; IMRT: Intensity-modulated Radiation Therapy; 5-FU: 5-Fluorouracil; MMC: Mitomycin; HPV: Human Papillomavirus; HIV: Human Immunodeficiency Virus; FDG-PET-CT: (F-18 fluorodeoxyglucose positron emission tomography-computed tomography); AJCC: American Joint Cancer Commission; APR: Abdominal-perineal Resection; RT: Radiotherapy; OS: Overall Survival; CFS: Colostomy-free Survival; LRC: Loco-regional Control; DFS: Disease-free Survival; PFS: Progression-free Survival; Cape: Capecitabine; RTOG: Radiation Therapy Oncology Group; AIDS: Acquired Immune Deficiency Syndrome; ESMO: European Society for Medical Oncology; ESSO: European Society of Surgical Oncology; ESTRO: European Society of Radiotherapy and Oncology

Introduction

Background

Carcinoma of the anus accounts for just 2.5% of all gastrointestinal system malignancies in 2015. The incidence, however, has shown an increasing trend [1,2]. The median age at presentation is the late fifties, into the mid-sixties although immunocompromised patients may present younger. Most patients have a history of bleeding with other findings such as hemorrhoids, fissures or a fistula [3]. These cancers develop at a higher incidence in patient populations using tobacco, having a history of multiple sexual partners, a history of sexually transmitted diseases, including human papillomavirus (HPV), and having had anal intercourse [2,3]. In an epidemiologic review of the Seattle SEER region from 1986-1998, 72.2% of anal cancers were of SCC histology and, of those, greater than 87% were HPV positive [4].

Superiorly, the anal canal begins where the rectum enters the puborectalis sling at the apex of the anal sphincter complex. The anorectal ring is approximately 1-2cm proximal to the dentate line. In the region of the dentate line, anal glands are subjacent to the mucosa, often penetrating through the internal sphincter into the intersphincteric plane. The distal zone of the anal canal extends from the dentate line to the mucocutaneous junction with the perianal skin [3,5]. Lymphatic drainage and nodal involvement of anal cancers above the dentate line spread primarily to the anorectal, perirectal, and internal iliac nodes. Below the dentate line lymphatic spread is primarily to the superficial inguinal nodes [5]. In up to 5% of cases, anal cancer patient can present as metastatic [3]. Metastasis frequently involves the liver and lungs [5-6].

Overall management approach

Nigro cultivated the approach of concurrent chemoradiotherapy (CRT) in the 1970's – 1980's as a curative therapy for carcinoma of the anus. CRT allowed for organ preservation in approximately 75% of patients reserving abdominal-perineal resection (APR) as salvage surgery for patients with persistent or recurrent disease [7,8]. The majority of patients treated with CRT were cured without an APR and the 5-year overall survival (OS) and colostomy-free survival (CFS) were reported at 67% and 59% [9].

Patient evaluation and investigations

History and physical examination are the initial assessment steps for work-up of an anal tumor. A physical exam should include an anoscopy and gynecologic exam with cervical cancer screening

Citation: Howell KJ, Lee YS and Kumar R. Carcinoma of the Anus: A Concise Review of Loco-Regional Therapy. Gastrointest Cancer Res Ther. 2016; 1(2): 1006.

in females. Further work-up for diagnosis and staging includes: pathology with consideration of biopsy of suspicious lymph nodes, chest X-Ray or CT thorax, CT scans of the abdomen/pelvis, MRI of the pelvis, ultrasound of the abdomen and/or bone scan where indicated, FDG-PET-CT (F-18 fluorodeoxyglucose positron emission tomography-computed tomography) when applicable, CBC/chemistry, human immunodeficiency virus (HIV) screen if indicated with CD4 level. Also consider hepatitis screen, thyroid function tests, CEA, or EKG when indicated. Sperm storage to be considered in men and hormone replacement therapy in women, pregnancy test when applicable [6]. The afore mentioned investigational studies will determine the staging as per the American Joint Cancer Commission (AJCC) criteria and guide further loco-regional versus metastatic management [4].

Chemotherapy

The Nigro technique was re-explored to evaluate radiotherapy (RT) alone versus a combination of CRT with 5-FU and a single dose of MMC. Although no OS significance was seen between the arms, a significant increase was seen in the complete remission rate, loco-regional control (LRC), disease-free survival (DFS) and CFS with CRT [10,11]. RTOG 87-04 explored 5-FU alone versus MMC and 5-FU. Both arms were concurrent with RT. Post-treatment biopsies were half as likely to be positive in the MMC arm. The DFS and CFS were also higher in the MMC arm [12]. Further investigations were held to determine if replacing MMC with cisplatin improved response and whether maintenance chemotherapy after CRT improved survival. The ACT II study investigated both of these points while RTOG 98-11 compared the standard chemotherapy arm to an experimental cisplatin-based arm. The experimental arm was initiated with 2 cycles of induction chemotherapy. Long-term analysis of RTOG 98-11 determined that both DFS and OS were better for the MMC arm and a trend continued towards improvement for CFS. ACT II found that neither of the two strategies if investigated – CRT with cisplatin, and further maintenance chemotherapy using 5-FU and cisplatin – is more effective than standard care with MMC for achieving complete response, progression-free survival (PFS), or OS [13,14,15].

As a pro-drug, Capecitabine (Cape) has started to be utilized in place of 5-FU with continued tumor response and an acceptable safety profile [16]. A retrospective review of 89 patients at Memorial Sloan Kettering Cancer Center suggests that Cape was associated with a decrease in hematological toxicity compared to 5-FU. Median treatment duration was also shortened by 3 days in the Cape group ($p=0.002$) [17]. Promitil® is a pegylated liposomal formulation of an MMC lipid-based prodrug. While not currently in clinical use for anal cancer, it has shown a significantly lower toxicity profile in the in vitro, preclinical, and phase I investigations [18].

Radiation therapy

The Radiation Therapy Oncology Group (RTOG) conducted a pilot study (RTOG 92-08) to examine radiation dose escalation with 5-FU/MMC [19]. Forty-six patients were given a radiation dose of 59.4Gy in 1.8Gy (2-week break). Results were compared to RTOG 87-04 trial in which patients were treated with 45Gy in a continuous schedule [12]. The two-year colostomy rate with 59.4Gy and a two week break was much higher than expected (30% vs. 9%). Because of this, an additional 20 patients were treated to 59.4Gy, but without a break. There were no treatment-related deaths, however, morbidity was significant. The authors concluded that, for higher doses to improve local control, radiation therapy might have to be given in a continuous fashion with 5-FU and MMC.

Further attempts to decrease acute toxicity were undertaken by planning and delivering a dose-painting intensity modulated radiation therapy (IMRT) technique as opposed to the previous conventional 2-dimensional or 3-dimensional techniques. In RTOG 0529 dose-painting IMRT yielded similar two-year outcomes as the RTOG 9811 conventional radiation, 5FU/MMC arm [9]. Although the primary endpoint of toxicity reduction was not achieved, there was a significant reduction in acute grade 2+ hematologic, and grade 3+ gastrointestinal and dermatologic adverse events. Treatment interruptions due to toxicity were also less frequent. The median duration of IMRT was 43 days, as compared to 49 days for the RTOG 9811 radiation 5FU/MMC arm ($p<0.0001$). Treatment breaks remained high, 49%, although decreased as compared to 62% on 9811 [20].

Unique to the therapeutic management of anal cancer, regions of microscopic disease tend to receive a dose lower than, or equal to, 45Gy at <1.8Gy per fraction. Despite the low dose per fraction there is no evidence of treatment failure to this region [21]. In contrast, regions of gross disease, lymph nodes >3cm, and larger tumors (T3/T4) may receive a dose as high as 60Gy to improve control. Despite the prior single-/multi-institutional trials and outcomes, however, variability continues to exist among the optimal dose painting IMRT dose fractionation schemes for anal cancer and may vary from institution to institution [22].

Radiotherapy techniques for patient set-up and radiation delivery also vary, but consensus has developed from RTOG and the national UK guidance for the identification of regions of clinical target volumes. In addition, the guidelines also offer several general recommendations by the consensus panel for normal organ constraints [23,24].

Results of Therapy

Complications of therapy

The high CFS rate associated with radiation and concurrent 5-FU and MMC has been tempered by significant acute toxicity in the form of painful moist skin desquamation, diarrhea, proctitis, cystitis, and hematologic decline. In addition to causing the patient distress these acute side-effects may result in hospitalization or self-imposed radiation treatment breaks that limit the delivery of the standard therapy. Long-term complications may be an extension of the acute effects and may additionally include bowel urgency, sterility, impotence, vaginal dryness, decreased hormonal levels and/or vaginal stenosis. HIV patients with acquired immune deficiency syndrome (AIDS) represent a patient population that, despite expectations of similar outcomes with regards to response, may still require extra consideration in regards to potential toxicities. The CD4 recovery in this patient population is prolonged after completion of therapy [25].

Follow-up policy

The current follow-up practice is to closely monitor the patient up to 12 weeks post therapy with serial biopsies of the anal region if gross disease remains. If the disease is clinically evident to have progressed or residual disease remains at the 12-24 week mark patients are taken

for resection of the primary site with APR and permanent colostomy placement [6]. In the most recent phase III RTOG trial, DFS was 67.8% in the MMC arm with a 5-year OS of 78.7% [15].

Molecular biomarkers (HPV/p16)

Of patients whom have acquired an HPV infection, a portion may advance from the permissive to the transforming infection stage, characterized by overexpression of viral oncogenes E6 and E7. Overexpression of p16 has been used as a surrogate marker for transformation. Data suggests that p16 positivity as a consequence of HPV infection confers a good prognosis and that p16 positivity without HPV infection is associated with reduced local control [26]. In a limited study of 41 patients retrospectively reviewed, 29 patients with positive HPV and p16 expression status the 4-year PFS and OS were 78% and 92%, respectively [27]. Of the four subgroups of HPV/p16 classification reviewed in a German retrospective study found those patients with HPV negative disease to have had the worst outcomes [26].

Imaging biomarkers (MRI & PET/CT)

The European Society for Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO) and the European Society of Radiotherapy and Oncology (ESTRO) (ESMO-ESSO-ESTRO) clinical guidelines encourage the use of pelvic MRI for staging of anal cancer [28]. MRI provides improved soft tissue contrast compared to CT, providing information on tumor size, local extent, and spread and invasion of adjacent organs, with a more accurate assessment of nodal involvement than clinical exam and endo-rectal ultrasound. Evidence was also presented that MRIs at 3- and 6-months post CRT predicted patients salvageable with R0 resection in early local relapses [29]. Post-therapy FDG-PET-CT also has evidence that it predicts clinical outcomes in patients with anal cancer treated with CRT. Initial post-treatment PET-CT was obtained on average 12.7 weeks after the last day of radiation in a single institutional review of 148 patients. The negative predictive value of a PET-CT performed at initial follow-up was 92.9%. And patients with a complete metabolic response on PET-CT within 25 weeks of treatment had significantly improved PFS and OS compared with patients who did not have a complete metabolic response (89.8% vs. 69.2%, p=0.004 and 94.8% vs. 79.3%, p=0.036 respectfully) [30].

Conclusion

Anal canal carcinoma is a success story of curative therapy with organ preservation. Well conducted trials have confirmed the necessary therapeutic management with concurrent radiation and 5-FU/MMC. Challenges, however, have always been noted in the toxicity profiles of treated patients, including patients requiring colostomies for long-term toxicities post therapy. Enhanced hematologic toxicities are of concern in the HIV/AIDS patient population where depressed CD4 counts can be prolonged even after the completion of therapy. Management of non-responsive or locally recurrent patients is by surgical removal with APR. Better identification of those patients failing organ preservation therapy could lead to enhanced therapies or reduced modalities of treatment. New directions include concurrent chemotherapies with promising toxicity profiles and molecular and imaging biomarkers. Even more promising is an identified association with HPV. Vaccines currently available can lessen the transmission of this pre-cancerous state.

References

1. Siegel R, Miller K, Jemal A. Cancer Statistics, 2015. Ca Cancer J Clin. 2015; 65: 5-29.
2. Salati SA, Al Kadi A. Anal Cancer – A Review. Int J Health Sci (Qassim). 2012; 6: 206-230.
3. Daling J, Madelenie M, Johnson L, Schwartz S, Shera K, Wurscher M, et al. Human Papillomavirus, Smoking, and Sexual Practices in the Etiology of Anal Cancer. Cancer. 2004; 101: 270-280.
4. Compton C, Byrd D, Garcia-Aguilar J, Kurtzman S, Olawaiye A, Washington M. American Joint Committee on Cancer AJCC Cancer Staging Atlas. 7th edn. New York: Springer. 2012.
5. Marshall D and Thomas C. Carcinoma of the Anal Canal. Oncol Rev 2009; 3: 27-40.
6. National Comprehensive Cancer Network. Anal Carcinoma (Version 2.2016).
7. Nigro N, Vaitkevicius V, Considine B Jr. Combined Therapy for Cancer of the Anal Canal: a Preliminary Report. 1974. Dis Colon Rectum. 1993; 36: 709-711.
8. Radiation Therapy Oncology Group. RTOG 0529: A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal.
9. Kachnic L, Winter K, Myerson R, Goodyear M, Willins J, Esthappan J, et al. Two-Year Outcomes of RTOG 0529: A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal. J Clin Oncol. 2011; 29: abstr 368.
10. UKCCCR Anal Cancer Trial Working Party. Epidermoid Anal Cancer: Results from the UKCCCR Randomized Trial of Radiotherapy Alone Versus Radiotherapy, 5-Fluorouracil, and Mitomycin. Lancet.1996; 348: 1049-1054.
11. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset J, Gonzalez D, et al. Concomitant Radiotherapy and Chemotherapy is Superior to Radiotherapy Alone in the Treatment of Locally Advanced Anal Cancer: Results of a Phase III Randomized Trial of the European Organization for the Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997; 15: 2040-2049.
12. Flam M, John M, Pajak T, Petrelli N, Myerson R, Doggett S, et al. Role of Mitomycin in Combination with Fluorouracil and Radiotherapy, and of Salvage Chemoradiation in the Definitive Nonsurgical Treatment of Epidermoid Carcinoma of the Anal Canal: Results of a Phase III Randomized Intergroup Study. J Clin Oncol. 1996; 14: 2527-2539.
13. James R, Glynne-Jones R, Meadows H, Cunningham D, Myint A, Saunders M, et al. Mitomycin or Cisplatin Chemoradiation with or without Maintenance Chemotherapy for Treatment of Squamous-Cell Carcinoma of the Anus (ACT II): A Randomized, Phase 3, Open-Label, 2x2 Factorial Trial. Lancet Oncol. 2013; 14: 516-524.
14. Ajani J, Winter K, Gunderson L, Pedersen J, Benson A, Thomas C, et al. Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal. JAMA. 2008; 299: 1914-1921.
15. Gunderson L, Winter K, Ajani J, Pedersen J, Moughan J, Benson III A, et al. Long-Term Update of US GI Intergroup RTOG 98-11 Phase III Trial for Anal Carcinoma: Survival, Relapse, and Colostomy Failure with Concurrent Chemoradiation Involving Fluorouracil/Mitomycin Versus Fluorouracil/Cisplatin. J Clin Oncol. 2012; 30: 4344-4351.
16. Deenen M, Dewit L, Boot H, Beijnen J, Schellens J, Cats A. Simultaneous Integrated Boost-Intensity Modulated Radiation Therapy with Concomitant Capecitabine and Mitomycin C for Locally Advanced Anal Carcinoma: A Phase I Study. Int J Radiation Oncol Biol Phys. 2013; 85: e201-207.
17. Goodman K, Rothenstein D, Lajhem A, Wu A, Cercek A, Saltz L. Capecitabine plus Mitomycin in Patients Undergoing Definitive Chemoradiation for Anal Squamous Cell Carcinoma. Int J Radiat Oncol Biol Phys. 2014; 90: S32-33.
18. Tian X, Warner S, Wagner K, Caster J, Zhang T, Ohana P, et al. Preclinical Evaluation of Promitil®, a Radiation-Responsive Liposomal Formulation of

Mitomycin C Prodrug, in Chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2016 [In press].

19. John M, Pajak T, Flam M, Hoffman J, Markoe A, Wolkov, et al. Dose Escalation in Chemoradiation for Anal Cancer: Preliminary Results of RTOG 92-08. Cancer J Sci Am. 1996; 2: 205-211.

20. Kachnic L, Winter K, Myerson R, Goodyear M, Willins J, Esthappan J, et al. RTOG 0529: A Phase II Evaluation of Dose-Painted Intensity Modulation Radiation Therapy in Combination with 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Cancer. Int J Radiat Oncol Biol Phys. 2013; 86: 27-33.

21. Call J, Haddock M, Quevedo J, Larson D, Miller R. Intensity-Modulated Radiotherapy for Squamous Cell Carcinoma of the Anal Canal: Efficacy of a Low Daily Dose to Clinically Negative Regions. Radiat Oncol. 2011; 6: 134-139.

22. Janssen S, Glanzmann C, Bauerfeind P, Stieb S, Studer G, Brown M, et al. Clinical Experience of SIB-IMRT in Anal Cancer and Selective Literature Review. Radiat Oncol. 2014; 9: 199-208.

23. Myerson R, Garofalo M, El Naqa I, Abrams R, Apte A, Walter B, et al. Elective Clinical Target Volumes for Conformal Therapy in Anorectal Cancer: A Radiation Therapy Oncology Group Consensus Panel Contouring Atlas. Int J Radiation Oncology Biol Phys. 2009; 74: 824-830.

24. Muirhead R, Adams R, Gilbert D, Glynne-Jones R, Harrison M, Sebag-Montefiore D, et al. Anal Cancer: Developing an Intensity-Modulated Radiotherapy Solution for ACT2 Fractionation. Clinical Oncology. 2014; 26: 720-721.

25. Alfa-Wali M, Allen-Mersh T, Antoniou A, Tait D, Newsom-Davis T, Gazzard B, et al. Chemoradiotherapy for Anal Cancer in HIV Patients Causes Prolonged CD4 Cell Count Suppression. Annals of Oncology. 2012; 23: 141-147.

26. Mai S, Welzel G, Ottstadt M, Lohr F, Severa S, Prigge E, et al. Prognostic Relevance of HPV Infection and p16 Overexpression in Squamous Cell Anal Cancer. Int J Radiat Oncol Biol Phys. 2015; 93: 819-827.

27. Belgioia L, Vagge S, Agnese D, Garelli S, Murialdo R, Fornarini G, et al. Intensified Intensity-Modulated Radiotherapy in Anal Cancer with Prevalent HPV p16 Positivity. World J Gastroenterol. 2015; 21: 10688-10696.

28. 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. Ann Oncol. 2014; 25: iii10-iii20.

29. Kochhar R, Renehan A, Mullan, Chakrabarty B, Saunders M, Carrington B. The Assessment of Local Response Using Magnetic Resonance Imaging at 3- and 6-Month Post Chemoradiotherapy in Patients with Anal Cancer. Eur Radiol. 2016 [In press].

30. Goldman K, White E, Rao A, Kaptein J, Lien W. Post-Treatment FDG-PET-CT Response is Predictive of Tumor Progression and Survival in Anal Carcinoma. Practical Radiation Oncology. Pract Radiat Oncol. 2016 [In press].

Gastrointest Cancer Res Ther - Volume 1 Issue 2 - 2016
Submit your Manuscript | www.austinpublishinggroup.com

Citation: Howell KJ, Lee YS and Kumar R. Carcinoma of the Anus: A Concise Review of Loco-Regional Therapy. Gastrointest Cancer Res Ther. 2016; 1(2): 1006.