ONCOLOGY. Vol. 24 No. 9

Intensity-Modulated Radiation Therapy for Anal Cancer: An Obvious yet Complicated Transition

By

Joseph M. Herman MD, MSC
Assistant Professor
Johns Hopkins University Department of Radiation Oncology and Molecular Radiation Sciences
Baltimore, Maryland

Charles R. Thomas, JR., MD
Professor and Chair
Department of Radiation Medicine
OHSU Knight Cancer Institute
Portland, Oregon
www.ohsu.edu/radmedicine

| August 24, 2010

In this issue of *ONCOLOGY*, Dr. Zagar and colleagues review the current role of intensity-modulated radiation therapy (IMRT) for anal carcinoma. Their thorough review serves as an excellent summation of how IMRT, when used properly, can result in improved toxicity profiles and similar outcomes.

Historical Perspective
Primary surgery with an abdominoperineal resection (APR) was historically the standard of care for localized anal squamous cell carcinoma. APR achieved 40%-70% survival rates at five years, with local failures from 27%-47%.[1,2] With modern technology and radiation dose escalation, external beam radiation therapy (EBRT) studies have improved complete response rates, decreased morbidity, and improved sphincter preservation rates. Nigro et al added 5-fluorouracil (5FU) and mitomycin C (MMC) to concurrent EBRT [3,4] and impressive complete response rates inspired other groups to investigate the role of chemotherapy as a component of sphincter-preserving therapy. The European Organization for Research and Treatment of Cancer (EORTC) and United Kingdom Coordinating Committee on Cancer Research (UKCCCR) studies reported improved local control and colostomy-free survival when

chemotherapy (5FU/MMC) was administered in conjunction with radiation.[5,6] The five-year survival rate for patients receiving standard chemoradiation approaches 70%; however, 20%-40% experience grade 3-4 toxicity, and administration with MMC causes profound hematologic toxicity.

In efforts to minimize the hematologic toxicity of chemoradiation and potentially increase the overall therapeutic ratio, cisplatin has been evaluated as a substitute for MMC. The compelling preclinical radiosensitizing data with cisplatin coupled with multiple favorable single institution studies led to the development of Radiation Therapy Oncology Group (RTOG) 98-11.[7] In RTOG 98-11, patients were randomized between *immediate concurrent* radiation with 5FU/MMC and *induction* 5FU/cisplatin chemotherapy followed by radiation with 5FU/cisplatin. Five-year disease-free survival was similar in both arms, but colostomy rates at five years were lower in the MMC arm (10% vs 19%, $P = .02$). There was no statistically significant difference in overall survival or overall toxicity; however, hematologic toxicity was significantly higher in the MMC arm ($P < .001$). The study has been criticized because it attempted to answer two questions in a single randomization study: (1) the role of cisplatin vs MMC in anal cancer and (2) the role of induction chemotherapy vs concurrent chemoradiation therapy. Induction chemotherapy may promote accelerated repopulation, thereby decreasing the efficacy of the cisplatin arm without assessing the true benefit of concurrent therapy with cisplatin vs MMC. Unlike RTOG 98-11, the Anal Cancer Trial (ACT) II study[8] randomized patients to conventional RT with *concurrent* 5FU/cisplatin or 5FU/MMC followed by a second randomization to an additional two cycles of 5FU/cisplatin or observation alone. With a median follow-up of three years, colostomy rates were similar in both arms while acute grade 3-4 hematologic toxicity rates were noted to be higher in patients receiving MMC (25%) versus cisplatin (13%). High-grade acute non-hematologic toxicities were elevated for both arms, but there were no statistically significant differences in the rates. Collectively, these studies suggest that conventional radiation can be delivered with concurrent 5FU/MMC or 5FU/cisplatin showing relatively similar non-hematologic toxicity. MMC, however, results in higher rates of hematologic toxicity. Hence, improved radiation delivery techniques with less toxic chemotherapeutic and/or targeted agents should be explored.[9]

Improved Radiation Delivery with IMRT

As outlined in the review by Zagar et al, there are several single institutional studies demonstrating encouraging toxicity profiles and equivalent outcomes with IMRT. However, the follow-up for such studies has been limited.[10,11] RTOG 0529 is a phase II study evaluating dose-painted IMRT in combination with 5FU/MMC in an attempt to reduce acute morbidity in patients with anal cancer. Preliminary results of 51 analyzable patients noted 76% experienced grade 2 GI/GU acute toxicity, which was equivalent to the MMC arm of RTOG-9811.[12] There was, however, a statistically significant reduction in grade 2 dermatologic and grade 3 GI/GU toxicity. Further analysis of outcomes and late morbidity in this trial will be presented at the upcoming ASTRO meeting in November 2010.

IMRT in patients with *rectal* cancer have demonstrated improvement in toxicity profiles, with local control rates apparently equivalent to conventional therapy.[13,14] However, one must remember that with rectal cancer, IMRT is used as an adjunct to surgery, unlike in anal cancer. Recurrent disease in the pelvis following IMRT for anal cancer can be difficult to manage, often resulting in a salvage APR. It is also more likely to result in worse toxicity than upfront surgical resection. Therefore, when IMRT is used for anal cancer, every effort should be made to ensure adequate coverage of all known and presumed disease. Standardized target delineation for anorectal cancer has been established by practicing radiation oncologists,[15] and exposure to a visual atlas prior to contouring can enhance volume conformity[16], thus decreasing the potential risk of error.

Toxicity Profile and Quality of Life

Although chemoradiation often avoids a permanent colostomy in anal cancer patients, the acute and long-term toxicities of this sphincter-preserving treatment approach can also be significant. With

conventional radiation fields, the entire pelvis is irradiated. Acute toxicities include radiation dermatitis, dysuria/cystitis, diarrhea, nadir of blood counts, vaginal irritation, and radiation enteritis. Long-term toxicities include fibrosis, radiation enteritis, femoral head fracture, sterility, pain, vaginal dryness, impotence, and second malignancies. Dose painting with IMRT can allow for sparing of normal structures and a reduction in many of these toxicities. Standardized, prospectively collected patient self-reported quality of life (QOL) measures such as the EORTC QLQ-C30 should be included in future IMRT studies in order to quantitatively compare global and site-specific effects of various treatment regimens.[17,18] Although several QOL and symptom measures exist, there is clearly a need for standardized systems that will allow for easier comparisons of treatments (IMRT vs 3-D conformal RT) internationally.

Patterns of Failure

With IMRT, dose painting is used to focus radiation to the primary tumor and spare adjacent organs at risk (OAR) from toxicity. In order to tailor the radiation with respect to these OAR, one must be cognizant of which areas are at a high risk of recurrence. Following standard 5FU/MMC-based chemoradiation, a study by Das et al reported that a majority of locoregional failures involved the anus and rectum, whereas inguinal recurrences were rare.[19] Another study by Wright et al also found local recurrence to be most common (78%); however, 44% had regional components of failure within the pelvis or inguinal nodes.[20] Initial patterns of failure of patients treated on RTOG 0529 with IMRT-based chemoradiation will be presented at the upcoming ASTRO meeting. With RTOG 0529, the anorectal contouring atlas was reviewed prior to radiation planning, yet a majority of these plans required revisions. The difficulty with planning IMRT anal cancer cases coupled with the limited data on long-term outcomes and patterns of failure suggest IMRT delivery should ideally be conducted in a prospective clinical trial.

Patient Selection, Comparative and Cost Analyses

The current National Comprehensive Cancer Network (NCCN) guidelines suggest that IMRT in addition to three-dimensional conformal radiation therapy may be used in the treatment of patients with anal cancer (www.NCCN.org). However, many insurance companies may still require a case-by-case review prior to approval of IMRT for anal cancer treatment because the data for IMRT in anal cancer are still maturing. It is unlikely that a prospective clinical trial comparing conformal RT with IMRT will ever be conducted. Nevertheless, comparative analyses may be used to assess differing treatment modalities and provide guidance as to which patients are more likely to benefit from IMRT.[21,22] Perhaps comparative analyses can better select patients for IMRT based on gender, age, stage of disease, and/or specific biomarkers.[19,23] A similar comparative analysis evaluating the cost-effectiveness of cisplatin and MMC in the treatment of anal cancer found that MMC may have a more favorable profile.[24] Additional comparative analyses like these may assist in further selecting which patients with anal cancer are more likely to benefit from specific radiation techniques and novel drug therapies.

New Frontiers

The addition of targeted therapies to IMRT may improve response rates but can also result in worse toxicity. Using select targeted therapies such as PARP inhibitors (inhibitors of poly[ADP-ribose] polymerase) may allow for radiation dose de-escalation with similar response rates and less toxicity.[25] Utilization of MRI and functional imaging (FDG/FLT-PET) may minimize the risk of “near radiation misses” and assist in selecting the optimal radiation delivery modality (IMRT vs CRT).[26-31]

Conclusion

This review by Zagar et al of IMRT for anal cancer points out the benefits and limitations of IMRT. Preliminary acute toxicity data is very favorable, although data on long-term toxicity and efficacy is

limited. Patient selection should be further delineated. Advanced imaging and integration of targeted agents should improve efficacy. Ideally, at this time, IMRT should only be done in a clinical trial and/or by clinicians with considerable experience.

References

1. Stearns MW, Jr, Urmacher C, Sternberg SS, et al: Cancer of the anal canal. *Curr Probl Cancer* 4:1-44, 1980.

2. Boman BM, Moertel CG, OConnell MJ, et al: Carcinoma of the anal canal: A clinical and pathologic study of 188 cases. *Cancer* 54:114-125, 1984.

3. Nigro ND, Seydel HG, Considine B, et al: Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer* 51:1826-1829, 1983.

4. Nigro ND, Vaitkevicius VK, Considine B, Jr: Combined therapy for cancer of the anal canal: A preliminary report. *Dis Colon Rectum* 17:354-356, 1974.

5. Bartelink H, Roelofsen F, Eschwege F, 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 Research and Treatment of Cancer radiotherapy and gastrointestinal cooperative groups. *J Clin Oncol* 15:2040-2049, 1997.

6. Epidermoid anal cancer: Results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR anal cancer trial working party. UK co-ordinating committee on cancer research. *Lancet* 348:1049-1054, 1996.

7. Ajani JA, Winter KA, Gunderson LL, et al: Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: A randomized controlled trial. *JAMA* 299:1914-1921, 2008.

8. James R, Wan S, Glynne-Jones R, et al: A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II). *J Clin Oncol* 27:170s, 2009.

9. Jiang Y, Mackley H, Cheng H, et al: Anal carcinoma therapy: Can we improve on 5-fluorouracil/mitomycin/radiotherapy? *J Natl Compr Canc Netw* 8:135-144, 2010.

10. Pepek JM, Willett CG, Czito BG: Radiation therapy advances for treatment of anal cancer. *J Natl Compr Canc Netw* 8:123-129, 2010.

11. Pepek JM, Willett CG, Wu QJ, et al: Intensity-modulated radiation therapy for anal malignancies: A preliminary toxicity and disease outcomes analysis. *Int J Radiat Oncol Biol Phys* Mar 16. Epub ahead of print, 2010.

12. Chan E, Kachnic LA, Thomas CR, Jr: Anal cancer: Progress on combined-modality and organ preservation. *Curr Probl Cancer* 33:302-326, 2009.

13. Ballonoff A, Kavanagh B, McCarter M, et al: Preoperative capecitabine and accelerated intensity-modulated radiotherapy in locally advanced rectal cancer: A phase II trial. *Am J Clin Oncol* 31:264-270, 2008.

14. Meyer JJ, Czito BG, Willett CG: Intensity-modulated radiation therapy for gastrointestinal tumors. *Curr Oncol Rep* 10:206-211, 2008.

15. Myerson RJ, Garofalo MC, El Naqa I, et al: Elective clinical target volumes for conformal therapy in anorectal cancer: A radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys* 74:824-830, 2009.

16. Fuller CD, Nijkamp J, Duppen JC, et al: Prospective randomized double-blind pilot study of site-specific consensus atlas implementation for rectal cancer target volume delineation in the cooperative group setting. *Int J Radiat Oncol Biol Phys* Apr 17. Epub ahead of print, 2010.

17. Tournier-Rangeard L, Mercier M, Peiffert D, et al: Radiochemotherapy of locally advanced anal canal carcinoma: Prospective assessment of early impact on the quality of life (randomized trial ACCORD 03). *Radiother Oncol* 87:391-397, 2008.

18. Das P, Cantor SB, Parker CL, et al: Long-term quality of life after radiotherapy for the treatment of anal cancer. *Cancer* 116:822-829, 2010.

19. Das P, Bhatia S, Eng C, et al: Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. *Int J Radiat Oncol Biol Phys* 68:794-800, 2007.

20. Wright JL, Patil SM, Temple LK, et al: Squamous cell carcinoma of the anal canal: Patterns and predictors of failure and implications for intensity-modulated radiation treatment planning. *Int J Radiat Oncol Biol Phys* Mar 27. Epub ahead of print, 2010.

21. Luo C, Yang CC, Narayan S, et al: Use of benchmark dose-volume histograms for selection of the optimal technique between three-dimensional conformal radiation therapy and intensity-modulated radiation therapy in prostate cancer. *Int J Radiat Oncol Biol Phys* 66:1253-1262, 2006.

22. Kato T, Obata Y, Kadoya N, et al: A comparison of prone three-dimensional conformal radiotherapy with supine intensity-modulated radiotherapy for prostate cancer: Which technique is more effective for rectal sparing? *Br J Radiol* 82:654-661, 2009.

23. Ajani JA, Wang X, Izzo JG, et al: Molecular biomarkers correlate with disease-free survival in patients with anal canal carcinoma treated with chemoradiation. *Dig Dis Sci* 55:1098-1105, 2010.

24. Walker GV, Fuller CD, Thomas CR, Jr, et al: A cost analysis of mitomycin- vs cisplatin-based definitive chemoradiotherapy for anal cancer (abstract). Gastrointestinal Cancers Symposium, 2010.

25. Loser DA, Shibata A, Shibata AK, et al: Sensitization to radiation and alkylating agents by inhibitors of poly(ADP-ribose) polymerase is enhanced in cells deficient in DNA double-strand break repair. *Mol Cancer Ther* 9:1775-1787, 2010.

26. Krengli M, Milia ME, Turri L, et al: FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma. *Radiat Oncol* 5:10, 2010.

27. Ford EC, Herman J, Yorke E, et al: 18F-FDG PET/CT for image-guided and intensity-modulated radiotherapy. *J Nucl Med* 50:1655-1665, 2009.

28. Konski A, Li T, Sigurdson E, et al: Use of molecular imaging to predict clinical outcome in patients with rectal cancer after preoperative chemotherapy and radiation. *Int J Radiat Oncol Biol Phys* 74:55-59, 2009.

29. Winton E, Heriot AG, Ng M, et al: The impact of 18-fluorodeoxyglucose positron emission tomography on the staging, management and outcome of anal cancer. *Br J Cancer* 100:693-700, 2009.

30. Kauczor HU, Zechmann C, Stieltjes B, et al. Functional magnetic resonance imaging for defining the biological target volume. *Cancer Imaging* 6:51-5, 2006.

31. Roels S, Slagmolen P, Nuyts J, et al: Biological image-guided radiotherapy in rectal cancer: Is there a role for FMISO or FLT, next to FDG? *Acta Oncol* 47:1237-1248, 2008.