Optimizing Outcomes of Chemoradiation in the Management of Squamous Cell Carcinoma of the Anal Canal

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Dr. Fakih and colleagues provide a detailed and thoughtful review of the role of chemoradiation in anal cancer treatment. They have included a comprehensive description of the epidemiology and risk factors for the development of squamous cell carcinoma of the anal canal, including the strong association with human papillomavirus (HPV) infection and increased incidence in human immunodeficiency virus (HIV)-positive individuals.

In the current issue of ONCOLOGY, Dr. Fakih and colleagues provide a detailed and thoughtful review of the role of chemoradiation in anal cancer treatment. They have included a comprehensive description of the epidemiology and risk factors for the development of squamous cell carcinoma of the anal canal, including the strong association with human papillomavirus (HPV) infection and increased incidence in human immunodeficiency virus (HIV)-positive individuals. As the authors discuss, the relationships between anal cancer and these two viruses have direct implications for the epidemiology, screening recommendations, potential primary prevention efforts, and toxicity of definitive chemoradiation.

In 1974, Nigro and colleagues reported their paradigm-shifting experience with three anal cancer patients treated with modest doses of preoperative radiation and concurrent chemotherapy. Two patients achieved a pathologic complete response, and a third showed no evidence for recurrence after refusing surgery.¹ This initial success spurred 30 years of intense investigation into sphincter-preserving strategies and the development of what is currently considered the standard of care for most patients: definitive radiotherapy (RT) with concurrent fluorouracil (5-FU) and mitomycin. The authors have thoroughly reviewed the major clinical trials and knowledge gained over this period. In seeking to optimize outcomes following chemoradiation, several issues are worthy of further discussion.

Is There a Role for Routine Staging PET Scan?

The National Comprehensive Cancer Network guidelines in clinical oncology currently recommend consideration of positron-emission tomography/computed tomography (PET/CT) in anal cancer staging. The benefits of PET are likely limited to nodal and distant metastatic disease detection. Although improved sensitivity of primary tumor detection has been documented, this is of questionable significance given the ability to perform a detailed clinical examination. As included in the review, several series have shown increased metabolic activity in regional lymph nodes for 17% to 20% of patients without nodal involvement by standard CT criteria.²-⁴ In the largest published, prospective assessment of the impact of pretreatment PET, 42% and 38% of patients with T2 and T3/4 tumors, respectively, had a change in nodal stage.³ The ability to identify otherwise occult metastases has direct implications for radiotherapy planning. According to Radiation Therapy Oncology Group (RTOG) 98-11 and Anal Cancer Trial (ACT) II, for example, the clinically negative inguinal lymph nodes were treated to a dose of 36 Gy and 30.6 Gy, respectively.⁵,⁶ In contrast, N2 staging mandates boosting gross disease to the final prescription dose of 59.4 Gy and 50.4 Gy, respectively. In the series mentioned above, PET staging resulted in the modification of RT planning for 13% of patients.

Based upon the lack of established specificity, Dr. Fakih and colleagues advise against the routine use of PET in the staging of anal cancer. We acknowledge the limitations of currently available data, including a lack of correlation with treatment outcomes. In particular, the use of PET following biopsy may increase the false-positive rate. Unindicated surgical nodal sampling would be required to establish false-positive rates specific to anal cancer. However, PET staging for other pelvic malignancies has demonstrated specificities of 95% and 90% for inguinal and pelvic nodes, respectively.⁷,⁸

As outlined in the review, the identification of regional nodal metastases in anal cancer is associated
with an approximately 20% overall survival decrement. Tumor control has long been recognized to be dosedependent. Improved nodal staging through the routine use of PET and treatment with tailored radiation doses may potentially improve disease-related outcomes, and can be accomplished with minimal additional treatment-related morbidity using modern techniques.

**Efforts to Enhance Chemoradiation**

Anal cancer is predominantly a locoregional disease. Higher T and N stages are associated with both local treatment failure and the development of distant metastases. Tumor size > 5 cm independently predicts for higher colostomy rates. The need for improved tumor control sparked interest in the use of induction chemotherapy. Initial phase II testing of cisplatin and 5-FU neoadjuvant chemotherapy followed by concurrent chemoradiation showed promising results and good treatment compliance, but the subsequent randomized RTOG 98-11 trial failed to show improved outcomes.

Based on the latest available evidence, Dr. Fakih and colleagues appropriately conclude that cisplatin-based induction chemotherapy followed by concurrent chemoradiation is no better than chemoradiation with 5-FU and mitomycin alone. The trial design of RTOG 98-11 was criticized for testing both an induction strategy and a novel drug combination in the experimental arm, which confounded the interpretation of higher colostomy rates observed in this arm. However, the recently reported ACT II trial demonstrated no difference in any disease-related endpoints between cisplatin or mitomycin and 5-FU concurrent chemoradiation, providing clarity on the efficacy of cisplatin in this disease.

An important lesson from RTOG 98-11 then, in light of the ACT II trial, is that induction chemotherapy not only failed to show a benefit, but may in fact be detrimental to sphincter preservation.

The precise mechanisms for the improvement in local control seen with chemoradiation alone are not fully understood, but appear to be influenced by time. In patients with locally advanced disease, the delivery of concurrent chemoradiation within 60 days has been shown to substantially improve the probability of local progression-free survival. The negative impact of extended durations of therapy and the introduction of treatment breaks has been confirmed in additional analyses. Potential explanations for these observations include the initiation of accelerated repopulation of tumor clonogens following cytotoxic insult and the development of resistance after induction chemotherapy.

As the authors suggest, some have advocated for the incorporation of non–cross-resistant drugs, such as taxanes, into induction strategies. Clearly, novel radiosensitizers and improved systemic therapies are needed, but at present, the use of induction chemotherapy appears to be a failed approach. Whether newer regimens or the addition of a third drug might overcome what appears to be a deleterious effect of induction chemotherapy remains to be seen. Furthermore, extrapolation from as yet unproven induction strategies in head and neck cancer are premature.

Alternative approaches such as adjuvant systemic therapy or novel concurrent regimens remain active avenues of investigation. Enthusiasm for adjuvant therapy has been dampened by ACT II results showing no benefit to "outback" 5-FU/mitomycin. However, alternative adjuvant agents may prove more promising. The addition of molecular targeted agents to traditional chemoradiation regimens may also prove useful. For example, the Eastern Cooperative Oncology Group (ECOG) is currently conducting a phase II study looking at the addition of cetuximab (Erbitux) to cisplatin/5-FU chemoradiation.

**A Reduction in Toxicity Is Needed**

Concurrent chemoradiation with 5-FU and mitomycin carries a substantial risk for both acute and late toxicity. Much of the increased acute toxicity risk is attributable to mitomycin myelosuppression. The addition of mitomycin to 5-FU and radiation is associated with a substantial improvement in disease-free survival, but also an increase in grade 4/5 toxicity from 7% to 23%. Treatment-related mortality approximates 3% with this regimen, although this may be improved with modern supportive care.

Understanding this toxicity profile makes the interpretation of the ACT II trial interesting. As mentioned above, there was no significant difference in complete response or colostomy rates between the cisplatin and mitomycin arms of the trial. However, the incorporation of cisplatin led to a statistically significant reduction in acute grade 3 or 4 hematologic toxicity, from 25% to 13%.

Currently, the investigators have concluded that 5-FU/mitomycin chemoradiation remains the standard of care. The ACT II trial was not designed to test equivalence and has not yet been published in full. However, it is the largest randomized controlled trial conducted to date.
investigating chemoradiation strategies for anal cancer. Pending final publication, the improved therapeutic index seen with cisplatin-based therapy may lead to practical conclusions that contradict those of the principal investigators.

Theoretically, intensity-modulated radiation therapy (IMRT) has the potential for reducing hematologic toxicity by sparing dose to the pelvic bones. In their study of cervical cancer patients receiving chemoradiation, Mell and colleagues identified bone marrow dosimetric parameters that correlated with reduced acute hematologic toxicity. However, hematologic progenitors are exquisitely sensitive to radiation, and the clinical utility of a marrow-sparing approach to anal cancer treatment remains to be defined.

Nonetheless, interest in IMRT remains high as a means of improving the tolerability of therapy, and by extension, limiting treatment interruptions. A recent multicenter study of IMRT as a component of combined-modality therapy reported a favorable reduction in gastrointestinal and dermatologic toxicity compared to historical controls. In addition to acute morbidity, late complications of pelvic radiotherapy can be significant. Common toxicities include sphincter dysfunction, chronic diarrhea, poor sexual function, and pelvic fractures. Limiting late sequelae by reducing dose to bowel, genitalia, and pelvic bones is a potentially beneficial use of IMRT, but mature data are lacking.

RTOG 0529, a phase II trial testing the feasibility and toxicity of IMRT with 5-FU and mitomycin, has completed accrual, and early results were recently reported at the 2010 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. No major protocol deviations were seen with respect to tumor or nodal treatment volumes. However, 79% of radiation treatment plans required modifications to elective nodal volumes prior to treatment following rigorous central review. This degree of variability in RT volumes is cause for concern. To facilitate broader implementation of high-quality IMRT, an RTOG consensus panel recently published a contouring atlas for clinical target volumes in anal cancer. Further follow-up is necessary to ensure that the transition to highly conformal radiotherapy does not compromise disease control.

Conclusions

Squamous cell carcinoma of the anal canal is highly responsive to chemoradiation, allowing radical surgery to be reserved for salvage. The current standard of care includes concurrent 5-FU/mitomycin with RT and results in high rates of sphincter preservation. The use of staging PET is an evolving strategy that has shown improved sensitivity over conventional CT for the detection of nodal and distant metastatic disease and has direct implications on treatment planning. Novel systemic therapies are needed to improve disease control rates for patients with locoregionally advanced disease, and current evidence suggests incorporation into concurrent regimens rather than induction or adjuvant regimens. Meanwhile, efforts should also focus on reducing the acute and late toxicities of therapy.

References:

REFERENCES:


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