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REVIEW ARTICLE

Management of Anal Cancer in 2010 Part 2: Current Treatment Standards and Future Directions

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ABSTRACT: The treatment of anal squamous cell cancer with definitive chemoradiation is the gold-standard therapy for localized anal cancer, primarily because of its sphincter-saving and colostomy-sparing potential. Studies have addressed different chemoradiation regimens in hopes of improving on the standard protocol of fluorouracil(Drug information on fluorouracil) (5-FU), mitomycin(Drug information on mitomycin), and radiation, but no alternative regimens have proven superior. Nevertheless, important conclusions have been derived regarding the continuity of radiation as well as the role of induction and maintenance chemotherapy in this setting. In the concluding part of this review, we consider the data on chemoradiation with 5-FU/mitomycin vs radiation alone, chemoradiation with 5-FU/mitomycin vs chemoradiation with 5-FU alone, neoadjuvant chemotherapy with cisplatin(Drug information on cisplatin)/5-FU followed by cisplatin/5-FU plus radiation vs mitomycin/5-FU plus radiation, the addition of induction or maintenance chemotherapy to chemoradiation, the effect of overall treatment time on tumor control, whether chemotherapy can be eliminated for early-stage anal cancer, and the impact of human immunodeficiency virus infection on treatment.

As noted in part 1 of this article, which appeared in the April 15th issue of *ONCOLOGY* (24:364-369, 2010), the treatment of anal squamous cell cancer with definitive chemoradiation is clearly the gold-standard therapy for localized anal cancer, primarily because of its sphincter-saving and colostomy-sparing potential. Studies conducted over the past 2 decades have addressed different chemoradiation regimens in hopes of improving on the standard Nigro protocol of fluorouracil (5-FU), mitomycin, and radiation. Although these studies failed to reveal any superiority of alternative regimens to the Nigro protocol, important conclusions were derived regarding the continuity of radiation as well as the role of induction (pre-chemoradiation) and maintenance chemotherapy (post-chemoradiation) in patients with anal cancer.

Part 1 of this review provided an overview of anal cancer epidemiology, risk factors, screening, prevention, and diagnosis. In part 2, we will focus on the current status of chemoradiation for anal cancer and reflect on potential areas for future treatment improvements.

Treatment

Prior to the 1980s, abdominoperineal resection of the anal canal and distal rectum, with the formation of permanent end-colostomy was the standard treatment of anal cancer and was associated with a 5-year survival of around 40% to 70%.[1-7]

Subsequent work by Nigro et al showed that the administration of preoperative 5-FU and mitomycin combined with radiation therapy resulted in a reduced surgical failure rate.[8,9] Given the high rate of complete pathologic response associated with the Nigro regimen, Nigro proposed an approach of initial chemoradiation followed by abdominoperineal resection only if residual tumor remained at the time of postradiation biopsy.[10] Combined-modality therapy using initial radiation therapy, 5-FU, and mitomycin followed by salvage surgery was subsequently established as the standard of care by retrospective and prospective studies, despite the lack of a randomized study comparing chemoradiation to surgery.[10-18] A randomized study comparing chemoradiation to abdominoperineal resection is generally not considered feasible, given the anticipated difficulties in patient accrual.

Chemoradiation With 5-FU/Mitomycin vs Radiation Therapy Alone

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial randomized 585 patients to radiation alone or radiation combined with chemotherapy (continuous 5-FU, 1,000 mg/m^2/d for 4 days or 750 mg/m^2/d for 5 days, during the first and final week of radiation treatment, with mitomycin, 12 mg/m^2 by bolus intravenous infusion on day 1 of chemoradiation).[18] The radiation dose was 45 Gy in 20 to 25 fractions over 4 to 5 weeks. Tumor response was assessed at 6 weeks after completion of the first radiotherapy course. Patients with at least a 50% tumor regression received an additional boost of 15 Gy in six fractions or by 25 Gy iridium-192 implant over 2 to 3 days. Poor responders with less than 50% tumor regression underwent surgical resection.

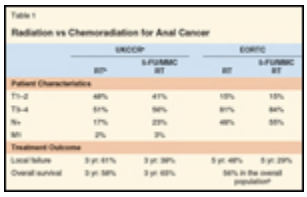
The response rate in the assessable population was 92% on both arms; most of these patients received the intended radiation boost. Approximately 65% of the poor responders underwent abdominoperineal resection, and the rest received other therapies. Local failure was defined as persistent disease following completion of therapy, anorectal surgery, or persistent colostomy at 6 months from completion of treatment. Local failure occurred in 265 of 562 evaluable patients, defined as those who were evaluable at 6 or more weeks from treatment start.

The 3-year local relapse rate was 61% in the radiation arm vs 39% in the chemoradiation arm. The incidence of anal cancer–related death was significantly higher in the radiation arm (39%) than in the chemoradiation arm (28%). The 3-year survival-rate for the radiation arm was 58%, compared with 65% for the chemoradiation arm, which was not a statistically significant difference because of the excess non–cancer-related mortality on the chemoradiation arm.[18]

In the European Organisation for Research and Treatment of Cancer (EORTC) study, 103 patients with locally advanced cancers of the anal canal were entered on a trial with a similar design.[16] A boost of 15 Gy for complete remission or 20 Gy for partial responders (ie, any shrinkage) was given after 6 weeks of completion of the initial 45 Gy. Chemotherapy consisted of 5-FU, 750 mg/m^2 daily as a continuous infusion on days 1 to 5 and 29 to 33, and mitomycin was given at 15 mg/m^2 on day 1 of the first course of 5-FU. Assessment of treatment effect was performed 6 weeks after completion of boost treatment. Complete response was higher in the chemoradiation arm (80%) vs the radiation arm (54%). At 5 years,

Kaplan-Meier estimates showed 18% more locoregional control (*P* = .02) and a 32% higher colostomyfree interval (*P* = .002) in favor of the chemoradiation arm. Evaluation of 5-year overall survival showed a trend in favor of the chemoradiation approach (*P* = .17).[16]

TABLE 1



Radiation vs Chemoradiation for Anal Cancer

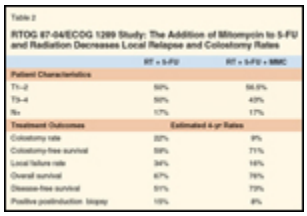
The results in the chemoradiation arm of the EORTC study were somewhat better than what was seen in the UKCCCR study, despite the inclusion of patients with more advanced disease and the exclusion of T1–2, N0 patients (Table 1). The improvement in outcome in the EORTC study may be related to more stringent inclusion guidelines (no metastatic disease patients were included), more prolonged and standardized radiation (45 Gy in 25 fractions in all patients), exclusion of patients older than 75 years, and application of a boost in all patients with disease regression, irrespective of its degree (UKCCCR mandated > 50% shrinkage). Both studies clearly indicate superior locoregional control and a decrease in colostomy rates with the addition of 5-FU and mitomycin to radiation therapy.

Chemoradiation With 5-FU/Mitomycin vs 5-FU Chemoradiation

In 1991, a meta-analysis of prospective clinical trials using radiation alone, with 5-FU, and with 5-FU/mitomycin reported a significant improvement in local control and 5-year overall survival in favor of 5-FU plus mitomycin.[13] Subsequently, the Radiation Therapy Oncology Group (RTOG) 87-04/Eastern Cooperative Oncology Group (ECOG) 1289 study—a phase III randomized clinical trial—confirmed the superiority of 5-FU plus mitomycin (Nigro regimen) over 5-FU plus radiation in the definitive treatment of anal cancer.[17] A total of 310 patients were randomized to radiation with 5-FU (1,000 mg/m^2/d as a continuous infusion for 96 hours on days 1 and 29) or radiation with the same 5-FU schedule and the addition of mitomycin (10 mg/m^2 on the first day of each 5 FU course). Radiation was given at 45 Gy in 5 weeks. Patients with palpable tumor at the end of the 45-Gy dose were given an additional 5.4 Gy. Patients with N0 disease received 45 Gy to the inguinal lymph nodes, while those with N1 disease were boosted to 50.4 Gy.

Response was documented with a mandated full-thickness tumor biopsy at 4 to 6 weeks after completion of this "induction chemoradiation." Salvage chemoradiation was administered if there was histologic confirmation of residual primary tumor. Salvage chemoradiation consisted of an additional radiation therapy boost of 9 Gy (5 fractions of 1.8 Gy) to the area of residual disease, along with concurrent 5-FU (1,000 mg/m^2/d for 4 days) and a single injection of cisplatin (100 mg/ m^2 on day 2 of 5-FU therapy). A total of 291 patients were assessable for disease outcome, 262 of whom underwent postinduction biopsy.

TABLE 2



RTOG 87-04/ECOG 1289 Study: The Addition of Mitomycin to 5-FU and Radiation Decreases Local Relapse and Colostomy Rates

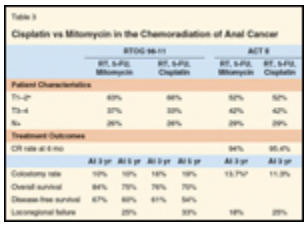
The negative biopsy rates were 86% and 92.2% in the 5-FU and 5-FU/mitomycin arms, respectively (*P* = .135). Colostomy rates at 4 years were lower in patients receiving 5-FU plus mitomycin (9%) vs patients receiving 5-FU (23%; *P* = .002). Similarly, the disease-free survival rate was significantly improved in favor of the mitomycin arm (4-year disease-free survival was 73% vs 51%; *P* = .0003). While these results did not translate into a survival advantage, a trend emerged in an overall survival benefit in the mitomycin group after 18 months. The assessment of the value of salvage chemoradiation was limited, as only 28 patients had positive biopsies postinduction. Of these 28 patients, 25 received salvage chemoradiation as per protocol. Twelve patients ultimately had a negative postsalvage treatment biopsy, and 4 of these 12 were disease-free 4 years later.[17] These results are summarized in Table 2. The RTOG 87-04/ECOG 1289 study firmly established 5-FU/mitomycin as part of standard chemoradiation therapy for anal cancer.

Neoadjuvant Chemoradiation With Cisplatin/5-FU vs Mitomycin/5-FU

Several phase II clinical trials showed promising results for 5-FU, cisplatin, and radiation combined in the treatment of anal cancer,[19,20] prompting the investigation of this combination in phase III clinical trials (Table 3).

RTOG 98-11 randomized 682 patients with T2–4, M0 anal cancer to 5-FU plus mitomycin and radiation vs neoadjuvant chemotherapy followed by 5-FU plus cisplatin with radiation.[21] The induction chemotherapy in the cisplatin arm consisted of two cycles of cisplatin plus 5-FU prior to definitive cisplatin plus 5-FU with radiation. The mitomycin arm did not receive any induction chemotherapy.

TABLE 3



Cisplatin vs Mitomycin in the Chemoradiation of Anal Cancer

Chemotherapy treatment in the mitomycin group consisted of mitomycin at 10 mg/m^2 on days 1 and 29 and 5-FU continuous infusion at 1,000 mg/m^2/d on days 1 to 4 and 29 to 32 (with radiation starting on day 1). Chemotherapy on the cisplatin arm consisted of cisplatin at 75 mg/m^2 on days 1 and 29 and repeated on days 57 and 85 (with radiation starting on day 57) and 5-FU continuous infusion at 1,000 mg/m^2/d on days 1 to 4, 29 to 32, 57 to 60, and 85 to 88. It is important to recognize that the total length of treatment with neoadjuvant chemotherapy followed by 5-FU plus cisplatin with radiation was 56 days longer than in the 5-FU plus mitomycin and radiation arm. Additionally, the initiation of radiation therapy was delayed 57 days.

Radiation was given to a minimum dose of 45 Gy in 25 fractions of 1.8 Gy using anteroposterior-posteroanterior or multifield techniques. Initial radiation fields included the pelvis, anus, perineum, and inguinal lymph nodes, with the superior border at L5-S1 and the inferior border to include the anus with a minimum margin of 2.5 cm around the anus and tumor.[21] Radiation fields were reduced further at 30.6 Gy and 36 Gy (for lymph node–negative patients). Patients with T3–4 disease, positive lymph nodes, or residual disease at the completion of 45 Gy, received an addition boost of 10 to 14 Gy (2 Gy fractions).[21]

The 3- and 5-year disease-free survival rates in the mitomycin arm were 67% and 60%, respectively. In the cisplatin arm, the 3- and 5-year disease-free survival rates were 61% and 54%, respectively. This mitomycin-favoring trend did not reach statistical significance ($P = .17$). The 5-year locoregional recurrence rates were 25% and 33%, and the 5-year distant relapse rates were 15% and 19% in the mitomycin and cisplatin arms, respectively. Similarly, a nonsignificant trend ($P = .10$) favored mitomycin therapy for 3-year survival (84% vs 76%) and 5-year survival (75% vs 70%). Treatment with 5-FU and mitomycin plus radiation resulted in a statistically significant reduction in the colostomy rate at 3 years (10% vs 16%) and 5 years (10% vs 19%).

Both treatments resulted in a 74% grade 3/4 toxicity rate in each arm. The mitomycin arm showed a significantly increased hematologic toxicity rate, even though the arm receiving neoadjuvant chemotherapy followed by cisplatin plus 5-FU with radiation got chemotherapy for almost 2 additional months.[21] RTOG 98-11 failed to show any superiority for neoadjuvant chemotherapy followed by the cisplatin plus 5-FU with radiation regimen over standard care in rectal cancer—ie, mitomycin plus 5-FU with radiation.

The addition of neoadjuvant chemotherapy to the cisplatin arm complicated the study design, as it did not allow a direct comparison of radiation with either mitomycin or cisplatin. The role of neoadjuvant chemotherapy in the treatment of anal cancer is unclear, especially as it prolonged the total duration of therapy by 56 days. Additionally, it is unknown whether the 57-day delay of initiating radiation influenced study outcomes, especially among patients who failed to respond to neoadjuvant chemotherapy.

The second UK Anal Cancer Trial (ACT II), as reported at the American Society of Clinical Oncology 2009 meeting, addressed the issues in the RTOG study design and directly evaluated the role of mitomycin vs cisplatin in the neoadjuvant chemoradiation of anal cancer.[22] A total of 940 patients (T1–4) were randomized to receive 5-FU plus cisplatin with radiation or 5-FU plus mitomycin with radiation. Both the mitomycin and cisplatin arms were randomized further to receive adjuvant cisplatin plus 5-FU for two cycles (maintenance) or to observation. Those patients randomized to maintenance therapy began adjuvant chemotherapy 4 weeks after completion of chemoradiation.[22]

The mitomycin chemoradiation arm in the ACT II trial consisted of a 5-FU continuous infusion at 1,000 $mg/m^2/d$ on days 1-4 and 29-32 and mitomycin at 12 mg/m^2 on day 1 of radiation, 50.4 Gy in 28 fractions. The cisplatin chemoradiation arm consisted of 5-FU continuous infusion at 1,000 $mg/m^2/d$ on days 1 to 4 and 29 to 32 and cisplatin at 60 mg/m^2 on days 1 and 29, with radiation starting on day 1.

The complete response rate at 6 months in the ACT II trial was similar in the mitomycin (94.5%) and cisplatin (95.4%) arms. The colostomy rate at 3 years was 13.7% on the mitomycin arm vs 11.3% on the cisplatin arm ($P = .26$). No difference was noted in locoregional recurrence between the mitomycin arm (11%) vs the cisplatin arm (13%). Nonhematologic toxicities were seen to the same extent in both arms, while hematologic toxicities were significantly higher in the mitomycin arm.[22] The ACT II study

showed that the outcomes and nonhematologic toxicities with cisplatin were equivalent to mitomycin while resulting in significantly lower hematologic toxicity (grade 3/4 hematologic toxicity during chemoradiation was 13.4% in the cisplatin-arm vs 24.7% in the MMC-arm).

Addition of Induction or Maintenance Chemotherapy to Chemoradiation

The relevance of induction chemotherapy prior to definitive chemoradiation was addressed by RTOG 98-11. This study, detailed above, did not show any advantage to neoadjuvant cisplatin plus 5-FU followed by cisplatin-based chemoradiation over mitomycin-based chemoradiation without induction.[21] The effect of an extended overall treatment time with neoadjuvant chemotherapy is unknown. The effect of a nearly 2-month delay in initiating radiation, especially among patients who do not respond to neoadjuvant chemotherapy, is also unknown.

Given that cisplatin- and mitomycin-based radiation were shown to be equivalent in the ACT II study, it would be highly unlikely that a beneficial effect of neoadjuvant 5-FU/cisplatin was negated by the effect of cisplatin-based radiation in RTOG 08-11.[21,22] This is supported further by a recent analysis of the efficacy data from the ACCORD 03 trial.[23] This was a 2×2 factorial design phase III study that randomized patients to two cycles of cisplatin plus 5-FU followed by chemoradiation (5-FU plus cisplatin with radiation) or to chemoradiation (5-FU plus cisplatin with radiation) alone. The induction arm consisted of cisplatin at 80 mg/m^2 on day 1 and 5-FU at 800 mg/m^2/d on days 1 to 4 of weeks 1, 5, 9, and 12, with radiation starting on week 9 of treatment. The upfront chemoradiation arm consisted of the same chemotherapy regimen but given only on weeks 1 and 5 of radiation. Radiation consisted of 45 Gy in 25 fractions. These arms were randomized further to a standard 15-Gy boost or to a higher-dose boost of 20 to 25 Gy.[23] Neither induction chemotherapy nor the additional boost of radiation resulted in any improvement in outcome measures (colostomy-free survival, event-free survival, local control, or overall survival).[23]

The relevance of maintenance (adjuvant) chemotherapy was addressed in the ACT II study (described above).[22] Patients were randomized to an arm receiving two cycles of cisplatin plus 5-FU (maintenance) or to a "no maintenance arm" following completion of chemoradiation. The 3-year disease-free and overall survival rates were 75% and 85% on the maintenance arm vs 75% and 84% on the "no maintenance" arm.[22] The lack of a clinical benefit for induction or maintenance chemotherapy does not support the implementation of these strategies in clinical practice outside the setting of a clinical trial.

Effect of Overall Treatment Time on Tumor Control

Multiple studies have shown the importance of time-related factors in the treatment of anal cancer, suggesting that accelerated repopulation of tumor clonogens during radiation therapy may be detrimental to tumor control.[24-26] It is likely that the lack of prolonged radiation treatment interruptions in anal cancer will have a similar beneficial effect on tumor control, as that has been well-documented for carcinomas of the head and neck, lung, and uterine cervix.[24,27]

Weber et al found that a treatment gap of more than 35 days correlated with lower locoregional control rates in patients with anal cancer.[24] Similarly, in a French study of 305 patients, Deniaud-Alexandre et al reported that a treatment interval greater than 38 days independently decreased the probability of disease-free survival in patients with anal cancer.[26]

A comparison of results from the RTOG 92-08 trial with those of the RTOG 87-04 trial showed that survival in the RTOG 92-08 cohort with no mandatory radiation treatment interruption was higher than

that in the mandatory 2-week treatment break cohort of RTOG 92-08, but similar to survival results in RTOG 87-04 and other published series with uninterrupted treatment.[17,28] The colostomy rate was fourfold higher in the mandatory treatment break cohort, despite the increase in overall radiation dose. These data demonstrated that prolonged treatment breaks resulted in poorer therapy outcome than continuous-course therapy, despite the higher total radiation dose delivered in the study that mandated a treatment break.

Combined-modality treatment of patients with anal cancer can cause considerable morbidity from acute skin and mucosal toxicity, potentially resulting in treatment interruptions. One way to decrease skin toxicity is to use intensity-modulated radiotherapy (IMRT), which delivers highly conformal doses of radiation that could potentially minimize toxicity and treatment breaks.[29] The RTOG is currently evaluating the feasibility of IMRT concurrent with chemotherapy in a phase II study.[30]

Can Chemotherapy Be Eliminated for Early-Stage Anal Cancer?

Although chemoradiation has been shown to be superior to radiation in terms of disease-free survival, local relapse, and colostomy-free survival, it is unclear whether these benefits apply to early-stage disease. Indeed, several retrospective series had previously reported excellent outcomes for patients with T1-2, N0, M0 disease with radiation alone.[26,31-34]

One recent retrospective analysis of 146 patients treated with radiation alone (71 patients) or chemoradiation (75 patients) raises doubts about the effectiveness of radiation alone.[35] Locoregional control was improved in the chemoradiation arm (hazard ratio = 2.24), but the difference did not reach statistical significance ($P = .064$).[35] This retrospective study, with heterogeneous treatment schedules and radiation dosing, however, limits the conclusions that may be drawn about radiation alone for earlystage anal cancer, especially among subgroups such as immunocompromised patients.

Unfortunately, neither the UKCCR nor the RTOG/EORTC studies analyzed the rate of primary tumor complete response based on T stage and treatment arm.[16,18] The RTOG 87-04 study that randomized patients to mitomycin plus 5-FU with radiation vs. 5-FU plus radiation did include tumor stage–based analysis.[17] In the RTOG 87-04 study, the colostomy rates decreased from 29% to 13% in the T3–4 population with the addition of mitomycin to 5-FU and radiation ($P = .019$). However, the reduction in colostomy rates from 15% in the mitomycin/5-FU plus radiation arm to 7% in the 5-FU plus radiation arm did not reach statistical significance in patients with stage T1–2, N0 disease.[17] Although these data suggest a trend for benefit from chemoradiation compared with radiation alone in T1–2 tumors, it is unknown whether patients with stage T1, N0 disease would derive any benefit from chemotherapy in addition to radiation in general. T1, N0 patients do very well with radiation alone or with chemoradiation.[13]

Since a direct comparison between chemoradiation and radiation alone for T1, N0 anal cancer does not exist, mitomycin plus 5-FU and radiation is still recommended for this population. However, for the extremely elderly population or for patients with significant comorbidities, the elimination of mitomycin and the administration of 5-FU alone or in combination with cisplatin may be a reasonable approach, especially among hematologically compromised patients.

Treatment of HIV-Positive Patients With Anal Cancer

Early reports, which included a small series of patients, suggested a poorer survival and increased toxicity for patients with CD4 counts < 200 cells/mm^3 and for patients who are not receiving highly

active antiretroviral therapy (HAART).[36-39] Full doses of chemoradiation (using 5-FU plus mitomycin or 5-FU plus cisplatin) were feasible, although at the cost of increased grade 3 and higher hematologic and gastrointestinal toxicities, treatment interruption, and the need for subsequent dose modification.[37,38,40,41]

The use of modern conformal radiation therapy with full doses of 5-FU and mitomycin in a HAART-treated population with a high median CD4 count and a low level of detectable viral titers was better tolerated, suggesting that early described toxicities were at least partly related to radiation techniques and uncontrolled HIV infection.[42] More definitive conclusions come from recent single- and multi-institution series comparing the outcome of HIV-positive and HIV-negative anal cancers.[43-46]

In a series of 87 patients (21 HIV-positive) treated with mitomycin and radiation, Hogg et al reported an increased rate of infectious and gastrointestinal toxicities in the HIV-positive group.[43] Both HIV-positive and HIV-negative groups were as likely to achieve a complete response (85% HIV-negative vs 81% HIV-positive). However, disease recurrence at 6 months was considerably higher in the HIV-positive group (29% vs 8%).

A multi-institutional, international, retrospective study compared the outcome of 40 HIV-positive anal cancer patients receiving HAART and chemoradiation to 81 HIV-negative anal cancer patients treated with mitomycin plus 5-FU and radiation.[46] Complete response to chemoradiation was high in both HIV-positive (92%) and HIV-negative (96%) groups. HIV-positive patients were more likely to experience grade 3/4 skin and hematologic toxicity. Furthermore, HIV-positive patients were more likely to experience local failure (61% vs 13%) and showed a trend toward dying from anal cancer (5-year cancer-free survival of 68% vs 79%; $P = .09$).[46]

In a larger series from the US Department of Veterans Affairs (VA) database, the outcome of 175 patients with HIV-positive anal cancer was compared to that of 1,009 patients who were HIV-negative.[45] No difference was reported between groups in terms of 2-year survival rates (77% for HIV-positive vs 75% for HIV-negative patients). There was also no difference in outcome based on HIV status in a multivariate analysis that considered HIV, age, sex, race, year of diagnosis, comorbidity score, and presence of metastases.[45] The VA study did not, however, report on cancer-free survival, colostomy rates, or local relapse in both populations. Furthermore, the VA study did not adjust for stage of disease (with the exception of presence of metastases in both groups) as a variable affecting overall survival.[45]

In summary, the treatment of HIV-positive patients in the HAART era is feasible and can result in long-term cures. In this population, and in the presence of a good performance status, it is recommended that patients receive a curative-intent full dose of mitomycin plus 5-FU and radiation. However, these patients need to be monitored more closely, as they may be prone to increased hematologic, gastrointestinal, and skin toxicity. Aggressive follow-up should be conducted after treatment completion, as a higher rate of local relapse with a need for salvage abdominoperineal resection has been described.

Future Directions

Improvement in radiation treatments through IMRT is actively being investigated and applied in anal cancer.[29,47] IMRT may reduce toxicity, allow for less treatment interruption, and therefore translate into better tumor control. This topic has been detailed in a prior issue of ONCOLOGY and will not be subject to discussion in this review.[30]

Improvements in systemic treatments are also being investigated. A particular area of interest is the targeting of epidermal growth factor targeting (EGFR). Targeting EGFR with the monoclonal antibody cetuximab(Drug information on cetuximab) (Erbitux) has been shown to improve the outcomes of squamous cell cancer of the head and neck when added to radiation therapy in a large phase III study.[48] Similarly, the addition of cetuximab to platinum-based therapy in squamous cell cancer of the head and neck improved overall patient survial.[49] This has led to the investigation of cetuximab with chemoradiation in anal cancer. A phase I study has shown the feasibility of adding this agent to cisplatin, 5-FU, and radiation therapy in anal cancer.[50] Several phase II studies are currently evaluating this combination in the US and Europe in immunocompetent and HIV-positive anal cancer patients.

While extensive efforts have been made to evaluate combination chemotherapy and induction/maintenance strategies in anal cancer, inadequate attention has been paid to the molecular characterization of this disease. HPV-positive head and neck cancers behave more favorably and respond better to treatment than HPV-negative tumors.[51] More efforts should be made to investigate the relevance of HPV-positivity in anal cancer in relationship to prognosis and treatment outcome.

REFERENCE GUIDE

Therapeutic Agents Mentioned in This Article

Cetuximab (Erbitux)
Cisplatin
Fluorouracil (5-FU)
Mitomycin

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

Furthermore, it is time to investigate more effective chemotherapeutic regimens if we are to seriously address the role of induction chemotherapy in this disease site. It has long been shown that a combination of a taxane, 5-FU, and cisplatin when followed by radiation therapy results in superior overall survival in head and neck cancers, compared to fluorouracil plus cisplatin and radiation.[52] Similar induction strategies and others incorporating anti-EGFR therapies need urgent investigation, particularly in patients with T3–4 or node-positive anal cancers.

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