Prognostic Factors for Squamous Cell Cancer of the Anal Canal

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ABSTRACT

Radiotherapy with concurrent chemotherapy is the standard of care for patients with nonmetastatic squamous cell anal cancer. Most patients treated with chemoradiotherapy have an excellent prognosis. However, some heterogeneity exists among anal cancer patients in their outcomes. This article reviews some of the clinical factors, treatment-related factors, and biologic factors that affect outcomes in patients with squamous cell anal cancer. The most important prognostic factors are the T and N stages. Some studies have suggested that women have better prognosis than men. Histologic subtypes and grade do not have a clear prognostic role. Response to treatment and duration of radiotherapy are likely to be important prognostic factors. Some molecular markers such as p53, p21, and cyclin A expression may have prognostic significance, but their role needs to be studied further. A better knowledge of prognostic factors could help us develop individualized therapies for patients and select high-risk patients for more aggressive and innovative treatments. A better understanding of molecular biology is required to characterize the inherent heterogeneity of anal cancer and thereby develop optimal therapies.

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Anal cancer is an uncommon malignancy, with an estimated 4,650 new cases expected to be diagnosed in the United States in 2007.[1] Radiotherapy with concurrent chemotherapy is the standard of care for patients with nonmetastatic squamous cell anal cancer.[2–4] Most patients who undergo chemoradiotherapy as primary treatment are spared from colostomy, with abdominoperineal resection necessary for salvage only in a small proportion of patients with recurrent or residual disease. Two randomized trials have shown that chemoradiotherapy improves local control compared with radiotherapy alone.[2,3] Another randomized trial showed that radiotherapy and concurrent 5-fluorouracil (5-FU) and mitomycin C improves disease-free survival and colostomy-free survival, compared with radiotherapy and concurrent 5-FU alone.[4]

Most patients treated with chemoradiotherapy have an excellent prognosis. Randomized trials in anal cancer have reported overall survival rates of 60% to 75% in patients treated with chemoradiotherapy.[2–5] However, some heterogeneity exists among anal cancer patients in their outcomes. This paper reviews some of the clinical factors, treatment-related factors, and biologic factors that affect outcomes in patients with squamous cell anal carcinoma.

CLINICAL PROGNOSTIC FACTORS

The most important prognostic factors for anal cancer are the T and N stages. Many studies over the past 25 years have demonstrated the importance of tumor size and extent and nodal involvement.[6–15] Data from randomized trials have further elucidated the role of T and N stage. The European Organisation for Research and Treatment of Cancer (EORTC) performed a randomized trial in which 110 patients with anal cancer were randomized to receive either radiotherapy alone, or radiotherapy with concurrent 5-FU and mitomycin C.[3] In this trial, patients with no nodal involvement had significantly higher rates of local control ($P = .0017$) and overall survival ($P = .045$) than patients with nodal involvement. In a multivariate analysis, nodal involvement was independently associated with both local control and survival. However, the extent of nodal involvement did not appear to affect outcomes, with N2-3 patients having similar outcomes as N1 patients. The size and number of involved nodes also did not affect outcomes. Moreover, in this trial, T stage, length of tumor, and circumferential extent of tumor were not significantly associated with local control or survival. Tumor thickness had a borderline significant association with survival ($P = .052$), but not with local control. Since this trial included only 110 patients, the power to detect the prognostic roles of these different variables may have been limited.

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Group (ECOG) conducted a randomized trial in which 310 patients were randomized to receive either radiotherapy with concurrent 5-FU, or radiotherapy with concurrent 5-FU and mitomycin C.[4] In this trial, patients underwent a biopsy 4–6 weeks after completion of chemoradiotherapy to assess tumor response. Tumor size was significantly associated with the rate of negative biopsies ($P = .02$). Patients with tumor size < 5 cm had a 93% rate of negative biopsies, while patients with tumor size ≥ 5 cm had an 83% rate of negative biopsies. In addition, nodal status was significantly associated with the colostomy rate ($P = .009$). Patients with no nodal involvement had a 13% colostomy rate, while patients with nodal involvement had a 28% colostomy rate.

Preliminary results were presented recently from the RTOG 98-11 trial, in which 682 patients were randomized to receive either radiotherapy with concurrent 5-FU and mitomycin C, or induction chemotherapy with 5-FU and cisplatin, followed by radiotherapy with concurrent 5-FU and cisplatin.[5,16] Multivariate analysis showed that clinical node-positive status ($P < .0001$) and tumor size > 5 cm ($P = .005$) independently predicted for worse disease-free survival.

Recent retrospective studies have confirmed the prognostic roles of T and N stage. Investigators from the M. D. Anderson Cancer Center reported a retrospective study of 167 patients with nonmetastatic squamous cell anal carcinoma treated with definitive chemoradiotherapy.[17] On multivariate analysis, higher T stage ($P = .023$) and higher N stage ($P = .030$) independently predicted for a higher rate of locoregional failure. The 3-year rate of locoregional control was 90% for Tx/T1, 86% for T2, 77% for T3, and 63% for T4 tumors. The 3-year rate of locoregional control was 84% to 88% for N0–2 and 39% for N3 tumors. On multivariate analysis, higher N stage also independently predicted for lower rates of distant control ($P < .001$) and overall survival ($P = .001$). The 3-year distant control rate was 94% for N0, 79% for N1, 75% for N2, and 76% for N3 patients. The 3-year overall survival rate was 93% for N0, 74% for N1, 74% for N2, and 56% for N3 patients.

A retrospective study from the Washington University School of Medicine evaluated 106 anal cancer patients treated with radiotherapy, with or without chemotherapy, and with or without surgery.[18] Univariate analysis showed that tumor mobility (a surrogate for depth of invasion by the primary tumor) was significantly associated with the rate of freedom from disease ($P = .009$). The 5-year ultimate freedom from disease rate was 89% for mobile tumors and 44% for tethered or fixed tumors. N stage ($P = .001$) and TN stage ($P < .001$) were also significantly associated with the rate of freedom from disease, on univariate analysis. The 5-year ultimate freedom from disease rate was 79% for node-negative and 27% for node-positive tumors. When T and N stages were taken together, the 5-year ultimate freedom from disease rate was 87% for T1–2N0, 78% for T3N0 and 43% for either T4N0 or any node-positive tumors. On multivariate analysis, extent of disease (T1–2N0 vs. T3N0 vs. T4 or N+) was the only factor that independently predicted for ultimate freedom from disease, local control, and freedom from relapse.

The studies discussed above clearly show the important prognostic role of T and N stage. In addition to T and N stage, certain other clinical factors may be associated with outcomes in anal cancer patients. Some studies have indicated that women have better prognosis than men. In the EORTC randomized trial, women had significantly higher rates of local control ($P = .0028$) and overall survival ($P = .0034$) than did men.[3] On multivariate analysis, gender was an independent predictor for both local control and survival. In the RTOG 98-11 trial, men had significantly lower rates of disease-free survival than women ($P = .014$).[5]

A retrospective study from the Washington University School of Medicine showed that gender was significantly associated with rates of ultimate freedom from disease ($P = .02$).[18] The 5-year ultimate freedom from disease rate was 54% for men and 80% for women. However, there were imbalances in stage between men and women in this study, and gender was not an independent predictor of freedom from disease on multivariate analysis. Other studies have not found a significant association between gender and outcome.[15,17] A large retrospective study from the M. D. Anderson Cancer Center reported that gender was not significantly associated with rates of locoregional control, distant metastasis, or overall survival.[17] Hence, the prognostic role of gender is not completely clear.

A number of studies have investigated whether the degree of differentiation and histologic subtype affect prognosis. In the EORTC randomized trial, the degree of differentiation and the histologic subtype (squamous vs. other) were not found to be significant prognostic factors.[3] A retrospective study of 242 patients from France reported that survival appeared to be better in patients with cloacogenic subtype; however, there was no significant difference in survival between three pathologic categories (cloacogenic vs. well-differentiated vs. moderately/poorly-differentiated).[12] Investigators from the Princess Margaret Hospital conducted a study in 192 patients, in which they reported a trend toward greater tumor control in basaloid tumors than in squamous tumors ($P = .13$)[15] In the Washington University retrospective study discussed earlier, the degree of differentiation was not significantly associated with the rate of ultimate freedom from disease.[18] There was a trend toward an improved 5-year rate of ultimate freedom from disease in patients with cloacogenic histology (84%), compared to those with squamous histology (66%), with a P value of .06. However, on multivariate analysis, histologic subtype was not an independent prognostic factor.

In the M. D. Anderson retrospective study, the degree of differentiation was not significantly associated with rates of locoregional control, distant metastasis or overall survival.[17] Basaloid subtype was significantly associated with a higher rate of distant metastasis, both on univariate and multivariate analysis (hazard ratio [HR] 4.23, $P = .003$). On the other hand, other studies have indicated that there are no significant differences in prognosis between different histologic subtypes.[6,19,20] Thus, conflicting data exist about the role of histologic subtypes, which is further complicated by the low reproducibility of identifying subtypes, even among experienced pathologists.[21] The 2000 World Health Organization classification recommends that the generic term squamous

cell carcinoma be used for all subtypes.[22] As discussed above, most studies indicate that the degree of differentiation is unlikely to have an independent prognostic role in anal cancer. The role of differentiation degree is also limited by the lack of clear, well-described grading criteria.[22]

Since patients with human immunodeficiency virus (HIV) infection have a higher risk for developing anal cancer, studies have evaluated the effect of HIV status in patients with anal cancer. Most studies on HIV-positive patients treated with chemoradiotherapy indicate that these patients have rates of tumor response and locoregional control that are comparable to HIV-negative patients.[23–29] However, HIV-positive patients experience higher rates of toxicity and demonstrate relatively lower rates of treatment compliance, which may affect outcomes.[23,30,31] HIV-positive anal cancer patients also appear to have lower overall survival rates compared to HIV-negative patients, but this difference is likely due to their underlying disease and comorbidities.[17,23]

Recent studies have investigated whether positron emission tomography (PET) could play a role in the evaluation of anal cancer patients. A prospective study in 21 patients with anal cancer showed that pretreatment PET scan identified involvement of pelvic lymph nodes in 4 (19%) patients and omental metastasis in 1 patient, which were not observed on computed tomography (CT) scan.[32] Investigators from the Washington University School of Medicine reported a study in 41 patients with anal cancer in which PET/CT scans detected abnormal uptake in pelvic nodes in 5 patients (12%) with normal pelvic CT scans.[33] Moreover, PET/CT scans detected abnormal uptake in 17% of groins that were negative by both CT and physical examination.[33] Another prospective study of 62 patients with anal cancer demonstrated that PET scan had higher sensitivity for detecting nodal disease (92% vs. 72%) than conventional imaging.[34] This study also showed that PET scan upstaged 15%, altered management intent in 3%, and altered radiation fields in 13% of patients.[34] The National Comprehensive Cancer Network (NCCN) now recommends PET scan as part of the evaluation for patients with anal cancer.[35]

TREATMENT-RELATED PROGNOSTIC FACTORS

Response to treatment could be an important prognostic factor for anal cancer. In a study from France in 305 patients treated mostly with radiotherapy alone, response to radiotherapy was significantly associated with disease-free survival, both on univariate and multivariate analysis.[36] Patients with a clinical complete response to radiotherapy had a 5-year disease-free survival rate of 80%, while those without a clinical complete response had a 5-year disease-free survival rate of 41%. In another study from France, 118 patients were treated with an initial course of external beam radiotherapy, with or without chemotherapy, followed by brachytherapy or external beam boost after 2 months.[13] Multivariate analysis showed that the response to the initial course of radiotherapy independently predicted for local control ($P = .007$), locoregional control ($P < .001$), and anal-cancer–specific survival ($P < .001$).

In a third study from France, 252 patients were treated with external beam radiotherapy, with concurrent chemotherapy in 67%, followed by brachytherapy or external beam boost.[37] Response to the initial course of radiotherapy was assessed about 4 weeks after completion of treatment in 221 patients. Response to radiotherapy was significantly associated with overall survival on both univariate ($P = .02$) and multivariate ($P < .01$) analysis. The 5-year overall survival rate was 81% for patients with tumor regression >80%, and 58% for those with tumor regression ≤80%. Response to radiotherapy was also significantly associated with disease-free survival on both univariate ($P = .0005$) and multivariate ($P < .001$) analysis. The 5-year disease-free survival rate was 70% for patients with tumor regression >80%, and 39% for those with tumor regression ≤80%. Response to chemoradiotherapy has been shown to be an important prognostic factor in other malignancies such as rectal cancer and esophageal cancer, and could play an important role also in the prognosis of anal cancer patients.[38–44]

Radiotherapy dose could affect the outcome of anal cancer patients. A recent study from Brazil in 43 anal cancer patients showed that patients treated with a radiation dose >50 Gy at the primary tumor had significantly higher local control than those treated with ≤50 Gy (crude rates 86% vs. 34%, $P = .012$).[45] Investigators from the Massachusetts General Hospital and Boston University Medical Center reported a study of 50 patients, in which radiation dose was significantly associated with higher rates of overall survival ($P = .02$) and local control ($P = .04$).[46] The 5-year overall survival rate was 84% in patients treated with ≥54 Gy and 47% in those treated with <54 Gy. The 5-year local control rate was 77% in patients treated with ≥54 Gy and 61% in those treated with <54 Gy.

Interruptions in treatment and prolonged courses of radiotherapy could reduce the biologic effectiveness of radiotherapy. In the study from Massachusetts General Hospital discussed above, there was a trend toward higher survival in patients with lower treatment time, but the difference was not statistically significant ($P = .14$). Patients with an overall treatment time <40 days had a 5-year survival rate of 86%, while those with treatment time ≥40 days had a 5-year survival rate of 66%. Other studies have also assessed the effect of treatment time and breaks during radiotherapy. A study from Switzerland of 90 patients treated with a split course of radiotherapy showed that patients treated with a longer gap between the two split courses of radiotherapy had significantly lower rates of locoregional control than those with a shorter gap (5-year rates 62% vs. 85%, $P = .02$).[47] On multivariate analysis, gap duration was an independent predictor of locoregional control. Similarly, a study from France of 305 patients treated with an initial course of radiotherapy, followed by a boost after a gap, showed that the duration of the gap independently predicted for disease-free survival.[36] A study from Germany evaluated 111 patients treated with chemoradiotherapy, with radiotherapy delivered as either a split course or a continuous course.[48] Patients with an overall treatment time >41 days had a significantly lower 5-year local control rate than patients with an overall treatment time ≤41 days (58% vs. 79%, $P = .04$). In contrast, a recent study of 68 patients reported that the length of treatment interruption did not affect local control or

overall survival.[49] However, the preponderance of evidence indicates that the duration of radiotherapy is an important prognostic factor for anal cancer.

MOLECULAR PROGNOSTIC FACTORS

Some studies have investigated the role of molecular and biologic prognostic factors in anal cancer. A study of 64 patients treated on the RTOG 87-04 trial showed a trend toward lower locoregional control (52% vs. 72%, $P = .13$) and overall survival (58% vs. 78%, $P = .14$) in patients with tumors overexpressing the tumor suppressor p53.[50] Investigators from the Princess Margaret Hospital reported that increasing p53 expression was associated with worse disease-free survival ($P = .01$) and locoregional control ($P = .02$), based on a multivariate analysis of 49 patients.[51] A recent study of 215 patients from Sweden showed that high expression of the cell cycle regulator cyclin A was significantly associated with higher rates of overall survival (77% vs. 59%, $P = .005$) and lower rates of locoregional failure (12% vs. 24%, $P < .05$).[52] In addition, this study showed that reduced expression of the cell cycle regulator p21 was associated with a significantly higher rate of locoregional failure (27% vs. 14%, $P < .05$), and a trend toward a lower overall survival rate (62% vs. 71%, $P = .08$).[52]

A study from the Norwegian Radium Hospital also indicated that lower p21 expression was associated with significantly lower overall survival ($P = .013$).[53] Investigators from Sweden reported that patients with tumor budding (detected by laminin-5 immunohistochemistry) had significantly higher rates of 5-year overall survival than patients without tumor budding (74% vs. 64%, $P < .05$), although tumor budding has been associated with poor prognosis in other cancers.[54] A German study showed that a higher proliferative potential, as measured by the MIB-1 labeling index, was associated with a significantly higher rate of colostomy-free survival (90% vs. 50%, $P = .04$).[14] However, another study did not detect any significant association between MIB-1 index and survival, disease-free survival, or locoregional control.[55]

DNA-ploidy was shown to be an independent predictor of anal cancer-related death in one study, but was not shown to be an independent predictor of outcomes in another study.[56,57] Most of these studies on molecular and biologic markers are based on a limited number of patients. Moreover, a lack of concordance exists between different studies regarding the role of molecular markers. Further studies are, therefore, warranted to evaluate the role of molecular and biologic prognostic factors in anal cancer.

DISCUSSION

Although many studies have attempted to identify prognostic factors for anal cancer, T and N classification remain the most important and reliable prognostic factors. Some studies have indicated that women may have a better prognosis than men, though this has not been confirmed by other studies. Histologic subtypes and degree of differentiation do not appear to have clear prognostic value, and their role is complicated by the lack of uniform criteria and reproducibility in determining subtypes and grades. Response to radiotherapy appears to be an important prognostic factor, and could serve as a marker for tumor biology. Treatment-related factors such as radiotherapy dose and radiotherapy treatment time likely have an important effect on outcomes. Some studies have shown the prognostic role of molecular markers, such as the tumor suppressor p53, the cell cycle regulators p21 and cyclin A, and the proliferation marker MIB-1 index, but most of these studies are based on a relatively small number of patients.

The rarity of anal cancer makes it particularly difficult to conduct investigations on prognostic factors, and our knowledge on the topic remains limited. Multi-institutional and collaborative group studies are warranted to determine prognostic factors, especially biologic and molecular factors. Although most patients with anal cancer have an excellent prognosis, poor outcomes are associated with a subgroup of patients. Prognostic models and nomograms should be developed to identify these patients. A better knowledge of prognostic factors would help us target high-risk patients in trials of newer and more aggressive local and systemic treatments. Moreover, a better understanding of molecular biology is needed to characterize the inherent heterogeneity of anal cancer and thereby develop optimal therapies.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.