Prognostic Factors Derived from A Prospective Database Dictate Clinical Biology of Anal Cancer

The Intergroup Trial (RTOG 98-11)

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BACKGROUND: Only 4 prospective randomized phase 3 trials have been reported for anal cancer. A prognostic factor analysis for anal cancer from a prospective database has been published from only 1 study (N = 110). To confirm and uncover new prognostic factors, we analyzed the prospective database of intergroup RTOG 98-11. METHODS: Univariate and multivariate analyses of the baseline characteristics for 5-year overall survival (OS) and disease-free survival (DFS) were carried out. Various combinations of tumor diameter and clinically positive nodes (N+) were analyzed to identify subgroups. RESULTS: A total of 644 were assessable and analyzed. Tumor diameter >5 cm was associated with poorer 5-year DFS (P = .0003) and poorer 5-year OS (P = .0031), and N+ was associated with poorer 5-year DFS (P ≤ .0001) and poorer 5-year OS (P ≤ .0001) in the multivariate analysis. In stratified analyses, N+ had more adverse influence on DFS and OS than did tumor diameter. Patients with >5-cm tumor and N+ had the worst DFS (only 30% at 3 years compared with 74% for the best group; <5 cm primary and N0) and OS (only 48% at 4 years compared with 81% for the best group; <5 cm primary and N0). Men had worse DFS (P = .02) and OS (P = .016). These factors maintained their influence in each treatment arm. CONCLUSIONS: This prospective prognostic factor analysis establishes tumor diameter as an independent prognosticator of poorer 5-year DFS and OS and confirms N+ and male sex as poor prognostic factors. This analysis also uncovers novel subgroups (derived from combining prognostic factors) with incremental worsening of DFS and OS. Cancer 2010;000:000–000. © 2010 American Cancer Society.

KEYWORDS: anal cancer, clinical biology, prognostic factors, prospective database, survival.

Anal carcinoma is a rare malignancy in the United States. Approximately 5070 new cases of anal canal were projected for the year 2008.1 The chemoradiation strategy for anal carcinoma results in disease-free survival (DFS) in ~65% of cases.2–6 Prognosis of patients varies considerably, and to some extent is based on prognostic factors. Some prognostic factors (nodal status, skin ulceration, and sex) have been identified from 1 small prospective study,7 but others (nodal status, sex, tumor diameter) have been identified by analyses of retrospective databases.7–16 Most published reports of predictive and prognostic variables for anal cancer include small numbers of patients, retrospective analyses of patients accrued over decades, and single-institution experiences.8 Retrospective reviews are fraught with their inherent limitations; therefore, to establish reliable prognostic factors, evaluation in a large number of prospectively accrued patients is desirable. Knowledge of clinical prognostic variables is critical in developing novel therapeutic strategies and in communication with patients/relatives and colleagues. In the future, established clinical prognostic factors may be combined with biomarkers for even better understanding of clinical biology of anal cancer and its susceptibility to chemoradiation.

Original Article

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The European Organization for Research and Treatment of Cancer (EORTC) phase 3 study, with 110 patients, presented a formal prognostic factor analysis and reported that nodal involvement, skin ulceration, and male sex were associated with poorer overall survival (OS) and local control. However, this prospective study could not identify tumor diameter as a prognostic factor for DFS or OS. Two other prospective randomized control trials of 585 patients and 310 patients have not reported their data for prognostic factors.

The US Gastrointestinal Intergroup trial RTOG 98-11 recruited 682 patients between 1998 and 2005, with participation by several US cooperative groups. The study compared the previously established standard of concurrent 5-fluorouracil plus mitomycin-C and radiation (mitomycin-based therapy) to 5-fluorouracil plus cisplatin (induction and concurrent) and radiation (cisplatin-based therapy). A total of 644 assessable patients were available for the analysis of prognostic factors. Intergroup RTOG 98-11 represents the largest prospectively collected, multicenter database. For this study, patients from the 2 treatment arms were combined for a prognostic factor analysis to confirm previously reported prognostic factors and to uncover any new ones. We were particularly interested in combining confirmed prognostic factors to identify if novel subgroups would more specifically define the clinical biology of anal cancer with regard to 5-year DFS and OS.

MATERIALS AND METHODS

Literature Review

Literature review was conducted by searching for prospective randomized controlled phase 3 studies by using the terms “anal cancer,” “anal canal cancer,” anal canal carcinoma,” and “epidermoid cancer or carcinoma of the anal canal.” Medline, www.clinicaltrials.gov, and online databases of large societies (American Society of Clinical Oncology and European Society of Medical Oncology) were searched. In addition, cross-references were searched from the published prospective randomized phase 3 trials and reviews.

RTOG 98-11 Infrastructure, Hypothesis, and Objectives

RTOG 98-11 was a US Gastrointestinal Intergroup trial with participation by the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group, Southwest Oncology Group, and Radiation Therapy Oncology Group (the coordinating group). The primary objective of the trial was to observe a DFS of 73% with cisplatin-based therapy compared with 63% with mitomycin-based therapy. In addition, the secondary objectives included time to colostomy, OS, and toxic effects. The protocol is available online for viewing (www.rtog.org).

The objective of the current analysis was to confirm the prognostic factors established by 1 small prospective study, establish new prognostic factors, and examine if a combination of prognostic factors will result in newly defined subgroups of anal carcinoma with differing clinical biology with regard to 5-year DFS and OS.

Patient Eligibility

All patients with histologically documented squamous, basaloïd, or cloacogenic carcinoma of the anal canal were eligible, provided they were > 18 years of age, had Karnofsky performance status > 60%, had T 2 to 4 with any N cancer, had adequate organ function, and were willing to provide a written consent.

Patients were excluded if they had a T1 or M1 cancer, severe comorbid conditions (including acquired immunodeficiency syndrome), or major malignancy treated within 5 years.

Evaluations

These have been previously described.

Randomization, Stratification, and Therapy

Patients were randomized to 5-fluorouracil plus mitomycin-C and concurrent radiation or induction 5-fluorouracil plus cisplatin followed by concurrent 5-fluorouracil plus cisplatin and radiation. Patients were stratified according to sex, clinical nodal status (positive or negative), and the size of the primary tumor (2-5 cm or > 5 cm).

The details of therapy have been previously described. Briefly, chemotherapy on Arm A included mitomycin-C 10 mg/m² intravenous bolus on Days 1 and 29 and infusion 5-fluorouracil 1000 mg/m² on Days 1 to 4 and 29 to 32. Chemotherapy on Arm B included cisplatin 75 mg/m² on Days 1 and 29, and also repeated on Days 57 and 85, and infusion 5-fluorouracil 1000 mg/m² on Days 1 to 4 and 29 to 32, and also repeated on Days 57 to 60 and 85 to 88 (Days 57 and 85 should correspond to Days 1 and 29 of radiotherapy).

All patients were to receive a minimum dose of 45 grays (Gy) in 25 fractions of 1.8 Gy over 5 weeks to the primary cancer with supervoltage radiation (photon energy of > 6 MV), using anteroposterior-posteroanterior or multield techniques. Uninvolved nodal sites at risk received 30.6 to 36 Gy in 17 to 20 fractions of 1.8 Gy over 3.5 to 4
weeks. For patients with T3, T4, N+ disease or T2 patients with residual disease after 45 Gy, the intent was to deliver an additional boost of 10 to 14 Gy in 2-Gy fractions to the primary tumor/involved nodal disease (total dose of 55-59 Gy in 30-32 fractions over 5.5-6.5 weeks).

**Statistical Methods**

For the purpose of this report, univariate and multivariate analyses were carried out for the entire population and populations in each treatment group. The main focus was on the rates of DFS and OS. Failures for the efficacy endpoints were as follows: OS, death due to any cause; and DFS, local, regional, or distant failure, second primary, or death from any cause (locoregional failure: local or regional relapse, progression, or persistence; distant metastases: appearance of distant metastases). All efficacy endpoints were measured from the date of randomization to the date of first failure for the given endpoint or date of last follow-up for patients who did not fail a given endpoint. OS and DFS were estimated univariately with the Kaplan-Meier method, and comparisons were tested using the log-rank test. Time to locoregional failure and distant metastases were estimated by the cumulative incidence method, and comparisons were tested using Gray’s test. All reported P values are 2-sided. Multivariate analyses were performed with Cox proportional hazard models to test for prognostic significance of treatment (Arm A vs Arm B), sex (female vs male), clinical nodal status (no vs yes), and tumor diameter (2-5 vs >5 cm). All variables were coded such that a hazard ratio (HR) >1 indicates an increased risk for the second level of the variable. For example, sex (female vs male) was coded such that a HR >1 indicates an increased risk of failure for males. The prognostic factors were assessed in each treatment arm (as described above) and in a similar manner when patients in 2 arms were combined. Two permutations of tumor diameters (<5 cm and >5 cm) were combined with 2 permutations of nodal involvement (N0 and N1) to create 4 subgroups to test their effect on DFS and OS.

**RESULTS**

**Patient Characteristics**

The study accrued 682 patients from October 1998 to June 2005. Pretreatment characteristics of 644 assessable patients were reported previously. Sixty-nine percent of patients were women, 27% had cancer size >5 cm in diameter (T3/T4), and 26% had clinically positive nodes. A total of 324 patients were randomized to mitomycin-based therapy, and 320 were randomized to cisplatin-based therapy.

**DFS and OS for the Entire Population**

The median DFS and OS for the 644 assessable patients have not been reached at a median follow-up time of 2.21 years.

**Prognostic factors for DFS and OS**

Multivariate analysis is presented in Table 1 with regard to treatment (5-fluorouracil/mitomycin-C vs 5-fluorouracil/cisplatin), sex (female vs male), clinical nodal status (negative vs positive), and tumor diameter (2-5 vs >5 cm). This table was modified from a previous one to include data on OS. We have previously demonstrated that tumor diameter >5 cm correlates well with the increased likelihood of colostomy, irrespective of the type of cytotoxic agents received by the patients.

**Sex**

DFS and OS of women were better than those of men. In the multivariate analysis, male sex was significantly associated with poorer DFS (P = .02) and OS (P = .016).

**Tumor diameter**

Tumor diameter >5 cm was associated with poorer outcome. In the multivariate analysis (Table 1), >5-cm
tumor diameter resulted in poorer 5-year DFS (log-rank \( P = .0003 \); Fig. 1) and poorer 5-year OS (log-rank \( P = .0031 \); Fig. 2).

**Clinical nodal status**

Clinically positive nodes were associated with poorer outcome. N1 status resulted in poorer 5-year DFS (log-rank \( P < .0001 \); Fig. 3) and poorer 5-year OS (log-rank \( P < .0001 \); Fig. 4).

**Subgroups derived from combining tumor diameter and nodal status**

Four subgroups were analyzed for DFS and OS by combining the 2 permutations of tumor diameters (<5 cm and >5 cm) and 2 nodal designations (N0 and N1). Tables 2 and 3 show the DFS and OS rates from 0 to 5 years. The most favorable prognostic subgroup was patients with ≤5-cm diameter, clinically lymph node negative tumors with 3-year and 5-year DFS of 74% and 66%, respectively, and 3-year and 5-year OS of 86% and 80%. The worst prognosis for DFS (Fig. 5) and OS (Fig. 6) were for patients with tumors >5 cm diameter and clinically positive nodal status, with 3-year DFS of only 30% and 4-year OS of 48%. Figures 5 and 6 and Tables 2 and 3 document a higher adverse effect of N\(^+\) status on all of the outcomes.

**DISCUSSION**

While reviewing the results of the literature search, we limited our focus to prospectively conducted phase 3
studies. Only 4 interventional anal cancer studies have been published to date.3-6 Table 4 summarizes the prognostic factors established thus far by prospective analyses. The British study4 (n = 585) and an RTOG study6 (N = 310) have not reported a prognostic factor evaluation; the EORTC study5 (N = 110) is the only 1 that has reported a formal prognostic factor analysis. The EORTC found that nodal status (local control, \( P = .003 \) and OS, \( P = .0003 \)), sex (male with worse outcome; DFS, \( P = .01 \) and OS, \( P = .011 \)), and skin ulceration (DFS, \( P = .0033 \) and OS, \( P = .005 \)) were prognostic, but tumor size was not. We now report our analysis from the second RTOG study3 (N = 644). For the RTOG 98-11 study, data for skin ulceration were not available.

Of all 4 reported randomized prospective phase 3 trials, the US Gastrointestinal Intergroup anal canal cancer trial RTOG 98-11 has the highest number of patients (N = 682; 644 analyzed) studied to date,3 and the current analysis for prognostic factors provides additional understanding of the clinical biology of anal carcinoma. Data in this analysis establish that tumor diameter is an independent pretreatment variable that predicts 5-year DFS and OS. The data also confirm 2 previously reported prognostic factors (nodal status and sex). In addition, the current analysis documents that anal cancer exhibits 4 subgroups of prognostic factor combinations. Greater understanding of clinical factors that drive clinical biology would reduce uncertainties that prevail today when treating patients with anal cancer. Knowledge that patients with \( >5\)-cm tumor and N1 status have only a 30% chance of being disease-free at 3 years allows more effective communication with colleagues, patients, and their relatives. Such knowledge would also lead to newer therapeutic algorithms. In addition, identification of poorly performing groups that

### Table 2. Disease-Free Survival for All Patients (N = 644)

<table>
<thead>
<tr>
<th>Years</th>
<th>Tumor Diameter</th>
<th>Positive Nodes</th>
<th>Tumor Diameter by Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5 (n=472)</td>
<td>&gt;5 (n=172)</td>
<td>Negative (n=477)</td>
</tr>
<tr>
<td>0</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>79%</td>
<td>63%</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>72%</td>
<td>57%</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>68%</td>
<td>53%</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>66%</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>60%</td>
<td>47%</td>
<td>64%</td>
</tr>
<tr>
<td>Total failed, No. (%)</td>
<td>153 (24.4)</td>
<td>79 (12.3)</td>
<td>135 (21.8)</td>
</tr>
<tr>
<td>Median, y</td>
<td>Not reached</td>
<td>3.5</td>
<td>Not reached</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.8, ∞</td>
<td>1.0, 2.4</td>
<td>1.4, 5.3</td>
</tr>
</tbody>
</table>

N/A indicates not applicable; CI, confidence interval.

### Table 3. Overall Survival for All Patients (n=644)

<table>
<thead>
<tr>
<th>Years</th>
<th>Tumor Diameter</th>
<th>Positive Nodes</th>
<th>Tumor Diameter by Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5 (n=472)</td>
<td>&gt;5 (n=172)</td>
<td>Negative (n=477)</td>
</tr>
<tr>
<td>0</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
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<td>2</td>
<td>89%</td>
<td>84%</td>
<td>90%</td>
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<td>3</td>
<td>83%</td>
<td>71%</td>
<td>83%</td>
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<td>4</td>
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<td>65%</td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td>77%</td>
<td>60%</td>
<td>78%</td>
</tr>
<tr>
<td>Total deaths, No. (%)</td>
<td>78 (14.8)</td>
<td>47 (27.3)</td>
<td>76 (15.9)</td>
</tr>
<tr>
<td>Median, y</td>
<td>Not reached</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.8, ∞</td>
<td>1.0, 2.4</td>
<td>1.4, 5.3</td>
</tr>
</tbody>
</table>

N/A indicates not applicable.

*Too few patients at risk, estimate unstable.
are likely to have treatment failure early could allow quick testing of novel therapy, because the endpoints are reached sooner in this group than in more favorable groups.

Reliable clinical prognostic parameters still do not account for inherent heterogeneity of outcome of individual patients. These unexpected patient outcomes, when patients are treated similarly, are multifactorial and can include type of therapy, toxicity, and treatment completion, but most likely include the degree of sensitivity to chemoradiation and to some extent patient’s genetic makeup. In the future, it will be important to combine clinical, epigenetic, genetic,22 and germ-line variables to develop a model that predicts response to therapy and prognosticates outcome. The first step in developing such sophisticated models could be the establishment of reliable prognostic factors and their interaction; the next step would be to conduct biomarker studies from tissue repositories that might be available.

Approximately 25% of newly diagnosed patients fall into the worst prognostic category (>5 cm tumor and N1 status). The current analysis does not provide any clue as to whether this group should be treated differently than the other 3 groups with lower risk of experiencing a DFS or OS event. Because anal cancer is rare, many trials cannot be proposed. However, newer tools such as positron emission tomography23-25 could be incorporated for early assessment of response in a poor prognostic group. If validated, it would help avoid the morbidity of chemoradiation in some patients who can be offered surgery. We acknowledge that there are no data to support this notion, and perhaps a combination of clinical and biology-based tools will provide some guidance in the future. It would appear that this group of patients is likely to end up with

![Figure 5. Disease-free survival by 4 subgroups of patients created by combining tumor diameter and nodal designation is shown (N = 644).](image)

![Figure 6. Overall survival by 4 subgroups of patients created by combining tumor diameter and nodal designation is shown (N = 644).](image)

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Prognostic Factor Evaluation</th>
<th>Prognostic Factors</th>
<th>Comments</th>
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<td>UKCCCR4</td>
<td>585</td>
<td>No</td>
<td>None listed</td>
<td>No follow-up analysis</td>
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<tr>
<td>EORTC5</td>
<td>110</td>
<td>Yes</td>
<td>Sex, nodal status, and skin ulceration but not tumor diameter for DFS and OS</td>
<td>Small sample size</td>
</tr>
<tr>
<td>RTOG 87-046</td>
<td>310</td>
<td>No</td>
<td>None listed</td>
<td>No follow-up analysis</td>
</tr>
<tr>
<td>RTOG 98-113</td>
<td>644</td>
<td>Yes</td>
<td>Sex, Tumor diameter, and nodal status for DFS and OS</td>
<td>Four prognostic subgroups identified</td>
</tr>
</tbody>
</table>

DFS indicates disease-free survival; OS, overall survival.
colostomy anyway, even after the completion of chemoradiation. On the other hand, one could also argue that patients with all the poor prognostic factors could benefit from more aggressive therapy.

In conclusion, our analysis of prospectively collected data establishes that tumor diameter is an independent prognosticator of DFS and OS. The analysis confirms that nodal status and sex are also independently prognostic. In addition, the analysis uncovers 4 subgroups, derived from combining prognostic factors, of anal cancers with differing clinical biology. Further understanding of the clinical biology of anal cancer could emerge from studying molecular biology and patient genetics along with clinical prognostic variables and imaging.

CONFLICT OF INTEREST DISCLOSURES

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Registration number: NCT00003596 (www.clinicaltrials.gov).

REFERENCES