Original Article

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 ($P \leq .0001$) and poorer 5-year OS ($P = \leq .0001$) 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,[5] 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.

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The European Organization for Research and Treatment of Cancer (EORTC) phase 3 study,[5] 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[4] and 310 patients[6] 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.[3] 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,[5] 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, basaloid, 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.[3]

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.[3] Briefly, chemotherapy on Arm A included mitomycin-C 10 mg/m^2 intravenous bolus on Days 1 and 29 and infusion 5-fluorouracil 1000 mg/m^2 on Days 1 to 4 and 29 to 32. Chemotherapy on Arm B included cisplatin 75 mg/m^2 on Days 1 and 29, and also repeated on Days 57 and 85, and infusion 5-fluorouracil 1000 mg/m^2 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 multifield techniques.[3] 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

Table 1. Multivariate Analyses (N=644)[a]

Adjustment Variables	Disease-Free Survival, Adjusted HR (95% CI), *P*	Overall Survival, Adjusted HR (95% CI), *P*
Treatment (5-FU/mitomycin-C vs 5-FU/cisplatin)	1.20 (0.93, 1.55), .17	1.28 (0.90, 1.84), .17
Sex (female vs male)	1.38 (1.05, 1.81), .02	1.57 (1.09, 2.27), .016
Clinical nodal status (negative vs positive)	2.66 (2.04, 3.46), <.0001	2.09 (1.45, 3.01), <.0001
Tumor diameter (2-5 cm vs >5 cm)	1.5 (1.14, 1.97), .004	1.62 (1.12, 2.33), .01

HR indicates hazard ratio; CI, confidence interval; 5-FU, 5-fluorouracil.
HR of 1 indicates no difference between the 2 subgroups. HR >1 indicates an increased risk of death for the second level of the variables listed.
P value is from chi-square test using the Cox proportional hazards model.
[a] Modified from Ajani et al.[21]

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 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,[17] and comparisons were tested using the log-rank test.[18] Time to locoregional failure and distant metastases were estimated by the cumulative incidence method,[19] and comparisons were tested using Gray's test.[20] 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.[3] 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[21] 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.[21]

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

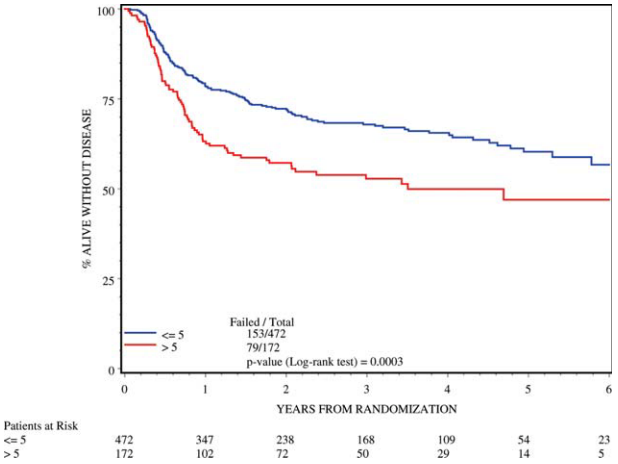

Figure 1. Disease-free survival by tumor diameter is shown (N = 644).

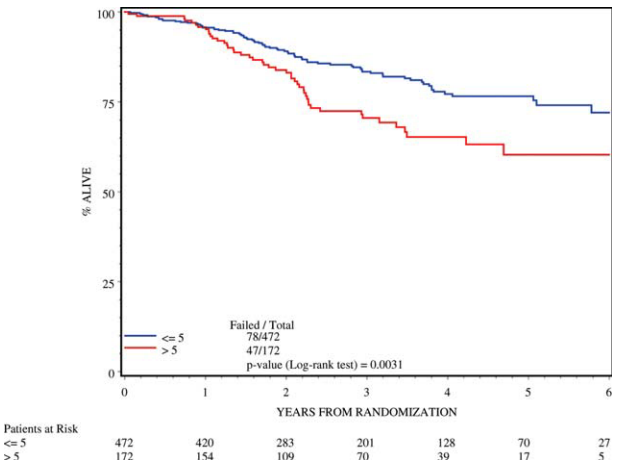

Figure 2. Overall survival by tumor diameter is shown (N = 644).

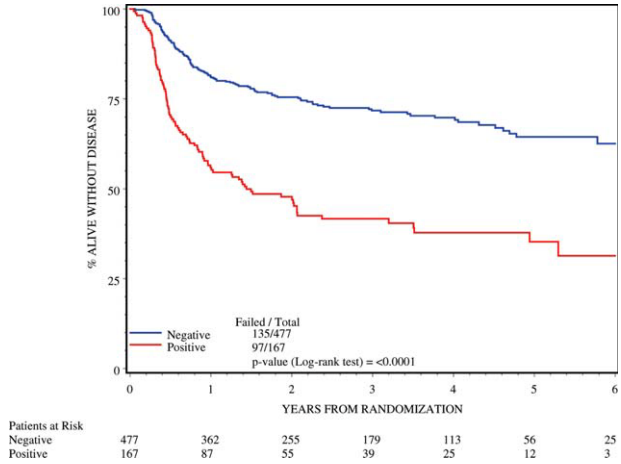

Figure 3. Disease-free survival by clinical nodal status is shown (N = 644).

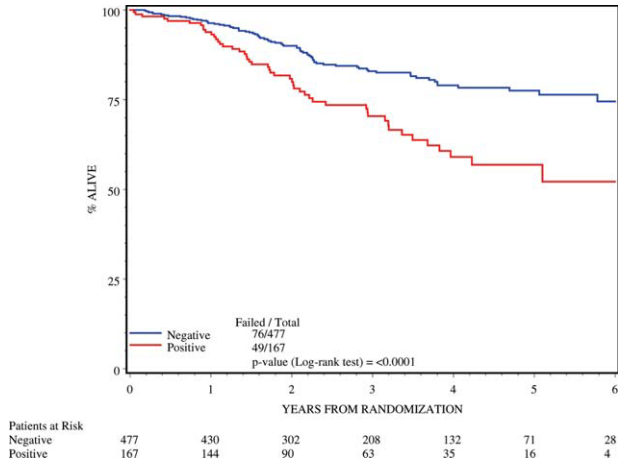

Figure 4. Overall survival by clinical nodal status is shown (N = 644).

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

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

Years	Tumor Diameter		Positive Nodes		Tumor Diameter by Nodes			
	≤5 (n=472)	>5 (n=172)	Negative (n=477)	Positive (n=167)	≤5, − (n=365)	>5, − (n=112)	≤5,+ (n=107)	>5, + (n=60)
0	100%	100%	100%	100%	100%	100%	100%	100%
1	79%	63%	81%	56%	84%	73%	62%	45%
2	72%	57%	76%	48%	78%	68%	53%	38%
3	68%	53%	72%	42%	74%	65%	48%	30%
4	66%	50%	70%	38%	72%	63%	45%	N/A[a]
5	60%	47%	64%	35%	66%	59%	41%	N/A[a]
Total failed, No. (%)	153 (32.4)	79 (45.9)	135 (28.3)	97 (58.1)	97 (26.6)	38 (33.9)	56 (52.3)	41 (68.3)
Median, y	Not reached	3.5	Not reached	1.4	Not reached	Not reached	2.0	0.9
95% CI		1.8, ∞		1.0, 2.4			1.4, 5.3	0.5, 1.4

N/A indicates not applicable; CI, confidence interval.
[a] Too few patients at risk, estimate unstable.

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

Years	Tumor Diameter		Positive Nodes		Tumor Diameter by Nodes			
	≤5 (n=472)	>5 (n=172)	Negative (n=477)	Positive (n=167)	≤5, − (n=365)	>5, − (n=112)	≤5,+ (n=107)	>5, + (n=60)
0	100%	100%	100%	100%	100%	100%	100%	100%
1	96%	96%	96%	94%	96%	97%	94%	93%
2	89%	84%	90%	81%	90%	90%	86%	72%
3	83%	71%	83%	70%	86%	75%	75%	63%
4	77%	65%	79%	59%	81%	73%	65%	48%
5	77%	60%	78%	57%	80%	69%	65%	N/A[a]
Total deaths, No. (%)	78 (14.8)	47 (27.3)	76 (15.9)	49 (29.3)	52 (14.2)	24 (21.4)	26 (24.3)	23 (38.3)
Median, y	Not reached	Not reached	Not reached	Not reached	Not reached	Not reached	Not reached	3.5
95% CI								2.4, ∞

N/A indicates not applicable.
[a] Too few patients at risk, estimate unstable.

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 study[4] (n = 585) and an RTOG study[6] (N = 310) have not reported a prognostic factor evaluation; the EORTC study[5] (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 study[3] (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

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 tomography[23-25] 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

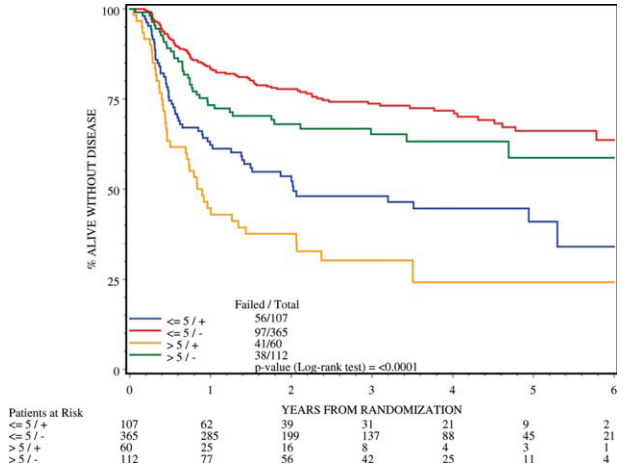

Figure 5. Disease-free survival by 4 subgroups of patients created by combining tumor diameter and nodal designation is shown (N = 644).

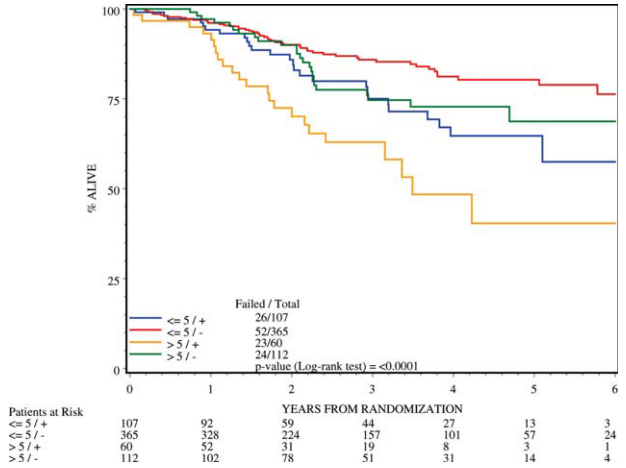

Figure 6. Overall survival by 4 subgroups of patients created by combining tumor diameter and nodal designation is shown (N = 644).

Table 4. Randomized Phase 3 Trials for Anal Canal Cancer and the Extent of Prognostic Factor Evaluation

Trial	No. of Patients	Prognostic Factor Evaluation	Prognostic Factors	Comments
UKCCCR[4]	585	No	None listed	No follow-up analysis
EORTC[5]	110	Yes	Sex, nodal status, and skin ulceration but not tumor diameter for DFS and OS	Small sample size
RTOG 87-04[6]	310	No	None listed	No follow-up analysis
RTOG 98-11[3]	644	Yes	Sex, Tumor diameter, and nodal status for DFS and OS	Four prognostic subgroups identified

DFS indicates disease-free survival; OS, overall survival.

colostomy anyway, even after the completion of chemoradiation.[21] 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

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71-96.
2. Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer*. 1983;51:1826-1829.
3. 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*. 2008;299:1914-1921.
4. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy5-fluorouracil and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet*. 1996;348:1049-1054.
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*. 1997;15:2040-2049.
6. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol*. 1996;14: 2527-2539.
7. Boman BM, Moertel CG, O'Connell MJ, et al. Carcinoma of the anal canal. A clinical and pathologic study of 188 cases. *Cancer*. 1984;54:114-125.
8. Das P, Crane CH, Ajani JA. Current treatment for localized anal carcinoma. *Curr Opin Oncol*. 2007;19:396-400.
9. 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*. 2007;68:794-800.
10. Greenall MJ, Quan SH, Urmacher C, DeCosse JJ. Treatment of epidermoid carcinoma of the anal canal. *Surg Gynecol Obstet*. 1985;161:509-517.
11. Sato H, Koh PK, Bartolo DC. Management of anal canal cancer. *Dis Colon Rectum*. 2005;48:1301-1315.
12. Peiffert D, Bey P, Pernot M, et al. Conservative treatment by irradiation of epidermoid cancers of the anal canal: prognostic factors of tumoral control and complications. *Int J Radiat Oncol Biol Phys*. 1997;37:313-324.
13. Longo WE, Vernava AM III, Wade TP, Coplin MA, Virgo KS, Johnson FE. Recurrent squamous cell carcinoma of the anal canal. Predictors of initial treatment failure and results of salvage therapy. *Ann Surg*. 1994;220:40-49.
14. Sischy B, Doggett RL, Krall JM, et al. Definitive irradiation and chemotherapy for radiosensitization in management of anal carcinoma: interim report on Radiation Therapy Oncology Group study no. 8314. *J Natl Cancer Inst*. 1989; 81:850-856.
15. Nilsson PJ, Svensson C, Goldman S, Ljungqvist O, Glimelius B. Epidermoid anal cancer: a review of a population-based series of 308 consecutive patients treated according to prospective protocols. *Int J Radiat Oncol Biol Phys*. 2005; 61:92-102.
16. Svensson C, Goldman S, Friberg B. Radiation treatment of epidermoid cancer of the anus. *Int J Radiat Oncol Biol Phys*. 1993;27:67-73.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Stat Assoc*. 1958;53:457-481.
18. Mantel N. Evaluation of survival data and 2 new rank order statistics arising in its consideration. *Cancer Chemother Rep*. 1996;60:163-170.
19. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: John Wiley & Sons; 1980.
20. Gray RJ. A class of K-samples test for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16: 1141-1154.
21. Ajani JA, Winter KA, Gunderson LL, et al. US Intergroup Anal Carcinoma Trial: Tumor Diameter Predicts for Colostomy. *J Clin Oncol*. 2009;27:1116-1121.
22. Bruland O, Fluge O, Immervoll H, et al. Gene expression reveals 2 distinct groups of anal carcinomas with clinical implications. *Br J Cancer*. 2008;98:1264-1273.
23. Schwarz JK, Siegel BA, Dehdashti F, Myerson RJ, Fleshman JW, Grigsby PW. Tumor response and survival predicted by post-therapy FDG-PET/CT in anal cancer. *Int J Radiat Oncol Biol Phys*. 2008;71:180-186.
24. Piperkova E, Raphael B, Altinyay M, et al. Impact of PET/CT on initial staging, restaging and treatment management of anal cancer: a clinical case with literature review. *J BUON*. 2006;11:523-527.
25. Nguyen BT, Joon DL, Khoo V, et al. Assessing the impact of FDG-PET in the management of anal cancer. *Radiother Oncol*. 2008;87:376-382.