

## US Intergroup Anal Carcinoma Trial: Tumor Diameter Predicts for Colostomy

Jaffer A. Ajani, Kathryn A. Winter, Leonard L. Gunderson, John Pedersen, Al B. Benson III, Charles R. Thomas Jr, Robert J. Mayer, Michael G. Haddock, Tyvin A. Rich, and Christopher G. Willett

### ABSTRACT

#### Purpose

The US Gastrointestinal Intergroup Radiation Therapy Oncology Group 98-11 anal carcinoma trial showed that cisplatin-based concurrent chemoradiotherapy resulted in a significantly higher rate of colostomy compared with mitomycin-based therapy. Established prognostic variables for patients with anal carcinoma include tumor diameter, clinical nodal status, and sex, but pretreatment variables that would predict the likelihood of colostomy are unknown.

#### Methods

A secondary analysis was performed by combining patients in the two treatment arms to evaluate whether new predictive and prognostic variables would emerge. Univariate and multivariate analyses were carried out to correlate overall survival (OS), disease-free survival, and time to colostomy (TTC) with pretreatment and treatment variables.

#### Results

Of 682 patients enrolled, 644 patients were assessable and analyzed. In the multivariate analysis, tumor-related prognosticators for poorer OS included node-positive cancer ( $P \leq .0001$ ), large ( $> 5$  cm) tumor diameter ( $P = .01$ ), and male sex ( $P = .016$ ). In the treatment-related categories, cisplatin-based therapy was statistically significantly associated with a higher rate of colostomy ( $P = .03$ ) than was mitomycin-based therapy. In the pretreatment variables category, only large tumor diameter independently predicted for TTC ( $P = .008$ ). Similarly, the cumulative 5-year colostomy rate was statistically significantly higher for large tumor diameter than for small tumor diameter (Gray's test;  $P = .0074$ ). Clinical nodal status and sex were not predictive of TTC.

#### Conclusion

The combined analysis of the two arms of RTOG 98-11, representing the largest prospective database, reveals that tumor diameter (irrespective of the nodal status) is the only independent pretreatment variable that predicts TTC and 5-year colostomy rate in patients with anal carcinoma.

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### INTRODUCTION

Anal carcinoma is an uncommon malignancy in the United States. Approximately 5,070 new cases of anal canal cancer were projected for the year 2008 of more than 1.44 million new cancer diagnoses.<sup>1</sup> The treatment strategy for anal carcinoma is unique and often effective in preserving the anal canal and its function because anal carcinoma is highly sensitive to chemoradiotherapy,<sup>2</sup> resulting in local control in approximately 65% of cases. The goal of therapy is to cure anal carcinoma without having to perform a colostomy. However, disease-free survival (DFS) and overall survival (OS) rates vary considerably, depending predominantly on the established pretreatment prognostic variables such as sex, clinical nodal status, and tumor diameter.<sup>3-6</sup> Approximately,

25% of patients have clinically node-positive cancer and/or  $\geq 5$  cm tumor diameter<sup>6</sup>; the larger the primary tumor, the higher the likelihood of lymph node metastases.<sup>7</sup>

Although the DFS rates can range from 55% to 65%, these do not necessarily correspond with the colostomy rates, which are often, fortunately, considerably lower.<sup>8</sup> The reasons for the discordance between the DFS and colostomy rates are multiple and include distant failures in a small percentage of patients, the broad definition of DFS that includes second primary and death resulting from any cause, effective secondary local salvage therapies, patient preferences, and unknown reasons. It would of considerable interest to identify pretreatment variables that can predict the probability of colostomy. If such variables are established, then it might be possible to develop new therapeutic strategies.

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Published reports discussing predictive and prognostic variables for anal canal cancer often include a small number of patients, retrospective analysis of patients accrued over a long duration, and single-institution experiences.<sup>8</sup> A prior Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Group prospective study of 310 patients suggested that the nodal status was associated with the colostomy rate (13% in clinically node-negative patients *v* 28% in node-positive patients)<sup>9</sup>; however, no univariate or multivariate analysis was reported. Thus pretreatment variables for predicting a probability of colostomy remain unknown.

The US Gastrointestinal Intergroup trial RTOG 98-11 recruited 682 patients between 1998 and 2005, with participation by several US cooperative groups.<sup>6</sup> The study compared the previously established standard of concurrent fluorouracil plus mitomycin and radiation (mitomycin-based therapy) with fluorouracil plus cisplatin (induction and concurrent) and radiation (cisplatin-based therapy). A total of 644 assessable patients were analyzed for the primary end point of DFS and secondary end points of OS and time to colostomy (TTC). The rates for DFS and OS were not statistically different between the two treatments, but the cumulative rate of colostomy was significantly higher for cisplatin-based therapy than mitomycin-based therapy (19% *v* 10%; *P* = .02).<sup>6</sup>

Intergroup RTOG 98-11 is unique and represents the largest prospectively collected, multicenter database that has been collected during a relatively short and modern time period on patients with anal canal carcinoma. For this analysis, patients in the two treatment arms were combined, and a comprehensive prognostic factors outcomes analysis was performed to further understand the clinical biology of anal canal carcinoma and to determine whether the results would lead to potential new therapeutic and investigative strategies.

## METHODS

### Infrastructure, Hypothesis, and Objectives

RTOG 98-11 was a US Gastrointestinal Intergroup trial with participation by Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group, Southwest Oncology Group, and RTOG (the coordinating group). The hypothesis of the trial was based on prior knowledge that DFS was better for lower T stage cancers. It was hypothesized that induction chemotherapy would reduce the bulk of the primary tumor before ensuing chemoradiotherapy and thereby result in a higher DFS.

The primary objective was to observe a DFS rate of 73% with cisplatin-based therapy, compared with 63% with mitomycin-based therapy. In addition, the secondary objectives included TTC, OS, and toxic effects.

The objective of the current analysis was to assess pretreatment variables that might predict the probability of colostomy and to further understand the clinical biology of anal canal cancer.

### Patient Eligibility

All patients with histologically documented squamous, basaloid, or cloacogenic carcinoma of the anal canal were eligible, provided that they were more than 18 years of age, had Karnofsky performance status  $\geq$  60%, had T2 to 4 with any N stage cancer, had adequate organ function, and were willing to provide written consent.

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

### Evaluations

These have been previously described.<sup>6</sup>

### Randomization, Stratification, and Therapy

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

The details of therapy have been previously described.<sup>6</sup> Briefly, chemotherapy on arm A included mitomycin 10 mg/m<sup>2</sup> administered as an intravenous bolus on days 1 and 29 and infusion of FU 1,000 mg/m<sup>2</sup> on days 1 through 4 and 29 through 32. Chemotherapy on arm B included cisplatin 75 mg/m<sup>2</sup> on days 1 and 29, and also repeated on days 57 and 85, and infusion of FU 1,000 mg/m<sup>2</sup> days 1 through 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 Gy administered in 25 fractions of 1.8 Gy over 5 weeks to the primary cancer with supervoltage radiation (photon energy of > 6 MV), using anterior-posterior-posterior-anterior or multifield techniques.<sup>6</sup> 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 to 59 Gy in 30 to 32 fractions over 5.5 to 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 timing and rates of DFS, OS, and TTC. Failures for the efficacy end points were as follows: OS, death from any cause; 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); colostomy failure, having a colostomy. All efficacy end points were measured from date of random assignment to date of first failure for the given end point or date of last follow-up for patients who did not fail a given end point. OS and DFS were estimated univariately with the Kaplan-Meier method,<sup>10</sup> and comparisons were tested using the log-rank test.<sup>11</sup> Time to locoregional failure, distant metastases, and colostomy were estimated by the cumulative incidence method,<sup>12</sup> and comparisons were tested using Gray's test.<sup>13</sup> All reported *P* values are two-sided. Multivariate analyses were performed with Cox proportional hazards models to test for prognostic significance of treatment (arm A *v* arm B), sex (female *v* male), clinical nodal status (no *v* yes), and tumor diameter (> 2 to  $\leq$  5 *v* > 5 cm). All variables were coded such that a hazard ratio (HR) greater than 1 indicates an increased risk for the second level of the variable. For example, sex (female *v* male) was coded such that an HR more than 1 indicates an increased risk of failure for male patients.

## RESULTS

### Patient Characteristics

The study accrued 682 patients from October 1998 to June 2005. Pretreatment characteristics of 644 assessable patients were reported previously.<sup>6</sup> Sixty-nine percent of patients were women, 27% had cancer size more than 5 cm in diameter (T3/T4), and 26% had clinically positive nodes. A total of 324 patients were randomly assigned to mitomycin-based therapy, and 320 patients were randomly assigned to cisplatin-based therapy.

### DFS and TTC for the Entire Population

The median DFS for the 644 assessable patients have not been reached at a median follow-up time of 2.21 years. The 5-year DFS rate

**Table 1.** Time to Colostomy for All Patients (n = 644)

Years	% of Patients							
	Tumor Diameter		Nodes		Tumor Diameter by Node Status			
	≤ 5 cm (n = 472)	> 5 cm (n = 172)	Negative (n = 477)	Positive (n = 167)	≤ 5 cm, Node Positive (n = 107)	≤ 5 cm, Node Negative (n = 365)	> 5 cm, Node Positive (n = 60)	> 5 cm, Node Negative (n = 112)
0	0	0	0	0	0	0	0	0
1	7	14	9	8	5	7	14	15
2	10	18	12	13	9	11	19	17
3	11	19	13	15	9	11	24	17
4	11	19	13	15	9	11	24	17
5	12	19	14	15	9	13	*	17
Total failed, n	49	31	58	22	9	40	13	18

\*Too few patients at risk; estimate unstable.

was 35% for node-positive patients (n = 169) and 64% for node-negative patients (n = 477) and was highest (66%) for node-negative, ≤ 5 cm tumors (n = 365).

The cumulative incidence 5-year colostomy rate (Table 1) was 9% for patients with node-positive disease and ≤ 5 cm tumors (n = 107) and 19% for patients with tumors more than 5 cm, regardless of nodal status (n = 172).

Patients with tumor diameter more than 5 cm had poorer DFS outcomes than those with tumor diameter ≤ 5 cm. Tumor diameter had a statistically significant influence on DFS (P = .0003 by the log-rank test), regardless of nodal status.

Patients with clinically positive nodes had poorer DFS outcomes than those with negative nodes. Clinical nodal status had a statistically significant influence on DFS (P ≤ .0001 by the log-rank test).

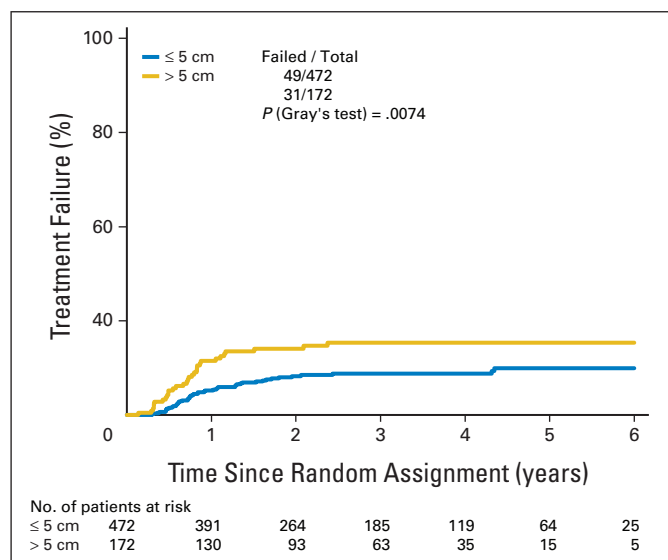
TTC was significantly influenced by the larger tumor diameter (Fig 1; P = .0074 by Gray's test); however, the clinical nodal status had no influence on TTC (Fig 2; P = .74 by Gray's test). In the cisplatin-based treatment group, patients with larger tumors had

shorter TTC (Fig 3; P = .05 by Gray's test) and there was a trend toward this same effect in the mitomycin-based treatment arm (Fig 4; P = .071 by Gray's test); TTC, however, was not influenced by the nodal status in the mitomycin-based arm (P = .79 by Gray's test) or the cisplatin-based arm (P = .59 by Grays' test).

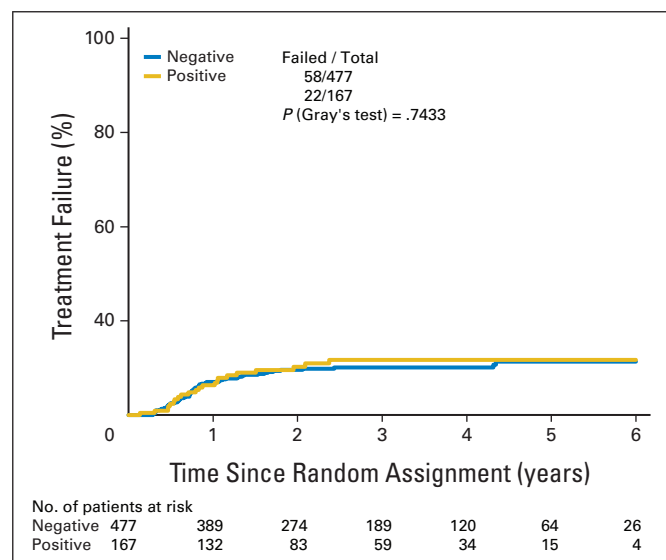
**Multivariate Analysis of the Entire Population (n = 644)**

In a multivariate analysis (Table 2), male sex (P = .02), clinically positive nodes (P ≤ .0001), and tumor diameter more than 5 cm (P = .004) were independent prognostic factors for poorer DFS, but the type of treatment (P = .17) was not.

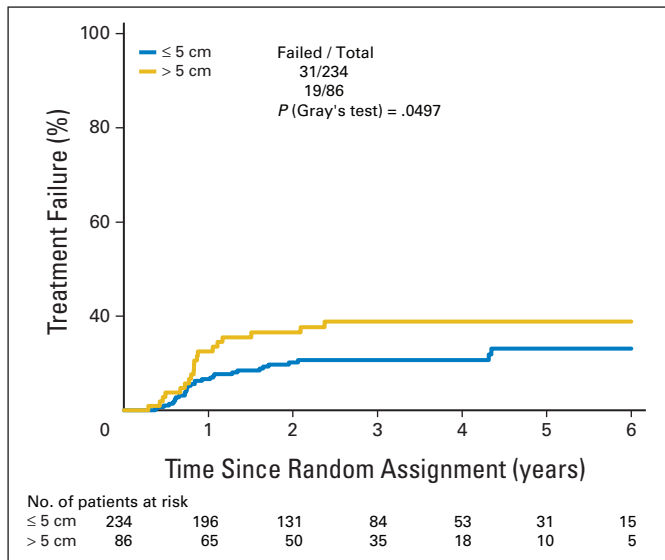
Cumulative incidence of colostomy was significantly higher for patients assigned to cisplatin-based therapy (P = .03). Among the three pretreatment variables, tumor diameter of more than 5 cm was an independent predictor for shorter time to colostomy (P = .008), but nodal status (P = .92) and sex were not (P = .92).



**Fig 1.** Time to colostomy by tumor diameter (n = 644).



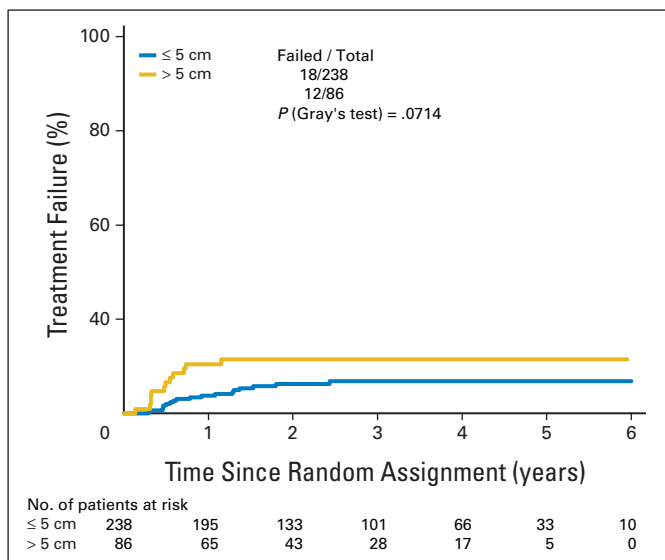
**Fig 2.** Time to colostomy by clinical nodal status (n = 644).



**Fig 3.** Influence of tumor diameter on time to colostomy within the cisplatin-based treatment arm (n = 320).

### Causes of Colostomy

Data were collected with regard to the reasons for colostomy in both treatment arms. Of the 80 patients with a colostomy, 62 (77.5%) were due to persistent or recurrent anal carcinoma, 16 (20%) were coded as treatment-related in patients with no evidence of disease (treatment complications, sphincter dysfunction as a result of prior tumor invasion/destruction), and the other two patients were coded as having both reasons for a colostomy. In the cisplatin-based arm, 42 (84%) of 50 colostomies were because of persistent or recurrent anal carcinoma, five (10%) were treatment-related, and three (6%) were due to both causes. In the mitomycin-based arm, 20 (66.7%) of 30 colostomies were due to persistent or



**Fig 4.** Influence of tumor diameter on time to colostomy within the mitomycin-based treatment arm (n = 324).

recurrent anal carcinoma, nine (30%) were treatment-related, and one (3.3%) was due to both causes.

### Event Rates After 2 Years

This combined analysis also demonstrated that although there is considerable heterogeneity in the colostomy event rates among various prognostic groups, most events occurred by the end of 2 years of follow-up for DFS and TTC.

## DISCUSSION

The US Gastrointestinal Intergroup anal canal cancer trial RTOG 98-11 has the highest number of patients (n = 682; 644 analyzed) studied to date,<sup>6</sup> and the current secondary analysis 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 for the probability of colostomy. The data also demonstrate that positive nodes influence OS and DFS rather than TTC and, intuitively, this makes sense. However, it is not clear whether this knowledge can be exploited to provide an advantage to patients who present for treatment with a tumor diameter more than 5 cm.

As shown in the current analysis, approximately 25% of patients who have more than 5 cm pretreatment tumor diameter have poor OS and DFS, as well as high colostomy rates. For a patient with tumor diameter more than 5 cm, potential options to improve outcomes of DFS and rate of colostomy include the following: galvanize clinical practice infrastructure to help the patient complete the prescribed dose of concurrent chemo-radiation, evaluate irradiation treatment factors (dose escalation, shorten duration of treatment) in an attempt to provide improved local control without compromise of anal function, continue to evaluate targeted agents in combination with concurrent chemo-radiation, observe patients more closely after chemo-radiation (team of surgeon/radiation oncologist) so that local surgical excision of persistent cancer may be feasible in select patients, and provide aggressive supportive care during therapy. Perhaps these and additional approaches would allow a reduction in the colostomy rate in this high-risk group of patients. This group of patients should continue to be enrolled in novel and potentially more effective treatment protocols that include attempts to find molecular markers that will more effectively guide individualized treatment strategies.

The strategies that would be most easily evaluated are changes in both dose and duration of the irradiation component of treatment with the use of sophisticated and/or novel irradiation techniques (intensity-modulated radiation therapy [IMRT], other). In view of improved perineal and small bowel tolerance with the use of IMRT for patients with anal cancer,<sup>14</sup> it may be feasible to escalate boost doses for patients with T3 to T4 anal cancers to the level of those used for patients with locally advanced squamous cell cancers of the head and neck region (70 Gy/35 fractions/7 weeks). With IMRT techniques, it may also be feasible to treat the primary tumor/involved nodal sites at  $\geq 2$  Gy/fraction while treating uninvolved nodal sites at 1.8 Gy/fraction, thus shortening the overall treatment time. Both total dose and treatment time have been shown to be of importance in obtaining improvements in locoregional control in phase III RTOG trials for

**Table 2.** Multivariate Analyses (n = 644)

Adjustment Variable	Disease-Free Survival			Time to Colostomy		
	Adjusted HR*	95% CI	P†	Adjusted HR*	95% CI	P†
Treatment, FU/mitomycin v FU/cisplatin	1.20	0.93 to 1.55	.17	1.66	1.06 to 2.62	.03
Sex, female v male	1.38	1.05 to 1.81	.02	0.97	0.60 to 1.58	.92
Clinical nodal status, negative v positive	2.66	2.04 to 3.46	< .0001	1.03	0.63 to 1.69	.92
Tumor diameter, 2 to 5 cm v > 5 cm	1.5	1.14 to 1.97	.004	1.85	1.17 to 2.91	.008

Abbreviations: HR, hazard ratio; FU, fluorouracil.

\*A hazard ratio of 1 indicates no difference between the two subgroups. HR > 1 indicates an increased risk of death for the second level of the variables listed.

†P value from  $\chi^2$  test using the Cox proportional hazards model.

patients with locally advanced squamous cell cancer of the head and neck.<sup>15</sup>

We have preliminary data with regard to the reasons for a colostomy. Data were collected with regard to the reasons for a colostomy in both treatment arms. In the cisplatin-based arm, 42 (84%) of 50 colostomies were because of persistent or recurrent anal carcinoma, five (10%) were treatment-related, and three (6%) were due to both causes. In the mitomycin-based arm, 20 (66.7%) of 30 colostomies were due to persistent or recurrent anal carcinoma, nine (30%) were treatment-related, and one (3.3%) was due to both causes. In the future, we plan to review the details of the causes of colostomy that are not directly related to anal carcinoma; this could provide some insight for reducing the colostomy rates in some patients.

Data in the current analysis also demonstrate that most of the outcome events (ie, OS, DFS, and colostomy) occur relatively early (by 2 years) during follow-up. This knowledge might be of value in modifying the design/end points of future phase II and III protocols. New treatment strategies could be evaluated initially in only high-risk patients with anal cancer (> 5 cm diameter and/or positive clinical nodes) using a phase II randomized study design with primary end points evaluated at 2 years (eg, DFS and colostomy rate at 2 years). If a potential advantage from a new therapy is established in this high-risk population of patients, the treatment approach can be evaluated more quickly in phase III trials, which may or may not include lower-risk patients (properly stratified, if included), using the same 2-year end points. Ultimately, potential improvements in treatment strategies could be more effectively evaluated and transferred to both high-risk and low-risk patient populations without having to conduct extensive/lengthy studies as done previously.

In conclusion, a secondary analysis of the US Gastrointestinal Intergroup RTOG 98-11 trial reveals that tumor diameter is an

important pretreatment variable for the prediction of rate of colostomy and DFS. In addition, most relevant outcome events occur by the end of 2-year follow-up. These findings warrant exploitation in developing novel strategies and treatments for patients with anal canal carcinoma.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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