Predictors of Nonadherence to NCCN Guideline Recommendations for the Management of Stage I Anal Canal Cancer

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Abstract

Background: Definitive chemoradiotherapy (CRT) is recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Anal Carcinoma for all patients with stage I anal canal cancer. Because these patients were not well represented in clinical trials establishing CRT as standard therapy, it is unclear whether NCCN recommendations are being closely followed for stage I disease. This study identified factors that predict for NCCN Guideline–concordant versus NCCN Guideline–discordant care. **Methods:** Using the National Cancer Data Base, we identified patients diagnosed with anal canal carcinoma from 2004 to 2012 who received concurrent CRT (radiotherapy [RT] 45.0–59.4 Gy with multiagent chemotherapy), RT alone (45.0–59.4 Gy), or surgical procedure alone (local tumor destruction, tumor excision, or abdominoperineal resection). Demographic and clinicopathologic factors were analyzed using the chi-square test and logistic regression modeling. **Results:** A total of 1,082 patients with histologically confirmed stage I anal cancer were identified, among whom 665 (61.5%) received CRT, 52 (4.8%) received RT alone, and 365 (33.7%) received only a surgical procedure. Primary analyses were restricted to patients receiving CRT or excision alone, as these were most common. Multivariable analysis identified factors independently associated with reduced odds of CRT receipt: low versus intermediate/high tumor grade (adjusted odds ratio [AOR], 0.21; 95% CI, 0.14–0.29; $P<.001$), tumor size <1 cm vs 1 to 2 cm (AOR, 0.24; 95% CI, 0.17–0.35; $P<.001$), age ≥70 versus 50 to 69 years (AOR, 0.36; 95% CI, 0.24–0.54; $P<.001$), male sex (AOR, 0.63; 95% CI, 0.45–0.90; $P=.009$), and treatment at an academic versus a non-academic facility (AOR, 0.58; 95% CI, 0.41–0.81; $P=.002$). **Conclusions:** Despite the NCCN recommendation of CRT for stage I anal cancer, at least one-third of patients appear to be receiving guideline-discordant management. Excision alone is more common for patients who are elderly, are male, have small or low-grade tumors, or were evaluated at academic facilities.

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Background

Anal cancer constitutes 2% to 3% of gastrointestinal malignancies, with approximately 8,000 new cases estimated for 2016 in the United States.[1] Currently, concurrent chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) and mitomycin-C (MMC) is considered standard-of-care therapy for all patients with nonmetastatic anal canal cancer.[2,3] Whether such an aggressive treatment is necessary for stage I (T1N0) disease has been less clear, however, because these patients were either excluded or underrepresented in the most influential anal cancer clinical trials.[4–9]

Radiotherapy (RT) or excision alone have been explored as less aggressive alternatives for early-stage anal canal cancers, although these studies have been primarily single-arm and retrospective.[10–14] Other studies have

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examined CRT with reduced doses of RT to minimize treatment toxicity.[15,16] Without strong prospective evidence available to support the efficacy and safety of RT or excision alone, NCCN has recommended definitive CRT for all patients with locoregional anal canal cancer since the inception of the second version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Anal Carcinoma in 2002.[2,17] Whether NCCN Guidelines are being followed specifically for patients with stage I anal canal cancer is unclear.

This study used the National Cancer Data Base (NCDB) to examine whether practice patterns for stage I anal canal cancer have been consistent with standard practice guidelines recommending CRT, as published by NCCN over the past decade. We then identify factors that predict the use of NCCN Guideline–concordant versus NCCN Guideline–discordant therapy.

Methods

Study Population

The NCDB is a joint project by the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. Established in 1989, the NCDB is a comprehensive, nationwide, facility-based oncology data set, capturing approximately 70% of all newly diagnosed malignancies in the United States. The data used in this study are derived from a deidentified NCDB file. The ACS and the CoC have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

We identified patients in the NCDB diagnosed from 2004 to 2012 with histologically confirmed clinical T1N0 anal canal cancer with the following histologies: squamous cell carcinoma, basaloid squamous cell carcinoma, or basaloid carcinoma (ICD-0-3 histology codes 8070–8078, 8083, 8123); anal margin cancers are not included within the anal cancer participant use file. Patients with unknown surgical status or those who underwent surgery >90 days after diagnosis were excluded. For the purposes of this study, surgical procedures were defined as "local tumor destruction alone" (photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, or thermal ablation), "excision alone" (polypectomy or excisional biopsy), or "APR" (abdominoperineal resection). Because specific chemotherapeutic agents are not specified within the NCDB, we limited our study to patients receiving multiagent chemotherapy, because this would be consistent with 5-FU/MMC use. Patients receiving RT were required to receive doses between 45.0 and 59.4 Gy and start RT within 90 days of diagnosis. Concurrent CRT was defined as initiation of multiagent chemotherapy and RT within 14 days of each other. Because the NCDB includes all methods of treatment received by patients as part of the first course of therapy, some patients were coded as undergoing a surgical procedure with subsequent definitive RT or CRT (eg, excisional biopsy followed by RT to 54 Gy within 90 days of diagnosis). These patients were included in either the RT or CRT subgroup, respectively. Patients were required to have known tumor grade and size for study inclusion. In order to minimize immortal time bias, which would affect treatment groups that did not complete a full course of RT, we excluded all patients who died within 3 months of diagnosis.[18]

Patients within our study cohort are shown in Figure 1. Notably, in order to prevent patient identifiability, the NCDB does not allow reporting of groups of <10 patients. For the initial analysis, only patients undergoing treatment with excision alone or CRT were examined. A sensitivity analysis was subsequently performed which reintroduced patients undergoing treatment with local tumor destruction, APR, or RT alone. "NCCN Guideline–concordant" patients were defined as those receiving CRT, whereas "NCCN Guideline–discordant" patients were defined as those undergoing local tumor destruction, excision alone, APR, or RT alone.

Statistical Methods

Patient demographic and clinical factors were compared using the chi-square test to identify predictors of receipt of therapy (excision alone or CRT). Patient demographic factors included age, sex, race, Charlson-Deyo comorbidity score, diagnosis year, insurance coverage, estimated income by county of residence, setting of residence, distance to treatment facility, academic or non-academic treatment facility affiliation, and geographic location. Clinicopathologic factors, including tumor size and tumor grade, were also included in chi-square analyses. Human papillomavirus (HPV) status was excluded from chi-

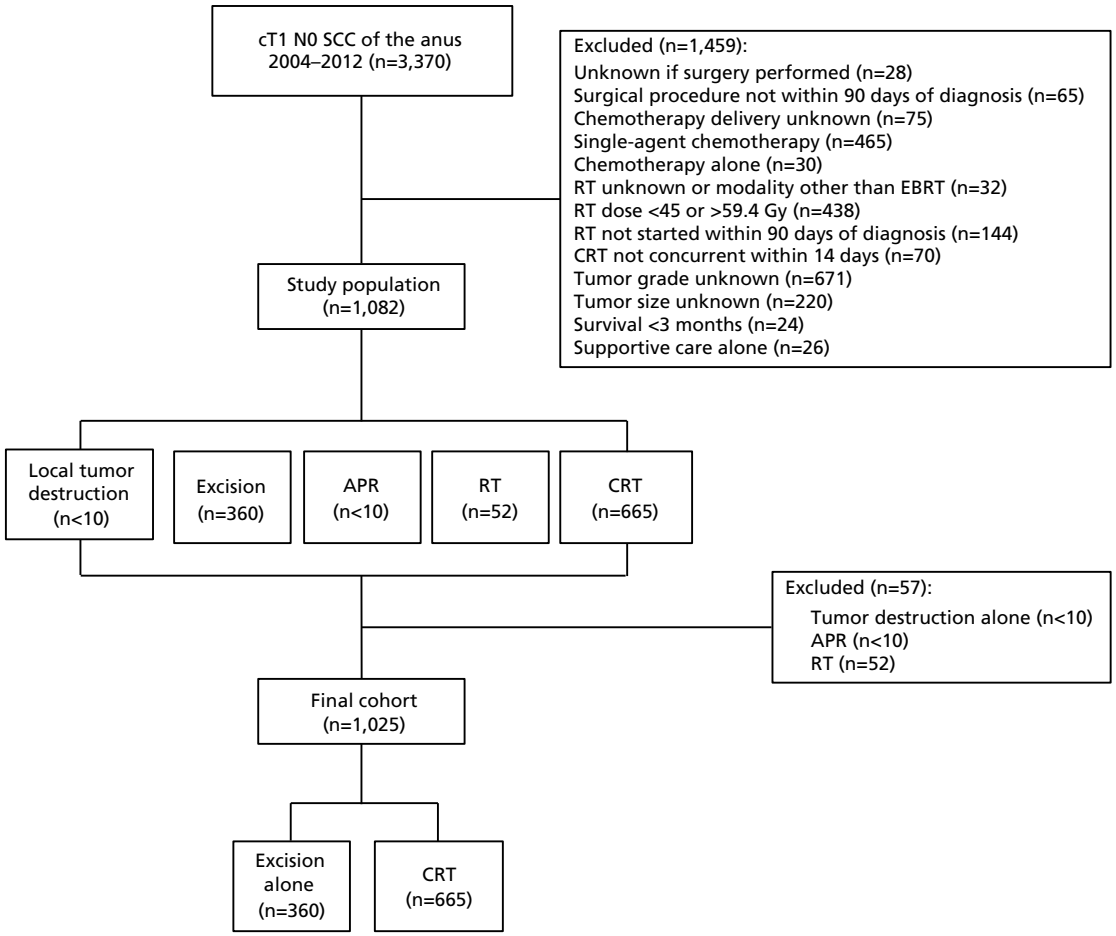

Figure 1. Flow diagram of inclusion criteria and treatment groups.
Note: The National Cancer Data Base does not allow reporting of groups of <10 patients.
Abbreviations: APR, abdominoperineal resection; CRT, chemoradiotherapy; EBRT, external-beam radiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma.

square testing due to limited data availability within the NCDB.

Clinicopathologic factors were dichotomized and univariable Cox regression was used to calculate unadjusted odds ratios (ORs) for receipt of CRT versus excision alone. Factors trending towards significance ($P<.10$) were included in a backward conditional stepwise multivariable logistic regression to identify adjusted ORs (AORs). Factors with $P<.05$ on multivariable regression were considered statistically significant predictors of receipt of CRT versus excision alone. Patients with missing data for variables of interest (detailed in Table 1) were omitted from univariable and multivariable analyses. HPV status was excluded from Cox regression models due to the high proportion of patients with unknown HPV status. We then repeated univariable and multivariable logistic regression as a sensitivity analysis including all patients who received either NCCN Guideline–concordant (CRT) or NCCN Guideline–discordant (local tumor destruction, excision alone, APR, or RT alone) care. Kaplan-Meier analyses were used to compare overall survival (OS) between treatment groups. Unadjusted hazard ratios (HRs) for survival were calculated with univariable Cox regression. Two-sided tests with a P value <.05 were considered to be statistically significant. All statistical analyses were performed using STATA/SE 13.1 (StataCorp, College Station, TX).

Table 1. Patient Cohort Demographic and Clinicopathologic Characteristics

Characteristic	n (%) (N=1,025)
Age, y	
Median	57
<50	257 (25.1)
50–69	587 (57.3)
≥70	181 (17.7)
Sex	
Male	339 (33.1)
Female	686 (66.9)
Race/Ethnicity	
White	817 (79.7)
Black	72 (7.0)
Hispanic	35 (3.4)
Other/Unknown	101 (9.9)
Charlson-Deyo comorbidity score	
0	852 (83.1)
≥1	173 (16.9)
Diagnosis year	
2004	60 (5.9)
2005	67 (6.5)
2006	69 (6.7)
2007	86 (8.4)
2008	124 (12.1)
2009	145 (14.2)
2010	150 (14.6)
2011	155 (15.1)
2012	169 (16.5)
Insurance coverage	
None	33 (3.2)
Private	587 (57.3)
Medicaid	60 (5.9)
Medicare	326 (31.8)
Government/Unknown	19 (1.9)
Estimated income	
<$38,000	169 (16.5)
$38,000 to <$48,000	236 (23.0)
$48,000 to <$63,000	273 (26.6)
≥$63,000	340 (33.2)
Unknown[a]	<10
Setting of residence	
Metropolitan	854 (83.3)
Urban	131 (12.8)
Rural	19 (1.9)
Unknown	21 (2.1)
Distance to treatment facility, miles	
<10	572 (55.8)
10–19	223 (21.8)
20–49	155 (15.1)
≥50	75 (7.3)
Treatment facility type	
Non-academic	626 (61.1)
Academic	279 (27.2)
Unknown	120 (11.7)
Geographic location	
Northeast	189 (18.4)
South	280 (27.3)
Midwest	285 (27.8)
West	227 (22.2)
Unknown	44 (4.3)
Tumor size	
<1 cm	239 (23.3)
1–2 cm	786 (76.7)
Tumor grade	
Low	256 (25.0)
Intermediate	486 (47.4)
High	283 (27.6)
HPV status	
Positive	56 (5.5)
Negative	56 (5.5)
Unknown	913 (89.1)

Abbreviation: HPV, human papillomavirus.
[a]The National Cancer Data Base does not allow reporting of groups of <10 patients.

Results

Within the NCDB, we identified 3,370 patients from 2004 to 2012 with histologically confirmed clinical T1N0 anal canal carcinoma. Patients were excluded if surgical status was unknown; the procedure was not performed within 90 days of diagnosis; they did not receive multiagent chemotherapy, as would be consistent with 5-FU/MMC; they received chemotherapy alone; nonstandard doses of RT were delivered; or those undergoing CRT did not receive RT within 14 days of chemotherapy (Figure 1). Given the prognostic significance of tumor grade and size,[19–21] an additional 671 and 220 patients were excluded, respectively, due to missing data. Our initial cohort included 1,082 patients. Definitive CRT was the most common treatment type received by patients in our study cohort (61.4%; n=665). Excision alone without subsequent additional therapy was observed in a large minority of patients (33.3%; n=360), whereas RT without chemotherapy was delivered to only 4.8% (n=52) of patients. Fewer than 10 patients received either local tumor destruction or APR as the only therapy. Approximately half of the patients within the CRT group (46.6%; n=310) had undergone initial surgery with excision or local tumor destruction before CRT. Because patients who received CRT or excision alone included nearly 95% of the total cohort, our initial analyses were restricted to these 2 most common treatment groups. Our final cohort included a total of 1,025 patients.

The median age for the entire cohort was 57 years. Most patients were female (66.9%), of white race (79.7%), had no significant comorbidities (83.1%), and were privately insured (57.3%). Tumors were primarily 1 to 2 cm (76.7%) and intermediate-to-high grade (75.0%). Tables 1 and 2 summarize all measured demographic and clinicopathologic characteristics and the association of these characteristics with treatment type, respectively. We assessed the use of CRT versus excision alone from 2004 to 2012 (Figure 2). Rates of CRT receipt did not change significantly over the study period (68.4% in 2004–2007 vs 63.5% in 2008–2012; P=.141).

Demographic and clinicopathologic factors were tested using univariable analysis for increased odds of CRT receipt (supplemental eTable 1, available with this article at JNCCN.org). Factors with a trend toward significance (age, sex, race, insurance

Table 2. Association of Treatment Type With Patient Demographic and Clinicopathologic Factors

Characteristic	N (%) Excision (n=360)	CRT (n=665)	*P* Value
Age, y (ref: 50–69)			<.001
<50	109 (42.4)	148 (57.6)	
50–69	171 (29.1)	416 (70.9)	
≥70	80 (44.2)	101 (55.8)	
Sex (ref: male)			<.001
Male	162 (47.8)	177 (52.2)	
Female	198 (28.9)	488 (71.1)	
Race/Ethnicity (ref: white)			.003
White	274 (33.5)	543 (66.5)	
Black	37 (51.4)	35 (48.6)	
Hispanic	18 (51.4)	17 (48.6)	
Other/Unknown	31 (30.7)	70 (69.3)	
Charlson-Deyo comorbidity score (ref: 0)			.276
0	293 (34.4)	559 (65.6)	
≥1	67 (38.7)	106 (61.3)	
Diagnosis year (ref: 2004–2007)			.650
2004	17 (28.3)	43 (71.7)	
2005	26 (38.8)	41 (61.2)	
2006	20 (29.0)	49 (71.0)	
2007	26 (30.2)	60 (69.8)	
2008	43 (34.7)	81 (65.3)	
2009	55 (37.9)	90 (62.1)	
2010	60 (40.0)	90 (60.0)	
2011	52 (33.6)	103 (66.5)	
2012	61 (36.1)	108 (63.9)	
Insurance coverage (ref: private)			.052
None	12 (36.4)	21 (63.6)	
Private	185 (31.5)	402 (68.5)	
Medicaid	24 (40.0)	36 (60.0)	
Medicare	129 (39.6)	197 (60.4)	
Gov't/Unknown[a]	10	<10	
Estimated income (ref: <63,000)			.031
<$38,000	68 (40.2)	101 (59.8)	
$38,000 to <$48,000	76 (32.2)	160 (67.8)	
$48,000 to <$63,000	79 (28.9)	194 (71.1)	
≥$63,000	135 (39.7)	205 (60.3)	
Unknown[a]	<10	<10	
Setting of residence (ref: metropolitan)			.045
Metropolitan	315 (36.9)	539 (63.1)	
Urban	36 (27.5)	95 (72.5)	
Rural[a]	<10	16	
Unknown[a]	<10	15	
Distance to treatment facility, miles (ref: <10)			.810
<10	203 (35.5)	369 (64.5)	
10–19	82 (36.8)	141 (63.2)	
20–49	50 (32.3)	105 (67.7)	
≥50	25 (33.3)	50 (66.7)	
Treatment facility type (ref: non-academic)			<.001
Non-Academic	190 (30.4)	436 (69.7)	
Academic	122 (43.7)	157 (56.3)	
Unknown	48 (40.0)	72 (60.0)	
Geographic location (ref: Northeast)			.005
Northeast	68 (36.0)	121 (64.0)	
South	99 (35.4)	181 (64.6)	
Midwest	79 (27.7)	206 (72.3)	
West	91 (40.1)	136 (59.9)	
Unknown	23 (52.3)	21 (47.7)	
Tumor size, cm (ref: <1)			<.001
<1	150 (62.8)	89 (37.2)	
1–2	210 (26.7)	576 (73.3)	
Tumor grade (ref: low)			<.001
Low	165 (64.5)	91 (35.6)	
Intermediate	145 (29.8)	341 (70.2)	
High	50 (17.7)	233 (82.3)	
HPV status			*
Positive	15 (26.8)	41 (73.2)	
Negative	29 (51.8)	27 (48.2)	
Unknown	316 (34.6)	597 (65.4)	

Abbreviations: CRT, chemoradiotherapy; HPV, human papillomavirus.
[a]The National Cancer Data Base does not allow reporting of groups of <10 patients.
*Chi-squared test not performed due to small sample size.

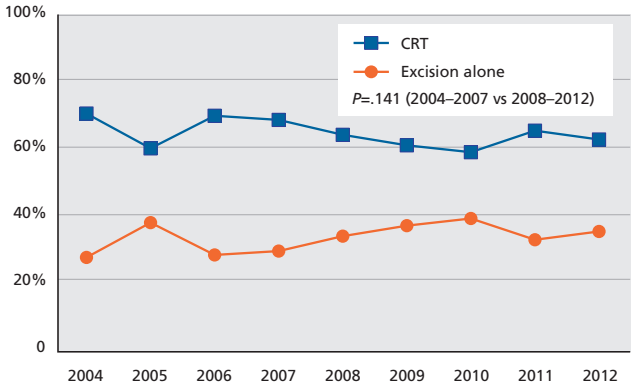

Figure 2. Unadjusted trends in use of CRT versus excision alone during the study period.
Abbreviation: CRT, chemoradiotherapy.

coverage, estimated income, setting of residence, treatment facility type, and tumor size and grade) were included in a multivariable logistic regression model. Multivariable modeling showed that patients who were significantly less likely to receive CRT included those aged ≥70 years versus 50 to 69 years (AOR, 0.36; 95% CI, 0.24–0.54; *P*<.001), male sex (AOR, 0.63; 95% CI, 0.45–0.90; *P*=.009), treatment at an academic versus non-academic facility (AOR, 0.58; 95% CI, 0.41–0.81; *P*=.002), tumor size <1 cm versus 1 to 2 cm (AOR, 0.24; 95% CI, 0.17–0.35; *P*<.001), and low versus intermediate/high tumor grade (AOR, 0.21; 95% CI, 0.14–0.29; *P*<.001) (Table 3 and Figure 3). OS was not statistically different between patients who underwent excision alone and CRT (5-year OS, 83.8% vs 87.3%; HR, 0.71; 95% CI, 0.48–1.04; *P*=.079) (Figure 4).

Because patients undergoing local tumor destruction, APR, or RT were excluded from the initial cohort, we performed a sensitivity analysis in which these patients were combined with those receiving excision alone (NCCN Guideline–discordant cohort). We then repeated univariable and multivariable regressions to identify independent factors associated with NCCN Guideline–concordant CRT versus other NCCN Guideline–discordant treatments. Results were similar to those of our initial analysis, with age ≥70 years, male sex, treatment at academic facility, tumor size <1 cm, and low-grade tumors more likely to be associated with nonstandard NCCN Guideline–discordant therapy (supplemental eTable 2).

Discussion

NCCN has recommended concurrent CRT for all patients with locoregional anal canal cancer, including stage I (T1N0) disease, since the second version of the NCCN Guidelines for Anal Carcinoma was published in 2002 (category 2A).[17] In this study, we used a large national hospital-based database to identify patient and tumor factors that predict for the use of NCCN Guideline–concordant CRT versus other NCCN Guideline–discordant therapies for patients with stage I anal canal cancer. We found that fewer than two-thirds of patients receive NCCN Guideline–concordant CRT as the initial course of therapy. Surgery has fallen out of favor for the primary treatment of anal canal cancer since the early discovery by Nigro et al[3] that sphincter and tumor removal via APR can be spared when patients receive CRT. However, in our cohort we found that a substantial proportion of patients (33%) with stage I anal canal cancer underwent excision alone as definitive therapy. Although NCCN recommends excision alone with adequate margins for patients with well-differentiated T1N0 cancers confined to the perianal skin or anal *margin*, the literature supporting this approach for cancers of the anal *canal* is limited to small retrospective series from the 1980s. For example, Boman et al[10] described a small series of patients with superficial anal canal cancers treated at the Mayo Clinic with excision alone, for which local control was achieved

Table 3. Multivariable Logistic Regression to Determine Odds of Receiving Chemoradiotherapy Versus Excision Alone

	Multivariable Analysis		
Variable	AOR	95% CI	*P* Value
Age, y			
<50 vs 50–69	0.74	0.50–1.09	.130
≥70 vs 50–69	0.36	0.24–0.54	<.001
Sex			
Male vs female	0.63	0.45–0.90	.009
Setting of residence			
Metropolitan vs non-metropolitan	0.68	0.43–1.09	.106
Treatment facility type			
Academic vs non-academic	0.58	0.41–0.81	.002
Tumor size, cm			
<1 vs 1–2	0.24	0.17–0.35	<.001
Tumor grade			
Low vs intermediate/high	0.21	0.14–0.29	<.001

Abbreviation: AOR, adjusted odds ratio.

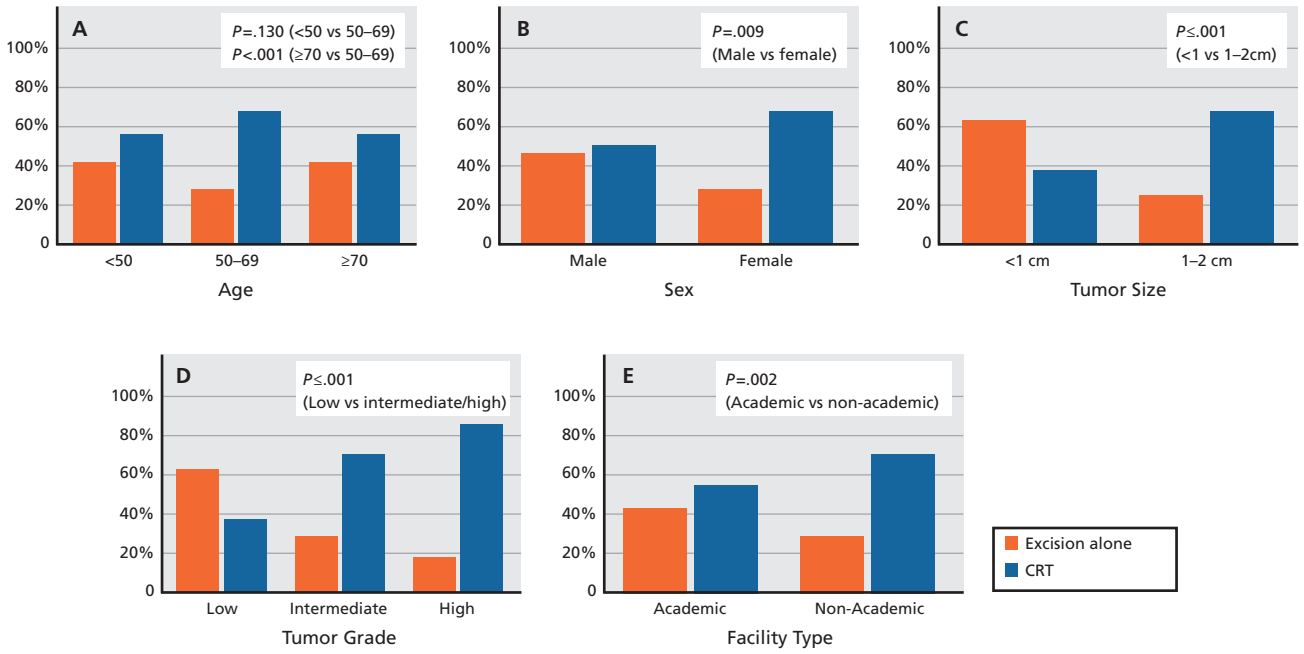

Figure 3. Rates of CRT and excision alone by (A) age, (B) sex, (C) tumor size, (D) tumor grade, and (E) treatment facility type.
Abbreviation: CRT, chemoradiotherapy.

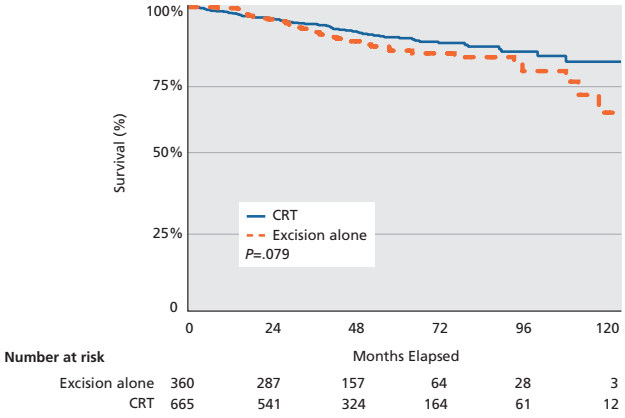

Figure 4. Overall survival for CRT and excision-alone treatment groups. Abbreviation: CRT, chemoradiotherapy.

in 92% (12 of 13). Others have observed higher rates of local failure, up to 40%, when excluding patients with microinvasive/in situ disease.[11,12]

Similarly, only small retrospective series have demonstrated acceptable local control with RT alone in small, node-negative anal tumors.[13,14,22–26] For example, Ortholan et al[14] reported a series of 66 patients with Tis or T1 anal canal cancer treated with RT alone, resulting in local control rates of 91%. Among 26 patients with T1 disease described by Deniaud-Alexandre et al,[13] RT alone resulted in local tumor control with sphincter conservation in 81%. Although RT alone is arguably the most widely accepted treatment as a potential alternative to CRT, we observed that only 4.8% of patients in our cohort received RT alone.

In this national study of patients with stage I anal canal cancer treated from 2004 to 2012, only 61% of patients appeared to receive NCCN Guideline–concordant CRT therapy. One reason why such a large proportion of patients receive NCCN Guideline–discordant care may be that less aggressive therapies are being delivered to patients with lower risk of disease recurrence. Indeed, the strongest predictors of NCCN Guideline–discordant care in our study were small tumor size and low grade, both of which have been associated with superior prognosis.[19–21] However, factors independent of prognosis also appear to be involved in treatment selection. For example, men appear to be more likely to undergo excision alone despite the poorer prognosis observed with male sex.[19,27]

Although we did not find an OS difference in patients receiving excision alone versus CRT, our data do not support changes to the management of stage I anal cancer. Importantly, local recurrence rates and salvage therapy use are not specified within the NCDB and remain unknown between these treatment groups. Especially in the setting of stage I anal canal cancer, for which survival is expected to be excellent, maintaining high rates of sphincter preservation and colostomy-free survival is a critical goal. Thus, before excision alone can be safely adopted into clinical practice, rates of local control and sphincter preservation should be prospectively tested and compared directly with CRT in a randomized trial or against historical controls.

Our study has several additional limitations. First, whether unmeasured factors may have affected treatment modality selection by the treating physician is unclear. For example, we lacked reliable data on several known prognostic factors for anal cancer, such as performance status and HPV status.[28,29] Second, it is important to note that the NCDB is not a population-based dataset; thus, bias with regard to patient inclusion in the NCDB could have an impact on our observations of NCCN Guideline–discordant care rates. For example, it is possible that patients receiving excision alone could be overrepresented if they were more likely to receive care at an NCDB-participating CoC member institution. Third, a small proportion of patients with missing data were excluded from Cox regression models. If these patients were more likely to receive a specific therapy, our exclusion may have introduced an unrecognized bias. Fourth, we were unable to control for underascertainment of data and errors in data reporting, which have been previously demonstrated in SEER registry data for breast and prostate cancers.[30–32] If analogous underascertainment occurred within our NCDB dataset, the proportion of patients undergoing excision alone could be overestimated.

Conclusions

Significant treatment variability exists nationally among patients with stage I anal canal cancer based on age, sex, treatment facility type, and tumor size and grade. Although most patients

(≈60%) receive definitive CRT, as recommended by NCCN, a significant proportion of patients receive nonstandard therapies, most commonly excision alone. Modern prospective studies that define the optimal management of stage I anal canal cancer are urgently needed to assess whether commonly used treatments not supported by national guidelines are safe and effective. Importantly, data on local control, colostomy-free survival, and quality of life are essential for understanding whether patients can safely receive nonstandard care with acceptable outcomes.

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