Impact of Surgical Resection on Survival Outcomes After Chemoradiotherapy in Anal Adenocarcinoma

Richard Li, MD^a; Ashwin Shinde, MD^a; Marwan Fakih, MD^b; Stephen Sentovich, MD, MBA^c; Kurt Melstrom, MD^c; Rebecca Nelson, PhD^d; Scott Glaser, MD^a; Yi-Jen Chen, MD, PhD^a; Karyn Goodman, MD^e; and Arya Amini, MD^a

ABSTRACT

Background: Anal adenocarcinoma is a rare malignancy with a poor prognosis, and no randomized data are available to guide management. Prior retrospective analyses offer differing conclusions on the benefit of surgical resection after chemoradiotherapy (CRT) in these patients. We used the National Cancer Database (NCDB) to analyze survival outcomes in patients undergoing CRT with and without subsequent surgical resection. **Methods:** Patients with adenocarcinoma of the anus diagnosed in 2004 through 2015 were identified using the NCDB. Patients with metastatic disease and survival <90 days were excluded. We analyzed patients receiving CRT and stratified by receipt of surgical resection. Logistic regression was used to evaluate predictors of use of surgery and to form a propensity score–matched cohort. Overall survival (OS) was compared between treatment strategies using Cox proportional hazards regression. **Results:** We identified 1,747 patients with anal adenocarcinoma receiving CRT, of whom 1,005 (58%) received surgery. Predictors of increased receipt of surgery included age <65 years, private insurance, overlapping involvement of the anus and rectum, N0 disease, and external-beam radiation dose $\geq 4,000$ cGy. With a median follow-up of 3.5 years, 5-year OS was 61.1% in patients receiving CRT plus surgery compared with 39.8% in patients receiving CRT alone (log-rank $P < .001$). In multivariate analysis, surgery was associated with significantly improved OS (hazard ratio, -0.59 ; 95% CI, 0.50 – 0.68 ; $P < .001$). This survival benefit persisted in a propensity score–matched cohort (log-rank $P < .001$). **Conclusions:** In the largest series of anal adenocarcinoma cases to date, treatment with CRT followed by surgery was associated with a significant survival benefit compared with CRT alone in propensity score–matching analysis. Our findings support national guideline recommendations of neoadjuvant CRT followed by resection for patients with anal adenocarcinoma.

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Background

Anal cancer is a rare malignancy, representing approximately 2% of all gastrointestinal malignancies.¹ Most cancers in this region are squamous cell carcinomas of the anus (SCCA); adenocarcinoma is a rare histology that represents 5% to 19% of anal canal cancers.^{2,3} The WHO classifies anal adenocarcinomas into subtypes of colorectal-type adenocarcinoma, anal gland adenocarcinoma, and fistula-associated adenocarcinoma.^{4,5} Prior analyses have indicated that adenocarcinoma of the anal canal is associated with substantially worse prognosis than more common histologies, such as SCCA or adenocarcinoma of the rectum.^{6,7}

Optimal treatment of anal adenocarcinoma is controversial due to a lack of data to guide management. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend that anal adenocarcinoma be managed with the rectal cancer paradigm, using neoadjuvant therapy followed by transabdominal resection for locally advanced disease.⁸ This differs from the guidelines for treatment of SCCA, which recommend definitive chemoradiotherapy (CRT) as first-line treatment; ESMO guidelines provide no specific recommendations regarding anal adenocarcinoma.⁹

There is a scarcity of data to guide management recommendations. No randomized trials exist, and the results of small retrospective case series have led to contradictory conclusions. A study by the Rare Cancer Network showed improved survival with CRT alone compared with surgery/radiotherapy (RT) or surgery alone; its recommendation was to reserve definitive surgery with abdominoperineal resection (APR) for salvage treatment.¹⁰ However, Papagikos et al¹¹ found that patients with anal adenocarcinoma treated with RT had high rates of both local and distant failure compared with those with SCCA, and they recommended preoperative CRT followed by APR to maximize disease control.

Thus, the role of surgery after CRT for locally advanced anal adenocarcinoma has not been fully defined. Given the limited data addressing management of this

^aDepartment of Radiation Oncology, ^bDepartment of Medical Oncology, ^cDepartment of Surgical Oncology, and ^dDepartment of Information Sciences, City of Hope National Medical Center, Duarte, California; and ^eDepartment of Radiation Oncology, University of Colorado, Denver, Colorado.

rare malignancy, we used the National Cancer Database (NCDB) to assess survival outcomes according to stage and treatment strategy in patients with anal adenocarcinoma. We focused our investigation on a comparison of survival outcomes between patients receiving definitive CRT and those receiving CRT followed by surgery.

Methods

The NCDB includes patient data from >1,500 accredited facilities and captures >70% of newly diagnosed cancer cases in the United States.¹² The data used in this study are derived from a deidentified NCDB file.

Patient Cohort Definition

A total of 59,543 patients diagnosed with anal cancer in 2004 through 2015 were identified in the NCDB. Patients were excluded if they had histology other than adenocarcinoma, had metastatic disease or unknown metastatic status at presentation, did not receive any treatment, or had missing information regarding treatment sequence or receipt of surgery, chemotherapy, or RT. Conditional landmark analysis was used, and patients who died or were lost to follow-up within 90 days were excluded. These criteria are summarized in Figure 1.

Descriptive statistics and analysis of national patterns of care were generated using the full cohort of 3,729 patients. We then performed a survival analysis focused on a smaller cohort of 1,747 patients with locally advanced disease (T2–T4 or node-positive) receiving CRT or CRT followed by surgery. For this analysis, the primary endpoint was overall survival (OS).

Variable Definitions

All variables were selected a priori. Sociodemographic variables, including age, year of diagnosis, race, insurance status, facility type, and facility location, were defined according to their respective data fields in the NCDB data dictionary.¹³ Race was categorized as non-Hispanic white, Hispanic white, black, or other (including Hispanic, Asian, and other); insurance status was grouped into government (Medicare/Medicaid/other), private, or uninsured; and facility locations were grouped into Northeast, South, Midwest, and West regions.

The T and N stages were defined by the clinical T and N stage fields, respectively. The AJCC stage was recorded based on the corresponding field; when missing, the stage group was classified based on clinical T and N staging. Histology of adenocarcinoma was defined using ICD-O-3 codes, including codes 8140–8145, 8200–8220, 8255–8263, 8320–8384, 8400–8490, and 8550–8574.¹⁴ For treatment variables, receipt of surgery, type of surgery performed, and chemotherapy and RT were defined by

Figure 1. Exclusion criteria and case selection for the patient cohort. Abbreviations: CRT, chemoradiotherapy; NCDB, National Cancer Database.

their respective fields in the data dictionary. Concurrent CRT was defined as initiation of chemotherapy and RT within a 14-day interval. Receipt of surgery was defined according to the corresponding codes in the data dictionary, with codes 20–27 representing local excision and codes 60–63 representing APR.

Statistical Analysis

Descriptive statistics were calculated for each of the demographic, pathologic, and treatment variables. OS was plotted using the Kaplan-Meier method, with differences across groups assessed using the log-rank statistic. Survival time was calculated from the date of diagnosis until the date of death or last contact if alive. Patients alive at the end of follow-up were censored at the last contact date. To handle missing data, the corresponding value was coded as “unknown” for all analyses, and a complete case analysis was performed.

Table 1. Baseline Patient Characteristics

Characteristic	Patients n (%)
Total, N	3,729
Sociodemographic factors	
Year of diagnosis	
2004–2006	913 (24.5)
2007–2009	976 (26.2)
2010–2012	893 (23.9)
2013–2015	947 (25.4)
Age, y	
<65	1,674 (44.9)
≥65	2,055 (55.1)
Race	
Non-Hispanic white	2,930 (78.6)
Hispanic white	472 (12.7)
Black	172 (4.6)
Other	124 (3.3)
Unknown	31 (0.8)
Insurance status	
Government	2,145 (57.5)
Private	1,362 (36.5)
Uninsured	147 (3.9)
Unknown	75 (2.0)
Facility type	
Academic/Research	1,632 (43.8)
Community/Comprehensive community	1,993 (53.4)
Unknown	104 (2.8)
Facility location	
Midwest	929 (24.9)
Northeast	819 (22.0)
South	1,360 (36.5)
West	517 (13.9)
Unknown	104 (2.8)

(continued)

Abbreviation: CRT, chemoradiotherapy.

Survival analyses were performed using the log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis to estimate hazard ratios (HRs). The final parsimonious multivariate Cox model was formed by using hierarchical backward selection of variables significant at $P < .10$. After hierarchical backward selection, variables included were age, comorbidity score, insurance status, facility type, T stage, N stage, and receipt of surgery. Patients with missing follow-up information were excluded from all survival analyses. The proportional hazards assumption was assessed for

Table 1. Baseline Patient Characteristics (cont.)

Characteristic	Patients n (%)
Clinical/Pathologic factors	
Primary site	
Anus or anal canal	2,163 (58.0)
Overlapping lesion of anus, anal canal, or rectum	1,566 (42.0)
Charlson-Deyo comorbidity score	
0	2,948 (79.1)
1	584 (15.7)
≥2	197 (5.3)
Clinical T stage	
T1	715 (19.2)
T2	873 (23.4)
T3	686 (18.4)
T4	242 (6.5)
Unknown	1,213 (32.5)
Clinical N stage	
N0	2,117 (56.8)
N1	388 (10.4)
N2	222 (6.0)
N3	94 (2.5)
Unknown	908 (24.3)
AJCC stage	
I	739 (19.8)
II	1,003 (26.9)
III	835 (22.4)
Unknown	1,152 (30.9)
Treatment factors	
Surgery	
Local excision	1,319 (35.4)
Abdominoperineal resection	1,671 (44.8)
None	739 (19.8)
Treatment modality sequence	
CRT	742 (19.9)
Surgery alone	1,253 (33.6)
Upfront surgery with adjuvant treatment	729 (19.5)
Neoadjuvant CRT, then surgery	1,005 (27.0)

Abbreviation: CRT, chemoradiotherapy.

all variables in the final multivariate analysis and was not violated.¹⁵

Multivariate logistic regression was performed to assess factors predictive of receiving surgery. This was also used to generate propensity scores, with all factors included in propensity score generation, regardless of statistical significance. We specified a subset analysis a priori to compare HR by AJCC overall stage and by primary site code.

Table 2. Comparative Use of Surgery in Patients Receiving CRT

Characteristic	CRT Alone n (%)	CRT + Surgery n (%)	Odds Ratio (95% CI)	P Value ^a
Total	742	1,005		
Sociodemographic factors				
Year of diagnosis				
2004–2006	170 (43.6)	220 (56.4)	Ref	
2007–2009	174 (40.7)	254 (59.3)	1.16 (0.86–1.56)	.346
2010–2012	170 (38.3)	274 (61.7)	1.36 (1.00–1.86)	.050
2013–2015	228 (47.0)	257 (53.0)	0.94 (0.69–1.27)	.676
Age, y				
<65	316 (35.2)	582 (64.8)	Ref	
≥65	426 (50.2)	423 (49.8)	0.69 (0.52–0.90)	.007
Race				
Non-Hispanic white	565 (41.6)	792 (58.4)	Ref	
Black	115 (48.5)	122 (51.5)	0.75 (0.55–1.02)	.063
Hispanic	36 (43.4)	47 (56.6)	0.81 (0.50–1.32)	.403
Other	22 (38.6)	35 (61.4)	1.04 (0.58–1.86)	.899
Unknown	4 (30.8)	9 (69.2)	0.94 (0.27–3.28)	.923
Insurance status				
Government	460 (49.1)	476 (50.9)	Ref	
Private	213 (32.0)	452 (68.0)	1.57 (1.19–2.08)	.002
Uninsured	46 (43.8)	59 (56.2)	0.89 (0.55–1.44)	.644
Unknown	23 (56.1)	18 (43.9)	0.43 (0.21–0.89)	.022
Facility type				
Academic/Research	306 (43.5)	471 (59.5)	Ref	
Community/Comprehensive community	326 (48.6)	496 (55.2)	0.82 (0.66–1.02)	.091
Unknown	146 (42.4)	38 (66.7)		
Facility location				
Midwest	188 (43.6)	243 (56.4)	Ref	
Northeast	154 (41.3)	219 (58.7)	1.05 (0.77–1.42)	.758
South	289 (44.5)	360 (55.5)	0.89 (0.69–1.17)	.413
West	92 (38.8)	145 (61.2)	0.97 (0.68–1.39)	.876
Unknown	19 (33.3)	38 (66.7)		

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Abbreviation: CRT, chemoradiotherapy.

^aBold indicates statistically significant *P* values.

Propensity score–matched analysis was performed. One-to-one nearest neighbor matching without replacement was performed for patients with complete follow-up to form the final propensity-matched cohort, with caliper width of 0.10. To further support the assumption of balance between groups, the propensity score was stratified into quintiles and a standardized difference between the treatment groups of <0.10 was validated. Cox proportional hazards regression was performed for survival analysis in the final matched cohort. All statistical analyses were

performed using SPSS Statistics, version 23 (IBM Corp.).

Results

Patient Cohort Characteristics

A total of 3,729 patients with a median follow-up of 41.1 months who met the inclusion criteria were identified in the NCDB (Figure 1). The demographic, pathologic, and treatment characteristics of the cohort receiving any treatment for anal adenocarcinoma are summarized in

Table 2. Comparative Use of Surgery in Patients Receiving CRT (cont.)

Characteristic	CRT Alone n (%)	CRT + Surgery n (%)	Odds Ratio (95% CI)	P Value ^a
Clinical/Pathologic factors				
Primary site				
Anus or anal canal	497 (51.7)	464 (48.3)	Ref	
Overlapping lesion of anus, anal canal, or rectum	245 (31.2)	541 (68.8)	2.25 (1.82–2.78)	<.001
Charlson-Deyo comorbidity score				
0	601 (42.3)	821 (57.7)	Ref	
1	103 (42.0)	142 (58.0)	1.13 (0.84–1.53)	.410
≥2	38 (47.5)	42 (52.5)	1.04 (0.64–1.69)	.887
Clinical T stage				
T1	65 (49.6)	66 (50.4)	Ref	
T2	242 (49.0)	252 (51.0)	0.99 (0.66–1.49)	.956
T3	197 (36.8)	338 (63.2)	1.37 (0.90–2.07)	.141
T4	86 (43.2)	113 (56.8)	1.07 (0.66–1.72)	.795
Unknown	152 (39.2)	236 (60.8)	1.06 (0.66–1.70)	.811
Clinical N stage				
N0	386 (42.8)	515 (57.2)	Ref	
N1	103 (34.7)	194 (65.3)	1.21 (0.90–1.62)	.203
N2	96 (57.1)	72 (42.9)	0.55 (0.38–0.78)	.001
N3	52 (62.7)	31 (37.3)	0.38 (0.23–0.62)	<.001
Unknown	105 (35.2)	193 (64.8)	1.33 (0.91–1.93)	.140
Treatment factors				
External-beam radiation dose, cGy				
<4,000	62 (61.4)	39 (38.6)	Ref	
≥4,000	601 (43.9)	769 (56.1)	2.03 (1.31–3.15)	.002
Unknown	79 (28.6)	197 (71.4)	3.93 (2.36–6.55)	<.001

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^aBold indicates statistically significant P values.

Table 1. Notably, 817 patients (21.9%) received local excision alone, 436 (11.7%) received APR alone, 742 (19.9%) received CRT, and 1,005 (27.0%) received neoadjuvant CRT followed by surgery.

Stratified by primary site, 2,163 patients (58.0%) had adenocarcinoma confined to the anal canal and 1,566 (42.0%) had overlapping lesions involving the rectum. No difference in survival was seen between these groups in either univariate or multivariate survival analysis (HR, 1.09; 95% CI, 0.96–1.24; $P=.185$). As a reference, we separately compared our study cohort with an NCCDB cohort of patients with stages I–III rectal adenocarcinoma (with no anal involvement), which had a significantly better prognosis (HR, 0.79; 95% CI, 0.72–0.87; $P<.001$).

Analyzing Predictors of Use for Surgery After CRT

We analyzed 1,747 patients receiving CRT. Of these, 742 patients (42%) received CRT alone and 1,005 (58%)

received CRT plus surgery (APR). The median radiation dose was 5,040 cGy (interquartile range [IQR], 4,500–5,580 cGy) in patients receiving CRT alone and 5,040 cGy (IQR, 4,800–5,400 cGy) in those receiving CRT plus surgery. In patients who received surgery, the median time between completion of RT and definitive surgery was 56 days (IQR, 44–74 days).

Table 2 illustrates the distribution of factors between patients who received CRT plus surgery and those who received CRT alone. We identified several factors predictive of use of surgery, including private insurance (odds ratio [OR], 1.57; 95% CI, 1.19–2.08; $P=.002$), overlapping involvement of the anus, anal canal, or rectum (OR, 2.25; 95% CI, 1.82–2.78; $P<.001$), and external-beam radiation dose of ≥4,000 cGy (OR, 2.03; 95% CI, 1.31–3.15; $P=.002$). Factors that predicted decreased use included age ≥65 years (OR, 0.69; 95% CI, 0.52–0.90; $P=.007$), and N2 disease (OR, 0.55; 95% CI, 0.38–0.78; $P=.001$) or N3 disease (OR, 0.38; 95% CI, 0.23–0.62; $P<.001$) compared with N0.

Assessing Survival Impact of Surgery After CRT

OS was strongly associated with receipt of surgery in univariate Kaplan-Meier analysis. Median survival was 79 months and 5-year OS was 61.1% for patients receiving CRT plus surgery compared with 42 months and 39.8%, respectively, for those receiving CRT alone (log-rank $P<.001$). Kaplan-Meier curves comparing CRT with or without surgery are depicted in Figure 2A.

Table 3 summarizes the results of multivariate survival analysis using Cox proportional hazards regression. Significant predictors of improved OS included age <65 years, Charlson-Deyo comorbidity score of 0, private insurance, lower T and N stages, and receipt of surgery. After adjustment in multivariate analysis, receipt of surgery remained a statistically significant predictor of OS (hazard ratio [HR], 0.59; 95% CI, 0.50–0.68; $P<.001$). To investigate the impact of missing data, a separate sensitivity analysis was performed including only patients with complete stage information ($n=1,399$); surgery remained a significant predictor of OS (HR, 0.57; 95% CI, 0.48–0.68; $P<.001$).

In subset analysis, receipt of surgery was associated with improved OS in subsets of 134 patients with stage I disease (HR, 0.45; 95% CI, 0.22–0.94; $P=.033$), 616 with stage II (HR, 0.55; 95% CI, 0.42–0.73; $P<.001$), and 649 with stage III (HR, 0.53; 95% CI, 0.41–0.69; $P<.001$) (data not shown). Receipt of surgery was associated with improved

OS in both 961 patients with anal involvement alone (HR, 0.70; 95% CI, 0.57–0.85; $P<.001$) and 786 with overlapping rectal/anal involvement (HR, 0.43; 95% CI, 0.34–0.55; $P<.001$).

Propensity Score–Matched Survival Analysis

Propensity score one-to-one matching was performed, adjusting for use of surgery. A total of 1,156 patients with complete follow-up data and meeting caliper width requirements were included in the final matched cohort: 578 receiving surgery and 578 not receiving surgery. Figure 2B shows Kaplan-Meier survival curves in the propensity-matched cohort. After adjustment for surgery use with propensity score matching, receipt of surgery was associated with improved survival by log-rank test ($P<.001$) and univariate Cox regression (HR, 0.58; 95% CI, 0.49–0.68; $P<.001$).

Discussion

To our knowledge, this is the largest published series of anal adenocarcinoma cases to date. Using propensity score–matched survival analyses, we found that surgery was associated with a significant survival benefit in patients who received CRT. Our analysis is supportive of national guidelines recommending neoadjuvant CRT followed by resection for patients with locally advanced anal adenocarcinoma.

Figure 2. Survival analysis of patients treated with CRT alone or CRT plus surgery. (A) Survival without adjustment. (B) Survival with adjustment using propensity score matching for surgery use.

Abbreviation: CRT, chemoradiotherapy.

Table 3. Multivariable Cox Proportional Hazard Models for Overall Survival Without Propensity Score Adjustment

Significant Factors	Hazard Ratio (95% CI)	P Value ^a
Age, y		
<65	Ref	
≥65	1.34 (1.09–1.63)	.004
Insurance status		
Government	Ref	
Private	0.65 (0.53–0.81)	<.001
Uninsured	1.01 (0.72–1.43)	.938
Unknown	0.82 (0.52–1.31)	.406
Facility type		
Academic/Research	Ref	
Community/Comprehensive community	1.36 (1.17–1.58)	<.001
Unknown	1.38 (0.88–2.16)	.155
Charlson-Deyo comorbidity score		
0	Ref	
1	1.26 (1.02–1.54)	.029
≥2	1.69 (1.24–2.29)	<.001
Clinical T stage		
T1	Ref	
T2	1.41 (1.00–1.99)	.047
T3	1.41 (0.99–1.99)	.054
T4	1.91 (1.30–2.80)	.001
Unknown	1.58 (1.08–2.30)	.018
Clinical N stage		
N0	Ref	
N1	1.13 (0.90–1.42)	.284
N2	1.47 (1.14–1.88)	.003
N3	2.55 (1.87–3.49)	<.001
Unknown	1.18 (0.91–1.53)	.212
Surgery		
Did not receive surgery	Ref	
Received surgery	0.59 (0.50–0.68)	<.001

^aBold indicates statistically significant *P* values.

Given the rarity of this disease, prior analyses have been limited to small retrospective series. A series from MD Anderson Cancer Center found poor outcomes, with a 5-year disease-free survival of 19%, in patients treated with CRT alone, and a later report from the same institution showed a survival benefit with the addition of surgical resection.^{11,16} A separate series from Memorial Sloan Kettering Cancer Center examined patients receiving surgery (either APR or local excision) and found a 63% local control rate in 13 patients at a median follow-up of

19 months.¹⁷ Both of these series concluded that CRT followed by APR is a reasonable treatment option. In contrast, Belkacémi et al¹⁰ analyzed 82 patients from the Rare Cancer Network, showing a 5-year OS rate of 58% in patients treated with CRT; they concluded that APR should be reserved for salvage treatment. However, their study did not include patients treated with CRT followed by surgical resection, which is the focus of our present analysis.

Our findings of improved survival with surgery are consistent with prior findings from analysis of the SEER database. Franklin et al⁶ analyzed 462 patients with all stages of anal adenocarcinoma and found that those who underwent surgical resection (vs no surgery or localized excision) had improved survival (HR, 0.71; 95% CI, 0.51–1.00; *P* = .05). However, this analysis was limited because it examined a smaller cohort of 462 patients and included all patients with anal adenocarcinoma, regardless of disease stage or neoadjuvant treatment; in addition, receipt of chemotherapy is typically not available in SEER. Kounalakis et al¹⁸ similarly analyzed patients from SEER and found that APR improved outcomes in nonmetastatic anal adenocarcinoma, although they did not account for sequencing of treatment.

We found a low rate of use of surgery, with only 58% of patients who received CRT subsequently undergoing surgical resection. These limited rates of surgery use are consistent with findings from prior national database analyses.^{3,6} No significant change was observed over time; APR was performed after CRT in 56.4% of patients in 2004 through 2006 versus 53.0% in 2013 through 2015. Notably, the first version of the NCCN Guidelines for Anal Carcinoma to recommend management of anal adenocarcinoma using the rectal cancer paradigm was published in 2004.¹⁹

One key limitation of this study was the coding of primary tumor location. Adenocarcinoma of the anal canal can be a difficult clinical entity to define, and there may be inconsistency in the classification of tumors as originating from this site. However, we attempted to mitigate the impact of coding error with supplementary analyses. In our subset analyses, receipt of surgery was found to be associated with improved OS in both 961 patients coded as having anal involvement alone and 786 coded as overlapping rectal and anal involvement. We also compared our cohort of patients with stages I–III anal adenocarcinoma with a cohort of patients with stages I–III rectal adenocarcinoma from the NCDB, and found that those with anal adenocarcinoma had significantly worse prognosis, suggesting that a distinction does exist. Unfortunately, there is no central histologic review mechanism within the NCDB for more definitive confirmation.

It is important to note some other limitations of our study. All data were collected retrospectively through the

NCDB, and therefore our study is subject to the usual biases of retrospective database studies. In particular, the NCDB does not contain any information regarding treatment intent. Therefore, patients who do not proceed to surgery after CRT due to circumstances, such as development of metastatic disease, are classified as receiving CRT alone even if they were initially intended to undergo surgery. Furthermore, guarantee-time bias could potentially skew our results, although we sought to mitigate this effect through a conditional landmark analysis excluding patients with follow-up of <90 days.

Despite these limitations, our study offers substantial value, given the lack of published data and the impracticality of randomized trials in this rare malignancy. This analysis provides a stronger basis for guidelines to recommend inclusion of surgery in the treatment paradigm for anal adenocarcinoma.

Conclusions

Results of our study showed that CRT followed by surgery was associated with improved survival compared with CRT alone in patients with nonmetastatic adenocarcinoma of

the anal canal. However, only 57% of patients receiving CRT subsequently had surgery. In the absence of prospective studies, our data support the NCCN recommendation of neoadjuvant CRT followed by surgery.

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Correspondence: Arya Amini, MD, Department of Radiation Oncology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010. Email: aamini@coh.org

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.
2. Basik M, Rodriguez-Bigas MA, Penetrante R, et al. Prognosis and recurrence patterns of anal adenocarcinoma. *Am J Surg* 1995;169:233–237.
3. Myerson RJ, Karnell LH, Menck HR. The National Cancer Data Base report on carcinoma of the anus. *Cancer* 1997;80:805–815.
4. Shia J. An update on tumors of the anal canal. *Arch Pathol Lab Med* 2010;134:1601–1611.
5. Hobbs CM, Lowry MA, Owen D, et al. Anal gland carcinoma. *Cancer* 2001;92:2045–2049.
6. Franklin RA, Giri S, Valasareddy P, et al. Comparative survival of patients with anal adenocarcinoma, squamous cell carcinoma of the anus, and rectal adenocarcinoma. *Clin Colorectal Cancer* 2016;15:47–53.
7. Bertelson N, Blumetti J, Cintron J, et al. Anal adenocarcinoma: outcomes in an uncommon malignancy. *Am Surg* 2015;81:1114–1117.
8. Benson AB III, Venook AP, Al-Hawary MM, et al. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 2.2018. To view the most recent version, visit NCCN.org. Accessed July 6, 2018.
9. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol* 2014;40:1165–1176.
10. Belkacémi Y, Berger C, Poortmans P, et al. Management of primary anal canal adenocarcinoma: a large retrospective study from the Rare Cancer Network. *Int J Radiat Oncol Biol Phys* 2003;56:1274–1283.
11. Papagikos M, Crane CH, Skibber J, et al. Chemoradiation for adenocarcinoma of the anus. *Int J Radiat Oncol Biol Phys* 2003;55:669–678.
12. Bilimoria KY, Stewart AK, Winchester DP, et al. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* 2008;15:683–690.
13. American College of Surgeons. National Cancer Database: participant user file data dictionary. Available at: ncdbpuf.facs.org. Accessed November 13, 2017.
14. International Classification of Diseases for Oncology; World Health Organization. International Classification of Diseases for Oncology: ICD-O-3 online. Available at: <http://codes.iarc.fr/>. Accessed November 13, 2017.
15. Bellera CA, MacGrogan G, Debled M, et al. Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer. *BMC Med Res Methodol* 2010;10:20.
16. Chang GJ, Gonzalez RJ, Skibber JM, et al. A twenty-year experience with adenocarcinoma of the anal canal. *Dis Colon Rectum* 2009;52:1375–1380.
17. Beal KP, Wong D, Guillem JG, et al. Primary adenocarcinoma of the anus treated with combined modality therapy. *Dis Colon Rectum* 2003;46:1320–1324.
18. Kounalakis N, Artinyan A, Smith D, et al. Abdominal perineal resection improves survival for nonmetastatic adenocarcinoma of the anal canal. *Ann Surg Oncol* 2009;16:1310–1315.
19. Engstrom PF, Benson AB III, Chen YJ, et al. NCCN Clinical Practice Guidelines in Oncology: Anal Cancer. Version 1.2005. To view the most recent version, visit NCCN.org. Accessed November 17, 2017.