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Local Excision and Chemoradiation for Clinical Node-Negative Anal Adenocarcinoma

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Abstract

Background: Given the lack of consensus in the surgical treatment of anal adenocarcinoma, practice-patterns demonstrate utilization of organ-preserving techniques. The adequacy of local excision compared to abdominoperineal resection (APR) as a surgical approach for stage II disease is unknown. Our study examines the utilization of local excision in the treatment of stage II anal adenocarcinoma, rates of R0 resection, and differences in overall survival compared to APR.

Materials and Methods: Using the National Cancer Database (2004–2016), we retrospectively analyzed patients diagnosed with clinical stage II anal adenocarcinoma who received chemoradiation and surgery. Patient cohorts were assigned based on the surgical procedure they received. Propensity score matching was used to offset selection bias and confounding factors. Treatment approach, pathologic margin status, and overall survival were assessed.

Results: Overall, 359 patients underwent resection of clinical stage II anal adenocarcinoma and received chemoradiation therapy. Of these patients, 87 (24%) underwent local excision, whereas 272 (76%) received an abdominoperineal resection. In a propensity score-matched cohort, patients who underwent local excision were less likely to achieve an R0 resection (40% vs 90%), and more likely to receive adjuvant instead of neoadjuvant chemoradiation. Overall survival was not significantly different between the propensity-matched groups. Surgical approach and pathologic margin status were not independently associated with overall survival.

Conclusions: Among patients with clinical stage II anal adenocarcinoma who received chemotherapy and radiation, complete resection was significantly less likely with local excision

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compared to abdominoperineal resection, however, overall survival was not affected. Prospective studies of neoadjuvant chemoradiation followed by local excision are warranted.

Micro-abstract

There is considerable practice-pattern heterogeneity in the resection of anal adenocarcinoma. Using the National Cancer Database, we analyzed the outcomes of local excision versus abdominoperineal resection for the treatment of clinical stage II anal adenocarcinoma. In propensity score-matched patients who received chemoradiation, complete resection was less likely with local excision compared to abdominoperineal resection, however, overall survival was not affected.

Keywords

Colorectal Cancer; Anal Cancer; Trans-anal Excision; Abdominoperineal Resection; Local control

Introduction

Adenocarcinoma of the anus is a rare but aggressive malignancy.¹ The National Comprehensive Cancer Network (NCCN) guidelines recommend treatment of anal adenocarcinoma according to the paradigm established for rectal adenocarcinoma, despite substantial differences in their staging paradigms. In anal adenocarcinoma, T-stage is determined by tumor diameter (T1: 2cm, T2: 2–5cm, T3: >5cm, T4: invasion of adjacent organs), whereas rectal adenocarcinoma is staged by depth of invasion.² The anatomic proximity of rectal and anal malignancies should not disguise the fact that they may differ significantly in cells of origin (i.e. rectal mucosa versus anal glands) and thereby their tumor biology. Despite such considerations, given the rarity of anal adenocarcinoma, separate treatment guidelines have not been developed. The NCCN panel encourages patient participation in clinical trials, underscoring the lack of data to strongly support any particular treatment strategy.³ As a result, there is considerable practice pattern heterogeneity surrounding anal adenocarcinoma management, particularly in the setting of resectable (stage I-III) disease.^{1, 3–5} Although some experts advocate for definitive surgical treatment in the form of an abdominoperineal resection (APR), others suggest that chemoradiation therapy alone is sufficient, with APR reserved as a salvage measure.⁶ The majority of studies, however, show that neoadjuvant chemoradiation followed by APR offers superior overall survival.^{7–11}

Encouraging outcomes with organ preservation for early-stage disease have led to increasing use of local excision (LE) in the treatment of rectal adenocarcinoma.^{12, 13} This approach may offer treatment-naïve patients with T1 tumors equivalent long-term and oncologic outcomes without the morbidity and potentially decreased quality of life associated with low anterior resection (LAR) or APR.¹⁴ Additionally, clinical trials suggest potential benefits of LE for highly-selected patients with T2 rectal adenocarcinoma following neoadjuvant chemoradiation.^{12, 13} For peri-anal squamous cell carcinoma, anal melanoma, and other less common histologic subtypes of cancer, LE has long been considered first-line surgical therapy, exhibiting equivalent overall survival compared to APR.^{15–17} Furthermore, LE has demonstrated equivalent cause-specific survival compared to definitive chemoradiation,

which is standard of care in small, well-differentiated anal squamous cell carcinomas.¹⁸ Extrapolating from these findings in other anal cancers, LE may be a reasonable treatment approach for localized anal adenocarcinoma, provided that it is able to achieve an acceptable oncologic outcome.

We first sought to characterize patients who underwent chemoradiation and either LE or APR for stage II anal adenocarcinoma. Next, we aimed to examine the adequacy of LE as a surgical approach, as assessed by rate of R0 resection, when compared to APR. Finally, we sought to compare the overall survival of patients who received LE to those who underwent APR.

Materials & Methods

Data Source

The National Cancer Database participant user files (NCDB PUFs) were the source of all data in our study. The NCDB is a nationwide repository of de-identified patient data related to cancer care metrics and outcomes in the United States derived from the submissions of over 1,500 Commission on Cancer (CoC)-accredited programs.¹⁹ The NCDB captures over 70% of new cancer diagnoses in the United States per year. The CoC is a multidisciplinary association maintained by the American College of Surgeons and the American Cancer Society that accredits US hospitals based on various aspects of cancer care. Due to our study's inclusion of only de-identified data, it was exempt from institutional review board review.

Patient Selection—The NCDB was queried for patients from 2004 to 2016 with adenocarcinoma of the anus using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography codes (C210, C211, C212, C218) and morphology codes (8140, 8210, 8215, 8255, 8260, 8261, 8263, 8480, 8481, 8490, 8560). Patient cohort selection is outlined in Figure 1. We isolated those with clinical stage II (cT2N0M0 and cT3N0M0) disease per the American Joint Committee on Cancer (AJCC), 7th Edition clinical staging system who received neoadjuvant or adjuvant chemoradiotherapy and a surgical procedure. LE was defined as local tumor excision with or without local tumor destruction, denoted by Facility Oncology Registry Data Standards site-specific procedure codes 20–27. Patients who received an APR were captured using site-specific procedure codes 60–63. We excluded patients with a prior history of malignancy or insufficient staging information. We collected information on clinicopathologic and treatment characteristics. Patients were divided into cohorts based on receipt of LE or APR.

Statistical Analysis—Descriptive statistics were calculated for clinicopathologic and treatment variables and analyzed by chi-square, Fisher's exact, or Mann-Whitney U test, as appropriate, to determine associations with surgical procedure. We performed greedy nearest-neighbor matching with a caliper width of 0.05 times the standard deviation of the logit of the propensity score using patient age, Charlson-Deyo score, and clinical T stage as covariates. Cox proportional hazards regression was performed using the matched cohort to evaluate the independent association of clinicopathologic variables with overall survival. Additionally, we estimated overall survival using the Kaplan-Meier method and compared

groups using the log-rank test. Statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 25.0 (IBM Corp., Armonk, N.Y., USA).

Results

Of the 5,803 patients with a diagnosis of anal adenocarcinoma, 359 received an operation and chemoradiation for clinical stage II disease (Figure 1). Most of the unmatched cohort (n = 359) underwent an APR (n = 272, 76%), while the remainder underwent LE (n = 87, 24%) (Table 1). Groups were well balanced with respect to patient sex, age, race, and Charlson-Deyo co-morbidity index. Patients who received LE were more likely to have cT2 disease and receive adjuvant chemoradiation (p < 0.05), whereas those who underwent an APR were more likely to have cT3 disease and receive neoadjuvant chemoradiation (p < 0.05). Median pathologic tumor size was correspondingly larger in the APR cohort, whereas other clinicopathologic factors, namely lymphovascular invasion and tumor grade, were similar between patient groups. Patients who underwent local excision were more likely to have positive resection margins than those who underwent APR (p < 0.05).

Propensity matching accounted for pre-matching differences in clinical T stage and pathologic tumor size and maintained pre-matching similarities in other patient and clinicopathologic factors (Table 1). In the propensity score-matched cohort, median overall survival was 85.8 months in the LE group versus 65.3 months in the APR group (Figure 2, p = 0.36).

Univariable and multivariable Cox regression analyses are shown in Table 2. Factors independently associated with decreased overall survival included more advanced T stage (cT3) and poorly differentiated or undifferentiated tumors. Surgical approach, sequence of treatments, and margin status were not associated with overall survival on either univariable or multivariable analysis of the matched cohort. In a sub-group analysis, there was no association between sequence of treatment and margin status in patients who underwent LE (p = 0.096). Of those who received a margin-positive LE, 81.8% received adjuvant chemoradiation and exhibited improved median overall survival (93 months vs. 46.6 months, log rank p = 0.036) compared to patients receiving neoadjuvant chemoradiation.

Discussion

We evaluated the outcomes of LE or APR in addition to chemoradiation in patients with clinical stage II anal adenocarcinoma. Patients who underwent LE were more likely to have cT2 disease, yet they had a lower rate of margin-negative resection. Furthermore, patients who underwent LE were more likely to receive adjuvant CRT. This suggests that efforts were made to spare patients with small (<5cm) anal adenocarcinomas from an APR, with perhaps *post hoc* decision-making regarding CRT. In contrast, patients who underwent APR had more advanced disease, for which they underwent neoadjuvant CRT followed by resection. Despite these treatment differences, we did not observe survival differences associated with either surgical approach or margin status among a propensity score-matched patient cohort. While only 40% of LE patients were able to undergo R0 resection, those who

were unable to achieve complete resection still demonstrated similar overall survival with the receipt of adjuvant chemoradiation. Given the lack of association between sequence of treatment and complete resection with LE, these data argue for extending recent clinical trials of neoadjuvant CRT followed by LE for rectal adenocarcinoma to include patients with anal canal adenocarcinoma and allow for adjuvant CRT.^{12, 20, 21} LE may provide adequate surgical treatment for localized low rectal cancer, sparing patients from APR and its attendant morbidity and quality-of-life impact, namely genitourinary dysfunction and permanent ostomy.²² Similarly, our results suggest that LE may be a reasonable surgical option for patients with appropriately sized, clinically node-negative anal adenocarcinoma.

While current recommendations endorse APR as the surgical procedure of choice for stage II-III anal adenocarcinoma, the data supporting this approach specifically for stage II disease are limited. Prior studies suggest that LE confers unacceptable oncologic outcomes, but these conclusions were drawn from limited, single-institution series that included patients with more advanced locoregional disease.^{8, 9} Perhaps most importantly, since their survival is limited primarily by distant recurrence and progression of metastatic disease, patients in these studies were treated prior to the advent of contemporary chemotherapy regimens. When compared to prior anal adenocarcinoma series, our findings suggest that, in the setting of modern systemic therapy, LE and CRT could spare patients the considerable morbidity of a more radical operation while conferring similar long-term survival, despite a low rate of complete resection.^{8, 9} This is important since OS is dictated by systemic relapse, not local recurrence.⁸ Additionally, APR remains available as a salvage therapy to patients who recur locally following LE for stage II disease. Furthermore, for patients who experience diminished quality of life due to the sequelae of anal chemoradiation therapy such as fecal incontinence, diverting ostomy or APR would be therapeutic options.²³ The decreased morbidity of LE, along with the lack of survival benefits from more aggressive surgical treatment, argues against APR for early stage anal cancer.

Despite our use of a large national database, our study is limited by its small sample size, and thus, may be underpowered to detect an overall survival difference. The retrospective nature of our analysis can be particularly problematic due to missing data, selection bias, and non-standardized follow-up. The rarity of anal adenocarcinoma may preclude the possibility of a randomized controlled trial, but prospective data collection would avoid much of the aforementioned bias. Notably, although it did not appear to impact overall survival, the disparity in R0 resections between groups may be clinically impactful on a larger scale. The NCDB does not track recurrence data or salvage therapy, which would have added value in assessing the adequacy of local control in these patients.

Based on our findings, we suggest that LE can be considered as a surgical option for highly-selected patients with stage II anal adenocarcinoma, particularly those with cT2 tumors, when coupled with chemoradiation. Although APR offers a higher chance of local control, patients often suffer life-limiting distant disease, which should prompt thoughtful patient selection when considering its morbidity. Finally, prospective evaluation of neoadjuvant chemoradiation and LE for localized cT2 anal adenocarcinoma may increase rates of local control using LE to be comparable to those of APR. Quality of life assessments would be important to optimally assess outcomes of this or another approach. In the absence of such

data, however, current practice will rely on expert consensus opinion and data from large cohort studies such as ours.

Clinical Practice Points

Current clinical practice guidelines recommend treatment of anal adenocarcinoma according to the paradigm established for rectal adenocarcinoma, despite substantial differences in their staging paradigms. This is largely due to the rarity of anal adenocarcinoma, and thus, the absence of randomized, controlled trials assessing its management. The rising popularity of organ-preservation treatment strategies has led to the increasing use of local excision in the treatment of early-stage rectal, and correspondingly, anal adenocarcinoma. In the absence of clinical trial data comparing the two, current practice will rely on expert consensus opinion and data from large cohort studies. Our retrospective, propensity score-matched analysis of patients with clinical stage II anal adenocarcinoma did not detect an overall survival difference between those who underwent local excision versus abdominoperineal resection, in addition to chemoradiation. These data suggest that local excision can be considered as a surgical option for highly-selected patients, particularly those who are unable or decline to undergo an abdominoperineal resection. Although the standard of care abdominoperineal resection offers a higher chance of local control, it carries a higher morbidity and patients may suffer life-limiting distant disease. Prospective evaluation of local excision will permit concurrent assessment of abdominoperineal resection as a salvage therapy. However, at this time, ours remains the largest analysis of local excision in anal adenocarcinoma to date.

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Highlights

- There is practice-pattern heterogeneity in the resection of anal adenocarcinoma.
- Organ-preserving treatment strategies are becoming more widely adopted.
- Retrospective analysis of patients with stage II anal adenocarcinoma was performed.
- Survival following local excision was comparable to abdominoperineal resection.
- Complete resection was less likely following local excision.

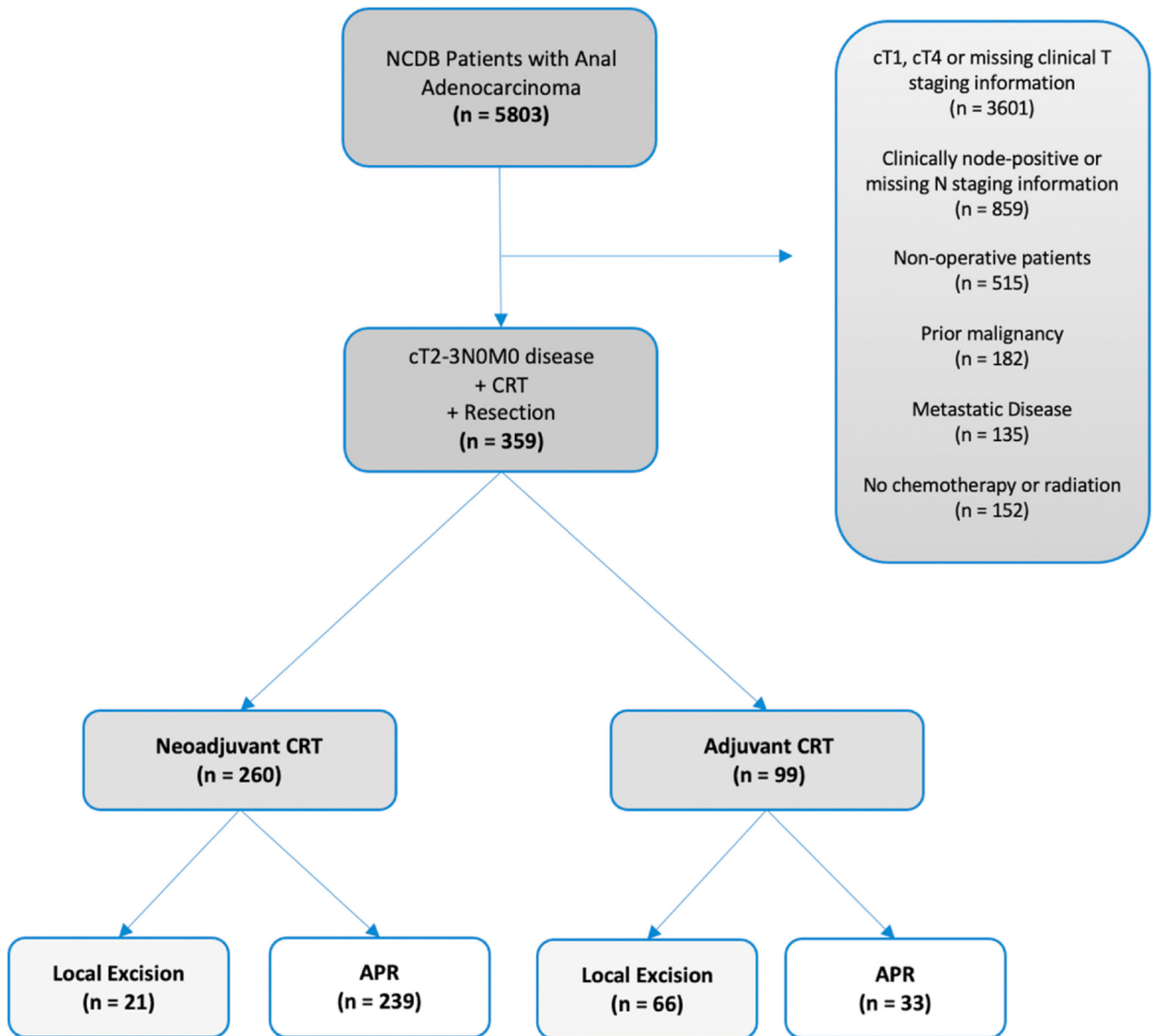


Figure 1. Exclusion criteria and case selection for the patient cohort. Abbreviations: NCDB, National Cancer Database; CRT, Chemoradiation Therapy; APR, Abdominoperineal Resection.

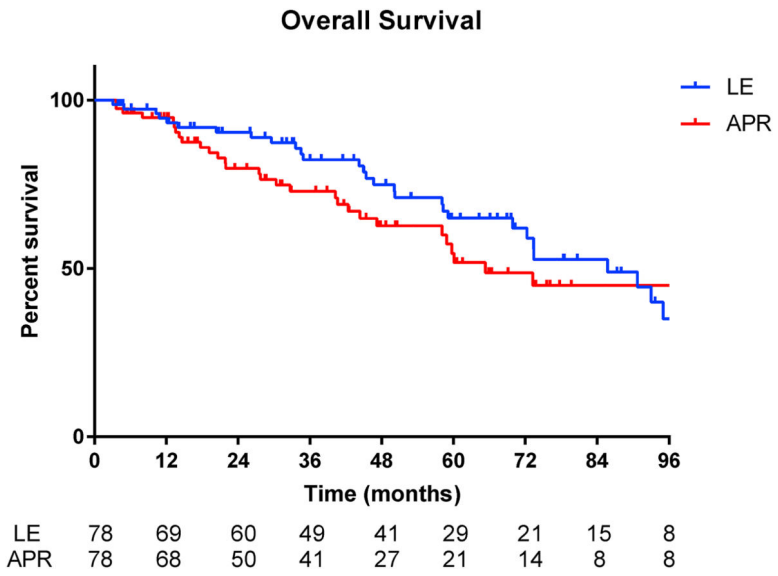


Figure 2. Kaplan-Meier survival curve for propensity score-matched patients with Stage II anal adenocarcinoma (p=0.36)

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Table 1
 Summary of unmatched patients and propensity score-matched patients from the NCDB with stage II anal adenocarcinoma.

	UNMATCHED			MATCHED		
	Local Excision [n = 87]	APR [n = 272]	p-value [ASD]	Local Excision [n = 78]	APR [n = 78]	p-value [ASD]
Sex			0.978			0.623
Female	51 (59%)	159 (59%)		49 (63%)	46 (59%)	
Male	36 (41%)	113(41%)		29 (37%)	32 (41%)	
Age (years)*			0.012			0.685
Median (interquartile range)	65 (20)	62 (16)	[0.32]	64 (18)	63 (19)	[0.09]
Race			0.843			0.757
Caucasian	72 (83%)	219 (81%)		64 (82%)	63 (81%)	
African American	12 (14%)	40 (15%)		11 (14%)	10 (13%)	
Other	3(3%)	13 (4%)		3(4%)	5 (6%)	
CDCC*			0.045			0.335
0	64 (72%)	221 (81%)	[0.09]	60 (77%)	67 (86%)	[0.09]
1	14 (16%)	39 (14%)	[0.02]	11 (14%)	6 (8%)	[0.06]
2	10 (12%)	12 (5%)	[0.07]	7(9%)	5 (6%)	[0.03]
Tumor Location			<0.001			0.019
Anus	31 (36%)	47 (17%)		29 (37%)	18 (23%)	
Anal Canal	29 (33%)	78 (29%)		26 (33%)	20 (26%)	
Overlapping	27 (31%)	147 (54%)		23 (30%)	40 (51%)	
Clinical T Stage*			<0.001			0.572
2	67 (77%)	123 (45%)	[0.32]	58 (74%)	61 (78%)	[0.04]
3	20 (23%)	149 (55%)		20 (26%)	17 (22%)	
Tumor Size (mm)			0.020			0.029
Median (interquartile range)	30 (25)	62 (16)		30 (26)	37.5 (25)	
Grade			0.211			0.484
Well Differentiated	14 (16%)	25 (9%)		11 (14%)	6 (8%)	
Moderately Differentiated	39 (45%)	150 (55%)		36 (46%)	44 (56%)	
Poorly Differentiated	16 (19%)	43 (16%)		14 (8%)	12 (15%)	

	UNMATCHED			MATCHED		
	Local Excision [n = 87]	APR [n = 272]	p-value [ASD]	Local Excision [n = 78]	APR [n = 78]	p-value [ASD]
Unknown	18 (20%)	54 (20%)		17 (22%)	16 (21%)	
Lymphovascular Invasion			0.061			0.195
Absent	25 (29%)	113 (42%)		23 (30%)	32 (41%)	
Present	4 (5%)	17 (6%)		3 (4%)	5 (6%)	
Unknown	22 (66%)	142 (52%)		52 (66%)	41 (53%)	
Margin Status			<0.001			<0.001
R0	35 (40%)	242 (89%)		31 (40%)	70 (90%)	
R1/R2	37 (43%)	23 (9%)		33 (42%)	7 (9%)	
Unknown	15 (17%)	7 (2%)		14 (18%)	1 (1%)	
Chemoradiation			<0.001			<0.001
Neoadjuvant	21 (24%)	239 (88%)		20 (26%)	74 (95%)	
Adjuvant	66 (76%)	33 (12%)		58 (74%)	4 (5%)	

* Variable used for propensity score-matching.
 ASD = Absolute Standardized Difference.

Table 2

Cox regression survival analysis of propensity-matched patients.

	Univariable					Multivariable				
	n	HR	Lower	Upper	Sig	HR	Lower	Upper	Sig	
Age	156	1.03	1.01	1.05	0.017	1.02	1.00	1.04	0.055	
Sex										
Male	95	ref	-	-	-					
Female	61	0.95	0.56	1.62	0.846					
Race										
White	127	ref	-	-	-					
African American	21	1.37	0.69	2.72	0.367					
Other/Unknown	8	0.64	0.16	2.64	0.536					
Surgical Procedure										
Local Excision	78	ref	-	-	-	ref	-	-	-	
APR	78	1.27	0.76	2.13	0.360	1.11	0.54	2.27	0.782	
Charlson-Deyo Score										
0	127	ref	-	-	-	ref	-	-	-	
1	17	1.76	0.88	3.52	0.110	1.81	0.82	3.99	0.139	
2	12	1.79	0.80	4.00	0.157	1.69	0.74	3.91	0.216	
Tumor Location										
Anus	47	ref	-	-	-	ref	-	-	-	
Anal Canal	46	1.63	0.79	3.38	0.187	1.61	0.75	3.46	0.225	
Overlapping sites of Anus/Anal Canal/Rectum	63	1.83	0.95	3.54	0.072	1.83	0.90	3.71	0.096	
Tumor Size	130	1.00	1.00	1.00	0.938					
Clinical T Stage										
cT2	58	ref	-	-	-	ref	-	-	-	
cT3	98	1.93	1.08	3.46	0.027	2.44	1.26	4.75	0.009	
Grade										
Well Differentiated	17	ref	-	-	-	ref	-	-	-	
Moderately Differentiated	80	3.04	0.93	9.99	0.067	2.08	0.61	7.07	0.241	
Poorly/Undifferentiated	26	3.70	1.01	13.52	0.048	3.73	1.01	13.81	0.049	
Unknown	33	3.38	0.98	11.70	0.054	2.54	0.72	8.99	0.150	
Lymphovascular Invasion										
Absent	55	ref	-	-	-					
Present	8	1.31	0.38	4.56	0.673					
Unknown	93	0.55	0.65	2.25	0.546					
Margin Status										
R0	101	ref	-	-	-					
R1/R2	40	1.34	0.76	2.35	0.309					
Unknown	15	0.69	0.21	2.23	0.533					

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	n	Univariable				Multivariable			
		HR	Lower	Upper	Sig	HR	Lower	Upper	Sig
CRT Sequence									
Adjuvant CRT	88	ref	-	-	-	ref	-	-	-
Neoadjuvant CRT	62	1.92	1.09	3.39	0.024	1.63	0.76	3.51	0.210