

Nomogram for Predicting Overall Survival and Salvage Abdominoperineal Resection for Patients with Anal Cancer

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BACKGROUND: Anal cancer treatment has evolved from abdominoperineal resection to chemoradiotherapy, which allows for sphincter preservation.

OBJECTIVE: The aim of this study was to develop an accurate model and nomogram to predict overall survival and the probability of salvage abdominoperineal resection for anal cancer patients.

DESIGN: This is a retrospective cohort study.

SETTINGS: Data were gathered from National Cancer Database entries from 1998 to 2010.

PATIENTS: Patients with de novo anal cancer were selected from the National Cancer Database in the years 1998 through 2010; 1778 patients were included, and their data were analyzed.

MAIN OUTCOME MEASURES: Variables included time to death, censoring indicator, age, race, sex, tumor size, year of diagnosis, surgery status, nodal status, TNM stage, and chemoradiation therapy. A stratified Cox proportional hazards model for overall survival and a logistic regression model for salvage abdominoperineal resection were developed. Our final models were internally validated for discrimination and validation.

RESULTS: Statistically significant variables in the salvage surgery model were tumor size and nodal status ($p \leq 0.001$). For overall survival model, statistically significant variables (all with $p \leq 0.005$), fitted across the strata of TNM clinical stage included age, sex, tumor size, nodal status, chemoradiotherapy treatment, and combination salvage surgery and chemoradiotherapy. Nomograms that predict events are based on our final models.

LIMITATIONS: Limitations included clerical database errors and nonmeasured variables, such as HIV status.

CONCLUSIONS: A nomogram can predict overall survival and salvage surgery for an individual with anal cancer. Such tools may be used as decision support aids to guide therapy and predict whether or not patients may need salvage surgery.

KEYWORDS: Anal cancer; Survival; Nomogram; Combined modality treatment; Abdominoperineal resection; Surgical salvage.

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Anal cancer is an uncommon GI cancer. Its incidence, however, has doubled over the past 30 years,¹ increasing as a public health concern. In 2014, in the United States alone, it was estimated that there would be an estimated 7210 newly diagnosed cases of anal cancer, with an estimated 950 cancer deaths.² Its treatment has evolved from abdominoperineal resection (APR) to combined chemoradiation (CRT), consisting of 5-fluorouracil, mitomycin C, and a radiation dosage of 54 to 59 Gy. Because anal cancers may regress slowly and well after completion of treatment, most physicians evaluate patients for the presence of residual local disease 12 to 26 weeks after the completion of CRT.^{3,4} Surgery (APR) remains the salvage therapy for persistent

and recurrent local disease. In a 235 patient cohort, 5-year cumulative incidence of tumor-related colostomy was 26% (95% CI, 21%–32%).⁵

Physicians and patients have little evidence to rely on in attempting to predict salvage APR and overall survival (OS) rates. Because most recurrences occur within the first 3 years, surveillance is important. Surveillance guidelines, however, vary among surgical and medical oncology societies.^{4,6,7} The specific aim of this study was 2-fold: 1) to construct a nomogram to predict the likelihood of needing salvage APR as a result of failure of chemoradiation treatment and/or recurrence, and 2) to construct an OS prediction model. To this end, we constructed a multiple logistic regression model and a stratified Cox proportional hazards multiple regression model, based on data captured at the National Cancer Database (NCDB).

MATERIALS AND METHODS

Study Population

The NCDB is a nationwide oncology outcomes database for more than 1500 commission-accredited cancer programs in the United States and Puerto Rico. It is the product of a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Begun in 1989, it now contains data on multiple types of cancers that are examined and analyzed. A large percentage of newly diagnosed cases of cancer are captured at the institutional level, and data reported to the NCDB include patient characteristics, cancer staging and tumor characteristics, treatment administered, and outcomes information. For this analysis, we examined data on patients with anal cancer during the years 1998 through 2010. The database included 53,523 patients. After excluding patients with anal margin cancer (*International Classification of Diseases, Ninth Revision* diagnosis codes 8000, 8010, 8070, 8071, 8072, 8076, 8083, 8120, 8124, and 8560 were kept, but all others were excluded), patients with class 00, per NCDB suggestion, and those with missing data points, 1778 patients were included, and their data were analyzed. Variables included time to death, censoring indicator, age, race, sex, tumor size, year of diagnosis, surgery status, nodal status, TNM clinical stage, and CRT. Because our primary goal was to evaluate the probability of treatment failure and/or recurrence, only patients with primary surgery site codes of 60 to 62 were included, because the focus of the study was on patients who underwent salvage APR, not those who received a colostomy for treatment toxicity.

Statistical Analysis

The 2 points of interest in our study were OS and APR salvage rates. Multiple regression analysis was performed

by using a TNM stage-stratified Cox proportional hazards model for the OS, and a logistic regression model for salvage APR. Variables were selected, according to known clinical prognostic factors, and availability in the NCDB, including age, sex, race, year of diagnosis, American Joint Committee on Cancer TNM stage (fifth, sixth, and seventh editions), surgery status (APR), and CRT.²⁰ We have used the data of staging as it is captured and coded in the database.

Age as a continuous variable was fitted to a smooth function per Harrell.⁸ We also trichotomized tumor size, per the American Joint Committee on Cancer guideline (T1: <20 mm; T2: 20–50 mm; T3: >50 mm). To find our final models, we used backward elimination, based on large *p* values from the full model without interaction terms. Once we removed variables with large *p* values (>0.3), we added all 2-way interaction terms. We then removed terms with large *p* values (> 0.1) one at a time. The prediction models were then implemented into a nomogram to enable use on plain paper.

Both OS and salvage APR prediction models were internally validated by measuring both discrimination and calibration. Discrimination was evaluated by using the concordance index (C-index), which is numerically identical to the area under the receiver operating characteristic curve. The C-index computes the proportion of pairs in which the predicted event probability is higher for the subject that experienced the event of interest than that of the subject that did not. The calibration curve displays predicted versus observed outcomes, making it possible to conduct further comparison of accuracy in estimating prognosis.⁸ Both discrimination and calibration were evaluated on the study cohort with the use of 100 bootstrap resamples for each model. All statistical analyses were performed by using an open-source statistical software, “R” (<http://www.r-project.org/>), with optional packages “rms” (regression modeling strategies) and “polspline.”

RESULTS

A total of 1778 patients were analyzed after they met the inclusion criteria. The patient and tumor characteristics are listed in Table 1. Overall, 65% were female, and 86% were white. The mean age of patients who received CRT was 57; the mean age for patients who did not receive CRT was 62, and the mean tumor size for both groups was approximately 45 mm. Two percent had stage 0 disease, 8% had stage 1, 28% had stage 2, 55% had stage 3, and 7% had stage 4. Fifty-three percent had node-positive disease. It was also determined that 26% of patients with stage 0, 67% of patients with stage 1, 72% of patients with stage 2, 89% of patients with stage 3, and 69% of patients with stage 4 disease received CRT.

TABLE 1. Patient and tumor characteristics

Variable	CRT (n = 1428)	No CRT (n = 350)	p
Age, mean	57	62	<0.0001 ^a
Sex, n (%)			
Male	487 (78)	140 (22)	
Female	941 (82)	210 (18)	0.045 ^b
Race, n (%)			
White	1229 (81)	293 (19)	
Black	166 (75)	54 (25)	
American Indian	33 (92)	3 (8)	0.041 ^b
Tumor size, mean	45.4	45.1	0.932 ^a
Clinical node status, n (%)			
Negative	601 (73)	229 (27)	
Positive	827 (87)	121 (13)	<0.0001 ^b
TNM stage, n (%)			
Stage 0	8 (26)	22 (74)	
Stage 1	94 (67)	47 (33)	
Stage 2	363 (72)	138 (28)	
Stage 3	882 (89)	107 (11)	
Stage 4	81 (69)	36 (31)	<0.0001 ^b

CRT = chemoradiation.

^a Welch 2-sample t test.^b χ^2 test.

A total of 1428 patients (80%) received complete CRT. Younger patients with stage 3 disease were more likely to receive treatment. As shown in Table 1, 82% of females and 78% of males received CRT, whereas 81% of white, 75% of black, and 92% of Native Americans received CRT for their disease. Of 1778 patients, 705 died, whereas 1073 were still alive at their last contacts. The 1-year, 2-year, 3-year, and OSs for the entire patient cohort were 86% (95% CI, 0.84–0.87), 72% (95% CI, 0.70–0.75), and 63% (95% CI, 0.60–0.65). The median OS for patients who received CRT was 71.9 months (95% CI, 63.0–97.3), compared with 47.1 months (95% CI, 31.8–71.8) for those who did not complete treatment (log-rank test p value < 0.0001). Statistically significant variables in our stratified Cox model were age, sex, tumor size, nodal disease, CRT, and APR*CRT p < 0.001 (Table 2). For those who did not receive CRT, there was no statistically significant difference in the hazard rate of death regarding whether or not one received salvage APR (95% CI, 0.70–1.36). For those who did receive CRT, there was a statistically significant difference in the hazards rate of death regarding whether or not one received salvage APR (95% CI, 1.58–2.35).

Of those patients who completed CRT (1428 patients), 326 patients (23%) received a salvage APR. Of the 350 patients who did not receive CRT for their disease, 169 patients (48%) received surgical treatment (APR). The reason patients did not receive CRT is not well captured within the database. We found that 14% of patients with stage 0 anal cancer, 38% of patients with stage 1 anal cancer, 67% of patients with stage 2 anal cancer, 41% of patients with stage 3 anal cancer, and 31% of patients with stage 4 anal cancer received APR for treatment of their dis-

TABLE 2. Stratified Cox proportional hazards regression analysis for OS

Variable	Regression coefficient	HR (95% CI)	p
Age	-0.0043	- ^a	0.5487
Age	0.0283	- ^a	0.0035
Sex (female vs male)	-0.3583	0.68 (0.58–0.80)	<0.0001
Tumor size = 2 vs 1	0.4314	1.54 (1.15–2.06)	0.0035
Tumor size = 3 vs 1	0.7066	2.03 (1.49–2.75)	<0.0001
Node positive	0.4775	1.61 (1.32–1.97)	<0.0001
APR vs not when CRT = 0	-0.0259	0.97 (0.70–1.36)	0.8777
APR vs not when CRT = 1	0.6548	1.93 (1.58–2.35)	<0.0001

APR = abdominoperineal resection; CRT = chemoradiation; OS = overall survival.

^aAge was modeled by using a restrictive cubic spline function, which yields an effective hazard ratio that varies continuously with age.

ease without CRT. We also found that fewer patients with node-negative disease completed CRT than those with node-positive disease (73% vs 88% with p < 0.001). Based on our multiple logistic regression model, statistically significant variables for having salvage APR after completion of CRT were size of tumor and nodal disease (p < 0.001) (Table 3).

Nomograms were constructed from the regression coefficients from these models. The first nomogram is of OS at 3 years after diagnosis, shown in Figure 1, whereas the second nomogram is that of salvage APR, shown in Figure 2. To use the nomogram, one first draws a vertical line up to the top points row to assign points for each variable. The total points are then added up, and a vertical line is drawn from the total points row to obtain the OS at 3 years after diagnosis. For the second salvage APR nomogram, one draws the line from total points to obtain the probability of surgery (salvage APR). Model performance was internally validated for discrimination and calibration. Discrimination, as measured by the bootstrap, corrected C-index was 0.66 for the OS and 0.70 for salvage APR. The calibration curves of both models are shown in Figures 3 and 4. In Figure 3, the bias-corrected calibration is relatively close to the original calibration, being only slightly different from the apparent calibration. The estimated mean absolute calibration error is 0.009, and 0.9 quantile of absolute error is only 0.017. In Figure 4, one can see that the bias-corrected calibration is close to both the original calibration and ideal line. The estimated mean absolute calibration error is 0.005, and 0.9 quantile of absolute error is only 0.021.

An example of interpreting the nomogram of OS is described here. A 70-year-old man who received CRT with T size of 35 mm and positive nodal status would receive 70 points from age, 1 from sex, 2 from T size, and 1 from N plus. As a result, he would receive point values of 32.5, 42.5, 47.5, and 52.5. If he did not undergo APR, he would earn none, whereas, if he underwent APR, he would earn an additional 72 points. His total score would be 175 if he did not have APR, and 247 otherwise. His corresponding

TABLE 3. Multiple logistic regression analysis for risk of salvage APR

Variable	OR (95% CI)	Variable	β -Coefficient	p
Tumor size: 1:2	0.67 (0.42–1.09)	Tumor size = 2	0.3935	0.1062
Tumor size: 3:2	1.90 (1.44–2.50)	Tumor size = 3	1.0334	<0.0001
Node positive	0.27 (0.20–0.35)	Node positive	-1.3257	<0.0001

survival probability at 3 years for stage 3 disease would be 28% if he received APR, compared with 52% if he did not.

On average, among those who received CRT, those who did not undergo APR had an approximately 22% higher predicted survival probability than those who underwent APR.

An example of interpreting the nomogram of salvage APR is described here. For a patient with T size of 35 mm and negative nodal status, the estimated probability for surgery is approximately 0.33. We obtain 30 points from tumor size (T size = 2), and 100 points from negative nodal disease to earn a total of 130 points. A point total of 130 predicts a 33% risk of receiving salvage APR. We obtained 32% (95% CI, 13%–52%), using R software.

DISCUSSION

Nomograms are accepted decision-making aids for use in predicting overall and disease-free survival, and have

been used for other systems/organs, including prostate,^{9,10} breast,¹¹ and pancreas.¹² Although nomograms do not replace the value of randomized clinical trials, they can be useful clinical tools to counsel patients about prognosis and therapy. Our goal is to construct a web browser-based nomogram that can be used in the clinical setting for all patients with newly diagnosed anal canal cancer. It is a significantly valuable tool for counseling our patients when we are predicting the success of chemoradiation treatment and overall survival. We currently plan to incorporate our model into an interactive Web tool (<http://skynet.ohsu.edu/nomograms>).

We developed and internally validated OS and salvage APR nomograms for patients with anal cancer. We did not include colostomy construction because of the toxicity of treatment. Although a colostomy construction due to toxicity of treatment can be life altering to the patient, we wanted to study the rate of failure of treatment for a

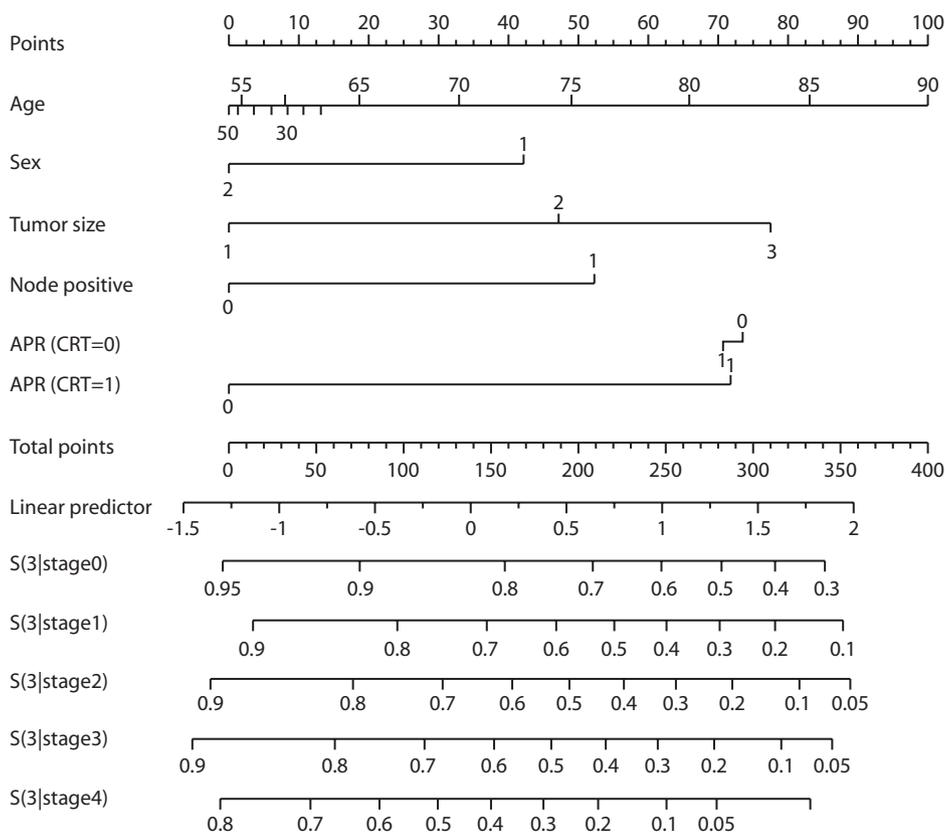


FIGURE 1. Nomogram at 3 years after diagnosis from OS model. (Sex = 1, male; 2, female.) APR = abdominoperineal resection; CRT = chemoradiation; OS = overall survival.

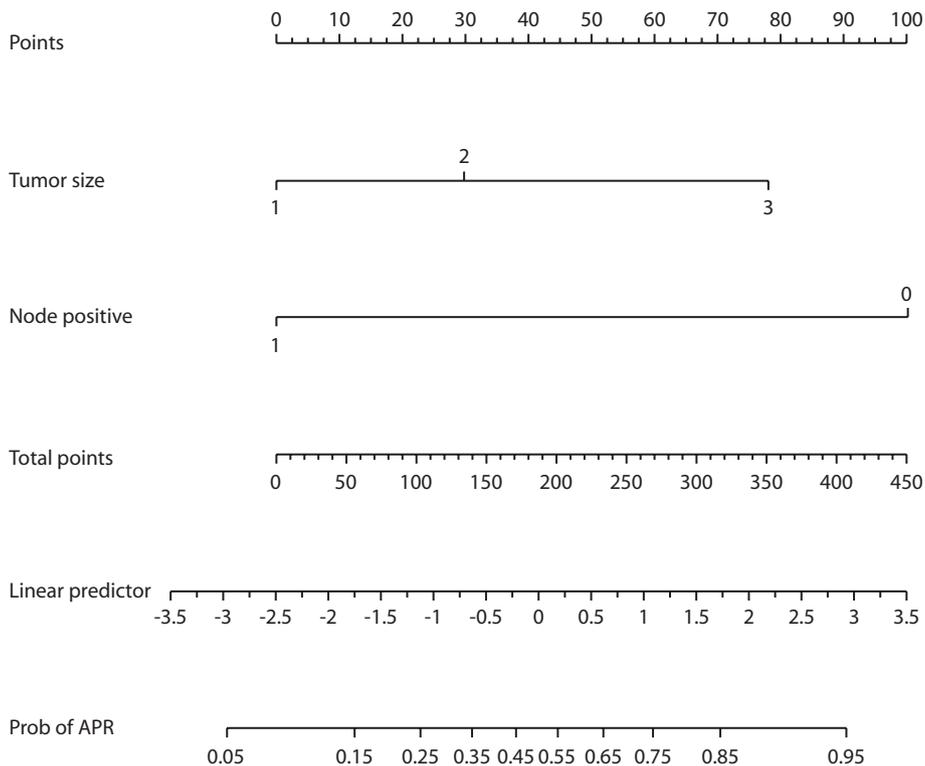


FIGURE 2. Nomogram from salvage APR model. APR = abdominoperineal resection.

better understanding of patient prognosis. We therefore examined the reason for the construction of a colostomy and included only the patients who had persistent/or recurrent disease. Statistically significant variables in the salvage APR model were nodal status and tumor size. The nomogram predicts with a C-index of 0.70 that the probability of salvage APR for a patient with a tumor size of 35 mm and clinically negative nodal status is about 33% after completion of CRT. Specifically, in our study, 23% of patients who completed CRT treatment received salvage APR for persistent or recurrent disease.

Consistent with our findings, in a 235-patient cohort, the 5-year cumulative incidence of colostomy rate was 26%, with size of tumor being the highest risk factor for tumor-related colostomy.¹³ Additionally, in the long-term update of the RTOG98-11 Phase III trial, the 5-year disease-free survival rate was close to 68%, and the multivariate analysis was significant for tumor diameter, treatment, and clinical nodal status.¹⁴ The NCDB database does not capture the type of chemotherapy received, whereas in the RTOG98-11 trial, chemotherapy regimens of 5-fluorouracil/mitomycin vs 5-fluorouracil/cisplatin were compared. We did find a higher proportion of patients with clinically negative nodal status receiving APR for recurrent or persistent disease. We attribute that to the fact that this group of patients in our cohort was more likely to receive APR because they did not complete their CRT treatment. Further, a series of salvage APRs showed

only clinically node-negative patients receiving APR for persistent/recurrent disease.³ The authors suggested that patients with positive nodal disease at diagnosis are more likely to be too advanced when CRT fails, to benefit from surgical salvage. In a different study, the ACT II trial,¹⁵ the

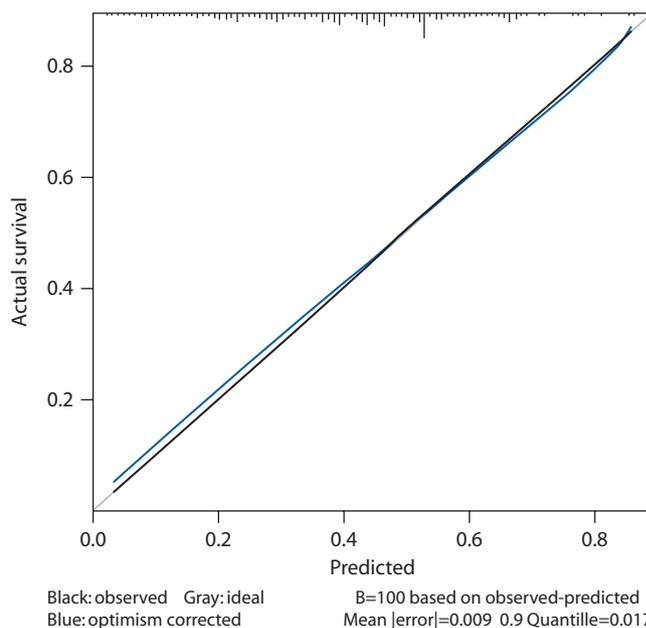


FIGURE 3. Bootstrap validation curve for OS model. Black line = apparent calibration accuracy; blue line = bootstrap estimates corrected for overfitting; gray line = ideal; OS = overall survival.

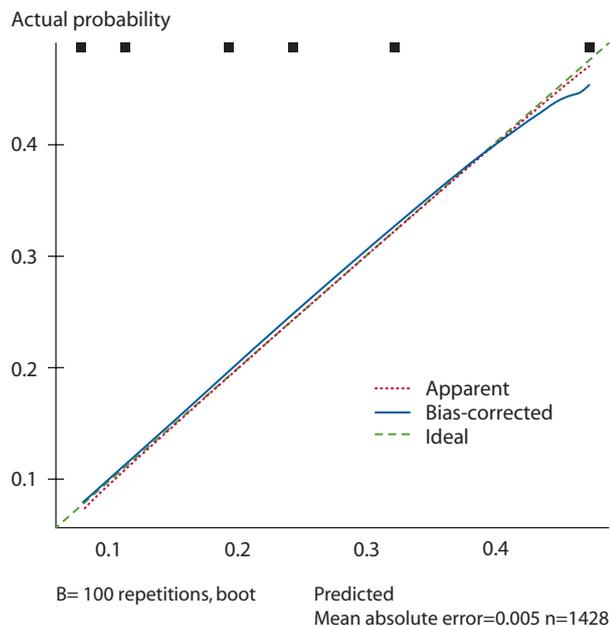


FIGURE 4. Bootstrap validation curve for salvage APR model. APR = abdominoperineal resection; dashed line = ideal; dotted line = apparent calibration accuracy; solid line = bootstrap estimates corrected for overfitting.

authors examined a cohort of 940 patients who completed the CRT treatment, and found that the 5-year rates for tumor and treatment-related colostomies had higher advanced T stages and clinically positive patients. The ACT II trial showed that treatment factors did not have significant impact on colostomy rates; in their study, however, they did include patients with anal margin cancer, and all the patients received and completed CRT, which is not the case in our study.

For our OS model, statistically significant variables fitted across the strata of TNM clinical stage included age, sex, tumor size, nodal status, CRT, and APR*CRT. The nomogram that predicts events is based on our final model; the OS model predicts that after adjusting for other covariates among patients who did not receive APR, patients who have received and completed CRT have a 49% survival advantage over patients who did not receive CRT or complete their treatment. We also found that for the patients who did not receive CRT, there was no statistically significant difference in OS regarding whether or not one received salvage APR (hazard rate of death 95% CI, 0.70–1.36). For those who did receive CRT, there was a statistically significant difference in the OS regarding whether or not one received salvage APR (hazard rate of death 95% CI, 1.58–2.35). For the former, perhaps receiving no CRT meant that a patient's disease status was either too mild or too advanced.

Comparably, in the ACT II trial, poor prognosticators included large tumor diameter, nodal involvement, and male sex.¹⁵ Likewise, in the RTOG 98-11 trial, the

authors demonstrated that in the multivariate analysis, OS was statistically significant for treatment, clinical node status, and sex.¹⁴

Several limitations of our study require consideration. The NCDB is limited in that it is retrospective data and subject to clerical error. HIV status was not reported in the NCDB during the years of this study period. We know that HIV-positive patients are at higher risk for treatment breaks that affect OS. A study with 98 patients with anal carcinomas demonstrated that the HIV-positive patients had poorer tolerance to combined therapy and shorter time to cancer-related death.¹⁶ Even with aggressive antiretroviral therapy, patients with anal cancer and HIV showed impaired tolerance to chemoradiotherapy and lower survival rates.¹⁷ Furthermore, HIV patients with anal cancer after CRT treatment can have prolonged CD 4 suppression that may contribute to a late death while they are in remission.¹⁸ In our study, we did not include grade status because there were many missing points. Further chemotherapy regimens and treatment breaks are not captured in the database.

Grade status has too many unknowns. In addition, to avoid selection bias, we only examined patients who had all data points of interest. Therefore, numerous patients with incomplete data were not included in this analysis. The C-index of our OS model is not as robust as the salvage APR model's index, because we could not include a global comorbidity score to increase the goodness of fit. Future efforts will include testing the performance of our models, using other patient databases to externally validate them. Efforts to establish a multi-institutional clinical data set with more detailed capture of comorbidities could improve the C-index of the OS model as well. Despite the limitations of the database, it has significant strengths. The NCDB is a nationwide oncology outcomes database that collects information on approximately 70% of all new invasive cancer diagnoses in the United States each year, and it is recognized as the largest clinical registry in the world.^{19,20}

CONCLUSION

We present an OS, as well as an APR salvage prediction model of patients with anal cancer who receive CRT treatment. These tools can assist physicians in counseling their patients and further assist patients in understanding the significance of their disease and treatment, as well as the odds of receiving salvage APR/permanent colostomy because of persistent or recurrent disease.

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