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ORIGINAL ARTICLE – COLORECTAL CANCER

Chemoradiotherapy with a Radiation Boost for Anal Cancer Decreases the Risk for Salvage Abdominoperineal Resection: Analysis From the National Cancer Data Base

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ABSTRACT

Background. Chemoradiotherapy (CRT), the primary treatment for anal cancer, achieves complete tumor regression in most patients. Abdominoperineal resection (APR) is reserved for persistent or recurrent disease. An additional boost dose of radiation after CRT often is used to improve the response rate for advanced local disease (T3, 4, and N+). This study examines the need for salvage APR after radiation boost.

Methods. Patients with de novo anal cancer in the National Cancer Data Base from the years 2004–2010 were analyzed. Patients with missing data points or who did not receive standard CRT were excluded. Variables included age, gender, race, primary tumor size, clinical nodal status, TNM stage, radiation boost, and APR. A logistic regression model assessing the relationship between boost radiation and APR was developed.

Results. Of 1,025 patients meeting inclusion criteria, 450 patients received CRT without a radiation boost and 575 patients received CRT with a radiation boost. The two groups were similar in age, gender, race, tumor size, nodal status, and TNM stage (p values all >0.05). Significant multivariate predictors of salvage APR were tumor size, negative nodal status, and boost RT (all $p < 0.05$), whereas gender, age, race, and TNM stage were not significant (all $p > 0.05$). When controlling for age, tumor size, and nodal status, salvage APR is less likely to occur after boost RT (odds ratio 0.63; 95 % confidence interval 0.47, 0.85; $p = 0.003$).

Conclusions. When controlling for age, tumor size, and nodal status, those who received boost radiation for anal cancer were less likely to require salvage APR.

Anal canal cancer is relatively uncommon, with just more than 7,000 estimated cases in the United States in 2013.[1] The incidence of anal cancer, however, has been increasing for years and has more than doubled over the past decade.[1,2] Fortunately, 93 % of patients present with localized or regional disease and are eligible for definitive treatment.[3] Historically, treatment for anal canal cancer consisted of surgical excision with abdominoperineal resection (APR), which commits a patient to a lifetime colostomy. In the 1970s, Nigro and colleagues introduced a combined chemoradiotherapy (CRT) approach, which allows for sphincter preservation.[4,5] Randomized trials performed by the United Kingdom Coordinating Committee on Cancer Research and the European Organization for Research and Treatment of Cancer Radiotherapy established CRT as standard of care with radical salvage APR if nonoperative intervention were to fail.[6,7] The Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group have defined the need for concurrent chemotherapy, including 5-fluorouracil and mitomycin C, in addition to radiation.[8,9]

To enhance tumor control, an additional dose of radiation (radiation boost) is commonly provided to a smaller treatment volume following an initial larger volume of

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radiation. A boost is typically used with more locally advanced tumors (T3, 4, and N+). However, the indications for administering a radiation boost vary widely between institutions and study protocols.[6,10,11]

The direct relationship between administration of a radiation boost and risk of future APR is unknown. Incomplete understanding of the effect of a radiation boost on clinical outcomes has likely contributed to the observed inconsistencies of its indications and use throughout treatment centers. The specific goal of this study was to determine the relationship between boost radiation treatment and future need for salvage APR.

METHODS

All patients with de novo anal cancer from the National Cancer Database (NCDB) from the years 2004 to 2010 were examined. We included all patients with anal canal squamous cell carcinoma. Patients with anal margin cancer or other histologic subtypes were excluded from the analysis. We then eliminated patients who had pertinent missing data points (age, gender, race, primary tumor size, clinical nodal status, TNM staging, treatment modalities, or occurrence of APR). Furthermore, we excluded those who did not receive standard CRT treatment. We chose to examine APR only in patients who had previously received CRT, because in this patient population it represents treatment for pelvic failure.

Variables included age, gender, race, primary tumor size, clinical nodal status, TNM stage, boost radiation, and APR. We assessed which patients received a radiation boost after standard CRT. Patient and tumor characteristics were compared for the two groups (those who underwent boost radiation and those who did not). For continuous variables, comparison of means between the two groups was analyzed using the Welch two-sample t test. Nominal variables were compared between the groups using Pearson's Chi squared test.

Tumor size was assessed as a continuous variable and a dichotomized variable using the median (those $\leq$50 mm and those >50 mm). Age was assessed in linear (age) and nonlinear (restricted cubic spline with 3 knots, age') terms, as described by Harrell.[12] A multivariate logistic regression model was developed to identify predictors of salvage APR. Using a backward elimination procedure, variables that did not have a statistically significant correlation ($p > 0.05$) were not included in the final multivariate model.

We examined relationship of total pelvic dose (range 30–59.4 Gy) to risk of salvage APR using a simple logistic regression model. Of those patients who had a radiation boost dose recorded as 5–20 Gy, the risk of boost dose and its effect on salvage APR was examined using logistic regression with radiation boost dose as a linear (boost dose) and nonlinear term (boost dose'). Rate of use of intensity-modulated radiation therapy (IMRT) as the boost modality compared to use of other modalities in each year was examined. Risk of salvage APR with IMRT boost compared with all other boost modalities were compared.

RESULTS

Of the 1,025 patients meeting inclusion criteria, 450 patients received CRT without a radiation boost and 575 patients received CRT with a radiation boost. The two groups were similar in age ($p = 0.24$), gender ($p = 1.00$), race ($p = 0.06$), tumor size ($p = 0.37$), clinical nodal status ($p = 0.66$), and TNM stage ($p = 0.57$; Table 1).

The overall number of patients who required salvage APR in this study was 247 (24 %). Of these, 117 patients had a radiation boost (20 % of those with a radiation boost) and 130 did not have a radiation boost (29 % of those without a radiation boost; $p < 0.002$). Boost administration was more likely in academic centers than in community facilities (59.3 vs. 48.2 %, $p < 0.002$); of note, the percent of patients with anal cancer receiving salvage APR between the two center types was no different (24.7 vs. 23.7 %, $p = 0.78$).

On initial multivariate analysis, gender ($p = 0.51$), race ($p = 0.48$), TNM stage ($p = 0.28$, 0.7, 0.23, 0.68, 0.07, and 0.17 for stage I, II, III, IIIA, IIIB, and IV respectively), and tumor size as a continuous variable ($p = 0.14$) did not have an effect on salvage APR rate and were eliminated from the final multivariate model. However, when dichotomizing tumor size at 50 mm, it was a statistically significant predictor of salvage APR and permanent colostomy ($p < 0.001$). Age ($p = 0.05$), age' ($p = 0.02$), negative clinical nodal status ($p < 0.001$), and lack of a radiation boost ($p = 0.002$) also were significant predictors of salvage APR.

On the final multivariate logistic regression model, variables included age, tumor size, nodal status, and radiation boost. Age was not a statistically significant predictor of salvage APR (odds ratio (OR) 1.03, 95 % confidence interval (CI) 0.83, 1.28). Tumor size >50 mm (OR 1.88, 95 % CI 1.39, 2.54; $p < 0.001$) was a significant predictor. There was a statistically significant decrease in occurrence of APR in patients with clinically node-positive disease (OR 0.28, 95 % CI 0.21, 0.39; $p < 0.001$). When controlling for age, tumor size, and nodal status, salvage APR is less likely to occur after a radiation boost (OR 0.63 with boost RT, 95 % CI 0.47, 0.85; $p = 0.003$; Table 2).

On a simple logistic regression, there was no significant relationship between total pelvic radiation dose or radiation

TABLE 1 Patient and tumor characteristics comparing the group who received boost radiation to those who did not receive boost radiation

Variable	Boost radiation ($N = 575$)	No boost radiation ($N = 450$)	p value
Age[a]	57 (49, 65)	56 (49, 66)	0.24[c]
Gender[b]			
Male	205 (36 %)	161 (36 %)	
Female	370 (64 %)	289 (64 %)	1.00[d]
Race[b]			
White	504 (88 %)	371 (82 %)	
Black	58 (10 %)	67 (15 %)	
American Indian	13 (2 %)	12 (3 %)	0.06[d]
Tumor size (mm)[b]			
≤50	343 (60 %)	260 (58 %)	
>50	232 (40 %)	190 (42 %)	0.37[d]
Clinical node status			
Negative	249 (43 %)	202 (45 %)	
Positive	326 (57 %)	248 (55 %)	0.66[b]
TNM stage[b]			
Stage 0	2 (<1 %)	3 (<1 %)	
Stage I	34 (6 %)	36 (8 %)	
Stage II	145 (25 %)	116 (26 %)	
Stage III	362 (63 %)	261 (58 %)	
Stage IV	32 (6 %)	34 (8 %)	0.57[d]
T stage			
X	16 (3 %)	11 (2 %)	
0	6 (1 %)	1 (<1 %)	
Is	2 (<1 %)	2 (<1 %)	
1	81 (14 %)	71 (16 %)	
2	238 (41 %)	175 (39 %)	
3	181 (31 %)	143 (32 %)	
4	51 (9 %)	47 (10 %)	0.66[d]
N stage			
X	17 (3 %)	12 (3 %)	
0	196 (34 %)	170 (38 %)	
1	90 (16 %)	60 (13 %)	
2	188 (33 %)	125 (28 %)	
3	83 (14 %)	83 (18 %)	0.84[d]

[a] Data are median and interquartile range

[b] Number and percent

[c] Welch two-sample t test

[d] Chi squared test

boost dose administered and risk for salvage APR ($p = 0.10$ and $p = 0.07$, respectively). Use of IMRT as the modality of boost radiation rose throughout the years examined from 1.2 to 34.2 %. Rate of salvage APR with IMRT boost modality was 13.7 %, whereas rate of salvage APR with non-IMRT boost modality was 21.7 % ($p = 0.10$).

DISCUSSION

In this population-based study using the National Cancer Data Base from the years 2004–2010, we have demonstrated that CRT with a radiation boost has been utilized for 56 % of patients as definitive primary treatment for anal canal cancer. Radiation boost has been administered to patients regardless of their demographics, tumor characteristics, or stage of disease. Older age, larger tumor size, negative clinical nodal status, and lack of boost radiation administrated were all independent risk factors for occurrence of salvage APR. When controlling for age, tumor size, and nodal status, those who received boost radiation were less likely to require APR.

The incidence of anal cancer has been rising steadily in the United States and has more than doubled in less than 15 years.[1,2] As a result of Nigro's work in the 1970s, sphincter salvage is achievable in most patients with definitive chemoradiation treatment. APR is a radical surgical treatment typically reserved for patients who fail CRT.[13] Although CRT is widely considered the standard treatment for this disease, there is broad variability in the radiation administration dose, schedule, and mechanism. This is especially true when it comes to radiation delivery.[6,10,11] Although many institutions report radiation boost delivery for specific tumor and staging characteristics including larger tumors or clinically positive nodal disease, in the National Cancer Database, we found no association between the use of a radiation boost and tumor size, nodal status or overall stage.

Anal cancer survival outcomes have been reported to be worse in men, African Americans, and older patients.[3,14,15] Despite differing survival in these groups, there has not been a known difference in colostomy-free survival.[16] The administration of a radiation boost to patients with different demographics is previously unknown. We have shown in this population-based study that patients who received a radiation boost and those who did not were no different in age, gender, or race.

Despite optimal treatment, approximately 10–15 % of patients fail CRT and another 10–30 % develop tumor recurrence.[17] These two clinical scenarios are the most common indications for salvage APR in a patient with anal canal cancer. This corresponds to 5-year, colostomy-free survival (CFS) rates after CRT of 66–87 %.[2,16,18] These rates may be slightly improved within the context of a clinical trial.[8] In this study, we have shown that the overall rate of APR after CRT was 24 %. When examining only those who received a radiation boost, this rate was lower at 20 % compared with 29 % of those who did not have radiation boost requiring radical surgery.

The role of radiation treatment intensification has been examined in a randomized, phase III study. The European UNICANCER ACCORD03 trial was designed to

TABLE 2 Multivariate logistic regression analysis for risk of salvage abdominoperineal resection

Variable	OR (95 % CI)	*p* value
Age	1.03 (0.83, 1.28)	0.044
Age'		0.020
Tumor size >50 mm	1.88 (1.39, 2.54)	<0.001
Clinically node positive	0.28 (0.21, 0.39)	<0.001
Boost radiation	0.63 (0.47, 0.85)	0.003

Adjusting for age, tumor size, and clinically positive nodal status, there is a statistically significant decreased need for lifetime colostomy when boost radiation was administered

determine 5-year CFS rates following treatment intensification by induction chemotherapy and/or dose escalation of radiation boost. Three weeks following whole pelvic radiotherapy to 45 Gy, the trial randomized patients to receive a "standard-dose" external-beam boost of an additional 15 Gy or "high-dose" external-beam or brachytherapy boost of an additional 20–25 Gy based on tumor response. This study did not demonstrate a benefit for radiation dosage escalation, with no difference in CFS.[19] However, the results of this trial are not directly comparable to our study, as CFS rates included treatment related complications, whereas our analysis only examined salvage APR rates secondary to pelvic failure.

The toxicity of treatment intensification by means of a radiation boost by both acute (diarrhea, dermatitis, anal pain, fatigue) and late effects (strictures, fistulas) are important to consider. A quality of life (QOL) study examining the patient cohort treated under the ACCORD 03 trial did not identify a significant difference in 2-month QOL assessments between the standard-dose and high-dose boost arms.[20] Late effects evolving over the course of months to years were not examined in this study or in our study. Because there is bias in our study and the randomized ACCORD 03 trial, the balance of benefit versus additional toxicity of treatment-intensification by means of a radiation boost can only be addressed in future randomized clinical trials with long-term follow-up.

On multivariate analysis gender, race and TNM stage were not significant predictors of APR. Age also was not a significant predictor of APR. Tumor size did not predict APR when analyzed as a continuous variable; however, when dichotomizing tumor size at 50 mm, it was a statistically significant predictor of requiring salvage APR. This suggests that when there is a large anal tumor burden, patients have a higher risk of persistent disease and/or disease recurrence requiring radical surgical excision. This is consistent with Call et al.,[10] who also found an increased risk of colostomy with increased tumor size, but differs from Grabenbauer et al.,[16] who found that T stage did not play a role in CFS.

Although positive nodal disease is known to correlate with worse survival and has been shown in some studies to correlate with higher rates of colostomy, our study demonstrated an inverse correlation between node positivity and requiring a salvage APR.[9,10,18,21] Our results are consistent with a series of salvage APRs reported by Pocard et al.,[22] in which 0 of the 21 patients in the study had clinically positive nodal disease on presentation or prior to APR. This may suggest that patients with positive nodal disease are not considered candidates for salvage APR due to recurrences and or local treatment failures that are too advanced to be amenable to surgical salvage.

When controlling for age, tumor size, and nodal disease, patients who received a radiation boost had a 37 % decreased odds of requiring an APR with lifetime colostomy compared with those who did not receive a radiation boost. The total pelvic radiation dose and the dose of boost delivered did not correlate with risk for salvage APR on logistic regression model. This suggests that those who received a radiation boost, regardless of the dose, may have better disease control, allowing these patients to avoid APR and its inherent major morbidity and mortality.[13,17] A possible confounding hypothesis could be that administration of boost radiation is a marker for a better treatment facility and better overall care. When examining this as a possibility, there was no difference in percent of patients receiving salvage APR between academic and community treatment centers, suggesting that boost is not a marker of quality of care.

Historically, external-beam radiotherapy for anal cancer has been planned and delivered using either two-dimensional or three-dimensional techniques.[4] However, more conformal pelvic radiotherapy with intensity-modulated radiation therapy (IMRT) is being increasingly used. Anal IMRT has been shown in multiple retrospective studies to have equivalent local control with possibly a decrease in radiation-related morbidity.[23–26] The rate of IMRT use for boost in the United States has dramatically increased over the years examined by almost 30-fold. Although not statistically significant, a trend was observed for a decreased salvage APR rate with an IMRT boost compared with a non-IMRT boost administered. Possible explanations for this trend include the improved dose conformality inherent to IMRT, allowing for increased localized radiation dose to the primary tumor while decreasing surrounding normal tissue toxicity. Additionally, with the rapid adoption of anal IMRT, the trend of decreased salvage APR rates with IMRT boost may be secondary to patients within this more recent time period receiving superior concurrent chemotherapy regimens per RTOG 9811 published in 2008.[8]

There are important limitations to this study. The NCDB is limited in that it is retrospective data and subject to clerical error. Importantly, HIV status is not reported in the

NCDB during the years of this study period. In order to avoid selection bias, we only examined those patients who had all data points of interest. For this reason, there are many patients with incomplete data that were not included in this analysis. Furthermore, we do not know how patients were selected for radiation boost; and for the patients who received a boost, we do not know the volume that was boosted (gross anal canal disease and/or clinically involved nodes). Additionally, the database does not include post-radiation toxicity or chemotherapy regimen used. It is possible that unmeasured confounders associated with the utilization of boost may influence the salvage APR rate.

In conclusion, we have demonstrated on multivariate logistic regression that patients who received a radiation boost have a decreased risk of requiring salvage APR. Because indications for a radiation boost administration are widely varied, this study suggests that the role of a radiation boost for sphincter salvage warrants validation as part of prospective clinical trial.

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