Published in final edited form as:

Cancer. 2016 August 15; 122(16): 2487–2495. doi:10.1002/cncr.30079.

Increased Tumor Response to Neoadjuvant Therapy Among Rectal Cancer Patients Taking Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers

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Abstract

BACKGROUND—Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used antihypertensive medications that have been reported to affect aberrant angiogenesis and the dysregulated inflammatory response. Because of such mechanisms, it was hypothesized that these medications might affect the tumor response to neoadjuvant radiation in patients with rectal cancer.

METHODS—One hundred fifteen patients who were treated with neoadjuvant radiation at the University of Wisconsin (UW) between 1999 and 2012 were identified. Univariate analyses were performed with anonymized patient data. In a second independent data set, 186 patients with rectal cancer who were treated with neoadjuvant radiation at the Queen's Medical Center of the

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Zachary S. Morris: Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, visualization, supervision, and project administration. **Sandeep Saha:** Formal analysis. **William J. Magnuson:** Validation, formal analysis, investigation, data curation, and writing—review and editing. **Brett A. Morris:** Formal analysis, investigation, data curation, writing—review and editing, and visualization. **Jenna F. Borkenhagen:** Investigation and writing—review and editing. **Alisa Ching:** Investigation and data curation. **Gayle Hirose:** Data curation. **Vanesa McMurry:** Writing—original draft. **David M. Francis:** Conceptualization, investigation, data curation, and writing—review and editing. **Paul M. Harari:** Conceptualization, writing—review and editing, and supervision. **Rick Chappell:** Conceptualization, methodology, formal analysis, writing—review and editing, and visualization. **Stuart Tsuji:** Conceptualization, methodology, investigation, resources, data curation, writing—review and editing, and supervision. **Mark A. Ritter:** Conceptualization, methodology, resources, writing—review and editing, visualization, and supervision.

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University of Hawaii (UH) between 1995 and 2010 were identified. These data were independently analyzed as before. Multivariate analyses were performed with aggregate data.

RESULTS—Among patients taking ACEIs/ARBs in the UW data set, a significant 3-fold increase in the rate of pathologic complete response (pCR) to neoadjuvant therapy (52% vs 17%, $P = .001$) was observed. This finding was confirmed in the UH data set, in which a significant 2-fold-increased pCR rate (24% vs 12%, $P = .03$) was observed. Identified patient and treatment characteristics were otherwise balanced between patients taking and not taking ACEIs/ARBs. No significant effect was observed on pCR rates with other medications, including statins, metformin, and aspirin. Multivariate analyses of aggregate data identified ACEI/ARB use as a strong predictor of pCR (odds ratio, 4.02; 95% confidence interval, 2.06–7.82; $P < .001$).

CONCLUSIONS—The incidental use of ACEIs/ARBs among patients with rectal cancer is associated with a significantly increased rate of pCR after neoadjuvant treatment.

Keywords

angiotensin; angiotensin-converting enzyme (ACE) inhibitor; neoadjuvant; radiation; rectal cancer

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are common medications that treat hypertension through inhibition of the renin-angiotensin system. Renin is an enzyme that cleaves angiotensinogen peptide to produce the decapeptide angiotensin I, which in turn is cleaved by angiotensin-converting enzyme (ACE) to produce the octapeptide angiotensin II.¹ Angiotensin II acts on angiotensin receptors to exert vasoconstriction and fluid retention. Multiple additional angiotensin peptides and ACE substrates have been identified, and this suggests the potential for additional and diverse physiologic functions.² In particular, ACE is specifically expressed at high levels in monocytes during the process of differentiation and maturation into macrophages or dendritic cells.^{3,4} In the setting of ischemic heart disease, ACEIs/ARBs confer a survival benefit, and this may be mediated through effects on angiogenic remodeling⁵ and through the modification of proinflammatory cytokine dysregulation and macrophage-mediated responses to lipoproteins.⁶

In the context of malignancy, preclinical pharmacologic and genetic studies suggest that ACEIs/ARBs may also affect tumorigenesis through effects on angiogenesis and immunosurveillance by macrophage and T-cell lineages.⁷ Select retrospective clinical studies support this possibility,^{8,9} whereas other studies have shown no association between ACEI/ARB use and the incidence of cancers.^{10–12} In the setting of an established tumor, retrospective clinical studies suggest that cancer-specific survival may be improved in the setting of pancreatic¹³ and non-small cell lung cancer¹⁴ among those patients taking ACEIs/ARBs. It remains unclear whether this results from a direct effect of ACEIs/ARBs or whether these agents modulate tumor responses to other therapeutics. Additional studies have demonstrated an impact of ACEIs/ARBs on the normal tissue response to radiation therapy and resulting reduced rates of cardiopulmonary, renal, and brain toxicity after local or total body radiation or chemoradiation.^{15–21}

Multiple preclinical studies suggest that agents targeting angiogenesis and/or tumor immune surveillance have the capacity to modulate tumor responses to radiation.^{22,23} However, it has not yet been determined whether ACEIs/ARBs, by affecting angiogenesis or immune tolerance, can affect tumor responses to radiation. Rectal cancer is commonly treated with neoadjuvant radiation therapy and, therefore, enables a direct pathologic assessment of responses to neoadjuvant therapy at the time of surgical resection. We hypothesized that ACEIs/ARBs might be able to modulate tumor responses to neoadjuvant chemoradiation among patients with locally advanced rectal cancer. To test this hypothesis, using 2 independent single-institution databases, we conducted a retrospective clinical review to evaluate the correlation of incidental ACEI/ARB use with pathologic response rates among rectal cancer patients receiving neo-adjuvant radiation.

MATERIALS AND METHODS

Data Collection

With institutional review board approval, we identified the medical records of 261 patients with rectal cancer treated at University of Wisconsin (UW) Hospital and Clinics between January 1, 1999 and July 1, 2012. Of these 261 patients, 115 underwent neoadjuvant radiotherapy or chemoradiotherapy followed by curative-intent surgery. The data collected for these 115 patients included the following: age, sex, date of diagnosis, prior diagnosis of inflammatory bowel disease or diabetes, use of specific medications at the time of the radiation consultation (ACEIs/ARBs, metformin, aspirin, or statins), clinical and pathological staging (American Joint Committee on Cancer, 7th edition), tumor grade at biopsy and surgery, pretreatment hemoglobin and carcinoembryonic antigen (CEA) levels, neoadjuvant radiation and chemotherapy treatment regimen, completion of neoadjuvant treatment, time from radiation to surgery, tumor size in the pathology specimen, surgical margin, number of lymph nodes sampled, number of lymph nodes positive for malignancy, lymphovascular space invasion, adjuvant chemotherapy regimen and number of cycles, acute and chronic toxicities (graded according to Common Terminology Criteria for Adverse Events, version 2.0), pathologic complete response (pCR), local recurrence (LR), distant recurrence, overall survival (OS), vital status, and date of last follow-up. Patients with a pCR were defined as having no evidence of a primary tumor on a posttherapy pathological examination (ypT0).

After the analysis of the UW data set, institutional review board approval was obtained to generate a second database from the medical records of 186 patients with rectal cancer treated with neoadjuvant radiotherapy or chemoradiotherapy followed by curative-intent surgery at the Queen's Medical Center of the University of Hawaii (UH) between 1995 and 2010. Data collected for this database included all the factors in the UW data set except for the adjuvant chemotherapy regimen and acute and late toxicities. The UH data set did incorporate additional data on patient ethnicity, biopsy histology, and the type of surgical procedure.

Statistical Analysis

The UW rectal cancer database was generated to test the hypothesis that ACEIs/ARBs might affect responses to neoadjuvant radiation in rectal cancer patients. Because of the modest size of the database, a decision was made to generate a second database from a distinct patient population to confirm the statistical significance of the association between the use of ACEI/ARB medications and the response to radiation among patients with rectal cancer. The UH database was then generated by investigators from UH.

Statistical analyses of anonymized patient data were conducted with JMP Pro 10 and SAS software (SAS Institute, Cary, NC). The chi-square test was used for a univariate evaluation of nominal variables versus binary outcomes (ACEI/ARB use or pCR), and a Student *t* test was used for a univariate analysis of continuous variables for the same. A 2-tailed Fisher's exact test was used for evaluating associations with acute and late toxicity. Missing data were excluded from analysis. In the UW data set, complete demographic, medication, treatment, survival, recurrence, and toxicity data were available for all patients. Two patients had missing data for clinical staging and pCR, and 4 patients were missing a component of pathology staging. Fifteen patients were missing the biopsy grade. Pretreatment CEA and hemoglobin levels were not available for 47 and 34 patients, respectively. In the UH data set, complete demographic, ACEI/ARB use, pCR, and survival data were available for all patients. Twenty-six patients were missing data for clinical staging, 37 were missing data for the biopsy grade, 34 were missing data for the pathologic stage, 2 were missing data for recurrence, 17 were missing data for chemotherapy, 70 were missing data for pretreatment CEA levels, and 81 were missing data for pretreatment hemoglobin levels. Multivariate logistic regression was used to evaluate correlates of pCR, and Cox proportional hazard models were used to evaluate correlates of time to LR and OS. OS, LR-free survival, and metastasis-free survival curves were estimated with the Kaplan-Meier method, and the log-rank test was used to compare survival in 2 or more groups. For all analyses, a 2-sided *P* value < .05 was considered to be statistically significant.

RESULTS

Enhanced Response to Neoadjuvant Radiation in Rectal Cancer Patients Taking ACEIs/ARBs

Between 1999 and 2012, 115 patients with rectal cancer were treated with neoadjuvant radiation therapy at UW. The median duration of follow-up was 4.1 years. Patient demographics and tumor characteristics are listed in Table 1. Twenty-five of the 115 patients (21.7%) were taking an ACEI/ARB at the time of their radiation oncology consultation. No significant difference was observed in this UW database between the cohort of patients taking an ACEI/ARB and those not taking these medications with respect to age (*P*= .16), sex (*P*= .23), pretreatment hemoglobin (*P*= .95), pretreatment CEA (*P*= .60), clinical stage (*P*=.94), or biopsy grade (*P*=.42; Table 1).

In the UW database, patients taking ACEIs/ARBs experienced a significantly increased rate of pCR to neo-adjuvant therapy in comparison with patients not taking an ACEI/ARB (52% vs 17%, *P*= .001; Fig. 1A). Although the analysis of variance was significant for the

association of pCR with the collective ACEI/ARB medications versus no ACEI/ARB therapy ($P=.0065$), we did not detect a significant difference when we compared pCR rates between patients taking different ACEIs/ARBs. Rates of pCR by medication were as follows: benazepril (2 of 3), candesartan (1 of 1), lisinopril (8 of 17), losartan (1 of 2), monopril (1 of 1), olmesartan (0 of 1), and no ACEI/ARB (15 of 90). All ACEIs in this cohort were of the dicarboxylate group except for monopril (phosphonate group). In contrast to ACEIs/ARBs, no significant difference was observed in the rate of pCR to neoadjuvant radiation among patients in this UW database who were taking statins ($n = 19$; pCR rate, 42% vs 21%; $P = .13$), glitazones ($n = 4$; pCR rate, 75% vs 22%; $P = .056$), aspirin ($n = 24$; pCR rate, 33% vs 22%; $P = .42$), or metformin ($n = 4$; pCR rate, 50% vs 23%; $P = .47$) versus those not taking these respective medications (Supporting Fig. 1 [see online supporting information]).

Treatment patterns and outcomes from the UW data set are listed in Table 2. No significant difference was observed between patients taking an ACEI/ARB and those not taking these medications with respect to the type of neoadjuvant chemotherapy ($P = .11$), the duration of radiation therapy ($P = .84$), the total dose of radiation therapy ($P = .56$), the time from neoadjuvant treatment to surgery ($P = .34$), or the use of adjuvant chemotherapy ($P = .48$; Table 2). Although no difference was observed in the distribution of clinical stages between the 2 groups (Table 1), the cohort taking ACEIs/ARBs exhibited a significant reduction in pathological staging in comparison with the cohort of patients not taking these medications ($P = .024$; Table 2). No significant correlation was seen between the use of ACEI/ARB medications and grade 3/4 acute ($P = .12$) or late toxicities ($P = .69$). In the Kaplan-Meier analyses, the use of ACEIs/ARBs did not significantly affect LR-free survival ($P = .89$), metastasis-free survival ($P = .49$), or OS ($P = .65$; Fig. 1B–D).

Independent Confirmation of the Impact of ACEIs/ARBs on the Response to Radiation in Rectal Cancer

In the UH database, 186 patients with rectal cancer were treated with neoadjuvant radiation therapy between 1995 and 2010. The median duration of follow-up for these patients was 5.3 years. Patient, tumor, and treatment characteristics for the UH database are listed in Table 3. Forty-nine patients (26.3%) in this database were taking an ACEI/ARB at the time of the radiation oncology consultation. No significant differences were observed in this UH data set between patients who were and were not taking ACEIs/ARBs with respect to the distribution of age ($P = .57$), sex ($P = .21$), pretreatment hemoglobin ($P = .95$), pretreatment CEA ($P = .31$), clinical stage ($P = .60$), or biopsy grade ($P = .44$; Table 3).

Similarly to the patients in the UW database, patients in the UH data set who were taking ACEI/ARB medications experienced a significant 2-fold increase in the rate of pCR to neoadjuvant therapy in comparison with those not taking these medications (24% vs 12%, $P = .03$; Fig. 2A). The mean duration of radiotherapy was approximately 38 days for both groups ($P = .84$), and there was no significant difference in either the total dose of radiation therapy ($P = .62$) or the time from radiotherapy completion to surgery ($P = .34$). In the Kaplan-Meier analysis, ACEI/ARB use did not significantly affect LR-free survival ($P = .43$), metastasis-free survival ($P = .13$), or OS ($P = .44$) in the UH database (Fig. 2B–D).

Aggregate Multivariate Analyses

Multivariate analyses were performed with the aggregate UW and UH data. In this combined data set, ACEI/ARB use was a stronger predictor of pCR ($P < .0001$) than the clinical stage ($P = .66$) or biopsy grade (0.20; Table 4). ACEI/ARB use, biopsy grade, and clinical stage did not predict LR-free survival, metastasis-free survival, or OS (Table 4). However, Kaplan-Meier analyses performed with this aggregate data set demonstrated that pCR to neoadjuvant radiotherapy also did not reach a significant level of association with LR-free survival ($P = .059$) or OS ($P = .087$; Supporting Fig. 2 [see online supporting information]), although there was a suggestion of a trend.

DISCUSSION

In 2 independent databases from very distinct rectal cancer patient populations, we report a significant positive correlation between the use of ACEI/ARB medications and pCR rates after neoadjuvant treatment (Figs. 1A and 2A). This effect was robust, and ACEI/ARB use was associated with 3- and 2-fold-enhanced rates of pCR in the UW and UH data sets, respectively. In the multivariate analysis, the use of ACEIs/ARBs more strongly predicted the likelihood of a pCR than the clinical stage or biopsy grade did (Table 4). Although the inclusion criteria for the design of this study specified patients undergoing neo-adjuvant radiation, the frequent use of concurrent chemo-radiation in the UW and UH data sets precluded our ability to determine whether the impact of ACEI/ARB use on pCR rates in this study might be mediated through an effect on tumor responses to radiation, chemotherapy, or both.

Patient and treatment characteristics were well balanced in both the UW database and the UH database between the cohort of patients who were taking ACEIs/ARBs and those not taking these medications. This list of identified covariates includes parameters such as the time to surgery and the pretreatment levels of CEA and hemoglobin, which have previously been identified as predictors of pCR in rectal cancer.^{24–27} In contrast to ACEIs/ARBs, other medications, including aspirin, statins, glitazones, and metformin, did not significantly affect pCR rates among rectal cancer patients, although patients taking these medications experienced nonsignificant trends toward higher pCR rates (Supporting Fig. 1 [see online supporting information]). These data support a potentially specific therapeutic effect for ACEIs/ARBs and argues against a confounding effect, although the impact of untested covariates, including comorbid medical conditions, cannot be excluded.

In these data sets, the use of ACEIs/ARBs did not significantly affect LR-free survival, metastasis-free survival, or OS. Prior studies have consistently identified a positive association between pCR and improved rates of locoregional disease control and OS.^{28–31} However, in these databases from UW and UH, the association of pCR with LR and OS rates did not reach significance. This suggests that our 2 data sets were underpowered with respect to patient numbers and/or the duration of follow-up for the purpose of detecting an association between ACEI/ARB use and LR or OS. Such associations were not considered primary endpoints in the design of this study. However, we do believe that if we had a greater number of patients in our database or additional databases, we would have the power necessary to detect significant changes in LR and OS rates. Indeed, the aggregate data set

combining the UW and UH data suggests a trend of increased OS and LR-free survival in rectal cancer patients with a pCR to neoadjuvant therapy (Supporting Fig. 2 [see online supporting information]).

The mechanism by which ACEI/ARB therapy may lead to improved pCR rates is not well understood. It is biologically plausible that ACEIs/ARBs might affect the response to neoadjuvant therapy among patients with rectal cancer. Prior studies suggest that ACEIs/ARBs may affect vascular remodeling by suppressing vascular endothelial growth factor production and improving defective angiogenesis.^{21–34} In the context of malignancy, multiple preclinical studies indicate that ineffective angiogenesis in tumors results in poor vascularization and leads to impaired perfusion and oxygenation with a resultant relative resistance to radiation and many chemotherapeutics.²² It is, therefore, possible that ACEIs/ARBs may antagonize aberrant angiogenesis within a tumor and that this may result in a pruning effect that could reduce vascular leakiness and thereby improve tumor perfusion and pCR rates after neoadjuvant treatment.

An alternative mechanism for how ACEIs/ARBs may increase pCR rates in rectal cancer patients after neo-adjuvant therapy could be related to the role of ACEIs/ARBs in modulating dysregulated inflammation and macrophage activity.⁷ Macrophages may have a protumor effect when they are localized within the necrotic center of colorectal tumors but may confer an antitumor effect when they are concentrated at the tumor periphery.³⁵ It is plausible that ACEIs/ARBs affect macrophages within the colorectal tumor microenvironment and that this could affect pCR rates to neoadjuvant therapy. Ongoing and anticipated studies examining biopsy and surgical pathology specimens from patients in our UW and UH databases may shed further light on these potential mechanisms.

The potential for ACEIs/ARBs to positively affect tumor responses to chemoradiation is all the more remarkable when it is placed in the context of prior studies showing a role for these agents in reducing certain normal tissue toxicities after radiation.^{15–21} The specific molecular and cellular mechanisms that may underlie this dichotomy remain obscure. We do not observe an effect of ACEIs/ARBs on radiation-related toxicities in the current study. However, prior preclinical studies have also not observed an effect of these medications on the gastrointestinal side effects of radiation,³⁶ which are likely to predominate in our patient population.

In conclusion, we present evidence from 2 independent and diverse patient data sets demonstrating a positive association between the use of ACEIs/ARBs and pCR after neoadjuvant treatment of rectal cancer. A weakness of this study is that this evidence is derived from retrospective data sets. In light of the low cost and established safety of ACEIs/ARBs, a prospective investigation is warranted to evaluate the capacity of these agents to enhance tumor responses to chemoradiation therapy in patients with rectal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING SUPPORT

Brett A. Morris was supported by the National Institute on Aging (grant T32-AG000213 24).

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Figure 1.

(A) Patients in the University of Wisconsin data set taking an ACEI/ARB experienced a significantly increased rate of pCR to neoadjuvant radiation in comparison with those not taking an ACEI/ARB ($P = .001$). ACEI/ARB use did not significantly correlate with (B) local recurrence-free survival ($P = .89$), (C) metastasis-free survival ($P = .49$), or (D) overall survival ($P = .65$) in Kaplan-Meier analyses. Dashed red lines indicate patients taking ACEIs/ARBs, and solid blue lines indicate patients not taking ACEIs/ARBs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; pCR, pathological complete response.

Figure 2.

(A) Patients in the Hawaii data set taking an ACEI/ARB experienced a significantly increased rate of pCR to neoadjuvant radiation in comparison with those not taking an ACEI/ARB ($P = 0.03$). ACEI/ARB use did not significantly correlate with (B) local recurrence-free survival ($P = .43$), (C) metastasis-free survival ($P = .13$), or (D) overall survival ($P = .44$) in Kaplan-Meier analyses. Dashed red lines indicate patients taking ACEIs/ARBs, and solid blue lines indicate patients not taking ACEIs/ARBs. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; pCR, pathological complete response.

TABLE 1

Patient and Tumor Characteristics in the University of Wisconsin Data Set

Variable	Level	ACEI/ARB Use		<i>P</i> ^a
		No (n = 90)	Yes (n = 25)	
Age at diagnosis, mean (SD), y		57.2 (12.6)	61.1 (11.5)	.16
Pretreatment hemoglobin, mean (SD), g/dL		13.3 (1.6)	13.3 (2.3)	.95
Pretreatment CEA, mean (SD), ng/mL		11.2 (6.1)	21.6 (9.1)	.60
Sex, No. (%)	Female	41 (45.6)	8 (32)	.23
	Male	49 (54.4)	17 (68)	
Clinical stage, No. (%)	IIA	40 (44.4)	10 (43.5)	.94
	IIC	1 (1.1)	0 (0)	
	IIIA	6 (6.7)	1 (4.3)	
	IIIB	42 (46.7)	12 (52.2)	
	IIIC	1 (1.1)	0 (0)	
Biopsy grade, No. (%)	1	24 (30.4)	8 (38.1)	.42
	2	49 (62)	10 (47.6)	
	3	6 (7.6)	3 (14.3)	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CEA, carcinoembryonic antigen; SD, standard deviation.

^aStudent *t* test for continuous variables and chi-square test for categorical variables.

Missing data are not shown but are accounted for in percentiles.

TABLE 2

Treatment Patterns and Outcomes in the University of Wisconsin Data Set

Variable	Level	ACEI/ARB Use		<i>P</i> ^a
		No (n = 90)	Yes (n = 25)	
Duration of radiation, mean (SD), d		38.46 (4.59)	38.60 (2.71)	.84
Radiation dose, mean (SD), Gy		50.5 (2.5)	50.6 (1.4)	.56
Concurrent chemotherapy, No. (%)	5FU	28 (31.1)	5 (20.0)	.11
	Capecitabine	61 (67.8)	18 (72.0)	
	No	1 (1.1)	2 (8.0)	
Adjuvant chemotherapy, No. (%)	No	23 (25.6)	5 (20.0)	.48
	Yes	62 (68.9)	20 (80.0)	
Time to surgery, mean (SD), d		48.2 (11.1)	50.5 (8.9)	.34
Pathological stage, No. (%)	0	15 (16.7)	13 (52.0)	.016
	I	26 (28.9)	3 (12.0)	
	IIA	22 (24.4)	3 (12.0)	
	IIC	1 (1.1)	0 (0.0)	
	IIIA	9 (10.0)	1 (4.0)	
	IIIB	11 (12.2)	5 (20.0)	
	IIIC	3 (3.3)	0 (0.0)	
Grade 3/4 toxicity at 90 d, No. (%)	No	89 (99.0)	23 (92.0)	.12
	Yes	1 (1.1)	2 (8.0)	
Grade 3/4 toxicity at >90 d, No. (%)	No	81 (90)	24 (96.0)	.69
	Yes	9 (10.0)	1 (4.0)	

Abbreviations: 5FU, 5-fluorouracil; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation.

^aStudent *t* test for continuous variables, chi-square test for categorical variables, and 2-tailed Fisher's exact test for toxicity.

Missing data are not shown but are accounted for in percentiles.

TABLE 3

Patient, Tumor, and Treatment Characteristics in the University of Hawaii Data Set

Variable	Level	ACEI/ARB Use		<i>P</i> ^a
		No (n = 137)	Yes (n = 49)	
Age at diagnosis, mean (SD), y		59.2 (11.9)	60.1 (8.8)	.57
Pretreatment hemoglobin, mean (SD), g/dL		13.3 (1.6)	13.3 (2.3)	.95
Pretreatment CEA, mean (SD), ng/mL		16.9 (40.5)	141 (704.8)	.31
Sex, No. (%)	Female	47 (34.3)	12 (24.5)	.21
	Male	90 (65.7)	37 (75.5)	
Clinical stage, No. (%)	I	11 (8.0)	4 (8.2)	.60
	IIA	67 (48.9)	26 (53.1)	
	IIB	3 (2.2)	0 (0.0)	
	IIIA	4 (2.9)	2 (4.1)	
	IIIB	29 (21.2)	5 (10.2)	
	IIIC	6 (4.4)	2 (4.1)	
Biopsy grade, No. (%)	1	5 (3.6)	4 (8.2)	.44
	2	80 (58.4)	29 (59.2)	
	3	9 (6.6)	5 (10.2)	
Radiation dose, mean (SD), Gy		47.5 (4.0)	47.9 (5.6)	.62
Concurrent chemotherapy, No. (%)	Yes	123 (89.8)	44 (89.8)	.72
	No	1 (0.7)	1 (2.0)	
	Unknown	13 (9.5)	4 (8.2)	
Pathological stage, No. (%)	0	16 (11.7)	12 (24.5)	.053
	I	14 (10.2)	10 (20.4)	
	IIA	19 (13.9)	7 (14.3)	
	IIB	2 (1.5)	0 (0.0)	
	IIIA	7 (5.1)	2 (4.1)	
	IIIB	30 (21.9)	2 (4.1)	
	IIIC	8 (5.8)	2 (4.1)	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CEA, carcinoembryonic antigen; SD, standard deviation.

^aStudent *t* test for continuous variables and chi-square test for categorical variables.

Missing data are not shown but are accounted for in percentiles.

TABLE 4

Multivariate Logistic Regression Analysis Evaluating Predictors of pCR and Multivariate Cox Model for Recurrence-Free Survival and Overall Survival

Outcome		pCR (Yes vs No)			LR-Free Survival			Metastasis-Free Survival			Overall Survival		
Variable	Level	Odds Ratio (95% CI)	P		Odds Ratio (95% CI)	P		Odds Ratio (95% CI)	P		Odds Ratio (95% CI)	P	
ACEI/ARB use		4.02 (2.06–7.82)	<.0001		0.76 (0.28–1.24)	.26		0.65 (0.41–1.01)	.06		0.73 (0.45–1.2)	.22	
Clinical stage	I	Reference	.66		Reference	.24		Reference	.75		Reference	.27	
	II	0.62 (0.11–3.43)			0.64 (0.3–1.38)			0.73 (0.35–1.78)			0.69 (0.32–1.49)		
	III	0.92 (0.17–5.02)			0.52 (0.23–1.17)			0.82 (0.38–2.01)			0.55 (0.25–1.24)		
	Unknown	0.56 (0.08–4.03)			0.92 (0.38–2.19)			0.93 (0.41–2.35)			0.97 (0.41–2.31)		
Biopsy grade	1	Reference	.20		Reference	.16		Reference	.20		Reference	.13	
	2	0.55 (0.24–1.26)			0.69 (0.37–1.29)			0.71 (0.42–1.28)			0.72 (0.38–1.36)		
	3	0.22 (0.04–1.15)			1.5 (0.64–3.54)			1.36 (0.62–2.87)			1.66 (0.69–3.96)		
	Unknown	0.85 (0.32–2.22)			0.89 (0.45–1.75)			0.88 (0.48–1.66)			0.95 (0.47–1.9)		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; LR, local recurrence; pCR, pathological complete response.