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Challenges to Delivery and Effectiveness of Adjuvant Radiation Therapy in Elderly Patients with Node-Positive Vulvar Cancer

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Abstract

Objective—To examine adjuvant radiation therapy (RT) use, patterns of RT delivery, and clinical outcomes in older patients with node-positive vulvar cancer.

Methods—Using SEER-Medicare linked data, we identified 444 patients (age ≥66 years) with node-positive squamous cell vulvar carcinoma, without distant metastases, and treated with primary surgery between 1991 and 2009. We used claims to examine RT use and the following delivery metrics: 1) completion of ≥20 fractions, 2) treatment duration <8 weeks, 3) <1 week of intra-treatment break, and 4) treatment interval from surgery to start of RT <8 weeks. We tested associations between RT use and metrics with overall (OS) and cause-specific survival (CSS) using multivariate proportional hazards regression.

Results—Median age was 78 years (interquartile range [IQR]=74–83). Median follow-up was 17 months (IQR=9–40). Three hundred six patients (69%) received RT. Three delivery metrics were associated with improved outcomes: completion of ≥20 fractions, treatment duration <8 weeks, and <1 week of intra-treatment break. Patients who achieved these 3 metrics demonstrated better disease outcomes compared with surgery alone (OS hazard ratio [HR] for death=0.62, 95% confidence interval [CI]=0.46–0.82, $P=0.001$; CSS HR=0.58, 95% CI=0.40–0.85, $P=0.005$). Patients not achieving RT metrics demonstrated marginal improvements in disease outcomes over surgery alone (OS HR=0.73, 95% CI=0.55–0.99, $P=0.04$; CSS HR=0.76, 95% CI=0.52–1.11, $P=0.16$). Notably, only 51% of patients who received RT achieved all benchmarks.

Conclusions—In this cohort of older women with node-positive vulvar cancer, achieving metrics for RT delivery was an important factor for optimizing disease benefits from treatment.

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Keywords

Radiation; Radiation quality; Vulvar cancer; Elderly

Introduction

In a landmark randomized trial, Homesley *et al* [1] established postoperative radiation therapy (RT) as a critical component of curative treatment for lymph node-positive vulvar cancer. In that trial, patients who received RT following radical vulvectomy and bilateral inguinal lymphadenectomy had improved overall survival (OS) and recurrence-free survival compared with patients treated with surgery alone. Unplanned subgroup analyses suggested that the benefit of adjuvant RT was limited to patients with clinically evident nodal disease or ≥2 positive nodes. However, the study was underpowered to show a benefit in patients with one occult positive node [1,2], and several subsequent retrospective studies have supported the use of RT in patients with any positive nodes [3–6].

The median age on the Homesley trial was 70 years old [2], and even though the demographics of vulvar cancer patients have changed since the publication of the Homesley trial more than 30 years ago [7–9], it remains primarily a disease of the elderly. Indeed, the incidence of vulvar cancer increases with increasing age, and over one-third of the nearly 6,000 new cases per year are diagnosed in patients over the age of 75 [10]. The propensity for this disease to affect the very elderly raises important considerations for treatment, as these patients may be less likely to tolerate curative therapy and more likely to die of intercurrent disease [11].

Limited data exist regarding the generalizability of the results of the Homesley study to elderly patients treated outside of the rigors of a randomized trial, yet such data are considerably needed, for several reasons. First, the delivery of vulvar RT is both clinically and technically challenging owing to patient age and frailty [11], skin reactions that may lead to treatment breaks, and complicated dosimetric considerations to ensure adequate target coverage [12,13]. It is not currently known how these challenges affect the delivery of quality RT in the community, and, in turn, affect outcomes such as overall and cause-specific survival, especially in elderly patients who face competing risks of death and comorbid illness. Therefore, we sought to define patterns of use and metrics for RT delivery, as well as examine the impact of RT on clinical outcomes in elderly patients with node-positive vulvar cancer treated in everyday practice in the United States.

Methods and Materials

Data Source

An Institutional Review Board waiver was obtained for the current study. The data were extracted from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Cohort Selection

To ascertain node-positive vulvar cancer patients treated with surgery, we initially identified 2,476 patients aged ≥ 66 years who were diagnosed with pathologically confirmed, invasive vulvar squamous cell carcinoma between 1991 and 2009. The age inclusion criteria of ≥ 66 years was based on the threshold for Medicare eligibility (65 years) plus the requirement of 1 year of continuous claims to define claims-based treatment and covariates. We excluded patients who had any prior history of pelvic/genital cancer or who had a diagnosis of any cancer within 5 years of their vulvar cancer diagnosis. We included only those who had a vulvectomy in the window from 1 month prior to 6 months after diagnosis to capture patients treated with a primary surgical approach. To ensure that complete claims data were available, we included only patients with fee-for-service Medicare Part A and B coverage in the 12 months before and 9 months after their vulvar cancer diagnosis and no Health Maintenance Organization coverage during the same period ($n=2,038$). Finally, we included only patients who had at least one pathologically confirmed positive node and who did not receive radiation before vulvectomy. The remaining 444 patients formed our study population (Table S1).

Treatment and Outcomes

We used Medicare claims to determine receipt of adjuvant RT and chemotherapy (Table S2). For patients who received RT, we used claims dates for RT delivery to determine the number of fractions received, the duration of RT, and the interval from surgery to the start date of RT. We obtained OS and cause-specific survival (CSS) from SEER and calculated all endpoints from the date of surgery.

Radiation Treatment Delivery Metrics

To evaluate RT delivery, we initially examined 4 candidate treatment parameters:

1. Treatment completion, defined by number of fractions. The metric for this parameter was receipt of ≥ 20 fractions of RT. We chose this metric based on the standard number of external beam fractions for curative-intent adjuvant pelvic RT in gynecologic cancer [1,14,15].
2. Treatment duration, defined by elapsed time between the first and last fractions of RT. The metric for this parameter was completion of all RT in <8 weeks. We chose this metric based on previous studies in other squamous cancers that have demonstrated a detrimental effect of RT duration >8 weeks [16–18].
3. Intra-treatment break, defined by ratio of RT treatment days to elapsed calendar days. The metric for this parameter was <1 week of treatment break (not counting weekends) over the course of RT. We arrived at this metric based on prior studies demonstrating associations between RT break and disease outcomes [19]. We chose to evaluate intra-treatment breaks along with treatment duration because a simple measure of elapsed days does not differentiate between patients whose treatment course was prolonged because of a higher prescribed dose (such as those who required boosting) and those who had intra-treatment delivery delays that protracted the overall duration of treatment.

4. Treatment interval, defined as time from vulvectomy to first fraction of RT. The metric for this parameter was initiation of RT within 8 weeks of surgery. We chose this metric based on a previous study in vulvar cancer that demonstrated a higher 5-year inguinal recurrence rate in patients for whom the interval from surgery to RT was ≥ 50 days [20].

Candidate treatment parameters were assessed for their univariate associations with OS and CSS. Parameters associated with absolute (but not necessarily statistically significant) improvements in either OS or CSS were considered for inclusion in the combined delivery metric. Survival analyses were conducted using a three-level RT variable (RT that met all delivery metrics, RT that failed to meet delivery metrics, and no RT).

Other Covariates

We obtained demographic and disease characteristics from SEER records and Medicare claims. Demographic covariates included age, race/ethnicity, geographic region, urban or rural residence, income quartile, and education quartile. Disease covariates included measures of comorbidity (performance status [21,22], cardiac disease, and diabetes), tumor size, number of pathologically confirmed positive nodes (and ratio to number of dissected nodes), length of postoperative hospital admission, infectious complications, and receipt of chemotherapy.

Statistical Analysis

To evaluate RT utilization, we identified univariate associations between RT use and patient and disease characteristics using the Pearson χ^2 test. We used multivariate logistic regression to test associations between RT use and covariates. Covariates for all multivariate models were chosen on the basis of clinical significance or statistical significance in the univariate analysis. We assessed trends in treatment use over time using the Cochran-Armitage test.

To evaluate OS and CSS, we used Kaplan-Meier estimates and compared treatment groups using the log-rank test. We used multivariate Cox proportional hazards models to test for associations between the treatment received and outcomes after adjusting for covariates. We tested interactions using the likelihood ratio test.

We performed sensitivity analyses to explore the potential impact of confounding from covariates, as patients receiving RT presumably had to be fit and healthy enough to undergo adjuvant treatment. First, we generated a multivariate Cox proportional hazards model in which we censored all patient deaths that occurred within 8 weeks of surgery to account for patients who may have experienced early mortality in the postoperative period that would have excluded them from being considered for radiation treatment. Second, because of the advanced age of the study population and resultant high risk of death not attributable to cancer, we performed a competing mortality analysis to estimate CSS after accounting for competing risks [23,24]. We also used propensity score-based matching to generate a new balanced cohort to minimize selection bias in evaluating survival outcomes. In an analysis of the three RT groups (RT delivery metrics met, RT metrics not met, and no RT), 2-step matching was employed to generate the final propensity score-matched cohort. In the first

step, we matched patients with RT metrics met with those with RT metrics not met, by applying an 8- to 1-digit algorithm using the predicted probability from the logistic model controlling for patients' demographic and clinical variables. Thereafter, we matched patients with RT metrics met with no RT by the same an 8- to 1-digit algorithm. In the second stage, patients with RT metrics met who were selected in both RT metrics not met and no RT matched cohorts served as an index from which the paired patients from two matched cohorts were extracted and then merged into the final propensity score-matched cohort, leaving 59 matched pairs for this analysis.

Analyses were conducted using SAS software version 9.4 (SAS Institute Inc.). All statistical tests were two-sided; a P value <0.05 was considered statistically significant. In all tables, cell counts were suppressed if there were fewer than 11 cases to avoid potential compromise of patient identities.

Results

Patient Characteristics

The median age was 78 years (interquartile range [IQR]=74–83 years). The median follow-up time was 17 months for all patients (IQR=9–40 months); 55 months (IQR=37–95 months) for surviving patients ($n=69$); and 15 months (IQR=8–28 months) for deceased patients ($n=375$). The median number of lymph nodes pathologically examined was 13 (IQR=7–19 nodes). Other patient characteristics are listed in Table 1.

Treatment Use

A total of 306 patients (69%) received adjuvant RT. Among the 170 patients with 1 positive node, 55% received adjuvant RT; among the 249 patients with 2 positive nodes, 78% received adjuvant RT. In univariate analyses, RT use varied by age, geographic region, number of positive lymph nodes, postoperative length of stay, and chemotherapy receipt (Table 1). In multivariate analysis, younger age, 2 positive lymph nodes, postoperative length of stay ≥ 7 days, and chemotherapy receipt remained significant predictors of RT use (Table 2). The frequency of RT use remained stable between 1991 and 2009 ($P_{\text{trend}}=0.86$; Figure S1).

Seventy-two patients (16%) received chemotherapy with RT and 12 patients (3%) received chemotherapy without RT. The likelihood of receiving chemotherapy increased with an increasing number of positive lymph nodes ($P<0.01$). The frequency of chemotherapy use generally increased between 1991 and 2009, although this trend did not reach statistical significance ($P_{\text{trend}}=0.15$, Figure S2).

Disease Outcomes for RT versus no RT

On analysis of the entire cohort, unadjusted 3- and 5-year OS rates were 32% and 24% for the RT group and 28% and 19% for the no RT group ($P=0.10$; Figure 1A). In multivariate analysis, the OS benefit of RT was significant, with a hazard ratio (HR) for death of 0.67 (95% CI=0.52–0.86, $P=0.002$) (Table 3). The interaction between the number of positive nodes and adjuvant RT was not significant in the OS model ($P=0.94$), suggesting that the

proportional benefit of adjuvant RT is not different for patients with one positive node compared with patients with 2 positive nodes.

On analysis of the entire cohort, unadjusted 3- and 5-year CSS rates were 44% and 41% for the RT group and 48% and 43% for the no RT group both groups ($P=0.79$; Figure 1B). In multivariate analysis for CSS, the benefit of RT was similar (HR=0.66, 95% CI=0.48–0.93, $P=0.02$) (Table S3).

In the sensitivity analysis in which deaths that occurred within the first 8 weeks following surgery were censored, the association between RT and OS as well as CSS were no longer significant (OS HR=0.80, 95% CI=0.63–1.03, $P=0.08$; CSS HR=0.83; 95% CI=0.61–1.14, $P=0.26$). In the competing mortality sensitivity analysis that accounted for the competing risk of non-cancer death, the association between RT and CSS was also not significant (HR=0.92; 95% CI=0.66–1.27, $P=0.61$).

Radiation Treatment Delivery Metrics

Of the 306 patients who received RT, 204 (67%) completed 20 fractions; 272 (89%) completed treatment in <8 weeks; 258 (84%) had <1 week of intra-treatment break over the course of RT; and 188 (61%) had an interval from surgery to the start of RT that was <8 weeks. Univariate analyses for each individual treatment parameter revealed absolute (but not statistically significant) improvements in OS and/or CSS for patients who received 20 fractions (compared to <20 fractions), completed treatment in <8 weeks (compared to 8 weeks), and had <1 week of intra-treatment break (compared to 1 week of intra-treatment break) (Table S4). In contrast, there were no absolute OS or CSS improvements observed in patients who had an interval from surgery to the start of RT <8 weeks (compared to 8 weeks).

Our combined variable for meeting RT delivery metrics included: completion of 20 fractions, completion of treatment in <8 weeks, and <1 week of intra-treatment break. Fifty-one percent of patients met all 3 metrics. In multivariate analysis, the strongest covariate independently predicting RT delivery meeting all metrics was use of IMRT (OR=7.10, 95% CI=0.2.05–24.6, $P=0.002$). Patients who received chemotherapy were less likely to meet the metrics (OR=0.48, 95% CI 0.24–0.96, $P=0.04$).

Unadjusted 3- and 5-year OS rates were 39% and 30% for patients who met all metrics, 32% and 20% for patients who failed to meet all metrics, and 31% and 20% for patients who received no RT ($P_{\log\text{-rank}}=0.06$; Figure 2A). In multivariate analysis, meeting all 3 RT delivery metrics was associated with improved OS compared to surgery alone, with a hazard ratio (HR) for death of 0.62, 95%CI=0.46–0.82, $P=0.001$). This OS benefit was confirmed in the propensity score matched subset (Figure 2C). However, patients who failed to meet all delivery metrics had only marginal improvements in OS compared to surgery alone in the multivariate model (HR=0.73, 95% CI=0.55–0.99, $P=0.04$) (Table 4).

Unadjusted 3- and 5-year CSS rates were 51% and 50% for patients who met all delivery metrics, 40% and 35% for patients who failed to meet all metrics, and 50% and 45% for patients who received no RT ($P_{\log\text{-rank}}=0.13$; Figure 2B). In multivariate analysis, meeting

all metrics was associated with improved CSS compared to surgery alone, with a HR of 0.58, 95% CI=0.40–0.85, $P=0.005$). In contrast, patients who did not meet all delivery metrics demonstrated marginally improved CSS compared to surgery alone (CSS HR=0.76, 95% CI=0.52–1.11, $P=0.16$) (Table S5). Propensity score matched subset analyses similarly found only RT patients who met all metrics with improved CSS compared to surgery alone (Figure 2D).

Discussion

In this population-based study of elderly women with node-positive vulvar cancer treated with primary surgery, adjuvant RT was associated with improved OS and CSS. Adjuvant RT that met basic delivery metrics demonstrated the greatest magnitude of OS and CSS benefit. Unfortunately, among patients receiving adjuvant RT in this study, only just over half actually achieved all RT metrics. An analysis accounting for the competing risks of comorbidity and death demonstrated a mitigating effect of these factors, suggesting that in elderly patients, some of the quantifiable survival benefit associated with RT was in part influenced by “healthy” selection bias; i.e., patients healthy enough to receive RT may have had other measured and unmeasured characteristics that favored survival. These results underscore, especially in this elderly patient population, the clinically impactful challenges of selecting patients up front who are fit for RT. Nonetheless, our results are also hypothesis-generating as to the importance of achieving RT delivery metrics to optimize disease benefit.

In our study, only 78% of patients with 2 positive lymph nodes received RT, despite the fact that this is a clinical scenario in which adjuvant RT has been demonstrated to improve OS. What is more, only 67% of patients received 20 fractions. In contrast, 90% of patients randomized to the RT arm of the Gynecologic Oncology Group (GOG) 37 study received complete treatment without modification [2]. These differences between our study and GOG 37 may reflect the challenges of RT delivery in elderly patients with vulvar cancer. For example, poor health and comorbid illness may lead to a prolonged recovery following surgery and decreased likelihood of receiving adjuvant RT. Indeed, we found that older age and longer postoperative hospitalization were negatively associated with RT receipt. In addition, for those patients who are able to initiate RT, delivering RT that meets basic delivery metrics can be clinically and technically difficult [11–13,25]. Empirically, our study showed that treatment breaks and treatment protraction are not uncommon in the elderly population.

Notably, our multivariate survival models suggested that RT failing to meet basic delivery metrics was little better to no better than surgery alone, indicating that inadequate RT in elderly patients may only add to toxicity with minimal disease benefit. Furthermore, our finding that the benefit of RT is no longer detectable in competing mortality analysis suggests that understanding life expectancy is important for stratifying patients for treatment in this clinical setting.

Our study had several strengths. First, the linkage of SEER data with Medicare claims allowed us to examine specific RT details (number of fractions, duration of treatment, etc.) that are not available in the SEER dataset. Our study therefore represents one of the first to

use population-level data to analyze the quality of RT delivered to patients with vulvar cancer. Second, by using a population-based dataset, we were able to analyze a large number of patients with a rare malignancy, as vulvar cancer accounts for only 0.6% of all cancers diagnosed in women in the United States annually [26]. We have also provided valuable outcomes data for the highest-risk age group (ages 75–84 years [10]), a group that is generally underrepresented in the published literature for vulvar cancer.

Our study also has several limitations. First, because we analyzed an elderly patient cohort, the generalizability of our results to younger patients is limited. The median age in our study was 78 years, which is 8 years older than the median age in the GOG 37 study (70 years) [1] and 9 years older than the median age of node-positive patients in the AGO-CaRE-1 study (69 years) [6]. Compared with the elderly patients in our study, younger patients are more likely to tolerate treatment and less likely to have competing mortality risks. Furthermore, the increased prevalence of human papillomavirus-positive vulvar cancer in younger age groups [8] introduces differences in the biology and radiosensitivity of the disease that further limit the applicability of our results to younger cohorts.

A second limitation is that the SEER-Medicare dataset does not include details of the radiation fields and dosages, and therefore other indicators of RT quality (total dose, target coverage) could not be assessed for their effects on outcomes. Therefore, these data need to be viewed as a complement to institution-based studies that may include additional details about RT but typically have smaller or less representative sample sizes. Prior studies have indicated that RT use is underreported in the SEER database alone [27], and our use of the linked Medicare database can help improve both the sensitivity and specificity of RT use. Nonetheless, because primary chart review was not used in this study, some use of adjuvant RT may have been missed, particularly if it was delayed beyond 9 months after surgery (our study window). Even so, such misclassification would have biased the results toward the null. Finally, margin status and extracapsular extension are not available in the SEER-Medicare dataset, and we were therefore not able to adjust for the potential effects of these variables on disease outcomes in this cohort.

Conclusion

In this population-based cohort of elderly women with node-positive vulvar cancer, achieving select delivery metrics for RT delivery optimized the OS and CSS benefits from adjuvant RT, while competing risks of death mitigated the benefits from adjuvant RT. Our results underscore the challenge and importance of patient selection in this elderly and often frail population, as well as the need to ensure the delivery of quality RT in those patients selected for treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conflict of interest statement: Dr. Meyer has received sponsor-paid travel from Astra Zeneca. Dr. Eifel holds a patent issued for an adaptive intracavitary brachytherapy applicator in conjunction with Nucletron/M.D. Anderson Cancer Center.

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Highlights

- In this cohort of 444 elderly patients with node-positive vulvar cancer, 69% received adjuvant RT.
- Only 51% who received adjuvant RT had RT adhering to basic delivery metrics.
- Adjuvant RT delivered according to metrics improved disease outcomes.

Figure 1.
(A) Overall survival and (B) cause-specific survival in patients who received no adjuvant radiation therapy (RT) and adjuvant RT.

Figure 2.

(A) Overall survival and (B) cause-specific survival in patients who received no radiation therapy (RT), RT metrics not met, and RT metrics met. (C) Overall survival and (D) cause-specific survival in propensity score matched sample.

Table 1

Patient characteristics by treatment group (n = 444).

Characteristic	No. of patients (%)		P
	No RT (n = 138)	RT (n = 306)	
Age group			0.03
65–69 years	15 (11)	26 (9)	
70–74 years	18 (13)	70 (23)	
75–79 years	33 (24)	87 (28)	
80+ years	72 (52)	123 (40)	
Race/ethnicity*			0.47
White	120 (87)	258 (84)	
Non-white	18 (13)	48 (16)	
Geographic region			0.04
West	47 (34)	108 (35)	
Northeast	31 (23)	89 (29)	
Midwest	26 (19)	66 (22)	
South	34 (25)	43 (14)	
Urban or rural			0.19
Urban	124 (90)	286 (93)	
Rural	14 (10)	20 (7)	
Income			0.89
\$35,721 (referent)	36 (26)	78 (26)	
\$35,722–\$46,564	31 (23)	79 (26)	
\$46,565–\$60,309	35 (25)	75 (25)	
\$60,310	36 (26)	74 (24)	
Education			0.91
First quartile	35 (25)	79 (26)	
Second quartile	37 (27)	73 (24)	
Third quartile	34 (25)	76 (25)	
Fourth quartile	32 (23)	78 (25)	
Charlson comorbidity score*			0.30
0 or unknown	87 (63)	212 (69)	
1	33 (24)	67 (22)	
2+	18 (13)	27 (9)	
Cardiac disease			0.11
No	52 (38)	140 (46)	
Yes	86 (62)	166 (54)	
Diabetes mellitus			0.44
No	85 (62)	200 (65)	
Yes	53 (38)	106 (35)	
Performance status			0.26

Characteristic	No. of patients (%)		P
	No RT (n = 138)	RT (n = 306)	
Normal	120 (87)	277 (91)	
Restricted	18 (13)	29 (9)	
Postoperative length of stay *			0.04
0–7 days	69 (50)	190 (62)	
8+ days	69 (50)	116 (38)	
Postoperative infection			0.64
No	99 (72)	226 (74)	
Yes	39 (28)	80 (26)	
Chemotherapy			<0.01
No	126 (91)	234 (77)	
Yes	12 (9)	72 (24)	
Tumor size (cm)			0.42
Median (interquartile range)	3.5 (2.5,5.0)	3.8 (2.5,5.0)	
No. of positive nodes *			<0.01
1	77 (56)	93 (30)	
2	55 (40)	194 (63)	

Abbreviations: RT = radiation therapy.

* Indicates characteristics for which some sub-categories were suppressed or removed from the table to avoid compromising patient identity.

Table 2

Multivariable model for use of radiation therapy in our study cohort (n = 444).

Variable	OR	95% CI	P
Age (per each year older age)	0.96	0.93–0.99	0.02
Race/ethnicity			
White (referent)	-		
Non-white	1.11	0.56–2.21	0.77
Geographic region			
West (referent)	-		
Northeast	1.69	0.87–3.26	0.12
Midwest	1.08	0.56–2.09	0.83
South	0.50	0.24–1.01	0.05
Urban or rural			
Urban (referent)	-		
Rural	0.58	0.25–1.36	0.21
Income			
\$35,721 (referent)	-		
\$35,722–\$46,564	0.90	0.46–1.77	0.76
\$46,565–\$60,309	0.59	0.29–1.19	0.14
\$60,310	0.52	0.25–1.09	0.08
Education			
First quartile (referent)	-		
Second quartile	0.97	0.50–1.87	0.28
Third quartile	1.10	0.55–2.20	0.79
Fourth quartile	1.25	0.60–2.57	0.55
Cardiac disease			
No (referent)	-		
Yes	0.85	0.54–1.35	0.50
Diabetes mellitus			
No (referent)	-		
Yes	0.89	0.56–1.42	0.63
Postoperative length of stay			
0–7 days (referent)	-		
8+ days	0.58	0.36–0.93	0.02
Postoperative infection			
No (referent)	-		
Yes	1.01	0.59–1.73	0.96
Chemotherapy			
No (referent)	-		
Yes	2.20	1.11–4.39	0.03
No. of positive nodes			
2 (referent)	-		

Variable	OR	95% CI	P
1	0.32	0.20–0.51	<0.001
Unknown number	0.81	0.29–2.24	0.69

Abbreviations: OR = odds ratio; CI = confidence interval.

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Table 3

Multivariable Cox model for overall survival in our study cohort with two radiation therapy (RT) categories (no RT and RT) (n = 416).

Variable	HR	95% CI	P
Radiation therapy			
No (referent)	-		
Yes	0.67	0.52–0.86	0.002
Age (per each year older age)	1.03	1.01–1.05	<0.001
Race/ethnicity			
White (referent)	-		
Non-White	0.48	0.34–0.70	<0.001
Geographic region			
West (referent)	-		
Northeast	1.04	0.75–1.46	0.80
Midwest	0.78	0.56–1.07	0.12
South	0.90	0.64–1.28	0.57
Urban or rural			
Urban (referent)	-		
Rural	1.30	0.85–1.97	0.23
Income			
\$35,721 (referent)	-		
\$35,722–\$46,564	0.70	0.50–0.97	0.03
\$46,565–\$60,309	0.79	0.56–1.12	0.18
\$60,310	0.66	0.45–0.97	0.04
Education			
First quartile (referent)	-		
Second quartile	1.16	0.83–1.62	0.38
Third quartile	1.23	0.88–1.71	0.23
Fourth quartile	0.99	0.69–1.43	0.97
Cardiac disease			
No (referent)	-		
Yes	1.23	0.97–1.55	0.09
Diabetes mellitus			
No (referent)	-		
Yes	1.28	1.00–1.63	0.05
Performance status			
Normal (referent)	-		
Restricted	1.34	0.90–1.97	0.15
Chemotherapy			
No (referent)	-		
Yes	1.36	0.98–1.88	0.06
No. of positive nodes			

Variable	HR	95% CI	P
2 (referent)	-		
1	0.57	0.43–0.76	<0.001
Nodal ratio			
0.1 (referent)	-		
>0.1 to 0.25	1.39	1.01–1.92	0.04
>0.25 to 1	1.97	1.40–2.76	<0.001
Size (per cm)	1.06	1.03–1.09	<0.001

Abbreviations: HR = hazard ratio; CI = confidence interval.

Table 4

Multivariable Cox model for overall survival in our study cohort with 3 radiation therapy (RT) categories (no RT, RT metrics not met, and RT metrics met) (n = 416).

Variable	HR	95% CI	P
Radiation therapy			
No (referent)	-		
RT metrics not met	0.73	0.55–0.99	0.04
RT metrics met	0.62	0.46–0.82	0.001
Age (per each year older age)	1.03	1.01–1.05	<0.001
Race/ethnicity			
White (referent)	-		
Non-White	0.47	0.33–0.68	<0.001
Geographic region			
West (referent)	-		
Northeast	1.05	0.75–1.47	0.77
Midwest	0.76	0.55–1.05	0.09
South	0.90	0.63–1.28	0.55
Urban or rural			
Urban (referent)	-		
Rural	1.30	0.85–1.97	0.23
Annual income			
\$35,721 (referent)	-		
\$35,722–\$46,564	0.69	0.50–0.96	0.03
\$46,565–\$60,309	0.78	0.55–1.10	0.16
\$60,310	0.66	0.45–0.97	0.03
Education			
First quartile (referent)	-		
Second quartile	1.17	0.84–1.64	0.35
Third quartile	1.27	0.91–1.78	0.16
Fourth quartile	1.02	0.71–1.47	0.91
Cardiac disease			
No (referent)	-		
Yes	1.23	0.97–1.56	0.09
Diabetes mellitus			
No (referent)	-		
Yes	1.30	1.02–1.65	0.04
Performance status			
Normal (referent)	-		
Restricted	1.35	0.91–1.99	0.14
Chemotherapy			
No (referent)	-		
Yes	1.33	0.96–1.84	0.09

Variable	HR	95% CI	P
No. of positive nodes			
2 (referent)	-		
1	0.58	0.44–0.76	<0.001
Nodal ratio			
0.1 (referent)	-		
>0.1 to 0.25	1.40	1.02–1.93	0.04
>0.25 to 1	1.98	1.42–2.78	<0.001
Size (per cm)	1.06	1.02–1.09	<0.001

Abbreviations: HR = hazard ratio; CI = confidence interval.