Scientific Article

The Association of Rural Residence With Surgery and Adjuvant Radiation in Medicare Beneficiaries With Rectal Cancer



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Received 15 June 2022; accepted 1 June 2023

Purpose: Radiation therapy and surgery are fundamental site-directed therapies for nonmetastatic rectal cancer. To understand the relationship between rurality and access to specialized care, we characterized the association of rural patient residence with receipt of surgery and radiation therapy among Medicare beneficiaries with rectal cancer.

Methods and Materials: We identified fee-for-service Medicare beneficiaries aged 65 years or older diagnosed with nonmetastatic rectal cancer from 2016 to 2018. Beneficiary place of residence was assigned to one of 3 geographic categories (metropolitan, micropolitan, or small town/rural) based on census tract and corresponding rural urban commuting area codes. Multivariable regression models were used to determine associations between levels of rurality and receipt of both radiation and proctectomy within 180 days of diagnosis. In addition, we explored associations between patient rurality and characteristics of surgery and radiation such as minimally invasive surgery (MIS) or intensity modulated radiation therapy (IMRT).

Results: Among 13,454 Medicare beneficiaries with nonmetastatic rectal cancer, 3926 (29.2%) underwent proctectomy within 180 days of being diagnosed with rectal cancer, and 1792 (13.3%) received both radiation and proctectomy. Small town/rural residence was associated with an increased likelihood of receiving both radiation and proctectomy within 180 days of diagnosis (adjusted subhazard ratio, 1.15; 95% CI, 1.02-1.30). Furthermore, small town/rural radiation patients were significantly less likely to receive IMRT (adjusted odds ratio, 0.62; 95% CI, 0.48-0.80) or MIS (adjusted odds ratio, 0.80; 95% CI, 0.66-0.97) than metropolitan patients.

Conclusions: Although small town/rural Medicare beneficiaries were overall more likely to receive both radiation and proctectomy for their rectal cancer, they were less likely to receive preoperative IMRT or MIS as part of their treatment regimen. Together, these findings clarify that among Medicare beneficiaries, there appeared to be a similar utilization of radiation resources and time to radiation treatment regardless of rural/urban status.

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Sources of support: This study was supported with Project Grant R01CA248470.

Research data are not available at this time.

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https://doi.org/10.1016/j.adro.2023.101286

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Introduction

An estimated 45,230 new cases of rectal cancer were diagnosed in the United States in 2021, approximately two-thirds of which presented with nonmetastatic disease.¹ For such patients, primary curative therapy requires total surgical excision of the mesorectum and its contents. Even with complete surgery, patients with stage II/III rectal cancer treated by surgery alone have high rates (up to 40%) of local and regional recurrence,² prompting multiple trials that showed decreased risk of recurrence when radiation therapy is added to surgery.³

Despite these benefits of adjunctive radiation therapy for rectal cancer patients, there still remain treatment disparities among multiple groups.^{4,5} For example, higher volume "centers of excellence," more routinely deliver radiation to patients with rectal cancer than lower volume centers,^{4,5} while Black patients are less likely to receive adjuvant chemotherapy and radiation therapy than White patients despite seemingly similar referral rates.⁵ To date, the role of rurality in receipt of radiation is less clear,⁶ as >90% of American College of Surgeons' Rectal Cancer Program "centers of excellence" are located in cities of at least 50,000 people.⁷ Furthermore, it remains unclear how newer techniques, such as intensity modulated radiation therapy (IMRT), are being adopted/used across rural settings.

For patients with cancer residing in rural areas, reduced access to surgical care has been well-documented in many settings. For example, rural patients undergo fewer lung and colon cancer-directed surgeries than urban patients, and those rural patients who do undergo surgery tend to have worse outcomes than urban patients.⁸⁻¹¹ Although these disparities may reflect differences in patient underlying health or the socioeconomic determinants of their health, decreased access to adjuvant cancer therapies may further exacerbate the gap in urban-rural outcomes.¹²⁻¹⁴

Given the known disparities in use of surgical and radiation treatment for other cancer sites, we hypothesized that rural patients with rectal cancer would be less likely than urban patients to receive radiation. We sought to test this hypothesis by examining patterns of care among a nationwide sample of patients with rectal cancer. In addition, we explored the association between rural residence and various technical aspects involved in the use of radiation and surgical therapies.

Methods and Materials

Study population

We identified a cohort of Medicare beneficiaries with incident, nonmetastatic rectal cancer using a previously described modification¹⁵ of the algorithm described by

Setoguchi et al¹⁶ (Fig. 1, Tables E1-3). We used fee-forservice Medicare claims from an observation window of April 1, 2016 to September 30, 2018, to identify the cohort. Beneficiaries were excluded if they were younger than 65 years and if they had end-stage renal disease, or evidence of stage IV rectal cancer. This observation period was preceded by a lookback period from October 1, 2015 to March 31, 2016 to exclude pre-existing cancers, including rectal cancers. To maximize sensitivity of detecting incident rectal cancers, subtotal rectal resections (such as transanal excision) were included in our initial cohort build. Given the uncertainty of treatment intent and staging associated with subtotal rectal resections, only patients who underwent a proctectomy were included in our surgical cohort analyses of adjuvant therapies, surgeon subspecialty, surgical modality, or surgical facility type.

Exposure variable

Patient place of residence (at the level of United States Census tract) was categorized as either metropolitan (\geq 50,000 people), micropolitan (10,000-49,999), or small town/rural (<10,000 people), using rural urban commuting area codes. Due to small cell size concerns, the rural and small town categories were collapsed into a single category for analysis.

Outcome variables

The primary outcome among the full cohort was a composite defined as receipt of both proctectomy (Table E2) and radiation therapy (Table E4) within 180 days of diagnosis. For the subset of patients receiving proctectomy, additional outcomes were receipt of preop radiation, preop chemotherapy (Table E5), and minimally invasive surgery (MIS) (Table E6).

Secondary outcomes included receipt of any surgery (including nonproctectomy rectal surgeries such as transanal excision); receipt of any treatment (any surgery, radiation, or chemotherapy); surgeon's subspecialty; receipt of concurrent chemoradiation without surgery (as a proxy for "watchful waiting"17,18); academic medical center (AMC) or National Cancer Institute (NCI) designation; and radiation characteristics including fractionation and modality. When available, the surgeon's specialty was also abstracted from claims and defined as either colorectal surgery or surgical oncology. The hospital where the surgery was performed was stratified by AMC and whether or not the facility was an NCI-designated cancer center. For the subset of patients receiving radiation, we documented radiation characteristics including use of IMRT, number of fractions delivered, timing (before vs after surgery) and use of concurrent chemotherapy.



Figure 1 Cohort build to identify incident of nonmetastatic patients with rectal cancer. *Includes all United-States-residing fee-for-service Medicare beneficiaries with continuous enrollment in Medicare Parts A and B between October 1, 2015 and December 31, 2018 (or until death).

Covariates

The following were candidates for inclusion in adjusted regression models: age; race/ethnicity; Medicaid eligibility; disability as original reason for entitlement; previous myocardial infarction, cerebrovascular accident, or transient ischemic attack; comorbid diabetes, congestive heart failure, chronic obstructive pulmonary disease, liver disease, or renal disease. Race/ethnicity was derived from the Research Triangle Institute Race Code¹⁹ and collapsed into the following: non-Hispanic White, non-Hispanic Black, Hispanic, or Other (which is comprised of the following: Asian/Pacific Islander, American Indian/ Alaskan Native, or Unknown). Analyses also adjusted for the overall health of the patient using the Hierarchical Condition Category (HCC) score,²⁰ and the socioeconomic characteristics of the beneficiary's neighborhood using the area deprivation index, which is a geographybased composite measure index of socioeconomic status calculated at the 9-digit ZIP code level, using 17 measures of poverty, housing, and employment.^{19,21,22}

Statistical analysis

Pearson χ^2 tests and analysis of variance were used to test for differences in baseline covariates. The Kruskal-Wallis test was used to compare median number of radiation fractions. To account for loss to follow-up due to death, associations with the primary outcome (receipt of radiation and surgery within 180 days of diagnosis) were determined using Fine-Gray competing risks regression,²³ and reported as an adjusted subhazard ratio; for this outcome, time to event was defined as days between diagnosis and later of the 2 components of the outcome (radiation and proctectomy). Logistic regression was used for outcomes with no loss to follow-up (preoperative radiation, preoperative chemotherapy, IMRT, MIS, and concurrent chemotherapy). Candidate covariates were included in regression models if they were determined to be associated with both the exposure (levels of rurality) and the outcome, using a conservative threshold of P < .2, and were dropped from final models if not significant at the P < .2 threshold. P < .05 was considered statistically significant.

3

Software

All statistical analyses were performed using Stata MP 17.0 statistical software (StataCorp LLC, College Station, TX).

Results

Patient characteristics

We identified 13,454 fee-for-service Medicare beneficiaries diagnosed with nonmetastatic rectal cancer over a 30-month period (Fig. 1). Of this cohort, 9797 (72.8%) were from metropolitan areas, 1813 (13.5%) from micropolitan areas, and 1844 (13.7%) from small town/rural areas (Table 1). In general, the patients were balanced in terms of mean age and sex. A greater proportion of small town/rural patients were white compared with metropolitan patients. Higher ADI and lower HCC scores were observed for small town/rural rectal cancer patients, reflecting lower socioeconomic status and relatively lower incidence of previously diagnosed medical comorbid conditions than urban beneficiaries.

Treatment characteristics

Of the 13,454 patients with rectal cancer, 5282 (39.3%) received a rectal surgery within 180 days of diagnosis. Of these, 1356 (25.7%) underwent nonproctectomy surgeries such as transanal excision, and 3926 (74.3%) underwent proctectomy (Fig. 1). The mean interval from diagnosis to proctectomy ranged from 81 to 87 days for all patients, varying only slightly across levels of rurality (Table 2). Fewer than half of all proctectomy patients (n = 1792, 45.6%) received radiation before their surgery, and 1334 (74.4%) of these preoperatively irradiated patients received chemotherapy concurrently. Fewer than 4% of proctectomy patients received radiation therapy postoperatively.

Most proctectomies were performed at AMCs (n = 2668, 68.0%). The type of performing surgeon varied with geography (described in the next section). Although the surgeon's subspecialty was not associated with rates of neoadjuvant radiation (Table E7), surgery at an NCI-designated cancer center (vs non-NCI-centers) was associated with higher rates of preoperative radiation among proctectomy patients (55.0% vs 44.8%; P < .01; Table E8).

Geography and receipt of treatment

Rural patients received treatment slightly later after diagnosis compared with those in more populated areas (mean 87 days, vs 81-83 days). Proportionally more proctectomy patients from small/rural areas received preoperative radiation therapy than those from more populated areas, although this was not statistically significant (Table 2). Radiation fractionation did not vary across geography; we noted scant (<0.5%) use of short course schedules overall during the study period. No differences were noted across geography in the proportions receiving concurrent chemoradiation without surgery (13.0%, 14.9%, 14.1%, P = .24). Among patients who received preoperative radiation, proportionally more metropolitan and micropolitan patients received IMRT than small town/rural rectal cancer patients (50.6% vs 47.9% vs 38.9%; P < .01; Fig. 2).

Metropolitan beneficiaries were more likely to undergo proctectomy from a surgical subspecialist than micropolitan or small town/rural beneficiaries (56.1% vs 45.0% vs 44.1%, P < .01). Proportionally more surgeries among metropolitan beneficiaries were coded as minimally invasive (61.6% vs 53.1% vs 53.8%, P < .01; Table 2, Fig. 2).

Multivariable regression results

Among the 13,454 patients who received a diagnosis of rectal cancer, residence across our 3 cohorts was not associated with likelihood of our composite outcome, receipt of both radiation and proctectomy within 180 days of rectal cancer diagnosis. However, when comparing small town/rural against metropolitan patients, there was a slightly increased likelihood (adjusted subhazard ratio, 1.15; 95% CI, 1.02-1.30) of rural patients' receipt of this treatment (Table 3). Similarly, small town/rural patients were more likely to undergo preoperative radiation than their metropolitan counterparts (adjusted odds ratio [AOR], 1.21; 95% CI, 1.01-1.45), although there was no overall association across the 3 levels of rurality.

Levels of rurality were not associated with differential receipt of concurrent chemotherapy (Table 4); however, as rurality increased, patients were more likely to receive sequential, neoadjuvant chemotherapy. Among the 3926 proctectomy patients who received preoperative radiation, small town/rural beneficiaries were least likely to receive IMRT (AOR, 0.62; 95% CI, 0.48-0.80) or receive MIS (AOR, 0.80; 95% CI, 0.66-0.97), compared with metropolitan patients.

Discussion

In this study using national Medicare claims data, we analyzed the treatment of 3926 elderly patients who underwent proctectomy for rectal cancer, of whom 1792 (45.6%) also received radiation therapy. When analyzing our full cohort, we found that, after adjusting for sociode-mographic and clinical characteristics, small town and

	Small town/rural (n = 1844)	Micropolitan (n = 1813)	Metropolitan (n = 9797)	P value
Age, mean (SD)	75.40 (6.9)	75.27 (7.0)	75.62 (7.3)	.10
Age, no. (%), y				<.01
65-74	933 (50.6)	919 (50.7)	4931 (50.3)	
75-84	711 (38.6)	686 (37.8)	3456 (35.3)	
85+	200 (10.8)	208 (11.5)	1410 (14.4)	
Race/ethnicity, no. (%)				<.01
White, non-Hispanic	1657 (89.9)	1636 (90.2)	8315 (84.9)	
Black, non-Hispanic	56 (3.0)	74 (4.1)	611 (6.2)	
Hispanic	55 (3.0)	63 (3.5)	414 (4.2)	
Other	76 (4.1)	40 (2.2)	457 (4.7)	
Sex, no. (%)				
Female	847 (45.9)	846 (46.7)	4610 (47.1)	.67
Past medical history, no. (%)				
Diabetes	388 (21.0)	384 (21.2)	1940 (19.8)	.24
Myocardial infarction	17 (0.9)	22 (1.2)	89 (0.9)	.47
CHF	97 (5.3)	123 (6.8)	647 (6.6)	.08
CVA/TIA	29 (1.6)	33 (1.8)	186 (1.9)	.63
COPD	135 (7.3)	172 (9.5)	733 (7.5)	.01
Liver disease	<11	<11	14 (0.1)	
Kidney disease	18 (1.0)	21 (1.2)	82 (0.8)	.38
Fully dual-eligible, no. (%)	138 (7.5)	115 (6.3)	627 (6.4)	.21
Disabled, no. (%)	211 (11.4)	200 (11.0)	864 (8.8)	<.01
Area deprivation index, mean (SD)	65.08 (19.5)	61.27 (20.7)	41.50 (26.6)	<.01
HCC score, mean (SD)	0.74 (0.6)	0.78 (0.7)	0.79 (0.7)	.02
Receipt of treatment				
Days to any treatment, mean (SD)	36.09 (27.3)	36.32 (29.8)	35.60 (29.1)	.67
Any treatment within 180 d of Dx, no. (%)	1239 (67.2)	1197 (66.0)	6475 (66.1)	.64
Any surgery within 180 d of Dx, no. (%)	772 (41.9)	695 (38.3)	3815 (38.9)	.04
Proctectomy within 180 d of Dx, no. (%)	613 (33.2)	514 (28.4)	2799 (28.6)	<.01
Radiation within 180 d of Dx, no. (%)	764 (41.4)	746 (41.1)	3901 (39.8)	.30
Chemotherapy within 180 d of Dx, no. (%)	714 (38.7)	666 (36.7)	3517 (35.9)	.07
Proctectomy and radiation within 180 d of Dx, no. (%)	329 (17.8)	262 (14.5)	1245 (13.7)	<.01
Concurrent chemoradiation without surgery within 180 d, no. (%)	240 (13.0)	271 (14.9)	1383 (14.1)	.24

Table 1 Characteristics of patients according to rurality of patients' residence (N = 13,454)

Abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; Dx = diagnosis; HCC score = Hierarchical Condition Category; SD = standard deviation; TIA = transient ischemic attack.

rural patients were slightly more likely than more urbandwelling patients to receive both radiation and proctectomy within 180 days of diagnosis. Of those patients who received proctectomy, >95% of radiation courses were received before surgery, across the rural-urban continuum. The vast majority of courses were traditional "long course" chemoradiation schedules and the only difference we detected in terms of the radiation modality regards use of IMRT, which was used least often for small town and rural patients.

Contrary to our hypothesis that rural patients with rectal surgery would be less likely to undergo radiation than urban dwellers, we did not detect an association between levels of rurality and receipt of preoperative radiation

	Small town/rural (n = 613)	Micropolitan (n = 514)	Metropolitan (n = 2799)	P value
Preop radiation, no. (%)	306 (49.9)	242 (47.1)	1244 (44.4)	.04
Preop concurrent chemoradiation, no. (%) †	238 (77.8)	187 (77.3)	909 (73.1)	.13
IMRT, no. (%) †	119 (38.9)	116 (47.9)	629 (50.6)	<.01
No. of preop radiation fractions, median ‡	28	28	28	.35
Postop radiation, no. (%)	23 (3.8)	20 (3.9)	101 (3.6)	.95
Preop chemotherapy, no. (%)	272 (44.4)	212 (41.2)	1054 (37.7)	.01
Postop chemotherapy, no. (%)	108 (17.6)	88 (17.1)	486 (17.4)	.98
Days from diagnosis to proctectomy, mean (SD)	87.0 (56.9)	82.9 (59.0)	80.7 (58.6)	.05
Minimally invasive surgery, no. (%)	330 (53.8)	273 (53.1)	1725 (61.6)	<.01
Surgeon's specialty*				<.01
Colorectal surgeon/surgical oncologist, no. (%)	269 (44.1)	230 (45.0)	1565 (56.1)	
General surgeon or other, no. (%)	341 (55.9)	281 (55.0)	1227 (43.9)	
Hospital type*				<.01
Academic and NCI-designated, no. (%)	76 (12.6)	59 (11.7)	318 (11.6)	
Academic but not NCI-designated, no. (%)	336 (55.6)	247 (49.1)	1632 (59.5)	
Neither academic nor NCI-designated, no. (%)	192 (31.8)	197 (39.2)	793 (28.9)	

Table 2 Treatment characteristics of patients undergoing proctectomy by rurality of patients' residences (n = 3926)

Abbreviations: IMRT = intensity modulated radiation therapy; NCI = National Cancer Institute.

* Some data could not be determined for surgeon's specialty and for hospital type.

[†] Denominator for these rows applies to preoperative radiation patients.

‡ Median is calculated for those who received preoperative radiation.



Figure 2 Treatment patterns for proctectomy patients by geographic location on univariate analysis χ^2 test. For the preoperative radiation, preoperative chemotherapy, and MIS groups, the denominator was 3926. Denominator for the IMRT group was 1792. For the specialist surgeon group, defined as either colorectal surgeons or surgical oncologists, the denominator was 3913. Error bars represent standard errors. * $P \le .05$. *Abbreviations*: IMRT = intensity-modulated radiation therapy; MIS = minimally invasive surgery; pre-op = preoperative.

	Receipt of radiation and proctectomy within 180 d* (N = 13,454)			Preop radiation ^{\dagger} (n = 3926)			Preop chemotherapy ^{\ddagger} (n = 3926)		
	ASHR	95% CI	P value	AOR	95% CI	P value	AOR	95% CI	P value
Place of residence Metropolitan	Reference		.05	Referen	nce	.10	Referen	nce	.01
Micropolitan	0.99	(0.88, 1.13)		1.08	(0.89, 1.31)		1.14	(0.94, 1.38)	
Small town/rural	1.15	(1.02, 1.30)		1.21	(1.01, 1.45		1.30	(1.08, 1.56)	

Table 3 Association of rurality with receipt of radiation and surgery within 180 days and preoperative radiation the
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Abbreviations: AOR = adjusted odds ratio; ASHR = adjusted subhazard ratio; CI = confidence interval; HCC = Hierarchical Condition Category. * Final model adjusted for disability as original reason for entitlement, congestive heart failure, HCC score, age groups, race/ethnicity, and area dep-

rivation index.

† Final model adjusted for HCC score, age groups, and race/ethnicity.

‡ Final model adjusted for HCC score and age groups.

Covariates assessed for inclusion included age, race/ethnicity, Medicaid eligibility, disability as original reason for entitlement, previous myocardial infarction and cerebrovascular attack/transient ischemic attack, comorbid diabetes, congestive heart failure, chronic obstructive pulmonary disease, liver disease, renal disease, HCC score, and area deprivation index for patient residence. Candidate covariates not associated (using conservative threshold of P < .2) with both place of residence/geography and outcome (ie, nonconfounders) were not included in final models.

therapy. Although rural areas may have fewer radiation resources, ^{12,24} it is possible that rural patients are referred to centers where surgeons are more likely to recommend neoadjuvant therapy. It is also possible that rural residents are more tolerant of long commutes for work, recreation, and medical care,²⁵ and therefore more willing to adhere to treating surgeons' recommendations regarding neoadjuvant therapy.

Although overall receipt and timing of radiation therapy did not differ across the rural-urban continuum, we found the use of IMRT varied across geography, as reported in other settings.^{26,27} Nonetheless, the routine use of IMRT for rectal cancer remains a source of ongoing controversy in the radiation oncology community^{28,29} and recent guidelines do not recommend it given mixed efficacy data³⁰⁻³² despite dosimetric studies showing reduced dose to small bowel, bladder, and bone marrow.³³⁻³⁶ Similarly, we found that surgeon training and surgical modality varied across geography, with rural and small town patients least likely to receive care from subspecialty-trained surgeons or minimally invasive surgical approaches, trends observed in other disease settings.³⁷ In contrast to the lack of consensus surrounding use of IMRT, data supporting MIS affirms quicker bowel recovery, decreased postoperative pain, improved cosmesis, and shorter length of hospital stay.³⁸ Reasons for the disparity in its use may be explained by lower supply of rural specialty surgeons or access to equipment and technology more readily available at high-volume, urban surgical centers.^{39,40}

7

There are limitations of this study, which should be considered. First, we acknowledge that our surgery rates appear low. There are inherent limitations in working with Medicare claims data; namely, the patients in our cohort are by definition elderly, and we do not have details regarding cancer staging (beyond notation of metastatic status), treatment intent, or radiation dose. A recent National Cancer Database analysis described rectal cancer surgery rates in the range of 60% to 70%.⁴¹ Other registry studies with access to staging information showed similar operative rates as well.⁴²⁻⁴⁴

Table 4	Association o	f rurality with type of	f surgery and features o	f radiation therapy delivery
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	IMRT* (n = 1792)		Concurrent chemotherapy ^{\dagger} (n = 1792)			Minimally invasive surgery [‡] (n = 3926)			
	AOR	95% CI	P value	AOR	95% CI	P value	AOR	95% CI	P value
Place of residence Metropolitan	Reference		<.01	Reference		.15	Reference		<.01
Micropolitan	0.90	(0.68, 1.19)		1.25	(0.90, 1.73)		0.78	(0.64,0.94)	
Small town/rural	0.62	(0.48, 0.80)		1.28	(0.95, 1.72)		0.80	(0.66, 0.97)	

Abbreviations: AOR = adjusted odds ratio; CI = confidence interval; HCC = Hierarchical Condition Category; IMRT = intensity modulated radiation therapy.

* Final model adjusted for: none.

† Final model adjusted for HCC score.

‡ Final model adjusted for HCC score, age groups, and area deprivation index.

Covariates assessed for inclusion included age, race/ethnicity, Medicaid eligibility, disability as original reason for entitlement, previous myocardial infarction and cerebrovascular attack/transient ischemic attack, comorbid diabetes, congestive heart failure, chronic obstructive pulmonary disease, liver disease, renal disease, HCC score, and area deprivation index for patient residence. Candidate covariates not associated (using conservative threshold of P < .2) with both place of residence/geography and outcome (ie, nonconfounders) were not included in final models.

Medicare beneficiaries are older, have more comorbid illnesses, and their diagnoses lack clarity in terms of stage, accuracy of diagnosis, and treatment intent, and therefore our results may not be generalizable to other populations. Despite low surgery rates in this unselected cohort, receipt of radiation among surgery patients should not vary with patient health, given that radiation is administered in a variety of settings and does not depend on patient age or functional status to the same extent as surgery. In other words, patients healthy enough for surgery are in nearly all cases healthy enough for radiation. Finally, subgroups within the 7.

rural and small town areas contained very few patients. This led us to combine these 2 groups, thus losing some granularity and ability to discern whether forces that drive medical decision making in small towns differ from those in more rural settings.

Conclusion

Using nationwide data, we found that Medicare beneficiaries with rectal cancer who live in rural areas and small towns are more likely to receive standard of care surgery and radiation than patients who live in more metropolitan areas. Rural radiation patients were less likely to be treated with IMRT. Lastly, there appeared to be a similar utilization of radiation modalities and time to radiation treatment regardless of geographic differences. Future studies should explore underlying causes for this observed geographic variation.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023. 101286.

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