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Geographic disparity in the use of hypofractionated radiotherapy among elderly women undergoing breast conservation for invasive breast cancer

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Abstract

PURPOSE—Research demonstrates that the use of short-course (hypofractionated) radiotherapy (RT) breast cancer in the US has lagged behind other countries, despite evidence from randomized trials. This study evaluates geographic heterogeneity in the delivery of hypofractionated radiotherapy among Medicare beneficiaries across the US.

METHODS—We identified 190,193 patients from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse. The study included patients over age 65 diagnosed with invasive breast cancer treated with breast conservation surgery followed by radiation diagnosed between 2000 and 2012. We analyzed data by hospital referral region based on patient residency zip code. The proportion of women who received hypofractionated RT within each region was analyzed over the study period. Multivariable logistic regression models identified predictors of hypofractionated RT.

RESULTS—Over the entire study period we found substantial geographic heterogeneity in the use of hypofractionated radiotherapy. The proportion of women receiving hypofractionated breast RT in individual hospital referral regions varied from 0% to 61%. We found no correlation between the use of hypofractionated RT and urban/rural setting or general geographic region. The proportion of hypofractionated RT increased in regions with higher density of radiation oncologists, as well as lower total Medicare reimbursements.

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CONCLUSIONS—This study demonstrates substantial geographic heterogeneity in the use of hypofractionated radiotherapy among elderly women with invasive breast cancer treated with lumpectomy in the US. This heterogeneity persists despite clinical data from multiple randomized trials proving efficacy and safety compared to standard fractionation, and highlights possible inefficiency in healthcare delivery.

Keywords

breast cancer; radiotherapy dose fractionation; breast-conserving surgery; physician's practice patterns; delivery of health care

BACKGROUND

Breast conservation therapy, involving lumpectomy and adjuvant radiotherapy (RT), is the treatment of choice for many women with early stage breast cancer¹. Postlumpectomy RT reduces the risk of local recurrence and long-term breast cancer mortality², with multiple randomized clinical trials showing overall survival equivalent to mastectomy. Clinical data established 5–7 weeks of whole breast RT as standard in the US, based on radiobiologic data suggesting that small daily doses of radiation (1.8–2.0 Gy per day) would preserve normal breast tissue^{2–5}. However, as early as 1992, Clark et al had demonstrated similar efficacy with a shorter 3–4-week radiotherapy regimen (using 2.66 Gy per day) for women with early stage disease⁶. This experience with short-course (also called hypofractionated) radiotherapy led to considerable variation in practice both in Canada and Europe^{7, 8}.

Such variation sparked three large randomized trials from Canada and the United Kingdom comparing hypofractionated RT to the standard longer course^{9–12}. Long-term results now confirm similar local control, overall survival, and side effects including acute breast swelling and long-term cosmetic outcomes. These trials are not without caveats, specifically regarding patients with node-positive disease, but they point to a large cohort of patients that qualify for a shorter course of RT.

The significance of radiotherapy course length impacts many potential stakeholders. From the patient's perspective, longer courses of RT require increased patient time and could impact a patient's decision about whether to pursue breast conservation therapy or mastectomy¹³. As of 2007, only 66% of women in the US with stage I–II breast cancer received breast conservation¹⁴, with main factors driving choice including surgeon recommendation and geography¹³. Furthermore, up to 15% of patients fail to receive radiotherapy when indicated after breast-conserving surgery¹⁵. From a societal healthcare standpoint, shorter courses of RT lead to decreased resource utilization and decreased cost, while potentially increasing quality of care on a population level^{16, 17}.

Therefore, as of 2008, the NCCN clinical guidelines have recommended the use of short-course RT as a treatment option for appropriate patients¹. In 2011, ASTRO published clinical guidelines describing a subset of patients deemed safe to treat with short-course breast RT¹⁸. Specifically, this recommendation included patients age 50 and older with T1-2, N0 tumors who did not receive chemotherapy and achieved dose homogeneity of $\pm 7\%$ in the central axis plane at the time of radiation planning. Notably, this was prior to publication of

long-term results of UK START trials in 2013 which included larger numbers of patients with pN1 disease who were treated with chemotherapy¹⁹. In 2013, ASTRO highlighted patient and physician discussion of short-course radiotherapy as the number one issue in the American Board of Internal Medicine's Choosing Wisely campaign¹⁸, a nationwide effort to promote effective use of health care resources.

Despite increased advocacy for its use, the rates of use of hypofractionated RT for early-stage breast cancer in the United States continue to be low. One publication of SEER-Medicare linked data shows that as recently as 2009–2010, the adoption rate of hypofractionated RT in the subset of patients meeting strict ASTRO guideline criteria remained as low as 14%²⁰. An even more recent study of private insurance claims data found rates of 8–11% in 2008 increasing to 21–35% in 2013¹⁶. This contrasts markedly to Canada where short-course RT in Ontario was up to 71% by 2008 in all patients postlumpectomy²¹. Of note, these initial studies in the US showed that tumor-related factors (including tumor size, grade, or breast laterality) were not associated with the low uptake of hypofractionated RT. They did, however, notice general regional trends.

Geographic heterogeneity in health care utilization has been rigorously studied in the US Medicare population and is thought to represent a symptom of inefficiency^{22, 23}. One study of Medicare expenditures found significant geographic variation that persists after controlling for demographics and health status of populations, and hypothesized that Medicare reform could reduce Medicare spending by 15%²⁴. Prior research studying the uptake of hypofractionated RT in the US has not thoroughly addressed the role of geography beyond general regional trends. The purpose of this study was to evaluate geographic variability in the delivery of hypofractionated RT across the US in a large representative cohort of women with breast cancer.

MATERIALS & METHODS

Study Population

This study identified Medicare beneficiaries with invasive breast cancer from the Centers for Medicare & Medicaid Services (CMS) Chronic Condition Data Warehouse. The Chronic Condition Data Warehouse contains demographic information, insurance coverage status, and comprehensive claims data for 100% of Medicare beneficiaries within the US. Our initial query of the database revealed 1,497,619 women with breast cancer over the age of 65 with evidence of an invasive breast cancer between January 1st, 2001, and December 31st, 2012. Unlike conventional cancer registries Medicare does not explicitly collect information on the diagnosis of breast cancer, therefore a validated algorithm was used to identify patients with breast cancer. Briefly, patients with breast cancer must have had at least 1 inpatient, skilled nursing facility, or 2 hospital outpatient or Carrier claims with the following ICD-9 codes: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3.^{25–28} In order to capture information on patient comorbidity and patterns of care after diagnosis we required continuous enrollment in Medicare Parts A and B, without enrollment in Part C for at least 1 year before and 1 year after diagnosis leaving 1,002,995 patients.

Medicare Part C includes managed care organizations which do not routinely submit billing claims. Further exclusion criteria are listed below, and the entire patient selection algorithm is demonstrated in Supplemental Figure 1.

Treatment variables

We used International Classification of Disease (ICD-9) codes and Healthcare Common Procedure Coding System (HCPCS) codes to identify lumpectomy and radiotherapy (see Supplemental Table 1 for codes). We restricted our analysis to women receiving cancer treatment within one year of diagnosis, including both lumpectomy (337,420) and radiotherapy (210,158). Additionally, we excluded the small fraction of patients who received mastectomy after lumpectomy (7,354 patients). For RT the number of fractions delivered was estimated from the number of unique days with a billing claim for each radiation treatment. Patients can receive multiple separate courses of RT over time if they develop progressive or metastatic disease; therefore, we assumed that any break in radiation treatment codes of more than 14 days indicated a separate course of radiotherapy. Among patients receiving multiple courses of RT we included only the first course of treatment as this was most likely delivered with adjuvant intent. Keeping consistent with existing research we defined hypofractionated RT as 13–24 total fractions and conventional RT as 25–36 total fractions²⁰. We excluded the small number of patients who received non-standard RT courses including <13, or >36 fractions, leaving 190,193 patients in our final analysis. Medicare does not record stage, though we hypothesized that women receiving lumpectomy followed by radiation would very likely have early stage breast cancer. We have independently assessed the patient selection algorithm on a separate dataset which found that 96% of cases had stage I–II breast cancer (see Supplementary Appendix for additional detail).

Other study variables

Demographic covariates included race (white, black and other), age at diagnosis (66–69, 70–74, 75–79, 80+), median income quartile, rural/urban location, and year of diagnosis. Median household income was defined from the 2000 US census, and divided into quartiles for analysis with missing data re-classified into the lowest quartile²⁹. Urban or rural status was defined using Rural-Urban Commuting Area codes with missing data classified as rural. We categorized the year of diagnosis into 2001–2003, 2004–2006, 2007–2009, 2010–2012 in order to correspond with the publication of the Canadian trial (2002)¹², and the START trials (2008)^{9, 10}. Comorbidity was defined from Medicare claims during the 12 months prior to diagnosis with the Deyo adaptation of the Charlson comorbidity index^{30, 31}. The use of intensity modulated radiation therapy (IMRT) was defined as the presence of an IMRT billing claim during radiation treatment (see Supplemental Table 1). Other study variables included the use of chemotherapy, breast magnetic resonance imaging (MRI) the year prior to surgery, receipt of screening mammogram (differentiated from diagnostic mammogram using methods per Fenton et al³²), and care delivered in a teaching hospital defined as the presence of an indirect medical education payment within 12 months after diagnosis.

Statistical Analysis

We performed a basic descriptive analysis of patient and hospital characteristics and evaluated patterns of hypofractionated RT over the study period. Beneficiary zip codes were used to assign women to a hospital referral region (HRR). There are 306 hospital referral regions spread across the US, and each distinct geographic region represents a pre-defined healthcare market for tertiary care services³³. We used ArcGIS (ESRI, Redlands CA) to map the proportion of women who received hypofractionated RT within each HRR. We mapped hypofractionated RT across the whole study period, and evaluated trends over time by separately mapping the years 2001–2003, 2004–2006, 2007–2009, and 2010–2012. We used pre-specified multivariable logistic models to assess factors that were potentially associated with the use of hypofractionated RT versus conventional RT (specific factors listed in demographic table). We searched for correlations in the regional use of hypofractionated RT and select aggregate regional healthcare characteristics including measures of healthcare density (number of acute care hospital beds per 1,000 residents), radiation oncologist density (number of radiation oncologists per 100,000 residents), and general overall healthcare expenditure (Medicare reimbursements per enrollee). Regional healthcare characteristics were obtained from the Dartmouth Atlas^{34, 35}. Healthcare density was estimated from the number of acute care hospital beds captured by the Annual Survey of Hospitals divided by the regional population according to the U.S. Census. Radiation oncologist density comes from the number of radiation oncologists in the American Medical Association Physician Masterfile divided by the regional population according to the U.S. Census.

Healthcare expenditure was estimated by summing Medicare reimbursement rates divided by the number of Medicare beneficiaries enrolled in Parts A and B on January 1 of the measurement year. Regional healthcare characteristics change yearly, though we evaluated these characteristics at a static timepoint in the year 2006 (midway through our study period). Associations between the use of hypofractionated RT and aggregate healthcare measures were assessed with Somers' D test^{36, 37}. Analyses were performed on the CCW server using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

RESULTS

Among the 190,193 patients in this study, the median proportion of hypofractionated breast RT increased steadily across the whole country over the study period, from 4.3% in 2001–2003, to 22.0% in 2010–2012. We did observe substantial geographic heterogeneity by healthcare referral region (HRR), with the proportion of women receiving hypofractionated RT varying from 0% to 61% during the entire study period from 2000–2012 (Figure 1). The vast majority (91%) of HRRs showed increased use of hypofractionated RT over the period between 2001–2003 and 2010–2012, though the geographic heterogeneity persisted (Figure 2). No single region was noted to have significantly higher or lower rates of use of hypofractionation than any other region except possibly a trend for increased use in the mountain west, especially notable in the years 2007–2009 and 2010–2012.

On multivariable analysis (Table 1) we found increased use of hypofractionated RT among non-White patients, older women, and those with higher median household income level. Treatment at a teaching hospital was also associated with a slight increase in the use of

hypofractionated RT. On the other hand, the use of chemotherapy, the use of IMRT, and history of breast MRI were all independently associated with decreased use of hypofractionated RT. Of note, neither Charlson comorbidity score nor urban/rural location were associated with hypofractionated RT.

Finally, we looked for correlations in the regional use of hypofractionated RT and select aggregate regional healthcare characteristics (Table 2). From a regional viewpoint the use of hypofractionated RT increased with a corresponding increase in the density of local radiation oncologists ($p=0.0003$). On the other hand, an increase in the use of hypofractionated RT was associated with a slight decrease in the number of regional hospital beds ($p<0.0001$), and decreased annual Medicare spending per enrollee ($p=0.0003$).

DISCUSSION

Publication of multiple randomized clinical trials show equivalent efficacy and toxicity of hypofractionated RT compared to standard fractionated RT for early stage breast cancer. Both the NCCN guidelines and ASTRO Choosing Wisely campaigns highlight the importance of considering hypofractionated RT among appropriate women with breast cancer. Nonetheless, we found that the rate of hypofractionated RT continues to be low in the US, with only 22% of women receiving hypofractionated RT by 2010–2012. Additionally, we demonstrate substantial geographic heterogeneity in the delivery of hypofractionated radiation across the US – with regional rates ranging from 0% to 61% – suggesting the potential for inefficient healthcare delivery.

Previous research by Jagsi, et al. involving the Surveillance Epidemiology and End Results (SEER)-Medicare linked data found little correlation between hypofractionated RT and tumor-specific characteristics including stage, grade, or breast laterality. This current study demonstrates substantial geographic heterogeneity in the use of hypofractionated RT in a very large population of Medicare patients across the US. The findings of our study in light of the Jagsi study²⁰ suggest that geography, and not tumor characteristics, drives the type of radiotherapy delivered in elderly women with breast cancer in the US.

One could argue that patients in rural settings stand to benefit more from shorter courses of radiation given the higher likelihood of living further from a radiation oncology treatment facility. Additionally, long courses of RT could create barriers to breast conservation altogether in rural settings¹³, leading to increased rates of mastectomy. Despite the rationale for short-course RT in rural settings we found that population density had no association with rate of hypofractionated RT use in our study, which agrees with previous research evaluating hypofractionated RT^{16, 20}. Geographic heterogeneity in healthcare delivery has been investigated in the US Medicare population and is thought to represent a symptom of inefficiency in health care delivery. Some reports estimate that decreased heterogeneity could reduce Medicare expenditures by 15–30% without compromising quality of care delivered^{22–24}.

Beyond geography we found that both treatment at a teaching hospital and treatment in communities with more radiation oncologists were associated with higher rates of

hypofractionated RT. This suggests that the healthcare environment and network of providers could play a role in shaping the patterns of radiotherapy delivery in their specific community. Factors influencing individual providers could include access to peer review and continuing medical education in an academic setting. Additionally, in a competitive environment, referring providers such as surgical and medical oncologists might preferentially refer to radiation oncologists more willing to deliver hypofractionated RT. One must also consider the influence of the individual radiation oncology provider on geographic heterogeneity. Wide variations in patterns of care are often not attributable to a small number of physicians, though one study of rate of carotid endarterectomy did find that a few surgeons in the high use areas may explain a large portion of the variation³⁸. Further research should focus on the influence of the radiation oncologist on treatment heterogeneity.

Meanwhile, financial incentives in the current fee-for-service reimbursement system tend to reward radiation oncologists for delivering longer courses of radiotherapy, regardless of efficacy. Our data suggests increased use of hypofractionated RT in regions with decreased Medicare spending. This finding does not imply that hypofractionated RT accounts for this decrease in spending, though this could indicate that hypofractionated RT delivery occurs in geographic regions which deliver more cost-effective care. Among the patients treated with hypofractionated radiation we found lower rates of more costly IMRT, which further supports the potential for regionalization of cost-conscious healthcare delivery.

The primary strength of this study arises from the wide breadth and large number of women in our study cohort. The study population extends across the US including regions not covered in standard registry-based studies. The primary limitation of these data includes the lack of clinical and tumor-specific information. On one hand, these unaccounted for confounding clinical and tumor variables could account for a part of the geographic variability in hypofractionated RT. On the other hand, prior research found that tumor size, tumor grade, and breast laterality did not influence the rates of hypofractionated RT^{20, 39}, suggesting the lack of clinical variables may not substantially impact our results. The possibility exists of erroneously including women with locally-advanced, or metastatic breast cancer. However, we did control for the use of screening mammography, and chemotherapy which could partially serve as surrogates for tumor stage. Mammographically detected tumors present at earlier stages⁴⁰, and chemotherapy is more frequently used with later stage tumors. Another limitation of this study relates to the lack of women under age 65. Elderly women were the best-represented population in the randomized clinical trials establishing the utility of hypofractionated RT, however we cannot extrapolate our findings to a younger population.

In conclusion, this study demonstrates substantial geographic heterogeneity in the use of hypofractionated radiotherapy among elderly women with breast cancer in the US. There are many potential factors underlying this heterogeneity including provider training and preferences, institutional practices and referral patterns, and patient preferences. Low utilization of hypofractionated radiotherapy coupled with geographic heterogeneity suggests inefficiency in our health care system in the face of strong data from randomized clinical

trials. Further studies should evaluate the role of the provider, healthcare system, as well as the influence of reimbursement policy on treatment decisions in radiation oncology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY

Among 190,193 women age 65 and older undergoing breast conservation for invasive breast cancer in the United States from 2000–2012, the proportion of women receiving hypofractionated radiotherapy (3–4 weeks) varied from 0% to 61%. In the setting of strong data from randomized clinical trials showing efficacy and safety compared to conventionally fractionated breast radiotherapy (5–7 weeks), the slow uptake of hypofractionated breast radiotherapy coupled with geographic heterogeneity suggests inefficiency in our health care system.

Figure 1.

Proportion of patients with breast cancer receiving hypofractionated RT following breast conserving surgery per hospital referral region (HRR) for all years combined. Shading of each region represents fraction of women who received hypofractionated (13–24 total fractions) compared to standard fractionated radiation (25–36 total fractions).

Figure 2.

Proportion of patients with breast cancer receiving hypofractionated RT following breast conservation per HRR by year. Shading of each region represents fraction of women who received hypofractionated (13–24 total fractions) compared to standard fractionated RT (25–36 total fractions).

Table 1

Radiotherapy by selected demographic and clinical characteristics

Characteristic	Radiotherapy (RT)		Adjusted OR (95% CI)	p-value
	Hypofractionated (13–24)	Conventional (25–36)		
	n (%)	n (%)		
Race				
White	17,356 (10.0%)	155,845 (90%)	1	–
Black	1,241 (10.4%)	10,749 (89.6%)	1.08 (1.01–1.15)	0.0172
Other	678 (13.6%)	4,324 (86.4%)	1.29 (1.18–1.40)	<0.0001
Age at diagnosis				
66–69 years	4,010 (7.8%)	47,139 (92.2%)	1	–
70–74 years	5,259 (9.0%)	53,148 (91.0%)	1.18 (1.13–1.24)	<0.0001
75–79 years	4,789 (10.4%)	41,466 (89.6%)	1.42 (1.36–1.49)	<0.0001
80+ years	5,217 (15.2%)	29,165 (84.8%)	2.13 (2.03–2.23)	<0.0001
Year of diagnosis				
2001–2003	2,245 (4.3%)	49,831 (95.7%)	1	–
2004–2006	2,391 (5.0%)	45,775 (95.0%)	1.18 (1.11–1.25)	<0.0001
2007–2009	4,908 (10.7%)	40,791 (89.3%)	2.81 (2.66–2.97)	<0.0001
2010–2012	9,731 (22.0%)	34,521 (78.0%)	6.86 (6.51–7.23)	<0.0001
Charlson comorbidity				
0	13,364 (9.3%)	130,162 (90.7%)	1	–
1	4,013 (11.9%)	29,839 (88.1%)	0.96 (0.93–1.00)	0.0547
2	1,258 (14.3%)	7,558 (85.7%)	1.00 (0.94–1.07)	0.9918
3 or more	640 (16.0%)	3,359 (84.0%)	1.00 (0.91–1.09)	0.9724
Chemotherapy				
No	16,680 (10.8%)	137,342 (89.2%)	1	–
Yes	2,595 (7.2%)	33,576 (92.8%)	0.65 (0.62–0.68)	<0.0001
RT technique				
non-IMRT	16,089 (9.9%)	147,177 (90.1%)	1	–
IMRT	3,186 (11.8%)	23,741 (88.2%)	0.93 (0.90–0.97)	0.0016
MRI				
No	14,033 (9.6%)	131,592 (90.4%)	1	–
Yes	5,242 (11.8%)	39,326 (88.2%)	0.95 (0.92–0.99)	0.0057
Teaching hospital				
No	14,093 (11.4%)	110,059 (88.6%)	1	–
Yes	5,182 (7.8%)	60,859 (92.2%)	1.06 (1.02–1.10)	0.0027
Median income quartile				
Bottom quartile	4,235 (8.9%)	43,303 (91.1%)	1	–
Second quartile	4,292 (9.0%)	43,239 (91.0%)	1.02 (0.97–1.07)	0.4555
Third quartile	4,581 (9.6%)	42,925 (90.4%)	1.09 (1.04–1.15)	0.0004
Top quartile	6,167 (13.0%)	41,451 (87.0%)	1.50 (1.43–1.58)	<0.0001

Characteristic	Radiotherapy (RT)		Adjusted OR (95% CI)	p-value
	Hypofractionated (13–24)	Conventional (25–36)		
	n (%)	n (%)		
Location				
Rural	3,879 (9.0%)	39,233 (91.0%)	1	–
Urban	15,396 (10.5%)	131,685 (89.5%)	1.03 (0.98–1.07)	0.2273

Table 2

Use of hypofractionated radiotherapy and corresponding regional healthcare characteristics

	Hypofractionated radiotherapy use by healthcare referral region					p-value for trend
	Bottom quintile	2 nd quintile	3 rd quintile	4 th quintile	Top quintile	
Proportion of hypofractionated RT – median (range)	3.2 % (0–4.2%)	5.4% (4.2–6.2%)	7.4% (6.3–9.0%)	10.8% (9.0–13.3%)	17.4% (13.3–46.6%)	–
Acute Care Hospital Beds per 1,000 Residents (2006)	2.87	2.58	2.37	2.37	2.36	<0.0001
Radiation Oncologists per 100,000 Residents (2006)	0.98	1.07	1.09	1.32	1.16	0.0003
Medicare reimbursements per enrollee (2006)	\$8,276	\$8,054	\$7,944	\$7,703	\$7,741	0.0003

* total Medicare reimbursements per enrollee were price, age, sex and race-adjusted