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Running Title: "Hospitalization-Associated RT Interruptions"

Independent Predictors for Hospitalization-Associated Radiotherapy Interruptions

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Abstract:

Purpose: Radiation treatment interruption associated with unplanned hospitalization remains understudied. The intent of this study was to benchmark frequency of hospitalization-associated radiotherapy interruptions (HARTI), characterize disease processes causing hospitalization during radiation, identify factors predictive for HARTI, and localize neighborhood environments associated with HARTI at our academic referral center.

Methods: Retrospective review of electronic health records provided descriptive statistics of HARTI event rates in our institutional practice. Univariable and multivariable logistic regression models were developed to identify significant factors predictive for HARTI. Causes of hospitalization were established from primary discharge diagnoses. HARTI rates were mapped according to patient residence addresses.

Results: Between January 1, 2015, and December 31, 2017, 197 (5.3%) HARTI events were captured across 3,729 patients with 727 total missed treatments. The three most common causes of hospitalization were malnutrition/dehydration (n=28, 17.7%), respiratory distress/infection (n=24, 13.7%), and fever/sepsis (n=17, 9.7%). Factors predictive for HARTI included African American race (OR, 1.48; 95% CI, 1.07-2.06; *P* = 0.018), Medicaid/uninsured status (OR, 2.05; 95% CI, 1.32-3.15; *P* = 0.0013), Medicare coverage (OR 1.7; 95% CI, 1.21-2.39, *P* = 0.0022), lung (OR 5.97; 95% CI, 3.22-11.44; *P* < 0.0001) and head and neck (OR 5.6; 95% CI, 2.96-10.93; *P* < 0.0001) malignancies, and prescriptions greater than 20 fractions (OR 2.23; 95% CI, 1.51-3.34; *P* < 0.0001). HARTI events clustered among 1) Medicaid/uninsured patients living in urban, low-income, majority-African American neighborhoods, and 2) patients from middle-income suburban communities, independent of race and insurance status. Only the wealthiest residential areas demonstrated low HARTI rates.

Conclusion: HARTI disproportionately impacted socioeconomically disadvantaged urban patients facing high treatment burden in our catchment population. Complementary geospatial analysis also captured risk experienced by middle-income suburban patients independent of race or insurance status. Confirmatory studies are warranted to provide scale and context to guide intervention strategies to equitably reduce HARTI events.

Introduction

Radiation therapy is an integral component of cancer care. Approximately 50% of all cancer patients will undergo at least one course of radiation treatment [1]. Optimal tumor control

requires strict adherence to daily treatment scheduling. Unplanned interruptions are associated with inferior outcomes, including reduced overall survival [2-8].

Hospitalization during radiotherapy is a severe, potentially preventable complication of treatment [9, 10]. Limited data are available to identify specific causes for hospitalization during radiotherapy [10]. The purpose of this study was to catalog hospitalization rates during radiation therapy and to identify patient-specific demographic, clinical, and treatment factors predictive for hospitalization-associated radiotherapy interruptions (HARTI) at our academic referral center. We also employed secondary geospatial analysis to identify residential neighborhood environments most closely associated with interruption events to localize potential need for interventional support to protect vulnerable populations [11].

Methods

Patient Population

Institutional IRB approval was obtained to examine electronic health records for patients receiving radiation treatment. Patients were included if they were scheduled to begin RT between January 1, 2015, and December 31, 2017. Only those who initiated therapy were included in the study.

Outcome Measures

The primary outcome of the study was frequency of hospitalization-associated radiotherapy interruption (HARTI). HARTI was defined as any unplanned cancellation of scheduled radiotherapy associated with hospitalization during radiotherapy. Hospitalization was

defined as emergency department visits as well as inpatient admissions with levels of care ranging from observation to the intensive care unit.

Secondary outcomes included causes of hospitalization defined by patient primary diagnoses at time of discharge, as well as identification of patient-specific demographic, clinical, and treatment factors significantly predictive for hospitalization-associated radiotherapy interruptions.

Data Collection

Patient demographic, clinical, and treatment information was compiled from electronic medical records. Patient predicted income (PPI) was categorized according to median household income from 2016 federal census information at the census tract level and was stratified into low (<$34,000), middle ($34,000-$67,000), and high (>$67,000) thirds for statistical analysis. Residence addresses were mapped at the zip code level for the purpose of geospatial analysis. The season in which patients began treatment was divided into winter (November through February) or non-winter (March through October). Travel distance to the treating facility for individual patients was measured from residence zip code centroids. Rurality of patients' home addresses was defined according to the United States Department of Agriculture 2013 Rural-Urban Continuum Codes.

Statistical Analysis

Descriptive statistical analyses were performed to classify the frequency of HARTI events across the demographic, clinical, and treatment variables. Chi-squared tests were performed to determine significance. Post-hoc pairwise chi-squared tests were utilized to further

identify significant factors within each categorical variable. Univariable logistic regression models were developed to determine significant factors from among those previously identified for predicting any interruption event [12-14]. Subsequent stepwise logistic regression models identified those variables most predictive for HARTI, and a multivariable logistic regression model was created to determine significant independent predictors. P values were two sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using RStudio version 1.3.959 (PBC, Boston, MA) and SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Geospatial Analysis

Frequency of HARTI was mapped at the level of residence zip codes and stratified according to patient race and insurance status to identify HARTI hotspots. Geographic data was plotted with RStudio version 1.3.959 (PBC, Boston, MA) using the GIS package ggmap: Spatial Visualization was performed with ggplot2 (Kahle and Wickham, 2013).

Results

Cohort Characteristics

A total of 3,729 patients received 72,964 fractions of EBRT between January 1, 2015, and December 31, 2017 with an average prescription of 20 fractions. Of the 3,729 patients, 3,487 (93.5%) completed the entire prescribed regimen. Patient characteristics are described in **Table 1.** Average patient age was 61.2 years. Two thousand sixty-five (55.4%) patients were female, 2,195 (58.9%) were below the age of 65, 2,032 (54.5%) were Caucasian, 1,577 (43.3%) African American, and 120 (3.2%) reported a race other than Caucasian or African American. Hispanic ethnicity was reported by 50 (1.3%) patients. One thousand nine-hundred and sixty-seven

(52.7%) patients were married. Insurance status was recorded as commercial for 1,794 (48.1%) patients, Medicare for 1,503 (40.3%), and Medicaid/uninsured for 432 (11.6%) (221 Medicaid and 211 uninsured patients, 5.9% and 5.7%, respectively). One thousand twelve (27.1%) patients fell within the low, 1,532 (41.1%) within the medium, and 1,149 (30.8%) within the high PPI categories. The most common sites being treated were breast (n=974, 26.1%), metastases (n=490, 13.1%), and prostate (n=413, 11.1%) with 976 (26.1%) patients receiving most commonly 26-30 fractions, 689 (18.5%) >30 fractions, and 586 (15.7%) 16-20 fractions. Most patients (n=2,455, 65.8%) began treatment in non-winter months. The mean distance between patient residence and the treatment facility was 23.7 miles with a median of 9.1 miles (standard deviation 103.3, interquartile range 5.4-15.6).

Hospitalization-Associated RT Interruption

HARTI was observed in 197 (5.3%) patients with a total of 727 scheduled treatments missed. Patients missed between 1 and 21 treatments with a median of 2 treatments and a mean of 3.69 treatments (standard deviation 4.13, interquartile range 1-5). Of the 197 patients, 83 (42.1%) missed only one treatment.

Causes of Hospitalization

Of the 197 patients to experience HARTI, an identifiable cause of hospitalization was found in 175 patients. **Table 2** details the most common principal problems associated with hospitalization as determined by primary discharge diagnoses. The most common primary disease processes leading to hospitalization were malnutrition/dehydration (n = 28, 28.7%),

respiratory distress or infection (n = 24, 13.7%), fever/sepsis (n = 17, 9.7%), inadequate pain control (n = 16, 9.1%), renal dysfunction (n = 15, 8.6%), and chest pain (n = 15, 8.6%).

Predictive Factors for HARTI

Table 1 details the proportion of patients who experienced HARTI among several demographic, clinical, and treatment factors. Chi-squared analysis identified statistically significant differences in the proportion of patients experiencing HARTI among each factor. Increased likelihood of HARTI was seen among African American (6.3% vs 4.4% for Caucasian, $P = 0.016$) and unmarried (6.4% vs 4.3% for married, $P = 0.007$) patients. Pairwise chi-squared analysis further demonstrated that patients treated for lung (10.8%) and head and neck (10.7%) malignancies were significantly more likely to experience HARTI when compared to patients treated for breast (1.7%) malignancies. Patients treated for malignancies with regimens composed of 26-30 (7.0%) and >30 fractions (8.1%) were more likely to experience HARTI compared to those with treatment regimens composed of either 1-5 (1.2%) or 16-20 (2.2%) fractions. Medicare patients were almost twice as likely to experience HARTI (6.3% vs 3.5% for commercially insured, $P = 0.0002$), and Medicaid/uninsured patients almost three times as likely (9.0% vs 3.5%, $P < 0.0001$) with 10.4% of uninsured patients experiencing HARTI ($P < 0.0001$ vs commercial).

Univariable and Multivariable Analyses of HARTI

Findings for both univariable analysis (UVA) and multivariable analysis (MVA) models predicting HARTI are described in **Table 3**. On MVA, African American patients had an almost 50% greater odds to experience HARTI (OR, 1.48; 95% CI, 1.07-2.06; $P = 0.018$) compared to

Caucasian patients. Additionally, both Medicare (OR 1.7; 95% CI, 1.21-2.39, *P* = 0.0022) and Medicaid/uninsured patients (OR, 2.05; 95% CI, 1.32-3.15; *P* = 0.0013) had greater odds of HARTI compared to patients with commercial insurance. Those treated more than 20 fractions were more likely (OR 2.23; 95% CI, 1.51-3.34; *P* < 0.0001) to experience HARTI than those receiving fewer than 20 fractions. Compared to patients treated for breast cancer, significantly higher odds of HARTI were seen among patients treated for lung (OR 5.97; 95% CI, 3.22-11.44; *P* < 0.0001), head and neck (OR 5.6; 95% CI, 2.96-10.93; *P* < 0.0001), gynecologic (OR 2.57; 95% CI, 1.20-5.40; *P* = 0.013), gastrointestinal (OR 2.55; 95% CI, 1.13-5.56; *P* = 0.02), CNS (OR 2.71; 95% CI 1.00-6.60, *P* = 0.036), metastatic (OR 3.46; 95% CI, 1.69-7.13; *P* = 0.0007), and skin malignancies (OR 4.37; 95% CI, 1.58-11.01; *P* = 0.0026).

Variables predictive for HARTI on UVA that did not reach statistical significance on MVA included marriage status and travel distance to treatment facility.

Geospatial Analysis of HARTI

The greater XXX metropolitan region has been historically shaped by racial and socioeconomic segregation. Central XXX is comprised predominantly of African American neighborhoods, clustered into areas with limited social resources apart from smaller majority White neighborhoods. Suburban/exurban XXX has gradually become more racially diverse but remains majority Caucasian with affluent regions interspersed with middle and low-income rural zip codes. Geospatial analysis of our patient's reported home addresses mapped at the zip code level (**Figures 1 and 2)** identified associations between HARTI and patient home location. The highest rates were observed in Medicaid/uninsured patients living in urban, low-income, majority-African American neighborhoods. Moving outward from downtown, elevated HARTI

rates were observed in middle-income suburban zip codes independent of patient race and insurance coverage. Only the wealthiest zip codes (the so-called “Poplar Corridor” of East XXX) demonstrated low rates of HARTI events.

Discussion

The Southeastern United States experiences some of the worst cancer outcomes in the country [15], attributable in part to socioeconomic burdens endemic to the region such as increased rurality and poverty, which are predictive for increased cancer mortality burden [16-18]. In our Mid-Southern academic referral practice, we have identified candidate risk factors for radiotherapy interruption associated with unplanned hospitalization. African American race, Medicaid/uninsured status, Medicare coverage, longer treatment regimens >20 fractions, and disease sites associated with high radiation toxicity were predictive for HARTI. Government-based coverage or lack of insurance was associated with up to 200% greater risk of HARTI compared to commercial insurance. African American patients faced nearly 50% increased risk, while patients with head and neck or lung cancer experienced almost 6 times the risk experienced by patients with breast malignancies.

The mechanistic pathways by which upstream social risk and health status factors impact radiation treatment quality are complex and difficult to disentangle. Various theories have been proposed to simplify explanation of persistent associations between social risk factors and health disparities in the face of ongoing improvement in public health and medical interventions over time [19]. The Fundamental Cause Theory is specifically relevant to our current study. As proposed and tested by Link and Phelan [20], this theory in simplest terms postulates that improvements in disease control fuel paradoxical health shortfalls in disadvantaged groups, since

advantaged individuals enjoy preferential access to such improvements. Privileged populations are less exposed to the causes of preventable disease and, when impacted, are better treated by virtue of better access to resources. Empirical data has supported the explanatory value of this model across numerous infectious, chronic disease, and mortality rate case examples [21-25], including race/ethnicity-specific COVID-19 transmission patterns observed in the United States [26]. In the case of HARTI, disadvantaged groups (e.g. minority race and/or those without commercial insurance) potentially face greatest risk exposure to preventable chronic disease, including cancer. When faced with the need for full-course radiotherapy for high-burden cancer diagnoses (e.g. head and neck, lung), these patients lack social, financial, and medical support to manage toxicity and comorbidities at home. Hospitalization and RT interruptions ensue, leading to preventable financial cost, morbidity, and outcomes disparities.

Although identification of specific root causes responsible for HARTI events in this study resided outside our scope of work, secondary geospatial analysis provided insight into residential environments associated with risk. HARTI impacted more patients living in urban low income, majority-minority neighborhoods, as well as suburban low-middle income areas. Expected income appeared to be more tightly associated with HARTI risk than race or insurance in the suburban setting. This echoes data demonstrating tight geographic association between entrenched county/zip code-level poverty and cancer mortality [17], even in the cooperative group trial setting [27]. Access to local assets and social networks intertwine with patient-level socioeconomic factors to determine individual vulnerability [11-13, 28]. Validated identification of specific social, financial, environmental, and health risks mechanistically responsible for HARTI risk in specific patients will be required to effectively triage supportive intervention strategies. Automated warehousing and linkage of high dimensional population-level social risk

data to individual-level electronic health record data is a realistic, testable strategy to achieve this [29, 30].

Previous studies have focused on Medicaid status or lack of insurance as predictive risk factors for radiotherapy interruption [12, 13]. We identified a novel risk for HARTI in our Medicare patient population, potentially attributable to co-existing health issues in this older population. Up to 70% of Medicare beneficiaries have at least two chronic conditions and 14% have six or more comorbidities requiring treatment [31]. It is reasonable to presume that such comorbidities predispose Medicare patients to increased radiation-related toxicity, thereby increasing their risk of hospitalization [32-34]; this would be a testable hypothesis in confirmatory studies.

Progression of toxicity to the point of unplanned hospitalization may signal inadequacies in supportive management and/or coordination with primary care providers. Individualized supportive care strategies employing real-time, automated collection of patient-reported toxicities and responsive supportive care have been shown to be effective during chemotherapy [35-37] and could be formally investigated in the radiation treatment setting. Many of the causes for hospitalization we found were preventable and could be identified by upfront patient risk stratification. Many hospitalizations could be preempted by primary care teams already familiar with patients. Formal coordination pathways between cancer and primary providers unfortunately remains relatively understudied and is a straightforward path towards holistic care [38-40]. Other institutions have investigated implementation of other interventions, such as patient symptom inventories and intensified visit schedules, and have found these to significantly reduce hospitalizations during cancer treatment [9, 41].

Reducing hospitalization during radiotherapy would potentially provide significant value. Patients would benefit from optimized cancer treatment outcomes and reduced suffering. All stakeholders, notably provider systems and insurers, would directly benefit from cost savings and improved capacity. From the perspective of Medicare, the average cancer diagnosis-related hospitalization can generate costs totaling more than twice the expected charges for a standard-fractionated radiation treatment course [42, 43]. All patients, insured or uninsured, share direct out-of-pocket expenses from hospitalizations. Stressed families and caregivers are additionally impacted by indirect costs and lost income opportunities.

Our study has limitations which impact interpretation and generalizability of our findings. First, this is relatively small study population sampled from a single metropolitan region, managed by one provider system, with only 197 HARTI events being captured. It is important to note that the full XXX region surrounding our academic care center is served by several hospital systems, each with siloed electronic health record platforms. If any patients were admitted to outside hospitals in the area, their respective HARTI events would not have been captured. Second, causes for hospitalization were cataloged retrospectively from discharge diagnoses; conclusive association (or lack of association) of hospitalization events with cancer-specific treatment was not possible to establish. Third, impact specific to hospitalization on downstream cancer outcomes relative to RT interruption was not addressed by this data. Finally, it is important to recognize that some zip codes in outlying suburban areas contained small total numbers of captured patients, so any single event would disproportionately impact our risk metric. Full regional sampling of all cancer patients treated with radiotherapy in the region would be required to correct for this. Prompted by COVID-19, we are creating a unified public health observatory for the full XXX region to achieve this goal in future studies [44]. We expect

our baseline results to focus more definitive work toward candidate neighborhoods and patient populations most in need.

Conclusion

In our academic referral practice, we found RT interruptions during unplanned hospitalizations to be associated with Medicaid/uninsured or Medicare coverage, African American race, prolonged treatment course, and treatment of sites with high symptomatic burden requiring intensive treatment. Complementary geospatial analysis identified risk hotspots in low income, urban, majority African American neighborhoods, as well as suburban low-middle income areas independent of race or insurance coverage. These findings are hypothesis-generating and will require additional context via scaled-up sampling from a wider assortment of U.S. cities. Nonetheless, this work promises to guide design and validation of individualized social interventions to meaningfully reduce RT outcome disparities.

Declaration of interests

☒ 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.

References

1. Delaney, G., et al., *The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines.* Cancer, 2005. **104**(6): p. 1129-37.
2. Ohri, N., et al., *Radiation Therapy Noncompliance and Clinical Outcomes in an Urban Academic Cancer Center.* Int J Radiat Oncol Biol Phys, 2016. **95**(2): p. 563-70.
3. Yao, J.J., et al., *The detrimental effects of radiotherapy interruption on local control after concurrent chemoradiotherapy for advanced T-stage nasopharyngeal carcinoma: an observational, prospective analysis.* BMC Cancer, 2018. **18**(1): p. 740.
4. Hunter, A.J. and A.S. Hendrikse, *Estimation of the effects of radiotherapy treatment delays on tumour responses: A review.* South African Journal of Oncology, 2020. **4**.
5. Hanna, T.P., et al., *Mortality due to cancer treatment delay: systematic review and meta-analysis.* BMJ, 2020. **371**: p. m4087.
6. Mehta, S., et al., *Impact of radiotherapy duration on overall survival in squamous cell carcinoma of the anus.* J Gastrointest Oncol, 2020. **11**(2): p. 277-290.
7. Giddings, A., *Treatment Interruptions in Radiation Therapy for Head-and-Neck Cancer: Rates and Causes.* J Med Imaging Radiat Sci, 2010. **41**(4): p. 222-229.

8. McCloskey, S.A., et al., *Radiation treatment interruptions greater than one week and low hemoglobin levels (12 g/dL) are predictors of local regional failure after definitive concurrent chemotherapy and intensity-modulated radiation therapy for squamous cell carcinoma of the head and neck.* Am J Clin Oncol, 2009. **32**(6): p. 587-91.
9. Hong, J.C., et al., *Predicting Emergency Visits and Hospital Admissions During Radiation and Chemoradiation: An Internally Validated Pretreatment Machine Learning Algorithm.* JCO Clinical Cancer Informatics, 2018(2): p. 1-11.
10. Waddle, M.R., et al., *Unanticipated hospital admissions during or soon after radiation therapy: Incidence and predictive factors.* Pract Radiat Oncol, 2015. **5**(3): p. e245-e253.
11. Holzer, J., et al., *Health Hot Spots: Mapping Hospital Costs and Social Determinants of Health.* Open Journal of Preventive Medicine, 2014. **04**(09): p. 717-722.
12. XXX
13. Ohri, N., et al., *Predictors of radiation therapy noncompliance in an urban academic cancer center.* Int J Radiat Oncol Biol Phys, 2015. **91**(1): p. 232-8.
14. Thomas, K., et al., *Interruptions of Head and Neck Radiotherapy Across Insured and Indigent Patient Populations.* J Oncol Pract, 2017. **13**(4): p. e319-e328.
15. Siegel, R.L., et al., *Cancer Statistics, 2021.* CA: A Cancer Journal for Clinicians, 2021. **71**(1): p. 7-33.
16. Blake, K.D., et al., *Making the Case for Investment in Rural Cancer Control: An Analysis of Rural Cancer Incidence, Mortality, and Funding Trends.* Cancer Epidemiology Biomarkers & Prevention, 2017. **26**(7): p. 992-997.

17. Moss, J.L., et al., *Persistent Poverty and Cancer Mortality Rates: An Analysis of County-Level Poverty Designations.* Cancer Epidemiol Biomarkers Prev, 2020. **29**(10): p. 1949-1954.

18. Erhunmwunsee, L., et al., *Neighborhood-level socioeconomic determinants impact outcomes in nonsmall cell lung cancer patients in the Southeastern United States.* Cancer, 2012. **118**(20): p. 5117-5123.

19. Cockerham, W.C., B.W. Hamby, and G.R. Oates, *The Social Determinants of Chronic Disease.* Am J Prev Med, 2017. **52**(1S1): p. S5-S12.

20. Phelan, J.C., B.G. Link, and P. Tehranifar, *Social conditions as fundamental causes of health inequalities: theory, evidence, and policy implications.* J Health Soc Behav, 2010. **51 Suppl**: p. S28-40.

21. Noppert, G.A., et al., *Contemporary Social Disparities in TB Infection and Disease in the USA: a Review.* Curr Epidemiol Rep, 2018. **5**(4): p. 442-449.

22. Chang, V.W. and D.S. Lauderdale, *Fundamental cause theory, technological innovation, and health disparities: the case of cholesterol in the era of statins.* J Health Soc Behav, 2009. **50**(3): p. 245-60.

23. Phelan, J.C., et al., *"Fundamental causes" of social inequalities in mortality: a test of the theory.* J Health Soc Behav, 2004. **45**(3): p. 265-85.

24. Lutfey, K.E. and J.D. Ketcham, *Patient and provider assessments of adherence and the sources of disparities: evidence from diabetes care.* Health Serv Res, 2005. **40**(6 Pt 1): p. 1803-17.

25. Daw, J., *Explaining the Persistence of Health Disparities: Social Stratification and the Efficiency-Equity Trade-off in the Kidney Transplantation System.* AJS, 2015. **120**(6): p. 1595-640.

26. Clouston, S.A.P., G. Natale, and B.G. Link, *Socioeconomic inequalities in the spread of coronavirus-19 in the United States: A examination of the emergence of social inequalities.* Soc Sci Med, 2021. **268**: p. 113554.

27. Unger, J.M., et al., *Persistent Disparity: Socioeconomic Deprivation and Cancer Outcomes in Patients Treated in Clinical Trials.* J Clin Oncol, 2021. **39**(12): p. 1339-1348.

28. Shavers, V.L., *Racial and Ethnic Disparities in the Receipt of Cancer Treatment.* CancerSpectrum Knowledge Environment, 2002. **94**(5): p. 334-357.

29. XXX

30. Shin, E.K., Y. Kwon, and A. Shaban-Nejad, *Geo-clustered chronic affinity: pathways from socio-economic disadvantages to health disparities.* JAMIA Open, 2019. **2**(3): p. 317-322.

31. U.S. Centers for Medicare & Medicaid Services, *Chronic Conditions Among Medicare Beneficiaries Chartbook: 2012 Edition*. 2012.

32. Nalbantov, G., et al., *Cardiac comorbidity is an independent risk factor for radiation-induced lung toxicity in lung cancer patients.* Radiother Oncol, 2013. **109**(1): p. 100-6.

33. Lee, J.H., et al., *Influence of Comorbidities on the Efficacy of Radiotherapy with or without Chemotherapy in Elderly Stage III Non-small Cell Lung Cancer Patients.* Cancer Research and Treatment, 2012. **44**(4): p. 242-250.

34. Hazell, S.Z., et al., *Hospitalization and definitive radiotherapy in lung cancer: incidence, risk factors and survival impact.* BMC Cancer, 2020. **20**(1).

35. Absolom, K., et al., *Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy.* J Clin Oncol, 2021. **39**(7): p. 734-747.

36. Doolin, J.W., et al., *Implementing Electronic Patient-Reported Outcomes for Patients With New Oral Chemotherapy Prescriptions at an Academic Site and a Community Site.* JCO Clin Cancer Inform, 2021. **5**: p. 631-640.

37. Patt, D., et al., *Implementation of Electronic Patient-Reported Outcomes for Symptom Monitoring in a Large Multisite Community Oncology Practice: Dancing the Texas Two-Step Through a Pandemic.* JCO Clin Cancer Inform, 2021. **5**: p. 615-621.

38. Grunfeld, E., *It takes a team: CanIMPACT: Canadian Team to Improve Community-Based Cancer Care along the Continuum.* Can Fam Physician, 2016. **62**(10): p. 781-782.

39. Tomasone, J.R., et al., *Interventions to improve care coordination between primary healthcare and oncology care providers: a systematic review.* ESMO Open, 2016. **1**(5): p. e000077.

40. Johnson, C.E., et al., *Randomized Controlled Trial of Shared Care for Patients With Cancer Involving General Practitioners and Cancer Specialists.* J Oncol Pract, 2015. **11**(5): p. 349-55.

41. XXX

42. U.S. Department of Health and Human Services, *Report to Congress: Episodic Alternative Payment Model for Radiation Therapy Services*. 2017.

43. Agency for Healthcare Research and Quality, *Statistical Brief #262. Healthcare Cost and Utilization Project (HCUP).* 2020.

44. Brakefield, W.S., et al., *An Urban Population Health Observatory System to Support COVID-19 Pandemic Preparedness, Response, and Management: Design and Development Study.* JMIR Public Health Surveill, 2021. **7**(6): p. e28269.

Figure 1. Geospatial analysis of hospitalization-associated radiotherapy interruption (HARTI) rates stratified according to patient race. Median household income is mapped at the census tract level according to pre-specified categories. Greater HARTI rates are denoted by larger bubbles plotted at zip code centroids.

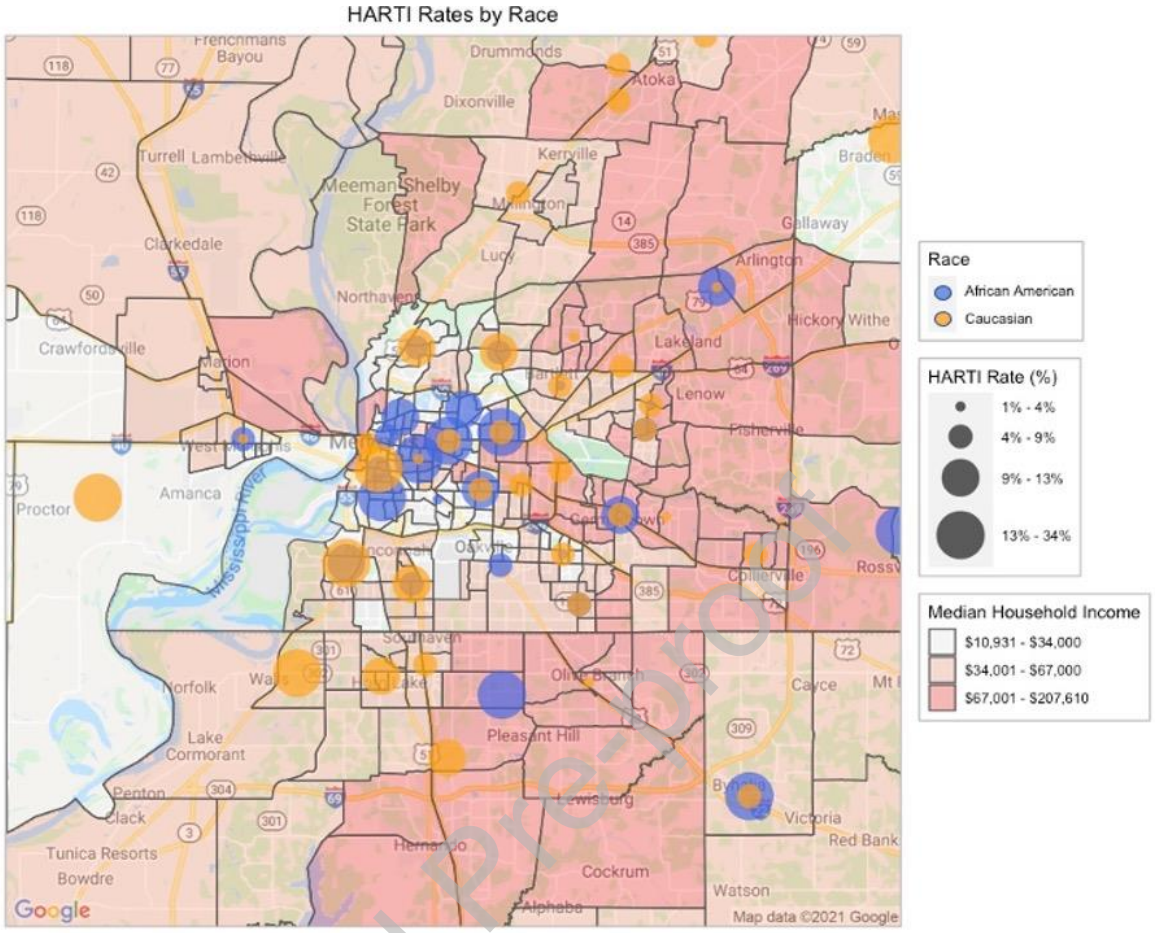

Figure 2. Geospatial analysis of hospitalization-associated radiotherapy interruption (HARTI) rates stratified according to patient insurance. Median household income is mapped at the census tract level according to pre-specified categories. Greater HARTI rates are denoted by larger bubbles plotted at zip code centroids.

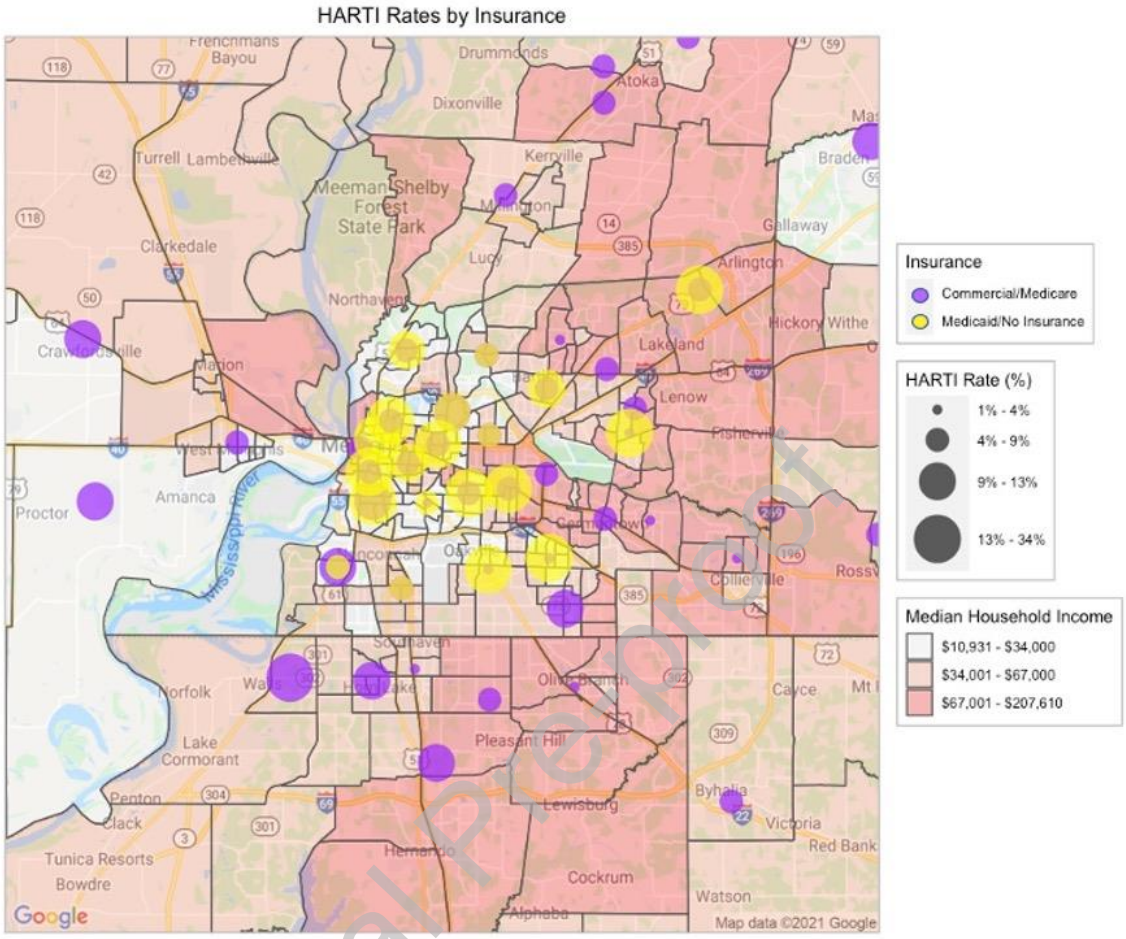

Table 1. Study Cohort Characteristics and Hospitalization Associated RT Interruption Likelihood

	Number (%)	Frequency of Hospitalization Associated Radiotherapy Interruption (%)
Total	3729	197 (5.3)
Gender		
Male	1664 (44.6)	6.0
Female	2065 (55.4)	4.7
Age (Mean, years)	61.2	
<65	2195 (58.9)	5.1
≥65	1534 (41.1)	5.6
Race		

Caucasian	2032 (54.5)	4.4*
African American	1577 (42.3)	6.3*
Other	120 (3.2)	6.7
Ethnicity		
Hispanic	50 (1.3)	6.0
Non-Hispanic	3540 (94.9)	5.2
Unknown	139 (3.7)	7.9
Marital Status		
Married	1967 (52.7)	4.3*
Unmarried	1648 (44.2)	6.4*
Unknown	114 (3.1)	5.3
Patient Predicted Income		
Low (<$34k)	1012 (27.1)	4.4
Middle($34-67k)	1532 (41.1)	5.6
High(>$67k)	1149 (30.8)	5.7
Unknown	36 (1.0)	5.6
Geography of residence		
Rural not by metro	114 (3.0)	0.9
Rural by metro	201 (5.4)	3.0
Metro	3428 (91.6)	5.6
Distance from RT (miles)		
0-5	1108 (29.9)	6.6
6-10	1175 (31.7)	5.6
11-15	503 (13.6)	3.8
16-20	220 (5.9)	6.9
21-30	253 (6.8)	4.8
31-40	110 (3.0)	1.9
>40	337 (9.1)	3.3
Insurance Type		
Commercial	1794 (48.1)	3.5*
Medicare	1503 (40.3)	6.3*
Medicaid/No Insurance	432 (11.6)	9.0*
Medicaid	221 (5.9)	7.7
No Insurance	211 (5.7)	10.4*
Diagnosis		
Breast	974 (26.1)	1.7*
Prostate	413 (11.1)	3.4
Lung	353 (9.5)	10.8*
GYN	226 (6.1)	6.2
H&N	402 (10.8)	10.7*
GI	238 (6.4)	5.0
CNS	148 (4.0)	4.7
Metastasis	490 (13.1)	4.1

Skin	123 (3.3)	5.7
Soft Tissue	53 (1.4)	3.8
Hematologic	146 (3.9)	2.7
Other	163 (4.4)	13.4
Treatment Season		
Non-Winter (Mar-Oct)	2455 (65.8)	5.7
Winter (Nov-Feb)	1274 (34.2)	4.6
Prescribed Fractions		
1-5	421 (11.3)	1.2*
6-10	494 (13.2)	5.7
11-15	195 (5.2)	5.1
16-20	586 (15.7)	2.2*
21-25	368 (9.9)	4.6
26-30	976 (26.2)	7.0*
>30	689 (18.5)	8.1*

* Denotes statistical significance

Table 2. Primary Causes of Hospitalization	
	Number (%)
Total	175 (100)
Principal Problem	
Malnutrition/Dehydration	28 (17.7)
Respiratory Distress/Infection	24 (13.7)
Fever/Sepsis	17 (9.7)
Pain Control	16 (9.1)
Renal Dysfunction	15 (8.6)
Chest Pain	15 (8.6)
Neurological Dysfunction	10 (5.7)
PEG Tube Complication	9 (5.1)
Radiation Mucositis/Dermatitis	9 (5.1)
Acute Bleeding Episode	7 (4)
Urinary Tract Infection	5 (2.1)
Soft Tissue Infection	5 (2.1)
Other	15 (8.6)

Table 3. Analysis of Hospitalization Associated Radiotherapy Interruptions by Study Cohort Characteristics

	Univariable Model		Multivariable Model	
	Unadjusted OR (95% CI)	***P***	**Adjusted OR (95% CI)**	***P***
Gender				
Male	*Reference*		*Reference*	
Female	0.77 (0.58-1.03)	0.076	1.33 (0.93-1.88)	0.12
Age (Mean, years)				
≥65	*Reference*		*Reference*	
<65	0.9 (0.67-1.20)	0.46	1.1 (0.71-1.70)	0.68
Race				
Caucasian	*Reference*		*Reference*	
African American	1.48 (1.10-1.98)	0.009	1.48 (1.07-2.06)	0.018
Other	1.56 (0.68-3.11)	0.24	1.49 (0.64-3.06)	0.32
Marital Status				
Married	*Reference*		*Reference*	
Unmarried	1.38 (1.03-1.85)	0.032	0.4 (0.02-4.36)	0.48
Patient Predicted Income				
High (>$67k)	*Reference*		*Reference*	
Middle ($34-67k)	0.98 (0.71-1.37)	0.92	0.97 (0.69-1.38)	0.88
Low (<$34k)	0.77 (0.52-1.13)	0.19	0.85 (0.56-1.28)	0.43
Geography of residence				
Metro	*Reference*		*Reference*	
Rural not by metro	0.15 (0.01-0.68)	0.061	0.15 (0.008-0.67)	0.058
Rural by metro	0.52 (0.20-1.09)	0.12	0.51 (0.20-1.09)	0.12
Distance from RT in miles				
0-5	*Reference*		*Reference*	
6-10	0.83 (0.59-1.17)	0.29	0.82 (0.57-1.17)	0.27
11-15	0.56 (0.32-0.91)	0.026	0.7 (0.40-1.16)	0.18
16-20	1.04 (0.57-1.81)	0.88	1.26 (0.67-2.24)	0.46
21-30	0.71 (0.36-1.27)	0.28	0.76 (0.38-1.40)	0.4
31-40	0.27 (0.043-0.86)	0.068	0.32 (0.05-1.09)	0.13
>40	0.48 (0.24-0.87)	0.025	1.32 (0.46-3.21)	0.58
Insurance Type				
Commercial	*Reference*		*Reference*	
Medicare	1.85 (1.34-2.58)	0.0002	1.7 (1.21-2.39)	0.0022
Medicaid/No Insurance	2.73 (1.79-4.11)	<0.0001	2.05 (1.32-3.15)	0.0013
Medicaid	2.29 (1.28-3.90)	0.0034	1.56 (0.85-2.73)	0.13
No Insurance	3.20 (1.89-5.24)	<0.0001	2.64 (1.53-4.43)	0.0003
Diagnosis				
Breast	*Reference*		*Reference*	
Prostate	1.98 (0.95-4.06)	0.061	1.73 (0.76-3.89)	0.19

Lung	6.82 (3.86-12.55)	<0.0001	5.97 (3.22-11.44)	<0.0001
GYN	3.73 (1.79-7.69)	0.0004	2.57 (1.20-5.40)	0.013
H&N	6.77 (3.88-12.34)	<0.0001	5.6 (2.96-10.93)	<0.0001
GI	3.00 (1.38-6.33)	0.0042	2.55 (1.13-5.56)	0.02
CNS	2.81 (1.07-6.63)	0.024	2.71 (1.00-6.60)	0.036
Metastasis	2.41 (1.25-4.69)	0.0087	3.46 (1.69-7.13)	0.0007
Skin	3.41 (1.30-8.09)	0.0076	4.37 (1.58-11.01)	0.0026
Soft Tissue	2.22 (0.35-8.02)	0.3	1.94 (0.30-7.23)	0.39
Hematologic	1.59 (0.45-4.37)	0.41	2.28 (0.63-6.57)	0.16
Other	7.67 (3.89-15.25)	<0.0001	8.4 (4.07-17.45)	<0.0001
Treatment Season				
Non-Winter (Mar-Oct)	*Reference*		*Reference*	
Winter (Nov-Feb)	0.77 (0.56-1.06)	0.11	0.81 (0.58-1.12)	0.22
Prescribed Fractions				
1-20	*Reference*		*Reference*	
>20	2.18 (1.60-3.02)	<0.0001	2.23 (1.51-3.34)	<0.0001

* Denotes statistical significance