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Preference of Choosing Intensity-Modulated Radiation Therapy (IMRT) in Breast Cancer Patients with Pre-existing Heart or Lung Disease

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Abstract Cover Page

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2017

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health
in Health Policy and Management
2019

Abstract

Preference of Choosing Intensity-Modulated Radiation Therapy (IMRT) in Breast Cancer Patients with Pre-existing Heart or Lung Disease
By Siyu Wang

Background: Currently, breast-conserving surgery (lumpectomy) followed by radiotherapy has become the most commonly used treatment combination for breast cancer patients who have been diagnosed at relatively early stages. Among breast cancer patients who take radiotherapy, the use of IMRT has increased dramatically. It is known that the use of IMRT makes it possible to protect surrounding tissues away from exposure to radiation doses and may decrease possible damage to patients' nearby organs. However, whether this advantage of IMRT could affect physician's behavior and patients' preference is uncertain, especially for breast cancer patients with pre-existing heart or lung disease.
Methods: Study sample derived from SEER-Medicare database. Women aged 66 years and older diagnosed with a primary invasive breast cancer and received some form of radiotherapy in the timeframe from 2007 through 2013 enrolled in the sample. Pearson Chi-square and logistic regression model were used to estimate the association between breast cancer patients with pre-existing heart or lung disease and the use of IMRT.
Results: 39181 subjects have been included in the model. 31.1% of them had previously diagnosed heart or lung disease before their diagnosis of breast cancer. 18.7% of enrolled breast cancer patients with previous heart or lung disease took IMRT. Among patients who took IMRT, patients with both left-sided tumors and heart disease had a higher proportion of taking IMRT (58.8%) compared to patients with right-sided tumors and same disease. Women with pre-existing heart or lung disease (unselected) were more likely (4.6 percentage point, 95% confidence interval (CI): 0.003-0.117) to use IMRT compared to conventional radiotherapy. Women with pre-existing heart disease had an even higher possibility (7.9 percentage point) of taking IMRT.
Conclusions: These findings suggested that patient' health status could affect their treatment options. Breast cancer patients who have pre-existing heart disease were more likely to choose IMRT. Differences could be explained by physicians prefer to be more conservative for breast cancer with previous cardiac risk. Further studies with deeper data and quality studies about patient's preference should be considered.

Cover Page

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Introduction

Breast cancer is the most common cancer among women, which also lead to the most cancer related mortality among women in most countries worldwide. In the United States, without considering several types of skin cancer, breast cancer accounts for most of cancer events among women regardless of race or ethnicity (CDC, 2018a). As for cancer mortality, although death rates of breast cancer have been decreasing since 1989, it still remains at the highest level of cancer related mortality with the exception of lung cancer (BREASTCANCER.ORG, 2018). Considering the incidence of breast cancer corresponds with aging, Medicare beneficiaries are especially vulnerable to breast cancer compared to younger women.

Following the implementation of organized cancer screening in the United States, more and more patients are being diagnosed at relatively early stages (R. A. Smith et al., 2017). Because of this trend, breast-conserving surgery (lumpectomy) followed by radiotherapy has become the most commonly used treatment combination. For patients who choose lumpectomy, taking radiation therapy after surgery could possibly become an inevitable choice. Breast cancer patients could take both conventional radiotherapy (3D-CRT) and advanced radiotherapy (IMRT). Compared to conventional radiotherapy, the characteristics of IMRT make it possible to protect surrounding tissues away from exposure to radiation doses and may decrease possible damage to patients' nearby organs (ASCO, 2017). Studies also proved that the use of IMRT has the potential to reduce heart injury after radiotherapy (Lohr et al., 2009).

However, no study has been done before to find out whether this advantage of IMRT will affect physicians' behavior and patients' preference of choosing radiotherapy treatment if they have pre-existing heart or lung disease before they have been diagnosed with breast cancer. What's more, guidelines also did not give any specific instructions for physicians of when and how to choose advanced RT techniques for their patients. Thus, current use of IMRT could be much subjective and might be largely affected by physicians' behavior and patients' preference.

Since we know that IMRT is an expensive treatment with unproven clinical benefits and the use of IMRT has increased dramatically, this could lead to unnecessary use of IMRT. I design this study to estimate whether patients with previous heart or lung disease are more likely to take IMRT. Aims of this study are to find out whether physicians will consider patient's potential benefits when they choose radiotherapy for their patients and come up with policy changes to reduce the use of IMRT for breast cancer patients.

Anderson Healthcare Utilization Model will be used to build up the conceptual framework of this study. I will derive a study sample from SEER-Medicare database. Pearson Chi-square and logistic regression model will be used to estimate the association between breast cancer patients with pre-existing heart or lung disease and the use of IMRT.

Literature review

Epidemiology of breast cancer

Breast cancer is a malignant tumor that derives from the epithelial tissues of the breast gland. 99% of breast cancers occur in women while males only account for 1%. Risk factors for developing breast cancer include aging, being female, obesity, family health history, major inheritance susceptibility, alcohol intake, breast tissue density, menstrual history (menstrual periods earlier than 12 years old and late menopause after 55 years old), reproductive history (having children late or not at all), hormone therapy history, personal history of breast cancer or benign breast disease, and radiation exposure to breast/chest (CDC, 2018c; NIH, 2018a). Among all risk factors, aging is considered as the most significant.

The female breast is composed of skin, connective tissue, breast gland and fat. The breast gland is made up of lobules and ducts. Types of breast cancer are dependent on which cells in different breast tissues turn into cancer. Most breast cancers derive from ducts or lobules (CDC, 2018d). Invasive ductal carcinoma is defined as cancer cells that grow outside the ducts and spread to other parts of the breast tissue (CDC, 2018d). Invasive lobular carcinoma is defined as cancer cells that grow outside the lobules and spread to surrounding breast tissues (CDC, 2018d). Both are considered as the most common breast cancers(CDC, 2018d). Invasive cancer cells can also spread outside the breast tissue and metastasize to other body tissues through lymph vessels and blood vessels. Carcinoma in situ such as ductal carcinoma in situ (DCIS) and lobules carcinoma in situ (LCIS) are breast diseases that have the possibility to develop into breast cancer where cancer cells have not invaded other breast surrounding tissues other than the mammary gland (CDC, 2018d).

The most common symptom of breast cancer is a new lump or mass (Healthline, 2017). Masses without pain and regular edges, hard and grow relatively fast are more likely to be cancer tumor, but this is not absolute. Masses with opposite characteristics can also be cancer tumor (Healthline, 2017). Other possible symptoms could be swelling of the tissue, skin change like orange peel or thickening, pain for breast or nipple, nipple shape change (retraction) and nipple discharge (ACS, 2017a). Sometimes lymph nodes outside the breast, such as under axillary or near the collar bone, can be affected earlier and show symptoms like lump or swelling even before the primary tumor in the breast tissue is able to be felt and detected (ACS, 2017a). Patients with distant metastasis may have symptoms as yellow skin, bone pain or difficulty breathing (Jassal, 2009).

Breast ultrasound, diagnostic mammogram, magnetic resonance imaging (MRI) and biopsy have been used for the diagnosis of breast cancer. Breast cancer is typically detected either during a screening examination before symptoms have developed or after a woman notices a lump. Most masses seen on a mammogram and most breast lumps turn out to be benign. When cancer is suspected, microscopic analysis of breast tissue is necessary for a diagnosis and to determine the extent of spread, referred to as the stage, and characterize the type of the disease (ACS, 2017b). The type and stage of breast cancer will direct physicians to choose proper treatments for their patients (CDC, 2018b).

Breast cancer in the U.S.

In the United States, without considering several types of skin cancer, breast cancer accounts for most of cancer events among women regardless of race or ethnicity (CDC, 2018a). Approximately one in eight women in the United States have the chance to develop invasive breast cancer during their lifetime (BREASTCANCER.ORG, 2018). The latest data shows that in 2018, the expected new cases of invasive breast cancer are more than 260,000 and the expected cancer mortalities caused by breast cancer are more than 40,000 (BREASTCANCER.ORG, 2018). In 2018, the number of women who used to have a diagnosis of breast cancer or currently live with breast cancer is more than 3.1 million (BREASTCANCER.ORG, 2018). Some of them are free of cancer now, while others still live with breast cancer and take treatments as needed. Although death rates of breast cancer have been decreasing since 1989, it still remains at the highest level of cancer mortality with the exception of lung cancer (BREASTCANCER.ORG, 2018).

The incidence of breast cancer corresponds with aging. 61 years old is the average age for women who are diagnosed of breast cancer. But the average age for most women whose death is related to breast cancer is over 65 years (Shachar, Hurria, & Muss, 2016). Because of the age factors associated with the disease, Medicare beneficiaries are especially vulnerable to breast cancer comparing to younger women.

Mammography for breast cancer

Mammography is a low-dose x-ray procedure that allows visualization of the internal structure of the breast. In 2015, the American Cancer Society (ACS) updated its breast cancer screening guidelines for women who are considered as average risk, which means women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer, or a history of previous radiotherapy to the chest at a young age (Oeffinger, Fontham, Etzioni, & et al., 2015). ACS strongly recommends that women with an average risk should take regular screening mammography beginning at 45 years of age (Oeffinger et al., 2015). Although screening guidelines are different between different medical associations, ultimately, the purpose of all guidelines is to recommend the right ages and screening intervals that will give women the highest likelihood of benefiting from the procedure. Proper guidelines can potentially minimize the probability of overdiagnosis and reduce false positives, which can lead to reduction of the rate of unnecessary biopsies (Fenichel, 2016).

Treatment for breast cancer

Treatment plan for breast cancer depends on the cancer stage and biological characteristics, the patient's age, menopausal status, as well as the preferences of physicians and patients (ASCO, 2017). Conventional treatments for breast cancer include surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy and systemic therapy, which is a combination of treatment options (WebMD, 2017). Among these treatments, surgery and radiotherapy are the most commonly used treatment combination since they are regular treatments for patients who have been diagnosed at relatively early stages. Most women with early-stage breast cancer will have some type of surgery, which is often combined with other treatments to reduce the risk of recurrence, such as radiation therapy, chemotherapy, hormone therapy, and/or targeted therapy (ACS, 2017b). Following the implementation of organized cancer screening in the United States, more and more patients are being diagnosed at relatively early stages (R. A. Smith et al., 2017). Because of this trend, breast-conserving surgery (lumpectomy, or BCS) followed by radiotherapy has become the most commonly used treatment combination. In most cases, BCS needs to be followed by radiation to the breast. For women with early breast cancer, studies indicate that BCS following by radiation therapy results in long-term outcomes equivalent to, and possibly better than, mastectomy (K. Chen et al., 2015; Fisher et al., 2002; van Dongen et al., 2000). Thus, for patients who choose surgery as BCS, taking radiation therapy after surgery could possibly become an inevitable choice. Past research has also confirmed that postoperative radiotherapy not only reduces the risk of recurrence, but also moderately reduces the risk of death caused by breast cancer (Clarke et al., 2005; S. Darby et al., 2011).

Radiation therapy kills cancer cells by using high-intensity beams or particles. It is often used after surgery to destroy cancer cells remaining in the diseased breast tissue, chest wall, or underarm area. As for radiotherapy, there are three main types of radiation: external radiation, internal radiation (brachytherapy) and intraoperative radiation (ASCO, 2017). For breast cancer patients who intend to take radiotherapy, external radiation therapy is the most commonly used one, which includes three-dimensional conformal radiation therapy (3D-CRT), image guided radiation therapy (IGRT), intensity modulated radiation therapy (IMRT), helical-tomotherapy, photon beam radiation therapy and proton beam radiation therapy (ACS, 2017c). Among external-beam radiotherapy for breast cancer, 3D-CRT and IMRT are the most common choice for patients.

Comparison of 3D-CRT and IMRT

Both 3D-CRT and IMRT use X-rays to damage diseased tissues. The difference between 3D-CRT and IMRT is that the radiation intensity of each beam varies in IMRT (ASCO, 2016). This characteristic of IMRT makes the radiation dose to target more exactly to the shape of the targeted tumor. Higher radiation doses can be focused on targeted diseased tissue while surrounding healthy tissues will be less affected by targeted doses (RSNA, 2017). In the current radiotherapy treatment system, 3D-CRT is considered as the conventional radiotherapy to give external-beam radiation therapy for breast cancer patients. IMRT is a more advanced radiotherapy to treat breast tumor.

The advantage and controversy of IMRT

The characteristics of IMRT make it possible to protect surrounding tissues away from exposure to radiation doses and may decrease possible damage to patients' nearby organs (ASCO, 2017). A significant amount of literature has found that IMRT can not only reduce the dose to the diseased breast but also to nearby tissues and the contralateral breast (Bhatnagar et al., 2006; Burmeister et al., 2008; Donovan et al., 2007).

The most obvious advantage of IMRT for breast cancer patients is the amelioration of acute skin toxicity. Patients taking IMRT have a lower risk of developing palpable induration in every area of the boost site (Ellen Donovan et al., 2007). The use of IMRT could decrease the severity of acute desquamation (an acute skin toxicity), reduce skin irritation and rashes, reduce the incidence of change in breast appearance and may have a beneficial effect on quality of life (Buwenge et al., 2017; Donovan et al., 2007; Freedman et al., 2006; Harsolia et al., 2007; Pignol et al., 2008).

The use of IMRT, however, is controversial because the clinical benefits of IMRT are largely uncertain. Little evidence supports the claim that IMRT could improve oncological outcomes of breast cancer patients. The rate of survival for patients who choose IMRT does not show a significant improvement. Also the rate of tumor recurrence and distant metastasis do not show a significant reduction (McDonald, Godette, Butker, Davis, & A.S. Johnstone, 2008). In other words, the oncological outcomes improvement or late toxicity reduction has not been proved. As a result, using IMRT for breast cancer patients should be carefully considered and this treatment should not be considered as a standard treatment technique for breast cancer (Buwenge et al., 2017).

The current use of IMRT

Overall, billing for IMRT treatment increased more than 10-fold from 2001 through 2005, contributing to a 33% increase in the cost of breast radiation. Radiation-related costs increased by 21% for non-IMRT patients and by 30% for IMRT patients. Overall Medicare billing for breast cancer patients who chose IMRT increased from less than 1 percent to more than 10 percent (B. D. Smith et al., 2011). Medicare billing for IMRT varied by regions. States with coverage favorable to IMRT had a much higher billing rates compared to states without coverage favorable (B. D. Smith et al., 2011).

Yet, given that IMRT is more expensive than conventional radiotherapy (for breast cancer, IMRT can be $5000 expensive than conventional radiotherapy) (Sheets et al., 2014), its use for post-lumpectomy may not be cost-effective compared with conventional 2-D radiotherapy.

NCCN guideline for radiotherapy

NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines) give clear instructions of when and how to use different radiation therapies like whole breast radiation, chest wall radiation, regional nodal radiation and accelerated partial breast irradiation (APBI). Meanwhile, guidelines give specific instructions of dose volume and fractions patients should receive. Guidelines also mentioned that advanced RT techniques (IMRT, IGRT, SBRT, SABR) facilitate the delivery of large doses of radiation to small target volumes while limiting the risk of radiation-induced damage to normal surrounding tissues and organs at risks. However, guidelines did not give any specific instructions for physicians of when and how to choose advanced RT techniques for their patients. Thus, current use of IMRT could be much subjective and might be largely affected by physicians' behavior (including financial incentives, if exists) and patients' preference.

Medicare coverage for radiotherapy

Medicare Part A and Part B may cover certain cancer treatments for beneficiaries with cancer, including but not limited to chemotherapy and radiation therapy (Medicare, 2018). Medicare costs will depend on whether a patient receives the cancer treatments as an inpatient or outpatient. Medicare covers radiation therapy for cancer patients. If patients are covered under Medicare Part A, they will pay the part A deductible as an inpatient and any copayment caused by their treatments (CMS, 2017). If patients get radiation therapy as an outpatient, they need to pay 20 percent of the Medicare-approved payment after they pay Part B deductible (CMS, 2017).

Medicare coverage policy for IMRT

Between 2006 and 2013 the Medicare program implemented several payment cut policies and reduced the payment for intensity modulated radiation therapy (IMRT) by 34%.

In 2007, CMS adopted a new method of calculating practice expense relative value units for each service. Under the new approach, CMS determined the practice expense relative value units based on the direct costs of the labor, supplies, and equipment for each service and a share of non-service-specific overhead costs (e.g., rent for the office space). This change resulted in a decrease in the payment for IMRT and an increase in the payment for conventional radiotherapy.

In 2010, CMS began using a new survey source for calculating overhead costs, which resulted in a further decline in the payment for IMRT.

In 2012 CMS cut the payment for IMRT code 77418 by 15% under the mis-valued code initiative. CMS justified this reduction based on the rapid growth in IMRT procedure volume and disparities in the IMRT procedure time between CMS's official estimate and patient education materials. CMS originally proposed to reduce the payment rate by 40%, but this huge cut was reversed by a campaign launched by the Society for Therapeutic Radiology and Oncology. Finally, CMS settled on a 15% reduction.

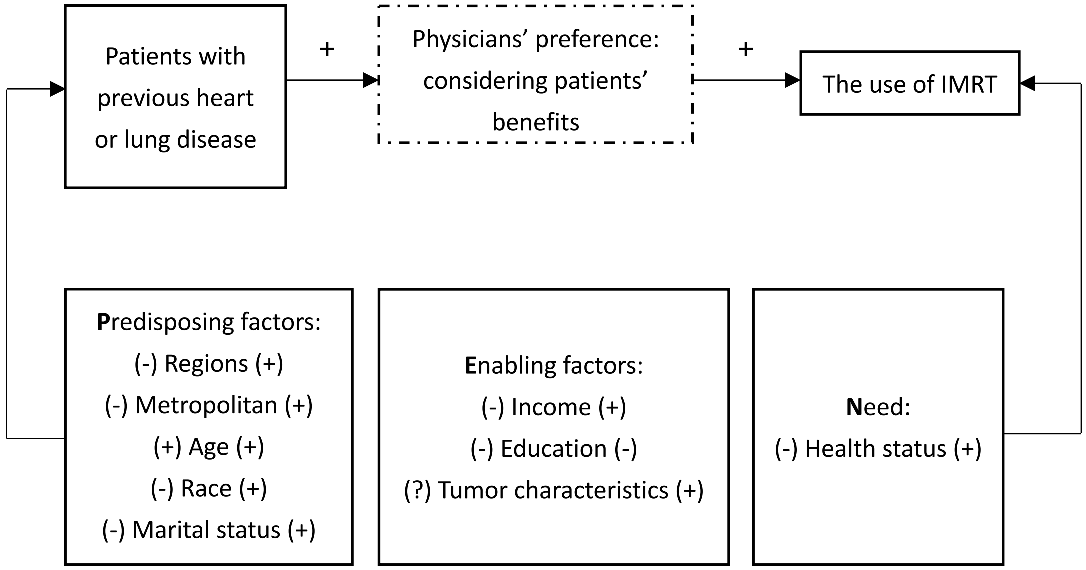
Literature gap

It is inevitable that radiotherapy usually involves some incidental radiation of patients' nearby normal organs, such as heart and lungs, which may lead to a higher risk of developing subsequent heart injury and lung injury. A large amount of studies indicated that radiotherapy for breast cancer could result in radiation-related mortality from cardiovascular disease and lung disease, and may increase the subsequent incidence of heart disease (Sarah Darby et al., 2003; Darby et al., 2013; S. C. Darby, McGale, Taylor, & Peto, 2005b; Henson, McGale, Taylor, & Darby, 2013). Moreover, one study showed that women with previous heart disease could have a higher risk of getting IHD (ischemic heart disease) after taking radiotherapy than women without any previous heart disease (S. C. Darby et al., 2013).

Many studies found that the characteristics of IMRT can reduce the exposure volume of radiation doses to patients' nearby tissues like heart and lungs. One study conducted by Lohr used a relative seriality model to calculate and predict the potential effect of IMRT for breast cancer only in left side on cardiac mortality and found that the use of IMRT could reduce the cardiac death risk (Lohr et al., 2009). This study assumed that the use of IMRT has the potential to reduce heart injury after radiotherapy.

However, no study has been done before to find out whether this advantage of IMRT will affect physicians' behavior and patients' preference of choosing radiotherapy treatment if they have existing heart and lung disease before they have been diagnosed with breast cancer. Since we know that IMRT is an expensive treatment with unproven clinical benefits and the use of IMRT has increased dramatically, this could lead to unnecessary use of IMRT. The result of this study has the potential to find out whether physicians will consider patient's potential benefits when they choose treatment for their patients.

Conceptual model



Conceptual model was built up based on Anderson Healthcare Utilization Model

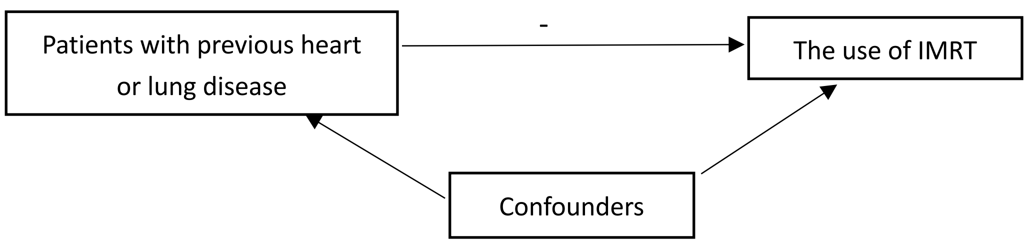
Focal relationship

The focal relationship of the conceptual model is the patients with previous heart or lung disease and the use of IMRT. The patients with previous heart or lung disease are defined as patients with pre-existing heart or lung disease before they are diagnosed with breast cancer. The usage of IMRT is defined as whether breast cancer patients and their physicians choose to take this advanced radiation therapy other than traditional radiotherapy. A body of literature suggests that radiotherapy (unspecified) for breast cancer would increase the subsequent rate of heart injury and lung injury, even resulting in mortality from cardiovascular disease (Sarah Darby et al., 2003; Darby et al., 2013; S. C. Darby, McGale, Taylor, & Peto, 2005a). Thus, in the light of these previous studies, it is logical to assume that there exists associative link between radiotherapy and the incidence of heart injury and lung injury. Further, the use of IMRT, as a more advanced radiotherapy treatment, could be logically assumed that is associated with the incidence of heart injury and lung injury. The gap here that this study wants to explore is whether patients with previous heart or lung disease are more likely to receive IMRT.

Hypotheses

The proposed study will test the following hypothesis derived from the conceptual model.

H1: There is a positive association between patients with previous heart or lung disease and the use of IMRT after controlling for predisposing, enabling and need characteristics.



Method

Data description

Data used for this proposed study comes from Surveillance, Epidemiology, and End Results (SEER)-Medicare database and the timeframe of the data used for this study is from 2007 to 2013. The SEER-Medicare database is a linkage of two large population-based sources of data, SEER Program and Medicare claims. This linkage database provide detailed demographic and claims information about Medicare beneficiaries with cancer, which can be used for epidemiological research and health services research (NIH, 2018c).

The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States (NIH, 2018b). Data have been collected since 1973, currently approximately 34.6 percent of the U.S. population have been covered by SEER Program (NIH, 2018b). During past years, more and more areas has been covered by the SEER Program. Currently the SEER areas include Connecticut, Hawaii, Iowa, New Mexico, Utah, Kentucky, Louisiana, New Jersey, California, Georgia, the metropolitan areas of Detroit, Seattle-Puget Sound. Data collection for registries located in Kentucky, Louisiana, New Jersey, and greater California began in 2000 (Ambs et al., 2008). The SEER Program registries routinely collect data on patient demographics and tumor characteristics (NIH, 2018b).

Medicare claims data are collected by Centers for Medicare & Medicaid Services (CMS), which contains detailed claims information about how Medicare pays for health care services provided to a Medicare beneficiary from the time when a beneficiary enrolls in Medicare until death. Data is available for each institutional claim, which are often utilized by hospitals, nursing facilities, inpatient and other facility providers, as well as and non-institutional claims, also known as professional claims and used by physicians, suppliers and other non-institutional providers (ResDAC, 2016). SEER-Medicare includes only fee-for-service Medicare beneficiaries who have both Part A and Part B.

Analytic sample derivation

The data used in this study comes from the SEER–Medicare database. Using this data, I derived an analytic sample of women aged 66 years and older diagnosed with a primary invasive breast cancer and received some form of radiotherapy in the timeframe from 2007 through 2013. Patients meeting following criteria were excluded: 1) breast cancer was not the initial primary tumor or Medicare claims indicated any cancer diagnosis within 1 year before the index diagnosis of breast cancer; 2) a second cancer was found within 12 months after the diagnosis of breast cancer or the patient died within 12 months after the diagnosis of breast cancer; 3) tumor histological examination was not of epithelial origin or stage was unknown; 4) breast cancer was lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS); 5) there was a distant metastasis at diagnosis; 6) patients had discontinuous fee-for-service Medicare Part A or Part B coverage; 7) patients were enrolled in Medicare Part C (excluded since managed care organizations do not submit detailed claims data); 8) patients who received brachytherapy and proton therapy; and 9) patients who received less than one or more than 40 fractions of radiation therapy , which reduces the risk of including patients with metastatic disease (J. Chen et al., 2012; Paravati et al., 2015; B. D. Smith et al., 2011).

A break ≥ 30 days between claims for external-beam radiation therapy was assumed to indicate multiple courses of radiation therapy (Paravati et al., 2015). For patients who received radiation therapy, only the first course was considered, since it was most likely delivered with definitive intent. Subsequent courses of radiation therapy were likely delivered in the setting of recurrent or metastatic disease (Paravati et al., 2015).

Measures

Heart disease

The incidence of cardiovascular conditions wes identified by using ICD-9-CM procedure and diagnosis codes, ICD-10 diagnosis codes and/or HCPCS codes (ICD-9-CM codes: 36.1x, 00.66, 36.01, 36.02, 36.05, 36.06, 36.07, 36.09, 410.x1, 411.1, 411.8, 411.81, 411.89, 413.x, 433.x, 434.x, 435.x, 401.x-405.x; ICD-10 codes: I21.09-I25.10 and I48.91-I65.29; HCPCS codes: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33520, 33521, 33522, 33523, 33525, 33533, 33534, 33535, 33536, 92973, 92980, 92981, 92982, 92984, 92995, 92996).

Lung disease

The incidence of lung conditions was identified by using ICD-9-CM procedure and diagnosis codes and/or ICD-10 diagnosis codes and/or HCPCS codes (ICD-9-CM codes: 490.x, 491.x, 493.x, 492.x, 494.x, 495.x, 496.x; ICD-10 codes: J40-J47, J80-J86, J90-J99).

The use of IMRT

Treatment with any radiation therapy was determined using a claim that indicates delivery of a radiation therapy within 1 year of breast cancer diagnosis (B. D. Smith et al., 2011). In this case, ICD-9-CM codes 9221-9229, CPT codes 77371–77373, 77401–77416, 77418, 77422, 77423, 77522–77525, HCPCS codes G0174 and revenue center codes 0330 or 0333 were used to identify all the radiation therapy. Among all these codes, CPT code 77418, HCPCS code G0174 were used to identify IMRT. CPT code 77413 accounted for 58% of the conventional radiotherapy treatment codes in the billing data.

Predisposing characteristics

Respondents were categorized into five age groups (65-69, 70-74, 75-79, ≥80 years of age and unknown) using the age at first diagnosis. However, women enrolled in the sample aged from 66 years old for the reason that one year has been reserved for identifying pre-existing heart or lung disease. Since original race/ethnicity has too many subdivisions, I integrated original race categories into five main racial groups (non-Hispanic white, non-Hispanic black, Hispanic, Asian, unknown). Marital status was assessed as married, unmarried (which includes never married, separated, divorced, or widowed) and unknown. The region category was measured based on the original registry category. Most of those regional remained the same as the original category and some has combined because of geographic proximity, such as Atlanta and rural Georgia registries. Metropolitan areas were assessed using three categories: metropolitan (metro, urban), rural (less urban, rural) and unknown.

Enabling characteristics

Socioeconomic status (SES) is an economic and sociological combined measure of a person's work experience and of an individual's or family's economic and social position in relation to others, based on income, education, and occupation (Saifullah Saifi 2011). In this study, socioeconomic status (SES) was assessed using income level and education level. Since the data of income level and education level are collected based on zip code census, the level of income and education were assessed at the community-level as a result. Education was categorized into two groups: lower than a high school diploma and higher than a high school diploma. Income was assessed with five categorical groups. The categorical criteria for income were based on median household income for zip code and using the 10^{th}, 30^{th}, 60^{th}, 90^{th} quantiles to represent the lowest to the highest income quantiles.

Need characteristics

Health status was measured by comorbidity index scores which are calculated from comorbid conditions. The comorbidity index score (also called Charlson comorbidity weights) was directly calculated using The Comorbidity SAS Macro (2014 version) which is provided by the NIH (NIH, 2016). Comorbidity index scores were categorized into five groups as 0, 1, 2, 3+ and unknown. When calculating comorbidity index scores, comorbidities related to heart and lung were excluded.

Tumor related variables

As for measurement of tumor characteristics, original numerical tumor sizes was categorized into four groups based on the continuous data (<2cm, 2-5cm, >5cm and unknown) (B. D. Smith et al., 2011). Lymph node involvement also was categorized into four groups based on the number of positive nodes (0, 1-3, 4+, no examined/unknown) (B. D. Smith et al., 2011).

Grade and differentiation codes are defined in ICD-O-2 and have four stages of grades. New measurements for grade were built based on this definition and had five groups (well differentiated, moderately differentiated, poorly differentiated and unknown) (B. D. Smith et al., 2011).

Laterality code for breast cancer patients describes which side of the breasts has developed tumors. Laterality was assessed using three groups: left, right and bilateral/unknown.

The following table shows original measurements in documentations and reclassified personal measurements. Original measurements report coding information directly from database codebooks. Personal measurements are reclassified and simplified based on original codes.

Table of constructs and their associated measures

Construct	**Measure in documentation**	**Personal measurement**	**Hypothesized relationship to the DV**
Heart disease	Use ICD-9-CM codes and/or ICD-10 codes to identify.	Dichotomous heart disease variable: • Heart disease • No heart disease	The incidence of cardiovascular conditions will help to identify the treatment group
Lung disease	Use ICD-9-CM codes and/or ICD-10 codes to identify.	Dichotomous lung disease variable: • lung disease • No lung disease	The incidence of lung conditions will help to identify the treatment group
The use of IMRT	Use ICD-9-CM codes, CPT codes, revenue center codes and HCPCS codes to identify.	The use of IMRT categorized as variables: • IMRT • Non-IMRT (traditional radiotherapy)	Dependent variable
Region	Registry has been categorized as: • San Francisco-Oakland	Geographic region categorized as: • Connecticut	+

	• Connecticut • Metropolitan Detroit • Hawaii • Iowa • New Mexico • Seattle (Puget Sound) • Utah • Metropolitan Atlanta • Alaska • San Jose-Monterey • Los Angeles • Rural Georgia • Greater California (excluding SF, Los Angeles & SJ) • Kentucky • Louisiana • New Jersey • Greater Georgia (excluding AT and RG)	• Detroit • Georgia • Greater California • Hawaii • Iowa • Kentucky • Los Angeles • Louisiana • New Jersey • New Mexico • San Francisco • San Jose • Seattle • Utah	
Metropolitan area	Urban/Rural area is classified as: Big Metro • Metro • Urban • Less Urban • Rural • Unknown	Metropolitan area categorized as: • Metro • Rural • unknown	+

Age	Code represents the patient's actual age in years at diagnosis: • Actual age in years • Unknown age	Age groups categorized as: • 66-69 years of age • 70-74 years of age • 75-79 years of age • ≥80 years of age • unknown	+
Race	Race/ethnicity has been classified into 45 categories (not all shown here): • White • Black • American Indian, Aleutian, Alaskan Native or Eskimo (includes all indigenous populations of the Western hemisphere) • Chinese • Japanese • Filipino • Hawaiian • … (HISPANIC ORIGIN) • Non-Spanish-Hispanic-Latino • Mexican • Puerto Rican • Cuban	Race/ethnicity categorized as: • Non-Hispanic White • Non-Hispanic Black • Hispanic • Asian • Others/unknown	+

	• … • Other • Unknown		
Marital status	Patient's marital status at the time of diagnosis is categorized as: • Single (never married) • Married (including common law) • Separated • Divorced • Widowed • Unmarried or domestic partner (same sex or opposite sex or unregistered) • Unknown	Marital status categorized as: • Married • Unmarried (never married, separated, divorced, or widowed) • Unknown	+
SES	*Income:* Median income for zip code. *Education:* Education level has been classified as: • < 12 years education • High school diploma • Some college education • At least 4 years of college education	Income level categorized as: • Lowest quartile • Second quartile • Third quartile • Highest quartile • unknown Education level categorized as: • Lower than high	+/-

		school diploma • Higher than high school diploma	
Health status	ICD-9-CM diagnosis, ICD-9-CM procedure, and CPT procedure codes should be used to identify comorbid conditions.	Comorbidity index categorized as: • 0 • 1 • 2 • 3+ • unknown	+
Tumor related variables	*Tumor characteristics:* • Tumor size records the largest dimension of the primary tumor in millimeters. Unknown size=999. • Lymph node involvement records the highest specific lymph node chain that is involved by the tumor. Allowable values = 0-9. *Grade:* Grade and differentiation are classified as: • Grade I; grade i; grade 1; well differentiated; differentiated, NOS	Tumor size categorized as: • <2cm • 2-5cm • >5cm • unknown Lymph node involvement categorized as: • 0 • 1-3 • ≥4 • No examined/unknown Grade categorized as: • Well differentiated • Moderately differentiated	+

	• Grade II; grade ii; grade 2; moderately differentiated; moderately differentiated; intermediate differentiation • Grade III; grade iii; grade 3; poorly differentiated; differentiated • Grade IV; grade iv; grade 4; undifferentiated; anaplastic *Laterality:* Laterality has been classified as: • Not a paired site • Right: origin of primary • Left: origin of primary • Only one side involved, right or left origin unspecified • Bilateral involvement, lateral origin unknown; stated to be single primary • Paired site: midline tumor • Paired site, but no information concerning laterality; midline tumor	• Poorly differentiated • Unknown Laterality categorized as: • Left • Right • Bilateral/unknown	

Statistical analysis

The demographic and tumor characteristics differences between treatment group and control group was tested by Pearson Chi-square. Unknown/not applicable or missing values have been cleaned before running logistic regression analysis. Covariates in the regression model included age, race, marital status, regions, metropolitan area, income, education, health status, tumor size, number of lymph nodes, grade differentiation and laterality. All statistical analyses were two-sided using an alpha level equal to 0.05. Analyses were conducted using SAS version 9.2 and Stata version 15.0.

Results

Table 1: Demographic and tumor characteristics

Characteristic	Patients without previous heart or lung disease		Patients with previous heart or lung disease		P-Value
	N	%	N	%	
Total	26939	68.9	12242	31.1	
Race					0.59
White	23970	90.0	11176	91.3	
Black	1620	6.0	673	5.5	
Hispanic	326	1.2	159	1.3	
Asian	404	1.5	208	1.7	
Other/unknown	619	2.2	25	0.2	
Age Group					0.10
66-69	7300	27.1	3538	28.9	
70-74	6842	25.4	2730	22.3	
75-79	6249	23.2	3146	25.7	
Over 80	6546	24.3	2827	23.1	

Regions					0.30
Connecticut	1104	4.1	490	4.0	
Detroit	1751	6.5	722	5.9	
Georgia	484	1.8	196	1.6	
Greater California	5280	19.6	2485	20.3	
Hawaii	323	1.2	110	0.9	
Iowa	646	2.4	269	2.2	
Kentucky	1373	5.1	673	5.5	
Los Angeles	4391	16.3	2019	16.5	
Louisiana	942	3.5	391	3.2	
New Jersey	4633	17.2	2240	18.3	
New Mexico	296	1.1	159	1.3	
San Francisco	1400	5.2	538	4.4	
San Jose	969	3.9	428	3.5	
Seattle	1777	6.6	869	7.1	
Utah	1481	5.5	649	5.3	
Metropolitan area					0.42
Metro	23841	88.5	10932	89.3	
Rural	3098	11.5	1310	10.7	
Marital status					0.55
Married	13793	51.2	6292	51.4	
Unmarried(never married, separated, divorced,or widowed)	13146	48.8	5950	48.6	
Income					0.24
Lowest quartile	4310	16.0	1897	15.5	
Second quartile	6896	25.6	3244	26.5	
Third quartile	7948	29.5	3758	30.7	
Highest quartile	7785	28.9	3342	27.3	
Education					0.39
Lower than high school	13200	49.0	6109	49.9	
Higher than high school	13739	51.0	6133	50.1	
Health status					0.13
comorbidity index	15678	58.2	7161	58.5	
0	6600	24.5	2889	23.6	

1	3044	11.3	1494	12.2	
2	1617	6.0	698	5.7	
3+					
Tumor size					0.77
2cm	16487	61.2	7639	62.4	
2-5cm	9590	35.6	4150	33.9	
>5cm	862	3.2	453	3.7	
Lymph nodes					0.68
0	14951	55.5	6966	56.9	
1-3	8082	30.0	3979	32.5	
4+	3906	14.5	1297	10.6	
Grade					0.41
Well differentiated	8000	29.7	3464	28.3	
Moderately differentiated	12526	46.5	6085	49.7	
Poorly differentiated	6413	23.8	2693	22.0	
Laterality					0.87
Left	14224	52.8	6243	51.0	
Right	12715	47.2	5999	49.0	

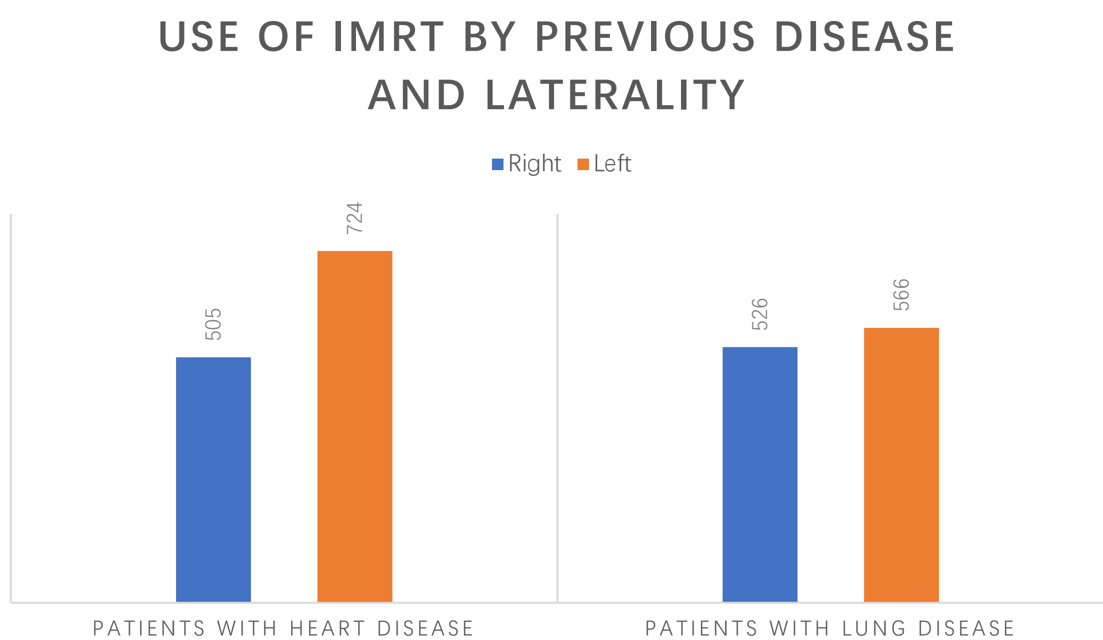
In this study 39181 subjects aged 66 years or older have been included in the model. 31.1% of them had previously diagnosed heart or lung disease before their diagnosis of breast cancer. In the sample, median age was 72.9 years old, more than 90% of women were white and around 90% of them resided in a metropolitan area. The majority of women had one or less comorbidity, less than 4 positive lymph nodes and their tumor size was usually less than 5cm.

Table 2: Radiotherapy treatment of patients with previous disease

	Patients with lung disease (%)	Patients with heart disease (%)	Patients with lung or heart disease (%)
Radiotherapy type			
IMRT	1092 (18.0)	1229 (19.6)	2290 (18.7)
Conventional	4973 (82.0)	5051 (80.4)	9952 (81.3)

In this study, 18.7% of enrolled breast cancer patients with previous heart or lung disease took IMRT. When patients with different disease were considered separately, breast cancer patients with previous heart disease have a little bit higher proportion of choosing IMRT as 19.6%, compared to patients with lung disease.

Figure 1: Use of IMRT for patients by pre-existing disease and laterality



This figure shows unadjusted use of IMRT by patients' previous disease and laterality. It indicated that breast cancer patients with left-side tumors are more likely to take IMRT, regardless of their previous disease. What's more, patients with both left-sided tumors and heart disease have a higher proportion of taking IMRT (58.8%) comparing to patients with right-sided tumors and same disease. For breast cancer patients with previous lung disease, patients with left-sided tumors are more likely to take IMRT, but this difference of proportion is not so huge.

Table 3: Marginal effects on different combinations of heart and lung disease

	Marginal Effects	95% CI	Marginal Effects	95% CI	Marginal Effects	95% CI
	DV: Combined previous disease		DV: Patients with previous lung disease		DV: Patients with previous heart Disease	
Radiotherapy type						
Conventional	Ref		Ref		Ref	
IMRT	.046*	(.003, .117)	.033	(.010, .109)	.079*	(.045, .124)

P<.05, **P<.01

Three logistic regression models have been estimated based on different combinations of heart and lung disease. The first model took women with combined previous disease as dependent variable and result showed that women with pre-existing heart or lung disease (unselected) were more likely (4.6 percentage point) to use IMRT compared to conventional radiotherapy. Then we estimated two other regression models taking patients with previous heart disease or lung disease separately. For women with pre-existing lung disease, they showed 3.3 percentage point higher preference of taking IMRT comparing to conventional radiotherapy. However, this difference is not significant. Women with pre-existing heart disease were 7.9 percentage point more likely to use IMRT compared to conventional radiotherapy and this difference is significant.

Discussion

Overall, the results of this study indicated that patient comorbid condition (lung or heart disease) could affect their treatment options. Breast cancer patients who have pre-existing heart disease were more likely to choose IMRT compared to patients without heart disease and this difference is significant. Patients with previous lung disease showed a little bit lower preference of choosing IMRT compared to patients with heart disease, but this difference is not significant. When we considered patients' pre-existing disease as combined, they showed a significantly higher preference of using IMRT. As we can see, different pre-existing diseases have different impact on patient' treatment preference. Based on our conceptual model, which assumed physicians' preference is the mediator of the focal relationship, this difference could be explained by physicians prefer to be more conservative for breast cancer with previous cardiac risk. Since we know that compared to most lung disease, cardiovascular disease is a more severe comorbidity. Most previous studies of radiation-related injury paid more attention to cardiovascular disease and less to lung disease. So it is reasonable if physicians tend to give a conservative treatment for their patients with previous cardiac risk. Overall, physicians prefer to choose IMRT for their patients who have pre-existing heart or lung disease. They assume their patients can benefit from this advanced radiotherapy.

Current guidelines do not give any specific instructions for physicians of when and how to choose advanced RT techniques for their patients. Thus, current use of IMRT could be much more subjective and largely affected by physicians' behavior and patients' preference. Under this background, unnecessary use of IMRT could be common. Nowadays using IMRT for breast cancer is controversial because of its uncertain long-term benefits and huge burden to healthcare system, especially for Medicare. An initiative called "Choosing Wisely", which is launched by ABIM Foundation, appeals to physicians that do not routinely use IMRT as part of breast conservation therapy. However, the result of reducing the use of IMRT is not very ideal. Physicians' behavior is very hard to change.

If healthcare systems want to reduce the use of IMRT for breast cancer patients through affecting physicians' behavior, a more clear and specific treatment guideline should be made. However, guidelines revision should be based on strong evidence from clinical trial. Thus, it is necessary for healthcare systems to organize a new clinical trial to examine and determine the clinical benefits and long-term outcomes of IMRT. Clinical trial also should estimate and determine the group of patients who really need to use IMRT. Based on the result from clinical trial, guidelines can be revised and physicians will have a better understanding of when and how to choose advanced radiotherapy for their patients.

In this study, we simplified the mediator as only physicians' preference. However, role of individual patients played in this focal relationship should be questioned. Since patient choice for radiotherapy could be provider driven or, perhaps, made jointly by provider and patient. Further quality study about patient preference should be considered.

Also, there were shifts in CMS payment policy for IMRT within the 2007-2013 interval, which could possibly affect physician/hospital incentives. However, these policy changes have not been considered in the regression model. Further studies should include these policy changes into analyses models.

This study has several limitations. First, the study sample is limited to older women who are Medicare beneficiaries and may not be generalizable to younger patients with breast cancer. It remains possible that younger women may receive IMRT more frequently because of concerns regarding late toxic effects or because of insurance coverage issues (B. D. Smith et al., 2011). Second, measurement error could occur when we use complicated code to identify the use of IMRT and comorbidities. Cardiovascular-related disease code is relatively easier to find references from past studies, but lung-related disease code is rare and may cause measurement error during data cleaning. What's more, severity levels of pre-existing heart or lung disease, which might affect the use of IMRT, could not been measured well in the data. Third, patient' preference, which could have a strong impact on the model, cannot be measured by SEER-Medicare data. Patients' preference also could be a mediator of the focal relationship, this will definitely affect the result of the study. Also, variables which are poorly measured, such as measuring health status by comorbidity index score, will limit the validity of study.

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