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Evaluating New Radiation Technologies In Older Women With Early Stage Breast Cancer: Understanding The Role Of Hospital Ownership Status And Estimating Cost-Effectiveness

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Evaluating New Radiation Technologies in Older Women with Early Stage Breast Cancer: Understanding the Role of Hospital Ownership Status and Estimating Cost-Effectiveness

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CHAPTER 1: INTRODUCTION

Innovation and development of new technologies have revolutionized cancer care by refining diagnosis, advancing treatment, and improving prognosis of many cancers previously associated with substantial morbidity and mortality. For example, the introduction of radiation therapy in conjunction with breast conserving surgery replaced previous dogma that insisted on radical and oftentimes disfiguring surgery in women with early stage breast cancer. [1-3] As such, the evolution of cancer technology has had a substantial impact in improving patient outcomes, safety, and quality of life.

As newer cancer technologies diffuse into clinical practice, it is important to rigorously evaluate both factors that drive adoption and the implications of such adoption in terms of clinical effectiveness, costs, and overall value. Such evaluation is critical to help inform clinical decision making and to ensure that high-quality and value-oriented care is achieved. Many factors can affect the adoption of new cancer technologies such as clinical evidence, hospital factors, patient and physician preferences, reimbursement incentives, as well as regional and health system characteristics. Given that newer cancer technologies are often more expensive and reimbursed more heavily than the standard of care, there have been questions about cost-conscious care and non-clinical factors driving adoption. After the initial adoption of newer cancer technologies, it is important to understand their implications in terms of costs, quality, and cost-effective care. These implications are often complicated by the fact that many newer cancer interventions often disseminate into clinical practice during times when there is scant comparative effectiveness data supporting their benefit. Using formal cost-effectiveness analysis offers one standardized way to evaluate existing trial tested cancer technologies and allows for estimating the incremental value of various cancer treatments relative to treatment guidelines. In addition, cost-effectiveness analysis is also valuable in assessing how much better newer technologies would have to be, and in particular those technologies that have been adopted in the absence of trial based evidence. Thus, an investigative framework that first evaluates factors that promote adoption of new cancer treatments and then assesses the cost-effectiveness of such adoption provides one way to longitudinally evaluate new technologies during different stages of clinical implementation.

When considering factors that drive adoption of newer technologies, non-clinical factors are particularly important to consider because the combination of higher reimbursements and limited clinical evidence raises questions about incentives driving their use. Hospital level factors such as ownership status is one example of a non-clinical factor that may drive adoption and use. Hospitals play an integral role in investing in new technological infrastructure and have real incentives to attract patients and secure financial viability. Thus, financial incentives related to hospital ownership status may be one factor that promotes the adoption of new cancer treatments. Financial incentives, in general, have been speculated as a contributing factor to increased adoption of highly reimbursed therapies in prostate and breast cancer care. [4,5] However, little is known about the role of hospital ownership status on the adoption of highly reimbursed cancer therapies.

In addition to financial incentives, enthusiasm and marketing of newer treatments may also affect the perception of newer cancer care technologies among both patients and providers and impact use and practice patterns. For example, enthusiasm for novel therapies may lead to new technologies being perceived as better than the current standard of care despite a lack of evidence demonstrating increased benefit. In addition, there may also be a notion that more care with newer technologies is better care and associated with improved outcomes. However, given the limited clinical evidence during early phases of adoption, the perception of new cancer technologies may not always be grounded with data proving their benefit. Therefore, it is important to comprehensively evaluate new technologies and understand factors that drive adoption such that new therapies are implemented responsibly and appropriately in clinical practice.

After initial adoption of these newer therapies, assessing the cost-effectiveness of these technologies offers one way to measure value and compare various newer treatments on a standardized scale. On the one hand, while costs may be higher, new technologies have the potential to improve patient quality of life and outcomes. However, in some settings new technologies have increased costs while having marginal or sometimes questionable benefit on clinical outcomes.[6] This may be particularly true in the early phase of adoption, when data on effectiveness is scant. Thus, assessing the cost-effectiveness of both the standard of care and of newer treatment options can help inform clinical decision making for both patients and providers and offer guidance towards value-oriented cancer care.

Towards this end, radiation therapy is a germane cancer technology to study because many new modalities are disseminating into clinical practice when there is scant evidence supporting their benefit. More specifically, radiation therapy in the treatment of older women with early stage breast cancer is a meaningful scenario to consider because use of radiation in this population confers no survival advantage, provides minimal benefit, and can be safely omitted according to current trial-based guidelines.[7-10] Moreover, newer radiation modalities have been increasingly adopted in the treatment of older women despite guidelines and trial-based evidence.[11,12] These patterns of care with newer radiation modalities raise questions about appropriate care, overuse, and cost-effective care. Two examples of newer breast radiation therapy modalities include brachytherapy and intensity modulated radiation therapy (IMRT). Modern breast brachytherapy involves catheter-based implantation of devices in the breast surgical cavity with later after-loading of high dose rate radiation sources to deliver radiation internally.[13] Breast brachytherapy condenses the treatment course from 5-6 weeks to 1 week. IMRT, on the other hand, is a variant of EBRT but allows for improved dose homogeneity and avoidance of some critical structures.[14,15] These newer therapies have the potential benefits of reducing treatment related acute side effects, reducing late toxicity, and decreasing toxicity to surrounding breast, heart, and lung.[13,16-18] However, clinical trial data comparing these newer modalities to the standard of care with external beam radiation has yet to mature with some preliminary studies suggesting that the risks may outweight potential benefit.[19,20]

Thus, determining factors that drive adoption and assessing the cost-effectiveness of newer and unproven radiation therapy modalities has important consequences in understanding and informing clinical decision making. Comparing newer modalities compared to the standard of care using cost-effectiveness analysis further enables a standardized method to assess potential value of newer radiation modalities and provide a quantitative framework that can speculate either how costly or effective newer modalities would have to be in order to be cost-effective. Therefore, we set out to determine the effect of hospital ownership status on the use of brachytherapy in the treatment of older women with early stage breast cancer. In a second study, we developed a decision analytic model to determine the incremental cost-effectiveness of a trial tested radiation therapy modality using external beam compared to guideline based treatment with no radiation in older women with early stage breast cancer. Finally, we determined the cost-effectiveness of newer radiation modalities (IMRT and brachytherapy) in this patient population and determined how much more effective they would have to be in order to be cost-effective.

CHAPTER 2: HOSPITAL OWNERSHIP STATUS AND USE OF BRACHYTHERAPY

2.1: ABSTRACT

BACKGROUND: Because the benefits of adjuvant radiation therapy (RT) for breast cancer decrease with increasing age, the use of expensive and unproven RT modalities such as brachytherapy in the treatment of older women has been questioned. In particular, patients and policy makers may be concerned that for-profit hospitals might be more likely to use therapies with higher reimbursements. Among both younger and older Medicare beneficiaries with breast cancer, we examined whether hospital ownership status is associated with use of adjuvant brachytherapy.

METHODS: We conducted a retrospective study of female Medicare beneficiaries aged 66-94 years old receiving breast-conserving surgery for invasive breast cancer in 2008 and 2009. We assessed the relationship between hospital ownership and receipt of brachytherapy, as well as overall RT (i.e. brachytherapy or whole breast irradiation (WBI)) using hierarchical generalized linear models.

RESULTS: The sample consisted of 35,118 women, 8.0% of whom had undergone surgery at for-profit hospitals. Among patients who received RT, those who underwent surgery at for-profit hospitals were significantly more likely to receive brachytherapy (20.2%) than patients treated at not-for-profit hospitals (15.2%; Odds Ratio (OR) for profit vs. not-for profit: 1.50, 95% CI: 1.23-1.84). Among women 66-79 years old, there was no relation between hospital profit status and overall RT use. However, among women age 80-94 years old, receipt of surgery at a for-profit hospital was significantly associated with higher overall RT use (1.22; 1.03-1.45) and brachytherapy use (1.66; 1.18-2.34), but not WBI use (1.14; 0.96-1.36)

CONCLUSIONS: Medicare beneficiaries undergoing breast-conserving surgery at for-profit hospitals were more likely to receive brachytherapy, a newer, less proven, and more expensive technology. Among the oldest women, who are least likely to benefit from RT, care at a for-profit hospital was associated with higher overall RT use, which was explained by higher utilization of brachytherapy in this subgroup

2.2: INTRODUCTION

The adoption of new unproven technologies and the associated increase in costs of cancer care has raised concerns about inappropriate care and overuse, especially in light of current value-oriented healthcare initiatives.[21-24] Many factors may affect the adoption of newer medical technologies including patient and physician preferences, reimbursement incentives, clinical evidence, and regional health system factors.[25-28] Hospitals play a major role in the adoption of new technologies, due to their ability to invest in infrastructure, their central role in the treatment of many conditions, and their being the focus of payer efforts to enhance quality and control costs. Hence, it is important to understand how hospital factors, such as ownership status, affect the adoption of new technologies.

The effect of ownership status is particularly relevant in clinical scenarios where evidence regarding treatment benefit is less definitive, and clinical decision-making is more discretionary. In this setting, hospitals owned by for-profit entities, which must return value to investors, may be more likely to encourage the adoption of highly reimbursed interventions. While both for-profit and not-for-profit hospitals have financial incentives to emphasize revenue-generating procedures, for-profit hospitals may be more responsive to these incentives given their fiduciary interests.[29-31] For example, for-profit hospital ownership has been associated with increased use of cardiac revascularization interventions independent of clinical outcome.[31] Similarly, receipt of care at for-profit hemodialysis centers has been associated with increased erythropoietin drug dosing in excess of recommendations from clinical guidelines.[32] However, these studies focused on the use of widely used treatment strategies that had already disseminated into clinical practice with evidence-based guidelines in place. Little is known about the effect of hospital ownership status on the adoption of new medical technologies that are reimbursed at higher rates than existing technologies.[33]

Breast brachytherapy for women with early stage breast cancer is an excellent example of a newer therapy with scant comparative effectiveness data and higher reimbursements compared to the standard whole breast irradiation (WBI). Given current trial based guidelines that recommend that radiation therapy using WBI after breast conserving surgery can be omitted in older women given limited clinical benefit, the use of a newer and unproven radiation modality, brachytherapy, raises questions about appropriate care and factors driving its adoption.[4,34,35] Although breast brachytherapy has diffused into clinical practice, some recent data suggest that harms may actually outweigh the benefits.[13,19,20,36-39] Furthermore, brachytherapy is more highly reimbursed than the standard of care, and some authors have suggested that financial interests are driving the adoption of brachytherapy in clinical practice. [4,40-42] It remains unknown whether care at a for-profit hospital is associated with the receipt of brachytherapy.

It is also important to consider how the adoption of brachytherapy might affect overall use of adjuvant radiation therapy (RT). That is, after disseminating into clinical practice in either profit setting, brachytherapy may substitute for the standard of care, WBI, without any increase in the overall use of RT. Alternatively, enthusiasm for brachytherapy could expand the pool of women who are assessed to be suitable candidates for RT and instead complement the standard of care, thereby increasing overall RT use. In this context, financial incentives and increased reimbursement for brachytherapy may lead to a higher overall use of RT. This may be particularly true among older women, and especially those above age 80 years, for whom the benefit of RT diminishes and thus may be more subject to provider preferences and discretionary judgment.[7-9,43] It remains unknown whether care at a for-profit hospital is associated with brachytherapy use as a substitute for standard RT or associated with a higher likelihood of RT use overall.

To further our understanding of the relation between hospital ownership status and cancer care, we used national Medicare data to assess the relation between for-profit hospital ownership and the adoption of brachytherapy among Medicare beneficiaries with breast cancer receiving breast-conserving surgery (BCS). We hypothesized that among women receiving adjuvant RT, those who had undergone BCS at a for-profit hospital would be more likely to receive brachytherapy. We also assessed whether women undergoing BCS at for-profit hospitals would be more likely to receive RT overall. That is, we hypothesized that the use of brachytherapy in for-profit hospitals increases the proportion of women who are receiving RT, rather than simply substituting for WBI. We also hypothesized that this relation between brachytherapy and overall RT use would be stronger among older women, the group for whom RT is more discretionary.

2.3: METHODS

Data Source and Study Sample

Using the Centers for Medicare and Medicaid Services Chronic Condition Warehouse (CCW) database, we identified a sample of female Medicare beneficiaries between ages 66-94 years who received BCS and adjuvant RT for invasive breast cancer in 2008 and 2009.[44,45] The CCW is a national database that contains 100% of fee-for-service Medicare claims for inpatient and outpatient institutional and non-institutional services for patients with certain chronic conditions. We identified beneficiaries with invasive breast cancer by the International Classification of Diseases, 9th revision (ICD-9) diagnosis code (174.x). Receipt of brachytherapy or other forms of adjuvant RT (external beam, intensity modulated) was identified according to Healthcare Common Procedure Coding

System codes (HCPCS; Appendix 2.1). We only included women who received BCS between January 2008 and June 2009 and were enrolled in fee-for-service Medicare Parts A and B during the study period. Approximately 93% of all Medicare beneficiaries are enrolled in both Parts A and B.[46] Women were excluded from this sample if they received an ICD-9 diagnosis code for any other cancer (including ductal carcinoma in situ) in the 9 months prior through 6 months after BCS (Appendix 2.2). This study used de-identified patient data and was classified by the Yale Human Investigation Committee as nonhuman subjects research and was exempted from a full review.

Radiation Therapy

Patients with any HCPCS codes indicative of brachytherapy treatment were considered to have received brachytherapy. Patients with at least four HCPCS codes indicative of the delivery of WBI with external beam RT (either standard or intensity modulated) were considered to have received WBI. In order to capture all patients for whom the decision was made to provide brachytherapy as a component of their therapy, patients with codes for both brachytherapy and WBI (less than 0.5% of the total sample) were assigned to the brachytherapy group.

Construction of Variables

Patient characteristics included age, race, year of surgery, residence in a metropolitan county based on Core Based Statistical Areas, and median household income at the zip code level. Clinical characteristics such as comorbid conditions, tumor laterality, lymph node evaluation, and receipt of chemotherapy were assessed using HCPCS and ICD-9 codes from the Medicare claims (Appendix 2.1). As proxies for access to care, we accounted for each of the following variables in the year prior to surgery: any hospital admission, screening mammogram, receipt of a flu shot, or primary care physician visit.

Comorbid conditions previously found to be associated with survival in non-cancer patients were assessed by searching claims in the 12 months through one month prior to BCS.[47] We included ICD-9 diagnosis codes that were on an inpatient claim or ≥2 outpatient/physician claims billed >30 days apart.

For each patient, we identified the hospital at which BCS was performed using the Medicare provider number. Hospital ownership was determined from the Medicare Hospital General Information dataset which is a self-reported measure by hospitals during enrollment with the Centers for Medicare and Medicaid Services.[48] All hospitals listed as ‘Proprietary’ under the hospital owner variable were considered for-profit. Hospitals listed as either ‘Government’ or ‘Voluntary Non-profit’ were considered not-for-profit. Patients for whom we could not identify a BCS-performing hospital or whose hospital was not included in the Hospital General Information dataset were excluded from analyses (n=6,194, 15%). Hospital volume was calculated as the number of patients in our sample who received surgery at each hospital during the study period. The sample was categorized into quintiles of volume such that each quintile had approximately the same number of patients. We assessed hospital volume to account for any confounding association between volume and use of RT. Conceivably, higher volume hospitals may prefer a shorter course radiation therapy modality such as brachytherapy regardless of profit-status to ensure a target operating volume.

Patients were assigned to hospital referral regions (HRR) based on zip-code of residence using a cross-walk available from the Dartmouth Atlas of Healthcare.[49] We assessed regional level factors that could be associated with the location of a for-profit hospital and use of brachytherapy including the presence of a state certificate of need (CON), two-year mammography rate, and radiation oncologist density for each HRR.

The CON variable was used to assess the presence of policies that regulated the opening of new radiation facilities during the study period. The presence of a state CON was determined using the National Conference of State Legislatures online resource and the American Health Planning Association National Directory annual report published during our study period.[50,51] We hypothesized that the presence of a state certificate of need may affect RT use by for-profit hospitals because there may be greater barriers in these states to open new radiation facilities and expand the referral base for radiation delivery. We hypothesized that both two-year mammography rate, an indicator for screening practices for a given HRR, and radiation oncologist density might be associated with the use of RT because these regional characteristics may increase both the incidence rate of invasive breast cancer and access to RT.

Statistical Analysis

We used chi-square tests to determine the unadjusted association between hospital ownership and each covariate. We used hierarchical generalized linear models (HGLMs) with a logit link function to assess the unadjusted and adjusted relationship between hospital ownership and receipt of brachytherapy among patients who received RT.[52] HGLMs allowed us to account for the non-independence of outcomes by clustering patients within hospitals, which were clustered within HRRs. In all HGLMs, hospital and HRR were specified as random effects, while all other covariates were specified as fixed effects. We estimated an analogous model using receipt of any RT as our outcome in the full sample. Because RT can be considered optional in many women ≥70 years of age, we hypothesized that the effect of hospital ownership on receipt of any RT might be moderated by patient age. For this reason, we repeated this model with the addition of interaction terms between hospital ownership and age category and re-estimated the model separately among age groups with and without significant interactions. Finally, in order to determine whether any association between hospital ownership and receipt of any RT was driven primarily by the differential use of brachytherapy rather than WBI among older women, we estimated two additional models in which the outcomes were receipt of brachytherapy (versus no RT) and receipt of WBI (versus no RT). All data analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC); HGLMs were estimated using the GLIMMIX procedure.

**CCW database queries and statistical analysis using SAS were performed by Ms. Pamela Soulos MPH*.

2.4: RESULTS

Overview of Study Sample and Hospital Characteristics

Our sample included 35,118 beneficiaries who received BCS. The mean age was 74.2 (SD: 5.9) and less than 6% of our sample was above age 85. The majority of women were white (91.1%). About 72% of the sample received adjuvant RT, of whom 22,496 (88.9%) had undergone BCS at a not-for-profit hospital and 2,816 (11.1%) at a for-profit hospital. Among women who received RT, there were significant differences between women receiving care at a for-profit compared to not-for-profit hospital with regards to race, residence in a metropolitan county, median household income, and receipt of a flu shot (Table 2.1). Patients from for-profit and not-for-profit hospitals were similar in all other patient characteristics.

Patients received care at 2,255 not-for-profit hospitals and 429 for-profit hospitals. Patients who received BCS at for-profit hospitals were more likely to receive surgery at lower surgical volume hospitals and reside in states without a CON for a radiation facility (63% of for-profit hospitals vs. 53% of not-for-profit hospitals, $p<0.001$). In addition, patients who received BCS at for-profit hospitals were more likely to reside in HRRs with a lower mammography rate and fewer radiation oncologists per capita.

Hospital Ownership and Receipt of Brachytherapy

Among beneficiaries receiving RT, 15.7% received brachytherapy. Women at for-profit hospitals who received RT were more likely to receive brachytherapy (20.2%) than women at not-for-profit hospitals (15.2%, adjusted OR: 1.50, 95% CI: 1.23-1.84, p<0.001, Table 2.2). Women who received BCS at higher surgical volume hospitals were also more likely to receive brachytherapy. In addition, patients who had left sided tumors, lymph node evaluation and screening mammograms were all more likely to have received brachytherapy (p<0.001). In contrast, patients receiving chemotherapy were less likely to receive brachytherapy.

Hospital Ownership and Receipt of Overall Radiation

There was no association between hospital ownership and the overall use of RT. That is, 73.1% of women undergoing BCS at a for-profit hospital subsequently received adjuvant RT, compared to 72.0% of women at not-for-profit hospitals (Figure 2.1, OR: 1.08, 95% CI: 0.97-1.20, p=0.18). However, the relation between hospital ownership and RT use varied across age groups.

Among the oldest women (aged 80-94 years), those undergoing BCS at a for-profit hospital were more likely to receive any RT compared to women receiving care at a not-for-profit hospital (Figure 2.1, 58.9% vs. 53.9%, OR: 1.22, 95% CI: 1.03-1.45, p=0.03). There was no significant difference in receipt of RT according to hospital profit status among women age 66-79 (78.1% vs. 78.8%, p=0.74)

The increased use of RT among older women at for-profit hospitals was associated primarily with receipt of brachytherapy. Specifically, women aged 80 and over receiving BCS at a for-profit hospital were more likely to receive brachytherapy (12.4% at for-profit vs. 8.0% at not-for-profit, OR for brachytherapy compared to no RT: 1.66, 95% CI: 1.18-2.34, p=0.003) while there was no relation between ownership status and the receipt of WBI (46.5% at for-profit vs. 45.9% at not-for-profit, OR for WBI vs. no RT: 1.14, 95% CI: 0.96-1.36, p=0.13).

2.5: DISCUSSION

We found that Medicare beneficiaries who underwent BCS at for-profit hospitals disproportionately received the more expensive and less proven brachytherapy over the less expensive standard of care (WBI). Furthermore, older women (≥80) at for-profit hospitals received more RT overall, with this difference largely driven by the use of brachytherapy. Thus, older women received more aggressive care at for-profit hospitals, despite being less likely to benefit from RT.[9]

Several factors may have contributed to the increased use of brachytherapy for women receiving care at for-profit hospitals. Financial incentives may be one driving factor.[12,40,53] Prior studies have highlighted the high reimbursement for brachytherapy, suggesting that it is more revenue generating than the standard of care. [4,42,54] While high reimbursements do not necessarily equate to high profit margins, there has been concern that higher reimbursements have fueled adoption of brachytherapy.[4,55-57] In response to these concerns, the Centers for Medicare and Medicaid Services reduced reimbursement for brachytherapy in 2008 and 2010. While we do not have actual profit margin estimates for brachytherapy in individual hospitals, our findings support previous reports suggesting that higher reimbursements may be contributing to the rapid adoption of brachytherapy.[55-57] In other cancer care settings, it has also been suggested that financial incentives drive the use of newer RT modalities such as intensity modulated RT in men with prostate cancer.[5] Reduced reimbursement of chemotherapy has been associated with significant changes in patterns of chemotherapy use by oncologists.[58-60] In addition to direct financial incentives, leaders at for-profit hospitals may prefer adopting novel therapies as a way to build market share. Indeed, hospital advertising has been shown to promote more advanced technology as a means to attract patients.[61,62]

It is important to note that a driving factor in the adoption of brachytherapy is the attempt to enhance convenience and tolerability of treatment. Brachytherapy has the potential of delivering RT to patients who otherwise may not seek treatment due to concerns about treatment length and toxicity, and may be a reason for some older women to choose brachytherapy over standard RT. However, it is unclear why patient preferences for radiation modality would vary with hospital ownership. Given that women older than 80 years of age are least likely to benefit from radiation overall in terms of improvements in cancer control, our analysis suggests that brachytherapy may be increasing accessibility to RT overall, but not necessarily for women who benefit from it the most. [9,10]

Our study has important limitations. First, we defined hospital ownership as either not-for-profit or for-profit which does not distinguish hospital behavior that can exist in both profit settings.[63] We grouped hospitals listed as ‘Government’ or ‘Voluntary Non-profit’ as not-for-profit because of our hypothesis that for-profit hospitals in particular might adopt brachytherapy to a greater extent compared to other hospital types.[63] However, hospital behavior can align with financial incentives within not-for-profit organizations as well.[63,64] Therefore, coarse classification of ownership into either for-profit or not-for-profit may obscure financial factors that affect brachytherapy use. Second, we examined only

Medicare beneficiaries, who may not be representative of the patterns of brachytherapy utilization in younger patient populations or in patients with private insurance or no insurance. Third, we did not consider the decreases in the Centers for Medicare and Medicaid Services reimbursement for breast brachytherapy, the first of which took effect in January 2009.[4] However, our study illustrates the pattern of brachytherapy use when reimbursement was higher. While our results suggest that the year when treatment occurred did not affect receipt of brachytherapy, future work exploring how these changes affect brachytherapy utilization will add to our understanding of financial incentives and adoption of new technologies of cancer care. Fourth, our analysis does not account for provider factors such as physician reimbursement structures that may differ between hospitals. Our analysis does not examine the effect of ownership status of free-standing RT facilities which also provide RT for patients and may respond differently to financial incentives. Instead, we chose to use hospital ownership where BCS was performed because patients who are referred for RT eventually seek treatment at either hospital-based facilities, freestanding facilities, or seek no RT treatment. Thus, determining the effect of hospital ownership rather than RT facility ownership captures an earlier point in the clinical decision making process. Finally, it is important to acknowledge that the long-term risks and benefits of brachytherapy are still being defined; the current work is focused on the adoption of brachytherapy during a time when there was scant comparative evidence concerning either benefits or risks. Future work should explore patterns of brachytherapy use in non-hospital based settings and how patterns of care respond to data forthcoming from ongoing clinical trials.

Our study extends the current literature by examining how hospital ownership affects the adoption of newer, more expensive cancer technologies and suggests that for-profit hospitals may be emphasizing revenue-generating RT interventions, leading to more aggressive care in patients who are likely to benefit less from treatment.

CHAPTER 3: COST-EFFECTIVENESS OF RADIATION THERAPY MODALITIES

3.1: ABSTRACT

PURPOSE

The use and limited benefit of radiation therapy in the clinical care of older women with favorable risk breast cancer have raised concerns about overuse, expenditure, and cost-effectiveness. Moreover, newer radiation therapy modalities such as intensity modulated radiation therapy (IMRT) and brachytherapy are diffusing into the clinical practice despite their increased costs and uncertain clinical benefit. We used Medicare data to: (1) estimate incremental cost-effectiveness ratios (ICERs) of external beam radiation therapy (EBRT) compared to no radiation; (2) incorporate age and comorbidity into cost-effectiveness estimates of EBRT; (3) evaluate the cost-effectiveness of newer radiation modalities.

METHODS

Using the Surveillance, Epidemiology, and End Results-Medicare database, we identified women who fulfilled the Cancer and Leukemia Group B C9343 trial criteria (>70 years of age, tumor size ≤2cm, estrogen-receptor positive status, node negative) and in whom the use of radiation can be safely omitted. We estimated the annual recurrence, annual metastasis and determined 10-year survival rates according to receipt of EBRT. We determined cancer-related costs to Medicare from a payer perspective. Assuming that all radiation modalities have equivalent effectiveness, we used a Markov decision model to calculate ICERs for each modality compared to no radiation therapy over a 10-year time horizon. We determined the ICERs for various radiation modalities by age and comorbidity status.

RESULTS

The median incremental radiation-related cost associated with EBRT compared to no radiation was $10,308. The cost-effectiveness ratio of EBRT compared to no radiation for the full study sample was $43,015/QALY, and increased with increasing age, ranging from $36,675 (ages 70-74) to $51,375 (ages 80-94) per QALY. The ICER for EBRT among the oldest women with the most comorbidities reached $343,333/QALY. The number needed to treat with radiation to prevent one recurrence was 125. The median incremental cost was $19,254 for IMRT and $18,249 for brachytherapy. Newer treatments would have to be at least 30% more effective to be cost-effective.

CONCLUSIONS

EBRT is cost-effective for a many older women with early stage breast cancer, but substantially less cost-effective for older women with multiple comorbidities. Newer radiation modalities would have to be less costly or substantially more effective in improving quality of life to be cost-effective.

3.2: INTRODUCTION

While the use of external beam radiation therapy (EBRT) after breast-conserving surgery (BCS) has been proven in clinical trials to improve local control and survival in women with early stage breast cancer, this effect has not been shown in an elderly population that typically has more indolent disease. [2,7,8,13,16,65-67] In fact, current trial-based recommendations suggest that adjuvant radiation therapy may be omitted in women >70 years of age with certain low-risk tumor characteristics. [34,35] Despite these guidelines, radiation therapy continues to be used in older women, raising concern about overuse. [11] The hesitation to change practice patterns in light of clinical evidence may be due to both the reduction in local recurrence associated with radiation therapy and the challenges inherent in incorporating the multifactorial effects of age and comorbidity into decision-making.

In our resource-strained healthcare system, we must consider the substantial costs and cost-effectiveness of radiation therapy in this population.[12,40] Formal cost-effectiveness analyses, integrating effectiveness data from well-designed clinical trials with cost data from clinical practice, are widely used tools for informing decision-making. Yet in some instances, new technologies diffuse into clinical practice in the absence of comparative effectiveness data. In this context, a framework is needed to allow practitioners and policy makers to assess newer cancer treatments in the absence of substantial clinical data. To address this need, cost-effectiveness analysis can be used in a different way by first traditionally assessing existing trial-tested interventions. Cost-effectiveness analysis can then be used to project how much more effective newer interventions would have to be in order to be cost-effective.

Radiation therapy in the treatment of older women with breast cancer is a salient example of a cancer technology that is continuously evolving and disseminating into clinical practice despite limited comparative effectiveness data. [55,68] Newer and high cost modalities such as brachytherapy and intensity modulated radiation therapy (IMRT) are being adopted while clinical trials comparing them to the standard of care (EBRT) are still ongoing. [4,12,16,41,55,69] These newer therapies have the potential benefits of reducing treatment-related side effects but are substantially more costly. [13,16-18,53] Notably, brachytherapy has not demonstrated any benefit on cancer control or overall or disease free survival compared to EBRT and may be inferior to EBRT in subsequent mastectomy rate and risk of complications. [19,20] IMRT has demonstrated a reduction in late toxicity and improvement in clinical measures of breast appearance, but it is unclear how IMRT affects patient reported quality of life. [14,70] Therefore, it is important to understand the balance between the costs of IMRT and brachytherapy and the potential benefits of reduced toxicity and improved cosmesis.

We therefore set out to estimate incremental cancer-related costs and cost-effectiveness for EBRT, using actual Medicare expenditures to estimate total cancer-related costs. Secondly, since life expectancy has a strong relation to the time at risk for breast cancer recurrence, and therefore of the effectiveness of radiation therapy, we used actual survival data of older women to estimate 10-year survival across life expectancy groups, defined by age and comorbidity burden. Finally, we explored the incremental costs for the newer radiation therapy modalities and projected how much more effective they would have to be relative to EBRT to be cost-effective.

3.3: METHODS
Basic Model

We designed a Markov decision model to simulate clinical outcomes, estimate quality-adjusted life-years (QALYs) gained, and determine the incremental cost-effectiveness ratio (ICER) of radiation therapy from a payer perspective over a 10-year horizon in older women (≥70 years of age) with early stage breast cancer. Our base case scenario was based on current treatment guidelines. That is, our base case scenario was of older women with early stage breast cancer who had undergone breast-conserving surgery but had received no radiation therapy. We used this model to compare the costs and health benefits of various radiation modalities (EBRT, IMRT, brachytherapy) compared to no radiation therapy. We estimated the cost-effectiveness of the newer modalities (IMRT and brachytherapy) compared to no radiation under the assumption that they had equal effectiveness to EBRT in terms of overall and recurrence-free survival and utility. We then estimated the improvement in effectiveness for the newer modalities that would be necessary in order for them to be below two commonly cited willingness to pay thresholds of $50,000/QALY and $100,000/QALY. Three hypothetical cohorts of women starting at ages 70, 75, and 80 were created to determine the effect of age. We assumed that all women enter the simulation in a no recurrence health state and subsequently transition to one of four health states (no recurrence, recurrence, metastasis, or death) each year (Appendix 3.1). We assumed the recurrence-related decrements in utility lasted for 2 years, during which a woman could transition to metastatic and death states or remain in the no recurrence state.[71] Alternate windows were explored in sensitivity analysis. We chose to use a 10-year time horizon to be conservative in our assumptions regarding the long-term benefit of radiation therapy in older women. Since current treatment guidelines are based on the results from the C9343 trial, which has accrued data for 10.5 years, we chose to constrain our model to a time-period during which radiation use has been proven to have no survival benefit. All analyses were performed on TreeAge Pro 2012 (Williamstown, MA) and SAS version 9.2 (SAS Institute Inc., Cary, NC).

Data Source and Model Assumptions

We determined cost inputs and transition probabilities for recurrence, metastatic, and death states by using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Using this database, we identified a sample of women who met eligibility criteria for the C9343 trial (≥70 years of age, tumor size ≤2cm, estrogen-receptor positive status, lymph node negative), were diagnosed in 1998-2007, and received BCS. The SEER-Medicare database is assembled from population-based cancer registries and links cancer incidence and survival information with Medicare claims [72]. We selected women who fulfilled C9343 criteria because the results from this randomized controlled trial shaped current recommendations that state radiation therapy can be safely omitted in these older women and thus our model parameters will reflect characteristics of a population for whom there are distinct trial based guidelines. We estimated 10-year survival according to age group in women who were diagnosed in 1998-1999, for whom we had 10 years of follow-up data and determined an annual mortality rate. We estimated recurrence and metastasis rates in our sample by using a previously validated administrative algorithm.[73] In brief, we used the high specificity, high positive predictive value algorithm to identify recurrences and metastatic events in our sample. Consistent with prior work, recurrences were estimated by determining the rate of secondary mastectomy, which has been shown to mirror randomized clinical trial data on effectiveness closely. [9,73] Of note, we assigned any patient with metastasis diagnosis codes and a subsequent non-breast cancer diagnosis in SEER to the "no metastasis" group. We used published SEER data to determine breast cancer specific mortality from metastatic disease and calibrated our model to obtain overall survival estimates that were consistent with our sample survival data. [74] Our input parameters were based on a sample of all women who fulfilled C9343 criteria but did not necessarily receive radiation therapy to account for any selection bias in choosing women who had either received radiation or no radiation therapy. All mortality, recurrence, and metastasis rates were converted to annual transition probabilities as model inputs (Table 3.1).

Radiation Therapy

Patients were considered to have received radiation therapy if their Healthcare Common Procedure Coding System codes indicated that they received at least four treatments of EBRT or IMRT or at least one treatment of brachytherapy (Appendix 3.2). Patients with codes for both brachytherapy and other modalities were assigned to the brachytherapy group because they were exposed to the incremental cost as well as potential for toxicity associated with brachytherapy.

Cost Inputs

Each cancer patient was matched to a non-cancer control based on age, race, comorbidity, region, and year of diagnosis (or year of randomly assigned index date for control patients). Total median costs were calculated as all costs to Medicare (including inpatient, outpatient facility, physician, home health, hospice, and DME claims) from a payer perspective in the 2 months before through 12 months after date of diagnosis/index date. We used median costs instead of mean costs to be more conservative in our cost estimates and prevent outliers from skewing the analysis. Each cancer patient's cancer-related cost was calculated as the difference between her total cost and that of her matched control (Table 3.1). The costs were adjusted to 2009 US Dollars using the Prospective Payment System and Geographic Adjustment Factor for inpatient services and the Medicare Economic Index and Geographic Practice Cost Index for outpatient services. [75,76] Cost of metastatic breast cancer care in Medicare beneficiaries was determined from the literature. [77] We estimated the continuing cost of care in the second through ninth year after diagnosis using the same approach. Within each year we restricted the sample used to calculate continuing cost to patients who fulfilled the following criteria through the end of the following year: continuously enrolled in fee-for-service Medicare and free from mastectomy, metastasis, and death. Costs in the year before death were also calculated for all cancer patients who were continuously enrolled in fee-for-service Medicare from diagnosis until death (Table 3.1).

Utility Inputs

We abstracted utility weights for each health state from the literature and then age-adjusted these utilities for older women at 5-year increments using previously reported trends [63,71,78]. For example, women who entered a simulation at age 70 would experience an initial set of utilities for various health states and these utility weights would decrease once a surviving member of the cohort turned 75 or 80. Utilities varied based on age, receipt of radiation therapy, and metastatic and recurrence status and were discounted at an annual rate of 3% (Table 3.1).

Life-Expectancy and Comorbidity Analysis

To assess the effect of varying survival and comorbidity burden, we constructed a separate non-cancer sample by randomly selecting a subset of 50,000 women aged 67-94 each year between 1998 and 1999 to allow for 10-year follow-up. We chose to use survival data from a non-cancer sample to determine age and comorbidity stratified cost-effectiveness estimates to allow for adequate sample size for each combination. Using our non-cancer sample, we determined age and comorbidity combinations that corresponded to different 10-year survival quartiles (0-25%, 25-50%, 50-75%, 75-100%). Combining these data, we estimated ICERs for EBRT by age and comorbidity.

Sensitivity Analysis

We performed a 1-way sensitivity analysis to assess the robustness of our model by determining the variability in incremental cost-effectiveness as a function of cost of radiation therapy, utility of radiation therapy, recurrence rate, metastasis rate, discount rate, cost of recurrence, and time-span of utility decrement upon entering a recurrence state. Recurrence and metastasis rates were varied between our estimates and trial-based data. Cost of radiation therapy was increased and decreased by 50%, the upper limit corresponding to the cost of the newer modalities. The incremental utility benefit of radiation therapy in both the recurrence and no recurrence state was varied by ±50%. We varied the number of years of decreased utility after experiencing a recurrence between one and five years. Using a threshold of $100,000/QALY, we determined how much more effective newer radiation modalities would have to be in terms of QALYs in order to be cost-effective.

**SEER-Medicare database queries were performed by Ms. Pamela Soulos MPH*.

3.4: RESULTS

We included 18,340 Medicare beneficiaries who met the C9343 eligibility criteria. The 10-year survival among all women varied between 73.6% for women aged 70-74 and 33.4% for women aged 80-94 (Table 3.1). We estimated the annual mastectomy probability to be 0.36% in patients receiving no radiation and 0.27% in patients receiving radiation.

We estimated the total costs for a 70-year old woman receiving EBRT during 10-years follow-up to be $41,703 compared to $31,434 for no radiation, resulting in an incremental cost of $10,269 (Table 3.2). Similarly, we estimated the QALYs experienced for a 70-year old woman to be 7.30 for EBRT and 7.02 for no radiation resulting in an ICER for EBRT of $36,675/QALY. ICERs for EBRT increased with increasing age, with an 80-year old woman experiencing 5.18 QALYs with EBRT and 4.98 with no radiation, corresponding to a cost-effectiveness ratio of $51,375/QALY. Using an age-weighted average, we calculated cost-effectiveness of EBRT for all women in our sample to be $43,015/QALY. The cost-effectiveness for EBRT varied by age and comorbidity status (Figure 3.1). Older women with more comorbidity had a decreased 10-year survival probability which corresponded to substantially less favorable cost-effectiveness for EBRT. Specifically, the ICER for EBRT was between $33,116/QALY and $44,652/QALY for women with predicted 10-year survival between 100% and 75% (corresponding to women aged 70-74 with no comorbidity). The ICER for EBRT increased between $57,122/QALY and $343,333/QALY women with predicted survival between 25% and 0%.

The median cancer-related costs per patient receiving newer radiation therapy modalities were $25,240 for IMRT and $24,235 for brachytherapy. Compared to no radiation, the incremental radiation-related costs were $19,254 per patient for IMRT and $18,249 per patient for brachytherapy (Table 3.1). Compared to EBRT, the incremental radiation-related costs were $8,946 per patient for IMRT and $7,941 per patient for brachytherapy. Assuming the newer modalities were equally effective to EBRT, the cost-effectiveness for a 70-year old woman was $68,625/QALY for IMRT and $65,036/QALY for brachytherapy when compared with no radiation (Table 3.2). The newer modalities were less cost-effective in 80-year old women and were estimated to be $96,105/QALY for IMRT and $91,080/QALY for brachytherapy. In our full sample, the cost-effectiveness of IMRT and brachytherapy was $80,478/QALY and $76,230/QALY, respectively. The cost-effectiveness of the newer modalities also increased with decreasing 10-year survival probability (Figure 3.1). Specifically, the cost-effectiveness estimates for the newer modalities were between $58,732/QALY and $79,178/QALY for women with a predicted survival between 100% and 75%. In women with a predicted survival between 25% and 0%, the cost-effectiveness estimates increased to be between $101,239/QALY and $608,033/QALY.

Using one-way sensitivity analyses our cost-effectiveness estimates were sensitive to the cost of radiation therapy. The incremental cost-effectiveness ratio increased by 80% to $65,771/QALY when the cost of EBRT was increased by 50% and approached the cost of the newer modalities. Our estimates were also sensitive to the utility of radiation therapy in women who had no recurrence. That is, when the incremental utility of radiation therapy was increased by 50% in women with no recurrence, the ICER for EBRT increased by 87% to $68,460/QALY. If we assigned zero utility benefit to radiation therapy compared to no radiation, then the base-case scenario of no radiation dominates our analysis. The ICER for EBRT was also sensitive to the number of years of decreased utility after experiencing a recurrence increasing to $50,831/QALY when we assumed the decreased utility would last for 5 years (Figure 3.2). Variations in the other variables changed our estimates by less than 5% (Figure 3.2). We found that IMRT and brachytherapy would have to improve QALYs by at least 28% or 56% in order to be cost-effective with a willingness to pay threshold of $100,000/QALY or $50,000/QALY, respectively (Figure 3.3).

3.5: DISCUSSION

We found that EBRT is a cost-effective therapy for older women with early stage breast cancer as the ICER of $43,015/QALY for EBRT falls below the willingness to pay benchmark of $50,000/QALY that is typically considered acceptable [79,80]. However, we found substantial variability in the cost-effectiveness of EBRT when considering variation in age and comorbidity. While there were many instances in which EBRT was cost-effective in older women, the cost-effectiveness ratios surpassed both $50,000/QALY and a more conservative cited benchmark of $100,000/QALY with increasing age and comorbidity. Thus, our cost-effectiveness analysis provides one way to clarify concerns regarding the unclear effects between life expectancy and breast cancer treatment choices. [43]

Our results raise important questions about the cost-effectiveness of IMRT and brachytherapy. Noting the absence of effectiveness data, our model facilitated cost-effectiveness estimates at various levels of clinical effectiveness. Notably, we found that if these newer modalities had similar effectiveness to EBRT, then their ICERs are above the benchmark of $50,000/QALY for women over 70 years with low-risk tumor characteristics. Moreover, at their current costs these newer modalities would have to be at least 30% more effective to be cost-effective. This study demonstrates a unique approach to evaluating newer cancer treatments as they are diffusing into clinical practice with limited effectiveness data. By using Medicare data to estimate both total cancer-related costs and clinical effectiveness parameters, this approach can be more broadly applied to other novel cancer treatments to inform patients, practitioners, and policy makers on cost-effective care and effectiveness goals of ongoing clinical trials.

Our study builds upon prior work by using the SEER-Medicare database to specifically consider total cancer-related costs and clinical effectiveness of radiation therapy in a population of older women in whom the necessity of radiation is more controversial. [81-83] In contrast, prior studies evaluating the cost-effectiveness of radiation therapy focused on younger women (aged 55-60) in whom the benefit and necessity of radiation therapy is more definitive and derived cost and effectiveness parameters mostly from the literature.[81-85] Our findings are consistent with prior work in that we also found EBRT to be cost-effective in women with early stage breast cancer with an ICER of less than $50,000/QALY. While prior work evaluating younger women estimated the ICER of radiation therapy to be $28,000/QALY, our results suggest that EBRT is less cost-effective in older women, which is not surprising given differences in survival. While our study estimated recurrence probability to be lower than previous trials, our sensitivity analysis suggests that these differences were minor drivers of cost-effectiveness.

There are important limitations to consider. First, our assumptions regarding utilities, while commonly cited in the literature, do not take into consideration different recurrence risks with current therapies, differential complication profiles of the newer therapies, and how patient preferences and functional status change among different age groups, factors that can all affect utility weights. [86,87] Instead, we assumed that the utilities for each mode of radiation were equivalent which may not be accurate. The health utilities we used were from a study in which patients reported a quality of life benefit to radiation therapy compared to no radiation, presumably from the peace of mind that radiation therapy allowed. Though this indicates that the long-term impact of standard breast radiation on overall quality of life is likely low, whether it actually improves quality of life for a patient for whom the benefit from radiation may be low is unclear. Despite the low risk of recurrence for most older women, there is a patient-specific risk tolerance which must be considered. Patients who are very risk averse are unlikely to accept a higher rate of recurrence by omitting radiation, and for these women, radiation may indeed have a long term quality of life benefit. While we can speculate how these parameters would affect our estimates, our projections would be strengthened with more information on how the utility function is affected by these parameters and with long-term data regarding the efficacy of these newer modalities.

Furthermore, studying cost-effectiveness using a cohort of long surviving patients may place less emphasis on short-term complications. Therefore, if patients place great importance on avoiding short-term toxicity or upon shorter radiation schedules (such as with brachytherapy), they may feel that more expensive treatment is justified, despite a lack of a large benefit as measured by improvement in the QALY forecast. For example, if brachytherapy is associated with less severe acute skin reactions compared to EBRT, this may lead to a transiently increased utility for brachytherapy. Despite this increased utility, however, the effect on the QALY forecast is likely minimal due to the relatively transient nature of skin reactions. In contrast, if brachytherapy significantly improves long-term breast outcomes such as cosmesis or late effects on the lung and heart, the effect on QALYs could be more significant. Other factors that may affect long-term utility and cost of these newer modalities include subsequent related procedures, screening and late toxicity. For example, several studies have reported that patients receiving brachytherapy receive more surgery post therapy while others have pointed out that a subset of patients have persistent seromas that may require ultrasound or even excision. [88-90] For IMRT, ongoing randomized controlled trials have reported a reduction in acute and long-term toxicity. [14] Therefore, if these factors change the utility or long-term costs of the newer modalities, then the target effectiveness will have to change correspondingly in order for these modalities to be cost-effective.

We also assumed that the recurrence risk is equivalent across all modalities. This is a tenuous assumption because brachytherapy may be less capable of treating occult multifocal disease compared to EBRT and is more prone to marginal miss (missing occult microscopic extension just beyond the excision cavity), which would ultimately lead to a larger difference in cost-effectiveness relative to EBRT. [91] Evidence from ongoing trials, thus, will be important to accurately build upon this model and to evaluate newer RT modalities.

In summary, EBRT is cost-effective for most older women with early stage breast cancer. However, newer modalities such as IMRT and brachytherapy are costlier than EBRT and would have to be substantially more effective in improving cancer control or quality of life to achieve equivalent cost-effectiveness. As newer technologies disseminate into clinical practice, it will be important to provide data on comparative effectiveness relative to costs to better inform clinical decision-making.

CHAPTER 4: CONCLUSIONS & FUTURE DIRECTIONS

4.1: SUMMARY

We assessed the effect of hospital ownership status on the adoption of brachytherapy and estimated cost-effectiveness of new radiation technologies in the treatment of older women with breast cancer. We found that hospital for-profit status was related to the receipt of not only brachytherapy but also was related to higher overall radiation therapy use leading to potentially overly aggressive care in this population. We also found that while the current standard of care, EBRT, is relatively cost-effective for older women, newer modalities would have substantially improve quality of life or be more effective in order to be cost-effective. We also found that cost-effectiveness of radiation therapy modalities vary substantially with increasing age and comorbidity. Overall, the increased adoption of these newer therapies in older women raises important questions about not only cost-effective care but also about provider preferences and financial incentives that may promote use despite limited data on effectiveness.

4.2: FUTURE DIRECTIONS

For-Profit Ownership and Receipt of Brachytherapy

While several factors may be related to the association between for-profit hospital ownership and receipt of brachytherapy, financial incentives may be one factor that can be tested further . Policy changes have led to decreased reimbursement and changes in coding structure for brachytherapy in breast cancer care. [4] Specifically, in 2008 Medicare reimbursement for each treatment delivered decreased. Also, the reimbursement structure changed to compensate number of catheters used instead of the number of dwell positions. In 2010, surgeon reimbursement for brachytherapy device placement was also decreased. These two events enable an interesting experiment to assess the role of financial incentives. That is, if financial incentives were driving increased use of brachytherapy in older women then decreases in reimbursement may lead to decreased use. On the other hand, if financial incentives are at play, then decreases in reimbursement may lead to changes in practice patterns in order to protect remuneration. For example, in order to protect compensation to levels commensurate with earlier reimbursement levels, practice patterns may shift towards more numerous catheter placement. However, if financial incentives are not driving increased brachytherapy use, then these effects may not be observed. Finally, determining the association between for-profit ownership status of free-standing radiation facilities and brachytherapy use may be another meaninful experiment to test the effect of financial incentives because free-standing radiation facilities may be more directly responsive to financial incentives than hospitals.

Cost-Effectiveness of Newer Radiation Therapy Modalities

We found that our cost-effectiveness estimates were particularly sensitive to utilities assigned to the various health states in our model. However, there is limited data characterizing utilities in women with early stage breast cancer receiving radiation therapy. We used utilities derived from the literature which may be dated and may not as accurately reflect the current perception of radiation therapy. The utilities used in our work also reflect a net benefit of radiation therapy over no radiation which is debatable in an older population given current evidence. Also, there have been no studies to our knowledge that have determined the utility of radiation therapy in older women specifically or the utility of the newer modalities. Thus, it will be important to direct future work towards understanding how older women percieve both the standard of care as well as the newer radiation modalities in terms of quality of life. In addition to the effects of age and technology, utility may change based on period in diagnosis, treatment, and post-treatment which will affect cost-effectiveness estimates. Finally, up to date utilities may be particularly important in characterizing the newer modalities which have many touted benefits in terms of toxicity and adverse effects. Together, these data will be important to strengthen future cost-effectiveness analyses and convey a more accurate and to date perception of the quality of life benefits of radiation therapy. However, collecting utility data can be laborious and challenging. Future work using existing survey instruments such as the Short Form (36) Health Survey (SF-36) may be one way to address this need because there are validated algorithms that are able to transform SF-36 data into utilities. [92] Conceivably, using this survey instrument we will be able to derive chronological changes in utility during various stages of cancer care for various radiation therapy modalities in women of varying ages. Finally, future work incorporating future trial-based effectiveness data will be critical to re-assessing cost-effectiveness of various radiation therapy modalities.

4.3: CONCLUSIONS

Proper evaluation of new technologies that considers benefits, risks, and costs in specific populations is critical towards promoting appropriate clinical care. As new technologies continually emerge into clinical practice, it will be important to comprehensively assess factors driving adoption, incentives affecting clinical decision making, and ultimately patient outcomes. Careful and thorough evaluation has influential consequences in spuring discussion and shaping policies that have positive impact on patient safety, quality, and outcome.

TABLE AND FIGURE LEGENDS

Table 2.1: Characteristics of patients who received radiation therapy according to hospital ownership where breast-conserving surgery was performed

Table 2.2: Associations between patient, clinical, and health system characteristics and the receipt of brachytherapy. Adjusted for patient, clinical, and health system characteristics

Table 3.1: Cost-Effectiveness Model Input Parameters

Table 3.2: Cost-Effectiveness Estimates

Figure 2.1: Percent of women receiving any radiation therapy or brachytherapy based on age and hospital ownership. **NFP**: not-for-profit; **FP**: for-profit

Figure 3.1: Cost-Effectiveness of EBRT and Newer Modalities based on Patient Age and Comorbidity (for example, a patient who is 77 years old with 1 comorbidity has a 10-year survival that falls between 25-50%. For EBRT, this estimated 10-year survival probability corresponds to a cost-effectiveness ratio between $44,678/QALY and $68,547/QALY.)

Figure 3.2: One way sensitivity analysis for EBRT in women aged 70-74

Figure 3.3: Incremental benefit in QALYs for newer modalities to be cost-effective

Appendix 2.1: Procedure and diagnosis codes used in analysis

Appendix 2.2: Sample selection algorithm

Appendix 3.1: Basic Model Bubble Diagram

Appendix 3.2: HCPCS and ICD-9 codes used in analysis

FIGURES

FIGURE 2.1 Percent of women receiving any radiation therapy or brachytherapy based on age and hospital ownership

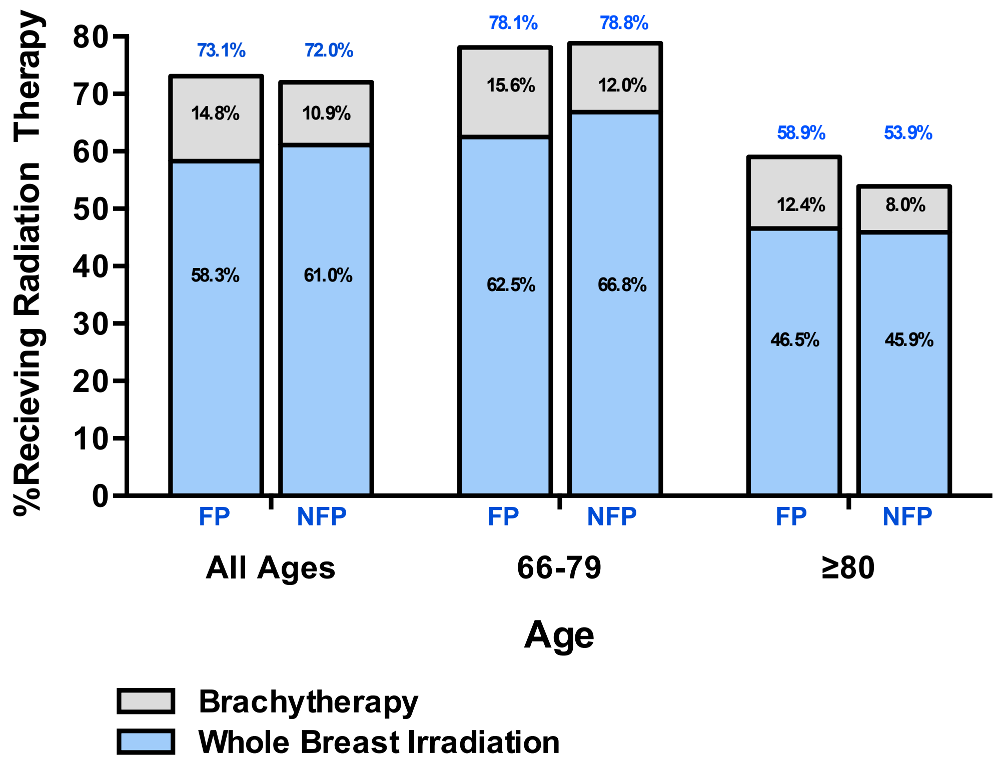
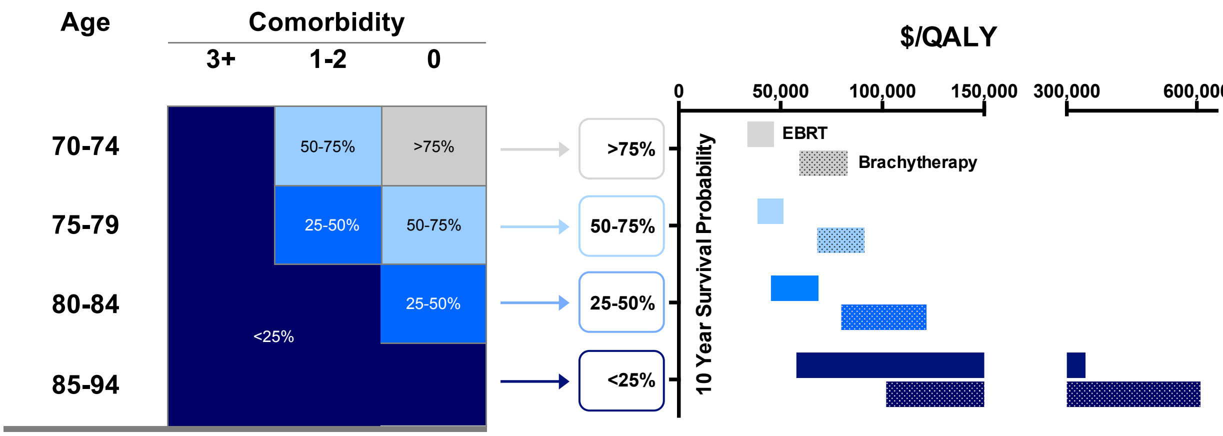
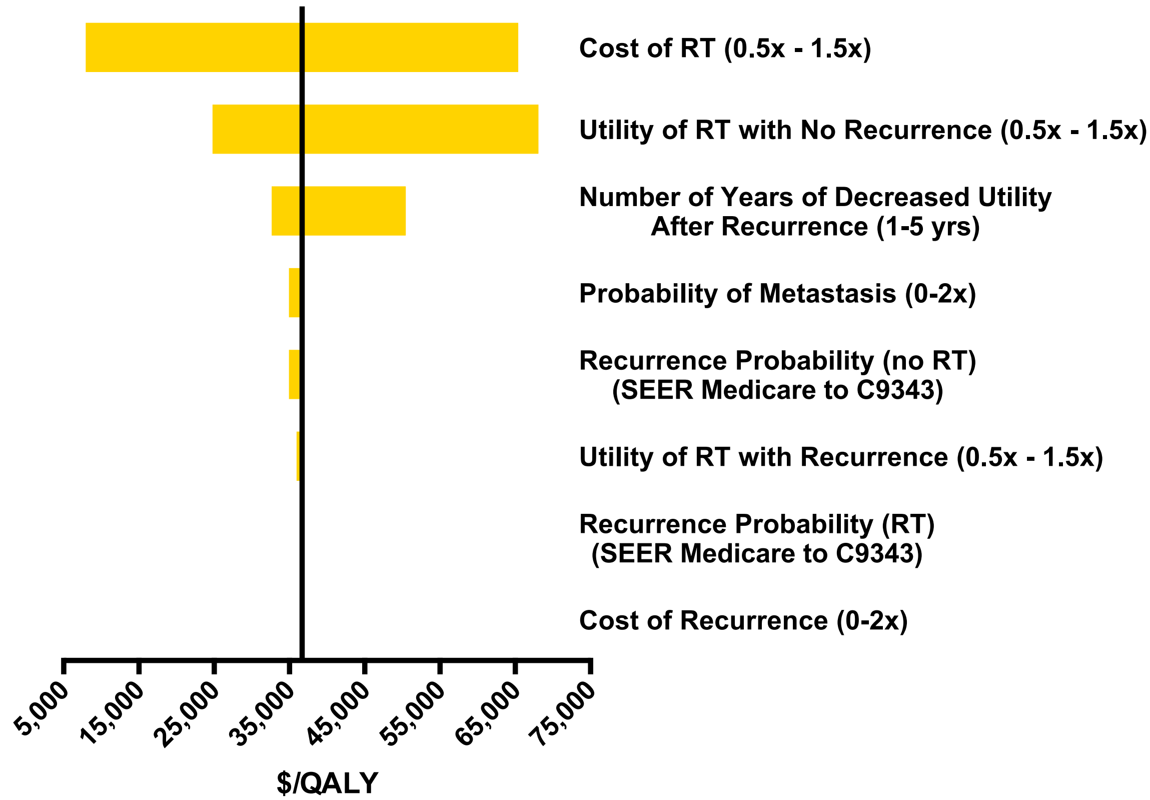


FIGURE 3.1: Cost-Effectiveness of EBRT and Newer Modalities based on Patient Age and Comorbidity (for example, a patient who is 77 years old with 1 comorbidity has a 10-year survival that falls between 25-50%. For EBRT, this estimated 10-year survival probability corresponds to a cost-effectiveness ratio between $44,678/QALY and $68,547/QALY.)



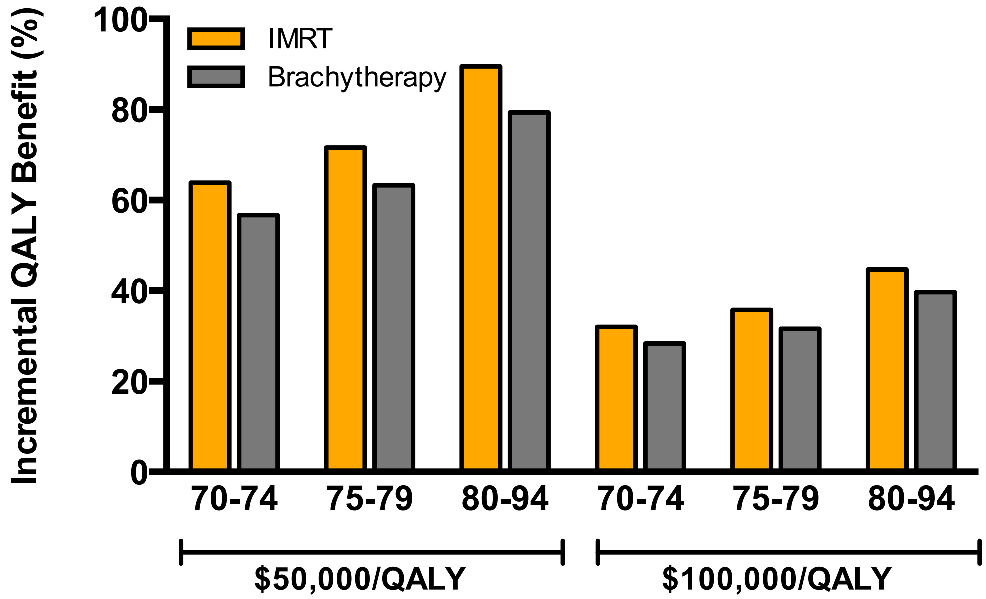
*Conditions used to create comorbidity categories included congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, renal failure, liver disease, AIDS/HIV, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen, coagulopathy, weight loss, fluid and electrolyte disorders, deficiency anemia, alcohol abuse, drug abuse, psychoses, depression.

FIGURE 3.2: One way sensitivity analysis for EBRT in women aged 70-74



*the incremental utility benefit of RT (versus no RT) in either a recurrence or no recurrence state was varied by ±50%

FIGURE 3.3: Incremental benefit in QALYs for newer modalities to be cost-effective



TABLES

Table 2.1 Characteristics of patients who received radiation therapy according to ownership of the hospital where breast-conserving surgery was performed.

	Non-profit			For-profit		
	N	%		N	%	p-value
Total	22496			2816		
Hospital characteristics						
Hospital volume						<0.001
Q1 (1-7)	4170	18.5		855	30.4	
Q2 (8-14)	4284	19.0		862	30.6	
Q3 (15-22)	4347	19.3		445	15.8	
Q4 (23-38)	5013	22.3		338	12.0	
Q5 (39-142)	4682	20.8		316	11.2	
Patient Characteristics						
Age at breast-conserving surgery						0.53
66-69	5964	26.5		765	27.2	
70-74	6673	29.7		834	29.6	
75-79	5209	23.2		619	22.0	
80-84	3412	15.2		428	15.2	
85-94	1238	5.5		170	6.0	
Race						<0.001
White	20542	91.3		2517	89.4	
Black	1375	6.1		183	6.5	
Other	579	2.6		116	4.1	
Year of surgery						0.83
2008	14610	64.9		1823	64.7	
2009	7886	35.1		993	35.3	
Residence in metro county						0.001
Yes	18038	80.2		2330	82.7	
No	4458	19.8		486	17.3	
Clinical characteristics						
Comorbidity						0.72
0 conditions	12761	56.7		1584	56.3	
1-2 conditions	7995	35.5		1021	36.3	
≥3 conditions	1740	7.7		211	7.5	
Tumor laterality						0.41
Right-sided	9715	43.2		1227	43.6	
Left-sided	10056	44.7		1228	43.6	
Unknown	2725	12.1		361	12.8	
Axillary node dissection						0.06
No	6285	27.9		740	26.3	
Yes	16211	72.1		2076	73.7	

	Non-profit			For-profit		
	N	%		N	%	p-value
Chemotherapy						0.04
No chemotherapy	19721	87.7		2429	86.3	
Chemotherapy started in month prior through month after surgery	920	4.1		115	4.1	
Chemotherapy started in 31-365 days after surgery	1855	8.3		272	9.7	
Hospital admission*						0.96
No	19460	86.5		2435	86.5	
Yes	3036	13.5		381	13.5	
Screening mammogram*						0.06
No	5102	22.7		683	24.3	
Yes	17394	77.3		2133	75.8	
Flu shot*						0.02
No	9390	41.7		1242	44.1	
Yes	13106	58.3		1574	55.9	
Visit to primary care physician*						0.12
No	686	3.1		71	2.5	
Yes	21810	97.0		2745	97.5	
Health system characteristics						
State certificate of need for radiation facility						<0.001
No	11820	52.5		1773	63.0	
Yes	10676	47.5		1043	37.0	
HRR-level two-year mammography rate among female Medicare enrollees 67-69, in quintiles						<0.001
Q1 (50.1-59.7)	3941	17.5		793	28.2	
Q2 (59.8-62.4)	4400	19.6		706	25.1	
Q3 (62.4-64.9)	4652	20.7		468	16.6	
Q4 (65.0-68.4)	4762	21.2		441	15.7	
Q5 (68.4-76.1)	4741	21.1		408	14.5	
Radiation oncologist density per 100,000 residents, in quintiles						<0.001
Q1 (0.2-1.0)	4397	19.6		688	24.4	
Q2 (1.0-1.1)	4078	18.1		660	23.4	
Q3 (1.1-1.2)	4531	20.1		624	22.2	
Q4 (1.2-1.4)	4818	21.4		293	10.4	
Q5 (1.4-2.5)	4672	20.8		551	19.6	

*In year prior to breast-conserving surgery

Table 2.2 Associations between patient, hospital, and health system characteristics and the receipt of brachytherapy

	Percent Receiving Brachytherapy	Unadjusted				Adjusted			
		OR	95% CI		P-value	OR	95% CI		P-value
Hospital characteristics									
Hospital profit status					0.01				<0.001
Non-profit	15.2	1.00	--	--		1.00	--	--	
For-profit	20.2	1.28	1.06	1.55		1.50	1.23	1.84	
Hospital volume					<0.001				<0.001
Q1 (1-7)	9.1	1.00	--	--		1.00	--	--	
Q2 (8-14)	13.2	1.40	1.15	1.69		1.38	1.13	1.67	
Q3 (15-22)	16.6	1.98	1.61	2.43		2.02	1.64	2.50	
Q4 (23-38)	20.0	2.21	1.79	2.72		2.24	1.80	2.77	
Q5 (39-142)	19.6	1.93	1.53	2.44		2.00	1.57	2.53	
Patient characteristics									
Age at BCS					0.52				
66-69	16.0	1.00	--	--					
70-74	15.6	0.99	0.89	1.09					
75-79	15.8	0.97	0.86	1.08					
80-84	15.7	0.90	0.80	1.03					
85-94	15.3	0.91	0.76	1.09					
Race					0.02				0.06
White	15.9	1.00	--	--		1.00	--	--	
Black	13.2	0.77	0.65	0.92		0.81	0.67	0.97	
Other	15.0	0.99	0.77	1.27		1.04	0.80	1.33	
Year of surgery					0.53				
2008	15.7	1.00	--	--					
2009	15.8	0.97	0.90	1.06					
Residence in metro county					0.51				
Yes	16.4	1.00	--	--					
No	12.9	0.96	0.84	1.09					

	Percent Receiving Brachytherapy	Unadjusted OR	Unadjusted 95% CI		Unadjusted P-value	Adjusted OR	Adjusted 95% CI		Adjusted P-value
Clinical characteristics									
Comorbidity					0.59				
0 conditions	15.6	1.00	--	--					
1-2 conditions	16.0	1.03	0.95	1.12					
≥3 conditions	15.4	0.96	0.83	1.12					
Tumor laterality					<0.001				<0.001
Right sided	15.6	1.00	--	--		1.00	--	--	
Left sided	16.7	1.10	1.02	1.20		1.11	1.02	1.21	
Unknown	12.9	0.81	0.71	0.93		0.83	0.72	0.96	
Axillary node dissection					<0.001				<0.001
No	11.6	1.00	--	--		1.00	--	--	
Yes	17.3	1.46	1.32	1.60		1.52	1.38	1.68	
Chemotherapy (composite)					<0.001				<0.001
No chemotherapy	16.3	1.00	--	--		1.00	--	--	
Chemotherapy started in month prior through month after surgery	7.2	0.33	0.25	0.43		0.32	0.24	0.41	
Chemotherapy started in 31-365 days after surgery	13.8	0.73	0.63	0.84		0.70	0.61	0.82	
Hospital admission (year prior to surgery)					0.04				
No	15.9	1.00	--	--					
Yes	14.3	0.89	0.79	1.00					
Screening mammogram (year prior to surgery)					<0.001				<0.001
No	13.4	1.00	--	--		1.00	--	--	
Yes	16.4	1.45	1.32	1.60		1.44	1.30	1.59	
Flu shot (year prior to surgery)					0.34				
No	15.4	1.00	--	--					
Yes	16.0	1.04	0.96	1.13					

	Percent Receiving Brachytherapy	Unadjusted				Adjusted			
		OR	95% CI		P-value	OR	95% CI		P-value
Visit to PCP (year prior to surgery)					0.03				
No	12.0	1.00	--	--					
Yes	15.8	1.32	1.03	1.71					
Health system characteristics State CON for radiation facility					0.09				
No	17.5	1.00	--	--					
Yes	13.6	0.85	0.71	1.02					
HRR-level two-year mammography rate among female Medicare enrollees 67-69, in quintiles					0.04				0.007
Q1 (50.1-59.7)	17.1	1.00	--	--		1.00	--	--	
Q2 (59.8-62.4)	17.2	1.05	0.76	1.44		1.04	0.76	1.44	
Q3 (62.4-64.9)	16.3	0.92	0.67	1.27		0.89	0.64	1.23	
Q4 (65.0-68.4)	16.1	0.80	0.58	1.10		0.75	0.55	1.04	
Q5 (68.4-76.1)	12.0	0.67	0.49	0.92		0.62	0.45	0.85	
Radiation oncologist density per 100,000 residents, in quintiles					0.26				
Q1 (0.2-1.0)		1.00	--	--					
Q2 (1.0-1.1)		0.92	0.69	1.23					
Q3 (1.1-1.2)		0.85	0.63	1.16					
Q4 (1.2-1.4)		0.84	0.63	1.13					
Q5 (1.4-2.5)		0.70	0.51	0.96					

*Adjusted for the following health system characteristics: state certificate of need (CON), HRR level 2-year mammography rate in quintiles, and radiation oncologist density per 100,000 enrollees

Table 3.1 Model Inputs

Model Assumptions		Ref
Utilities		71, 78
Conservative Surgery and Radiation Therapy with No Recurrence	0.92-0.758	
Conservative Surgery and Radiation Therapy with Isolated Local Recurrence	0.82-0.676	
Conservative Surgery Alone with No Radiation Therapy with No Recurrence*	0.88-0.725	
Conservative Surgery Alone with No Radiation Therapy with Isolated Local Recurrence*	0.81-0.667	
Distant Metastases	0.7-0.577	
Survival (All Women)		
5 year survival		
70-74	91.1%	
75-79	86.6%	
80-94	70.3%	
10-year survival		
70-74	73.6%	
75-79	61.2%	
80-94	33.4%	
Annual Recurrence Probability		
No RT*	0.0036	
RT	0.0027	
Annual Metastasis Probability		
1-3 years	0.0064	
4-10 years	0.0096	
Annual Death Probability from Metastatic Breast Cancer	0.210-0.238	74
Annual Discount Rate	3%	
Cancer Related Costs per patient		
No RT*	$5,986	
EBRT	$16,294	
IMRT	$25,240	
Brachytherapy	$24,235	
Other Costs		
Recurrence (Mastectomy)	$5,534	
Metastatic Care	$35,000	77
Continued Phase Costs	$156-$705	
Death (last year of life)	$28,580	

* Base case estimate

Table 3.2 Cost and Effectiveness Estimates

	Age	No RT	EBRT	IMRT	Brachytherapy
Costs ($)	70-74	31,434	41,703	50,649	49,644
	75-79	40,907	51,177	60,123	59,118
	80-94	71,803	82,078	91,024	90,019
ΔQALY	70-74	-	0.28	*(0.28)*	*(0.28)*
	75-79	-	0.25	*(0.25)*	*(0.25)*
	80-94	-	0.20	*(0.20)*	*(0.20)*
Incremental Cost-Effectiveness Ratio ($/QALY)*	70-74	-	36,675	68,625	65,036
	75-79	-	41,080	76,864	72,844
	80-94	-	51,375	96,105	91,080
	All	-	43,015	80,478	76,270
Number Needed to Treat to Prevent One Recurrence	All	-	125		

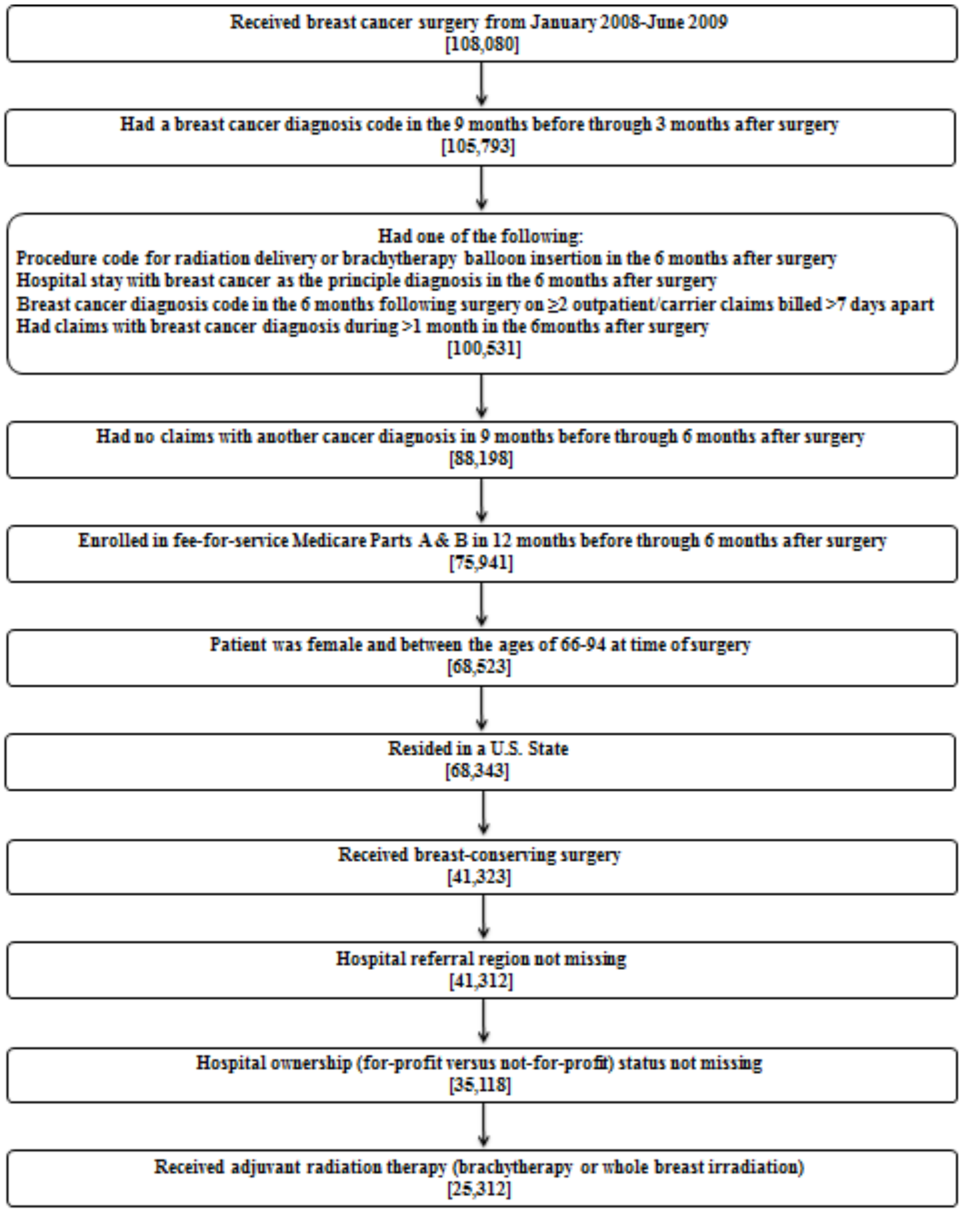
- denotes base case scenario;
italics indicates model assumption that effectiveness of newer modalities is the same as EBRT
* Incremental Cost-Effectiveness Ratios for newer modalities (IMRT, brachytherapy) are compared to no RT

APPENDICES

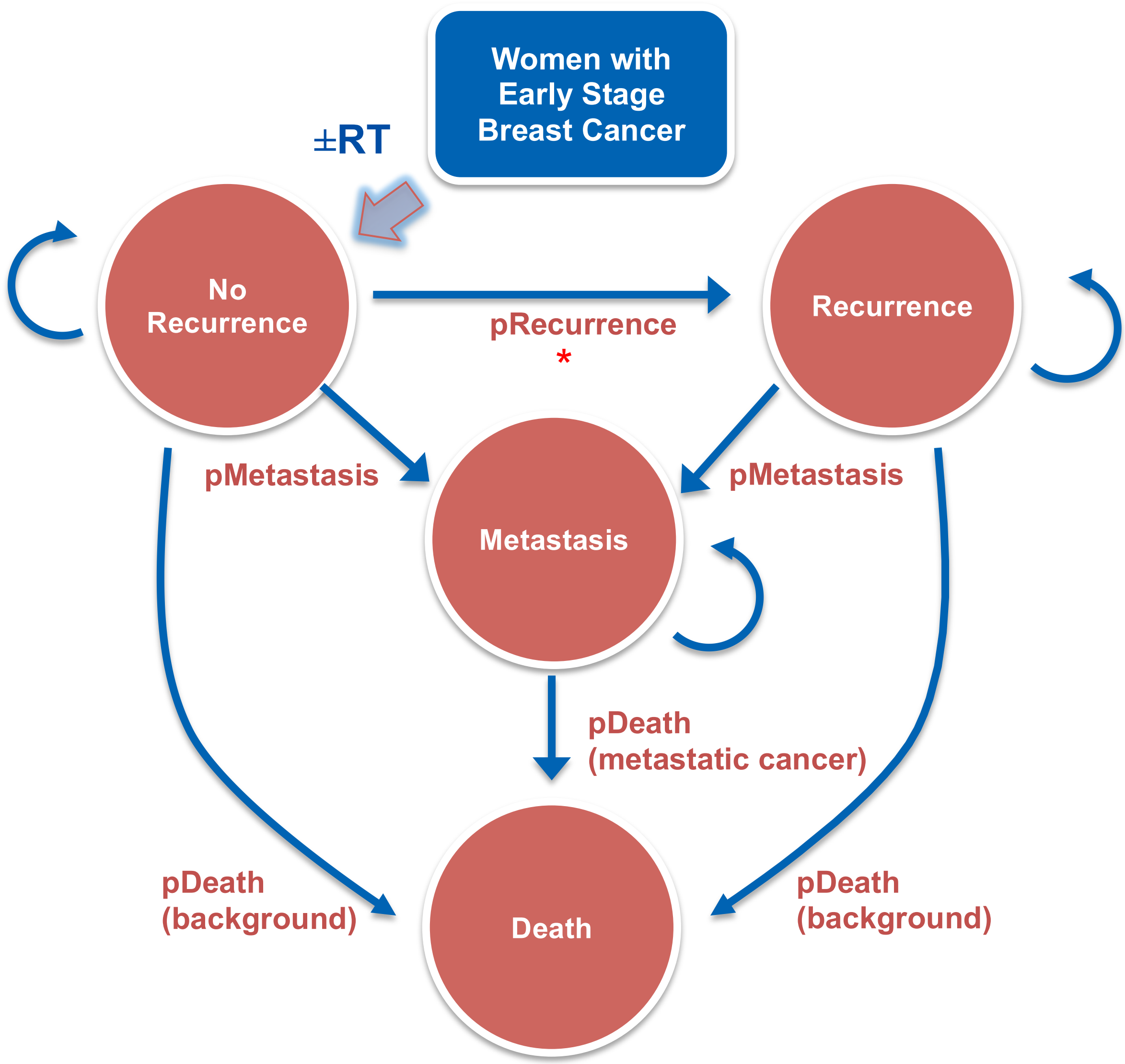
APPENDIX 2.1 Procedure and diagnosis codes used in analysis

	HCPCS	ICD-9 PROCEDURE	ICD-9 DIAGNOSIS
Breast Surgery	19110, 19120, 19125, 19126, 19160, 19162, 19301, 19302	85.20, 85.21, 85.22, 85.23, 85.25,	
Whole-Breast Irradiation	77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77418, 0073T, G0174		
Brachytherapy	77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77785, 77786, 77787, 77799, 0182T		
Tumor laterality	This was using the HCPCS modifier codes for left and right side, which is optionally included for procedures		
Axillary node dissection	19302, 38740, 38745, 38525, 38500	40.23, 40.51	
Chemotherapy	96400-96549, Q0083-Q0085, J9000-J9999, G0355-G0362, J8510, J8520, J8521, J8530, J8560, J8565, J8600, J8610, J8700	99.25	V58.1
Screening mammogram	76092, 77057, G0202, G0203		V76.1, V76.11, V76.12
Flu shot		90656, 90658, 90659, 90660, 90661, 90662, 90724	V04.81
Visit to primary care physician		99202, 99203, 99204, 99205, 99212, 99213, 99214, 99215, 99387, 99397	

APPENDIX 2.2 Sample Selection Algorithm



APPENDIX 3.1



*Upon experiencing a recurrence, there is a two-year decrease in utility
pDeath (background): annual probability of death (refers to background mortality)
pDeath (metastatic cancer): annual probability of death from metastatic breast cancer
pRecurrence: annual probability of recurrence
pMetastasis: annual probability of metastasis

APPENDIX 3.2

Treatment	**Healthcare Common Procedure Coding System**	**International Classification of Diseases, 9th revision**
Breast-conserving surgery	19110, 19120, 19125, 19126, 19160, 19162, 19301, 19302	85.20, 85.21, 85.22, 85.23, 85.25,
External beam radiation therapy	77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416,	
Intensity modulated radiotherapy	77301, 77418, 0073T, G0174	
Brachytherapy	77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77799, 0182T, 19296, 19297, 19298, C9714, C9715	

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