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Comprehensive Investigation of Radiation Techniques for Whole Breast and Post-Mastectomy Irradiations

Yibo Xie

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COMPREHENSIVE INVESTIGATION OF RADIATION TECHNIQUES FOR WHOLE BREAST AND POST-MASTECTOMY IRRADIATIONS

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Physics and Astronomy

by

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LIST OF ABBREVIATIONS

3D-CRT: 3D-conformal radiotherapy

CEA: Cost-effectiveness analysis

FIF: Field-in-field

HT: Helical Tomotherapy

ICER: Incremental cost-effectiveness ratio

IMPT: Passive scatter proton therapy

IMRT: Intensity modulated radiation therapy

MA-VMAT: Multiple arc VMAT

NC-VMAT: Non-coplanar VMAT

NED: Non evidence of disease

PMRT: Post-mastectomy radiotherapy

PSA: Probabilistic sensitivity analysis

PSPT: Intensity modulated proton therapy

QALY: Quality adjusted life years

SOC: Standard of care

VMAT: Volumetric modulated arc therapy

WBRT: Whole breast radiotherapy

WTP: Willingness to pay

ABSTRACT

Purpose: The purpose of this dissertation is to compare treatment outcomes and cost-effectiveness of various radiotherapy techniques for post-mastectomy radiotherapy (PMRT) and whole breast radiotherapy (WBRT) patients.

Methods: Treatment planning comparison of standard volumetric modulated arc therapy (STD-VMAT), multiple arc VMAT (MA-VMAT), non-coplanar VMAT (NC-VMAT), intensity modulated radiotherapy (IMRT), helical tomotherapy (HT), mixed beam therapy and proton therapy was performed for 9 PMRT patients, and cost-effectiveness of those PMRT techniques compared to standard of care (SOC) were evaluated using a Markov model. Treatment planning comparison of SOC, field-in-field (FIF), hybrid IMRT, full IMRT, STD-VMAT, MA-VMAT and NC-VMAT was performed for 15 WBRT patients, and cost-effectiveness of those WBRT techniques were also evaluated.

Results: For PMRT patients, IMRT exhibited the lowest lifetime attributable risk (LAR) of contralateral breast cancer; NC-VMAT exhibited the lowest LAR of lung cancer; mixed beam therapy exhibited the lowest risk of coronary events (RCE). Probability sensitivity analyses (PSAs) show that all advanced PMRT techniques are more cost-effective than SOC at a willingness-to-pay (WTP) threshold of 100,000 \$/QALY, while only IMRT has a 30.7% probability of being more cost-effective than SOC at a WTP threshold of \$50,000/QALY. For WBRT patients, MA-VMAT exhibited the lowest LAR of lung cancer, contralateral breast cancer and RCE. NC-VMAT plans provided the second lowest LAR of lung cancer and RCE. PSAs show FIF is more cost effective than SOC at WTP threshold of 50,000 \$/QALY, while FIF, hybrid IMRT and MA-VMAT are more cost-effective than SOC at WTP of 100,000 \$/QALY, respectively.

Conclusions: IMRT, NC-VMAT, and mixed beam therapy could be the optimal radiation techniques for certain PMRT patients, and MA-VMAT and NC-VMAT could be the optimal radiation technique for WBRT patients. Advanced PMRT techniques are more cost-effective for breast cancer patients at a WTP threshold of 100,000 \$/QALY, and IMRT might be the most cost-effective option for PMRT patients at a WTP of 50,000 \$/QALY. FIF, MA-VMAT and NC-VMAT are more cost-effective for WBRT patients at a WTP of 100,000 \$/QALY, and FIF might be the most cost-effective option at a WTP of 50,000 \$/QALY.

CHAPTER 1. INTRODUCTION

1.1. Breast Cancer

About 1 in 8 women will develop invasive breast cancer over the course of her lifetime in the US. The American Cancer Society estimated that 268,600 cases of breast cancer were diagnosed in the US during 2019 [1]. One fifth of the cases were in situ breast cancer cases while the rest of the cases were invasive [2]. As shown in figure 1.1, it is estimated that 30% of new cancer cases among females are breast cancer and 15% of cancer related deaths among women will be attributed to breast cancer in 2019.

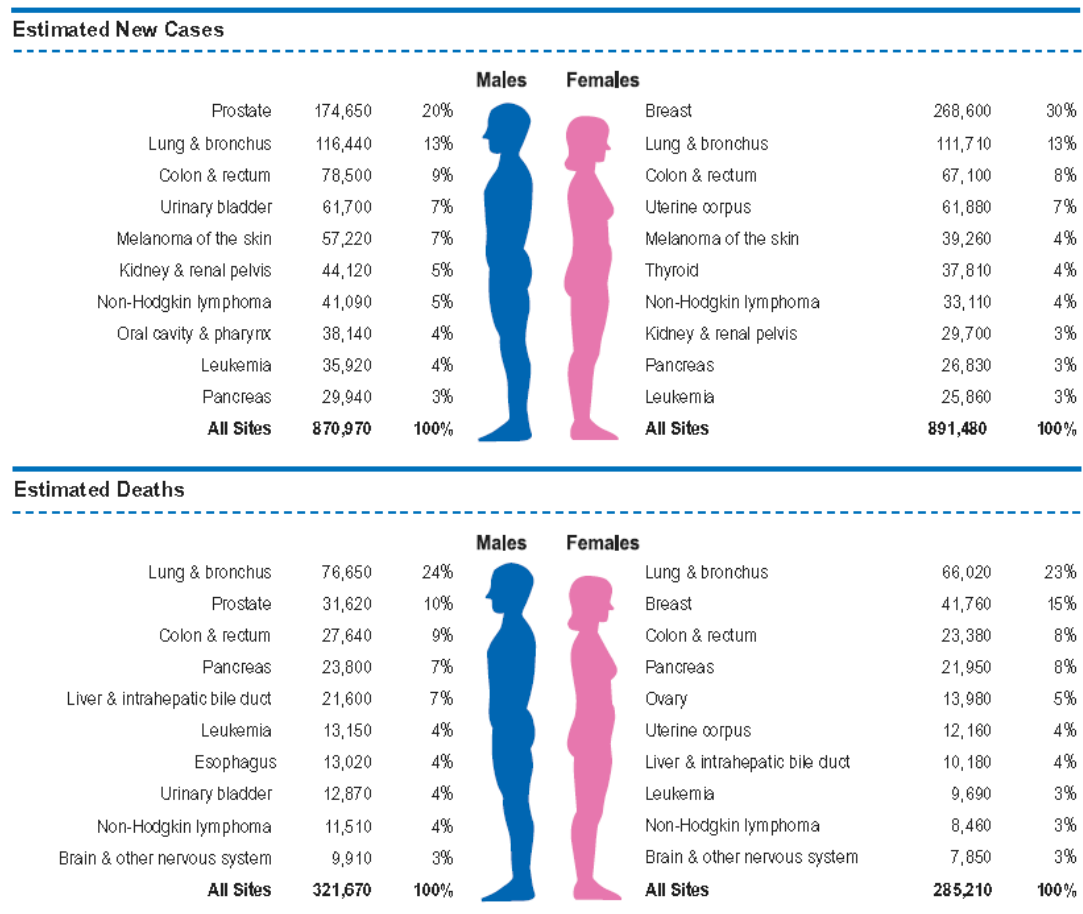


Figure 1.1. Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2019. [1]

1.2. Radiotherapy techniques

Radiotherapy has been used over decades as a supplemental treatment after surgery for breast cancer, and randomized clinical trials have shown that radiotherapy can improve local control and overall survival [3-7]. Doctors generally agree that patients with 4 or more positive axillary nodes, skin involvement, or chest wall involvement have a significantly higher risk for the cancer to recur locally at the surgical site or regionally in the nodal basin. Because of this, post-mastectomy radiotherapy (PMRT) is currently the standard of care (SOC) for all patients with locally advanced breast cancers [8-11]. Treating the chest wall is mandatory according to the American Society of Clinical Oncology (ASCO) because the chest wall is the site at the greatest risk of recurrence in patients undergoing mastectomy. A PMRT prescription dose of 50 Gy in 2 Gy or 50.4 Gy in 1.8 Gy daily fractions given over 5-6 weeks is commonly used in most US institutions [5, 12].

Whole breast radiotherapy (WBRT) after breast conserving surgery (BCS) has been established as the standard treatment for early stage breast cancer. The intent of WBRT is to treat the entire ipsilateral breast to ensure that the lumpectomy cavity is dosimetrically covered within the irradiated volume and any residual cancer cells are eradicated. A clinical trial (Protocol B-06) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) showed that WBRT after lumpectomy results in comparable survival outcomes as those treated with PMRT [6]. Typical WBRT uses conventionally fractionated radiation after breast-conserving surgery, such as 2 Gy per fraction for a total dose of 50 Gy or 1.8 Gy per fraction for a total dose of 50.4 Gy followed by an optional boost to 60 Gy or 66.6 Gy [13].

The current SOC for WBRT in the US and in our clinic is using 3D parallel-opposed tangential conformal photon fields to treat the whole ipsilateral breast and chest wall, plus additional photon/electron fields to treat supraclavicular, axillary and internal mammary nodes

when necessary [14]. The current SOC for PMRT in the US is using 3D parallel-opposed tangent photon fields to treat the lateral chest wall shown in Figure 1.2, where the green triangle represents wedge was used to modify the radiation beam to optimize the dose distribution within the target volume. The internal mammary chain lymph nodes, axillary lymph nodes, and the supraclavicular lymph nodes may be treated using additional anterior photon/electron fields based on the diagnosis [15, 16].

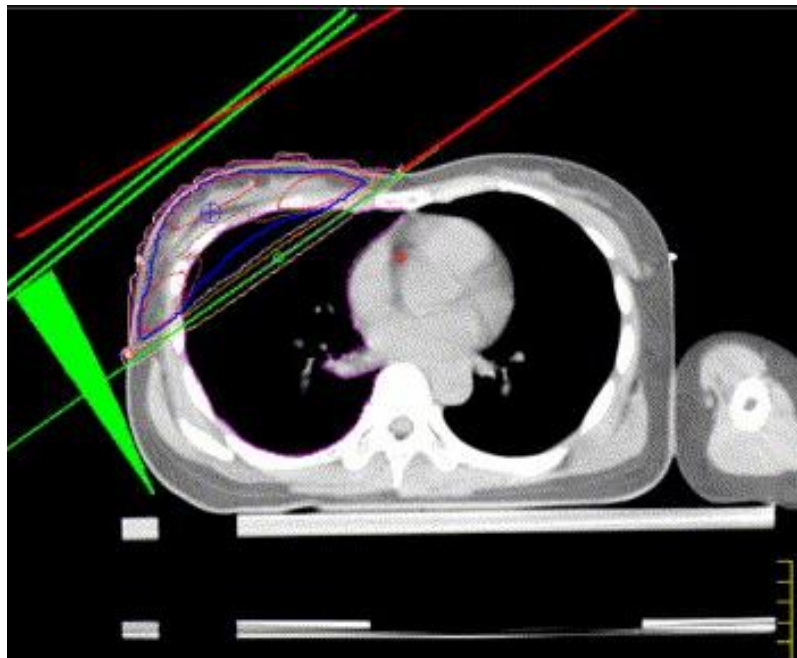


Figure 1.2. 3D parallel-opposed tangent photon fields to treat the lateral chest wall. Source: Seung *et al.*, 2004 [17]

Helical tomotherapy (HT) is an arc-based, photon intensity modulated radiotherapy (IMRT) delivery system that utilizes a rotating helical fan beam with a multi-leaf collimator (MLC) containing 64 binary leaf-pairs. Ashenafi *et al.* [18] performed a treatment planning study comparing HT with conventional mixed-beam therapy for PMRT. They showed that HT achieved significantly better PTV dose homogeneity while maintaining acceptable sparing of organs at risk

(OARs). However, there are several shortcomings associated with HT, including long treatment delivery time and increased stray radiation dose etc.[19].

VMAT is also an arc-based photon IMRT delivery system, but unlike HT the entire treatment volume can be covered by a single rotation of the gantry. VMAT is capable of varying the MLC leaf position, dose rate and gantry rotation speed simultaneously during delivery [20, 21]. Our clinic has found that for more complex treatment sites like chest wall, two arcs are necessary to obtain the desired dosimetric results [22]. Multiple arc VMAT (MA-VMAT) showed good feasibility and OAR sparing [23] for WBRT but has not been evaluated for PMRT. Non-coplanar VMAT (NC-VMAT) has been shown to improve OAR dosimetry for intracranial tumors [24, 25], but has not been investigated for breast cancer. The details of MA-VMAT and NC-VMAT will be further illustrated in Chapter 2 and Chapter 4.

Another technique for treating breast cancer is bolus electron conformal therapy (BECT). As high-energy electrons have a relative short range in tissue, which allows electron therapy to have a sharp dose fall-off and create a conformal isodose line around the target volume [26]. This makes BECT suitable for treating a superficial target volume such as the chest wall, or for treatments where organs at risk (e.g., lungs and heart) are close to the target. BECT mixed with IMRT and VMAT (mixed beam therapy) for PMRT was recently evaluated by our group, and it can potentially reduce risks of normal tissue complications [27]. A machinable wax bolus used in BECT is shown in Figure 1.3.

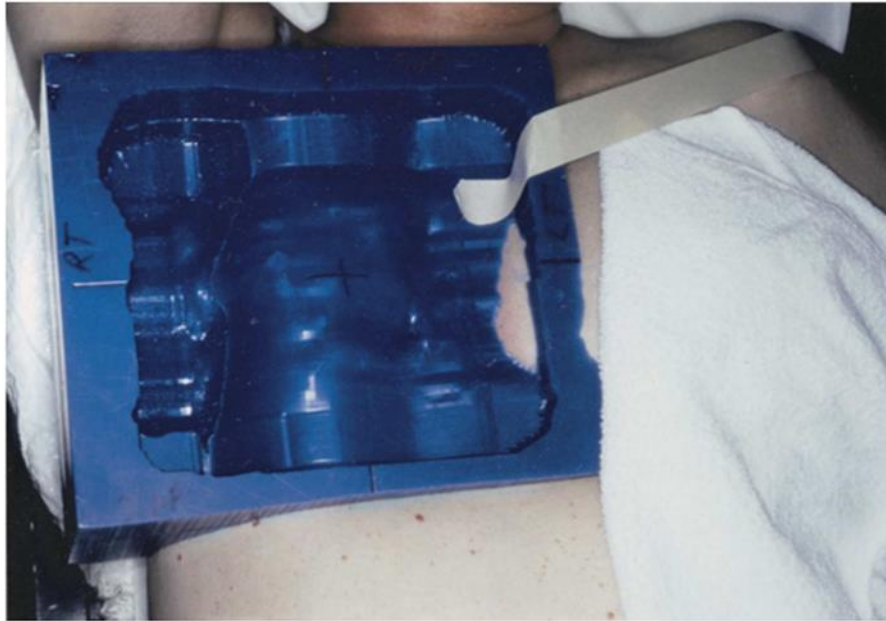


Figure 1.3. Machinable wax bolus on patient surface used in BECT. [28]

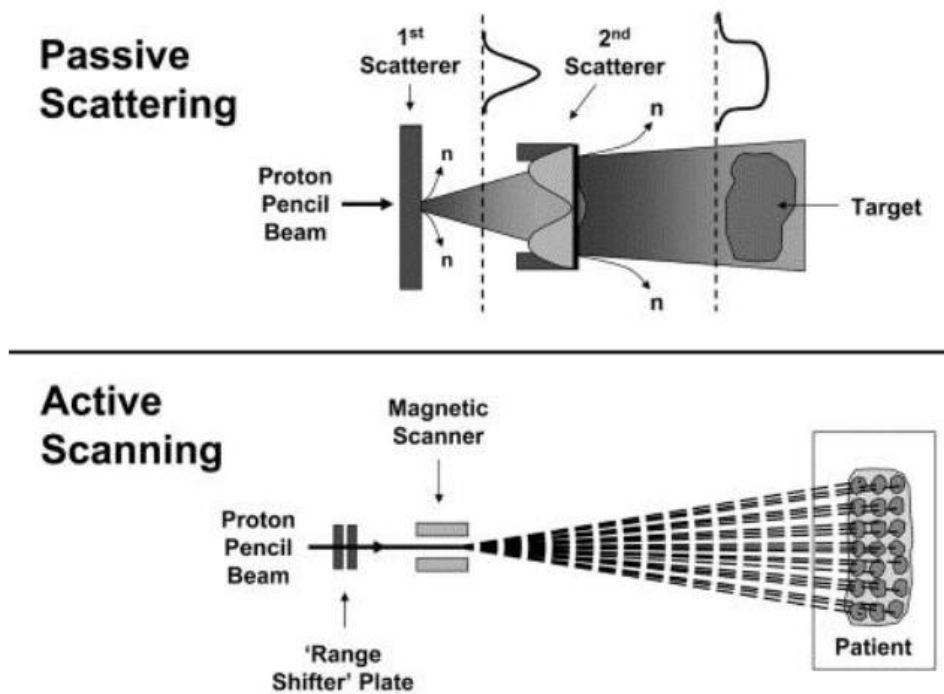


Figure 1.4. Passively scattered proton therapy (PSPT) and intensity modulated proton therapy (IMPT). [29]

Irradiation of breast cancer with proton beams has also been investigated to spare the total healthy tissue [30-33]. The advantage of proton therapy over photon is its rapid increase in energy loss rate near the end of its range shown, which means it'll significantly reduce the dose to normal tissue compared to photon due to the absence of exit dose. There are two main methods for proton radiotherapy delivery: passively scattered proton therapy (PSPT) and intensity modulated proton therapy (IMPT). The differences between the two proton therapy modalities are shown in Figure 1.4. For PSPT, a pencil beam can be scattered out by a dual scattering system and be conformed to the shape of the target by using a collimator and compensator; For IMPT, two orthogonal scanning magnets are used to scan a narrow pencil beam in three dimensions and deposit dose spot to spot through the target volume. In a study by Johansson *et al.* [33], PSPT appeared to have major advantages in terms of lower complication risks of cardiac mortality and pneumonitis compared with conventional radiation techniques for treating node-positive left-sided breast cancer after breast-conserving surgery. In another study, Ares *et al.* [31] found IMPT was advantageous for complex left-sided whole breast target volumes. Hernandez *et al.* [20] found that passive scatter proton therapy and intensity modulated proton therapy showed significant advantages in terms of sparing OARs and lower complication risks when compared to VMAT. However, the main drawbacks of proton therapy are its limited availability and much higher cost.

1.3. Radiogenic side effects

On average more than 80% of breast cancer patients live for 10 years or longer [7]. Given the favorable oncologic outcomes, it is increasingly paramount to minimize radiogenic side effects and improve survivorship for these patients.

Although radiotherapy can improve local control and overall survival [7], long-term breast cancer survivors may develop acute and chronic treatment-related morbidities and mortality after

radiotherapy [34, 35]. Pneumonitis [36, 37], hair loss [38, 39] and skin toxicity [35, 40, 41] are common acute effects which usually occurred within weeks after radiotherapy. Cardiac toxicities [42-46], secondary cancers [47-49] are common late effects which may occur months, years or even decades after radiotherapy.

Using conventional 3D conformal therapy with photon beams for breast cancer is often challenging: considerable volumes of heart and ipsilateral lung are likely to receive high doses which may lead to radiation-induced toxicity such as pneumonitis, lung fibrosis, coronary heart disease and secondary malignancies [50]; significant dose inhomogeneity can also occur within the irradiated volume and can cause poor cosmetic outcomes [51, 52]. In order to avoid high dose exposure to surrounding and underlying healthy tissues, various advanced radiotherapy techniques have been introduced as explained in section 1.2.

1.4. Cost concerns and cost-effectiveness analyses

There are increasing concerns about national healthcare cost. Among all cancer sites, expenditures for female breast cancer remain the highest. Depending on the individual case and type of treatments required, the total cost of breast cancer treatment on average can be around \$100,000. It has been reported that breast cancer cost about \$16.5 billion in the United States in 2010, which is higher than any other type of cancer. And by 2020, annual breast cancer treatment costs are projected to reach \$20 billion [53]. Although more advanced radiotherapy technologies like IMRT, VMAT and proton therapy may improve radiobiological dosimetric outcomes under certain circumstances, their much higher cost may not justify their advantages, e.g. most proton beam facilities can cost more than \$225 million each depending on the number of rooms and other factors [54], while evidence on the effectiveness and safety of proton therapy from clinical trials is lacking and will not be available until years or decades later.

Cost effectiveness analysis (CEA) can be used to assess and potentially improve the performance of health systems, since it can be used to guide utilization away from procedures that produce little benefit at a higher cost—in other words, to improve the efficiency of health care. The most commonly used health status measure is “utility”, which ranges from 0 to 1, where a utility of “1” means the patient is in optimal health and utility of “0” means patient is deceased [55]. Quality-adjusted life years (QALY) is commonly used to measure health outcome that equals to utility times the number of years, where one QALY equates to one year in perfect health [56].

Cost-effectiveness is typically expressed as an incremental cost-effectiveness ratio (ICER), in terms of a ratio where the denominator is a gain in QALY from a new medical intervention (Q_1) compared to a reference medical intervention (Q_0), and the numerator is the cost difference between the two medical interventions (C_1 and C_0) shown in the following equation[57].

$$ICER = \frac{C_1 - C_0}{Q_1 - Q_0}$$

Willingness to pay (WTP) threshold of 50,000 \$/QALY is commonly used [58, 59] for ICER to assess the cost-effectiveness of a new medical intervention. As WTP threshold value depends on both academic literature and country-specific government health insurance programs allowed for source reliability and information cross-checking [60], World Health Organization that suggested WTP threshold of 1 to 3 times the gross domestic product (GDP) per capita [61], which is reported to be \$ 65,462 per capita in 2019 at US [62], and WTP threshold of 100,000\$/QALY is more commonly used in cost-effectiveness studies nowadays [63, 64].

The Markov model is commonly used to simulate randomly changing systems in CEA, due to its ability to combine health status and cost information together. The transition states (e.g., local recurrence, distant metastasis, and death) in the Markov model need to be defined first for patients who underwent radiotherapy, followed by the transition probabilities, utilities, and costs

which are assigned for each state, and the number of cycles, which typically corresponds to the number of years that will be run to simulate change in the system.

Since the uncertainties exist among transition probabilities, utilities and costs in the model, sensitivity analysis is commonly implemented to determine how different values of an independent variable will impact a particular dependent variable. One-way sensitivity analysis [65] and probabilistic sensitivity analysis (PSA) [66, 67] are included in our study.

One-way sensitivity analysis examines the impact on the outcomes (e.g., ICER) of changing the value of a specific variable (e.g., based on its uncertainty) while keeping all other variables constant at their baseline value, which are typically shown by tornado diagram. Figure 1.5 shows an example of the one way analysis results for standard VMAT compared to SOC for PMRT patients, the X axis represents the ICER value, the dashed line represents the initial calculated values, and the width of the bar represents the uncertainty changes that will affect the ICER value. The wider the bar represents the variable has more significant impact on the ICER value. As shown in Figure 1.5, among the probabilities of developing cardiac toxicity, secondary lung cancer and contralateral breast cancer using VMAT, the probability of developing cardiac toxicity using VMAT has the most significant effect on the ICER value, which means the uncertainties in the probability of developing cardiac toxicity using VMAT is a key factor that may affect the final decision of choosing the most cost effective radiotherapy technique.

PSA is performed to assess the uncertainty and robustness of the model by assigning specific distributions for model parameters, i.e. the probabilities, utilities, and costs of radiogenic side effects can be varied simultaneously across their distributions using Monte Carlo simulation. Recommended by Briggs *et al.* [68], we used beta distribution for transition probabilities and utilities estimates, and used gamma distributions for cost parameters.

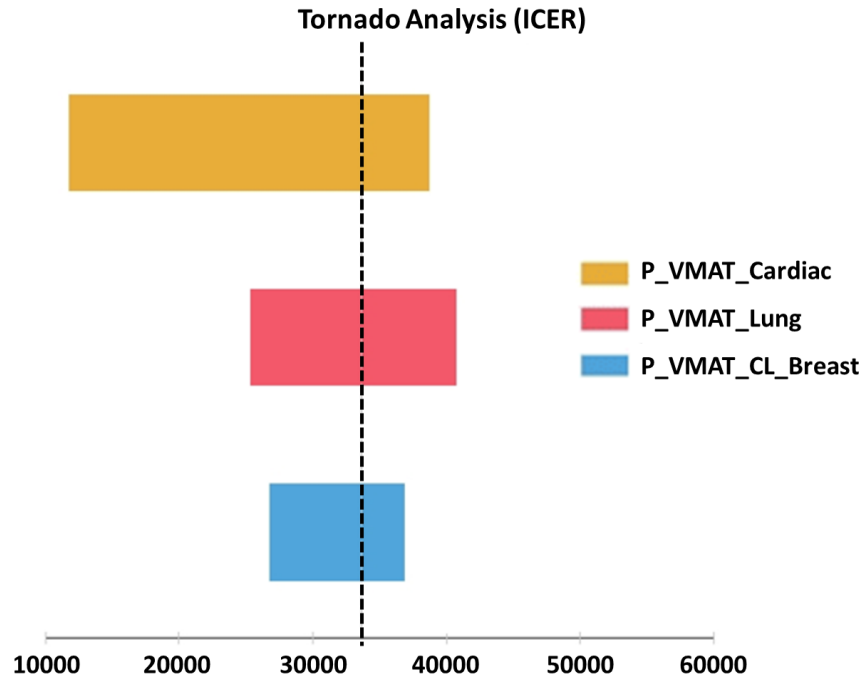


Figure 1.5. Tornado diagram of one way analysis results comparing STD-VMAT to SOC for PMRT patients

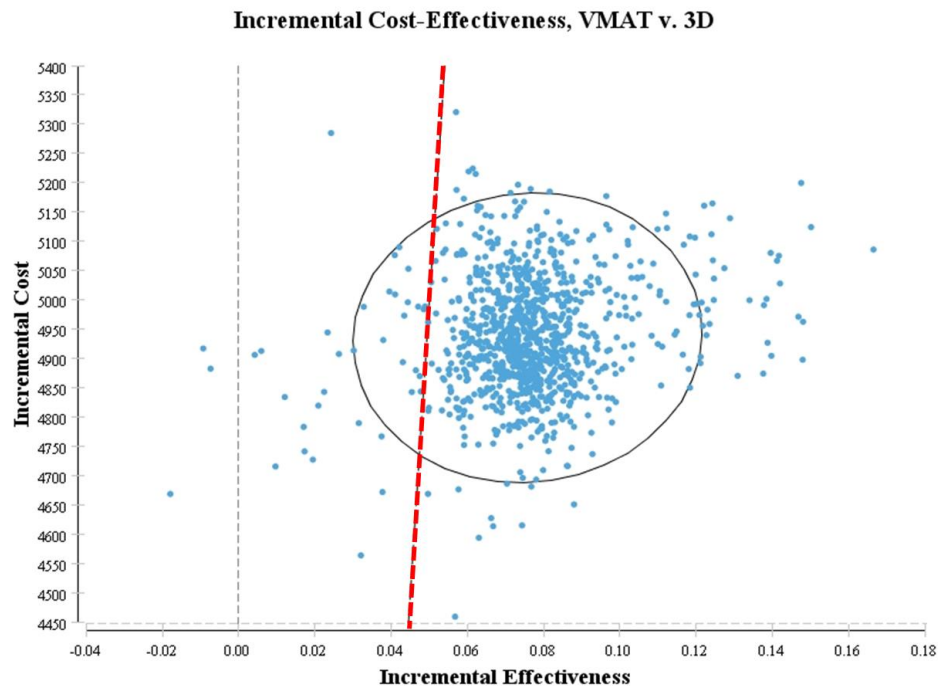


Figure 1.6. Scatter plot of PSA that comparing the cost-effectiveness of STD-VMAT to SOC at WTP of 100,000 \$/QALY

Scatter plot and WTP acceptance curve are commonly used in PSA [65]. Figure 1.6 shows a scatter plot comparing the cost-effectiveness of standard VMAT with 3D conformal therapy where X axis represents QALY (incremental of effectiveness), and Y axis represents the incremental of the cost. One dot in the scatter plot represents one value being selected from the distribution of certain variables and an ICER is calculated. 100,000 iterations are performed to form the scatter plot. The circle represents 95% of the 100,000 dots fall into, and the red dash line represents the WTP of 100,000 \$/QALY. The percentage of 100,000 dots under the line represents the probability of VMAT being more cost effective than 3D conformal. As shown in Figure 1.6, majority of the dots (over 90%) within the circle are under the red dashed line for WTP threshold of 100,000 \$/QALY, which emphasizes that VMAT has a higher probability to be more cost effective compare to 3D conformal therapy.

WTP acceptance curve can be acquired by varying the slope of WTP line shown in Figure 1.6. The probability of VMAT or 3D conformal being more cost effective at various WTP threshold can be calculated and are shown in Figure 1.7. The two dashed lines shown in Figure 1.7 highlight the WTP threshold at 50,000 \$/QALY and 100,000 \$/QALY respectively.

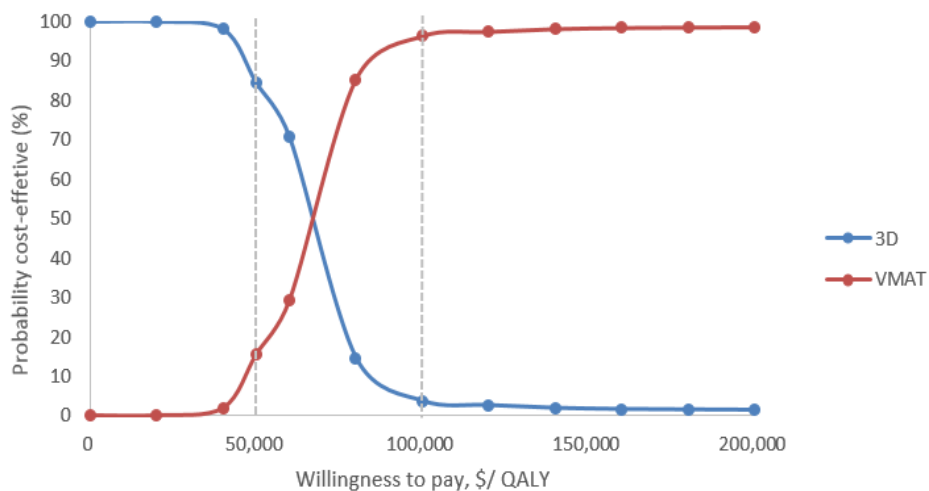


Figure 1.7. WTP acceptance curve of PSA that comparing the cost-effectiveness of STD-VMAT to SOC at different WTP threshold

1.5. Statement of the problem

Most radiotherapy techniques provide comparable target coverage. While the more advanced ones have the potential to improve treatment quality by constraining therapeutic doses to radiosensitive organs, they also have drawbacks, like increased low-dose volume, which could increase the risk of developing side effects [69, 70], and higher costs etc. Also, most previous studies only compare one or few techniques for breast cancer [71-79], a comprehensive comparison study including all advanced techniques is lacking. There have been some treatment planning studies of breast cancer radiotherapy [30, 80-86], but most of them only included one or a few advanced RT, and none of them considered stray radiation doses because dose reconstruction in low dose areas is challenging [87-89]. Evidence from clinical trials will not be available until years or decades later, and the literature is largely incomplete regarding systematic comparison of advanced RT for breast cancer. These advanced RT techniques are implemented with very little evidence for safety or efficacy [33, 71, 90-98].

There have been some cost effectiveness studies about breast cancer radiotherapy: some compared radiotherapy versus non-radiotherapy [99, 100]; others compared partial breast irradiation versus whole breast irradiation [99, 101]. Moreover, most cost effectiveness studies only considered local recurrence and metastasis, and only a few studies assessed the radiogenic side effects by interpolating risk values in the literature [102-105]. Cost-effectiveness studies up to now completely lack consideration of late radiation-induced side effects and do not compare all available advanced radiotherapy technologies.

1.6. Hypothesis and specific aims

The specific purpose of this dissertation is to compare treatment outcomes and cost-effectiveness of various radiotherapy techniques for PMRT and WBRT patients. The hypothesis

of this study is advanced radiotherapy techniques can improve normal tissue sparing while maintaining PTV coverage, and also be more cost-effective compared with the current SOC for selected WBRT and PMRT patients.

There are 2 specific aims of this dissertation. First the predicted treatment outcomes for PMRT and WBRT patients are compared; and secondly, the cost-effectiveness of advanced radiotherapy techniques for PMRT and WBRT patients are evaluated. Chapter 2 describes a treatment planning comparison study using standard VMAT, MA-VMAT, NC-VMAT, IMRT, Tomotherapy, mixed beam therapy and proton therapy for 9 chest-wall cancer patients who underwent radiotherapy after mastectomy. Chapter 3 evaluates the cost-effectiveness of the PMRT radiotherapy techniques. Chapter 4 reports a treatment planning comparison study using 3D conformal RT, field-in-field, hybrid IMRT, full IMRT, standard VMAT, MA-VMAT and NC-VMAT for 15 patients who underwent WBRT after lumpectomy. Chapter 5 evaluates the cost-effectiveness of the WBRT radiotherapy techniques.

1.7. References

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CHAPTER 2. POST-MASTECTOMY RADIOTHERAPY FOR LEFT-SIDED BREAST CANCER PATIENTS: COMPARISON OF ADVANCED TECHNIQUES¹

2.1. Introduction

About 1 in 8 women will develop invasive breast cancer over the course of her lifetime in the US (www.cancer.org). Due to the prevalence of microscopic diseases after the mastectomy, post-mastectomy radiotherapy (PMRT) is commonly performed on these patients to sterilize the residual tumor cells, and has been shown to improve the overall survival for invasive breast cancer patients by reducing the risk of tumor recurrence and cancer mortality.[1]

The role of PMRT in breast cancer care is evolving rapidly with the adoption of new radiotherapy technologies: fixed beam intensity-modulated radiotherapy (IMRT) has been shown to be a preferred technique for PMRT patients and has a good balance of target coverage and normal tissue sparing;[2] the standard of care for PMRT at our institution has been volumetric modulated arc therapy (VMAT) or Helical Tomotherapy (TOMO).[3, 4] Both modalities provide good target coverage and dose homogeneity, but the stray radiation dose to organs at risk (OARs) is a concern;[5] bolus electron conformal therapy (BECT) mixed with IMRT and VMAT (mixed beam therapy) for PMRT has been recently evaluated for real patients' treatment planning by our group and can potentially reduce risks of normal tissue complications.[6] Apart from these previously reported PMRT techniques, multiple arc VMAT (MA-VMAT) which consists of 6 small partial arcs showed good feasibility and OAR sparing[7] for whole breast radiotherapy but has not been evaluated for PMRT; non-coplanar VMAT (NC-VMAT) has been shown to improve

¹Xie Y, Bourgeois D, Guo B, Zhang R. Postmastectomy radiotherapy for left-sided breast cancer patients: Comparison of advanced techniques. Medical Dosimetry. 2019 May 23. Copy right (2019) Medical Dosimetry. Adapted with permission.

OAR dosimetry for intracranial tumors,[8, 9] early stage Hodgkin's lymphoma,[10] liver cancer[11] and prostate cancer,[12] but has not been investigated for PMRT either.

There have been some treatment planning studies of PMRT,[2-4, 6, 13-18] but most of them did not include any or only one advanced PMRT technique. The literature is largely incomplete regarding the systematic comparison of advanced technologies for post-mastectomy patients and these techniques are therefore implemented with very little evidence for safety or efficacy.

The purpose of this study was to compare predicted treatment outcomes (target coverage and risks of developing of radiogenic side effects) for a sample of PMRT patients using various advanced PMRT modalities, including fixed-beam IMRT, NC-VMAT, MA-VMAT, and TOMO. Standard VMAT and mixed beam therapy for PMRT have been reported by our group previously[6] for the same sample of patients, and the outcome results using these modalities will be compared with the PMRT techniques investigated in this study.

2.2. Methods and materials

Patient selection

Nine consecutively sampled left-sided post-mastectomy patients were retrospectively selected. All patients received a modified radical mastectomy and were treated at our institution. Computed tomography (CT) scans had been acquired and all patients were scanned in the supine position with the free breathing CT data sets including all anatomy from the top of the head down to the lower abdomen. All CT data sets were anonymized[19] and assigned a unique research identifier, CW1 to CW9. The planning target volume (PTV) and organs at risk (OARs) for each patient were previously contoured by the same radiation oncologist. PTV included the left chest wall, left supraclavicular and axillary area, and internal mammary chain area. The patients had a

1-cm thick Superflab bolus (Radiation Products Design, Inc., Albertville, MN, USA) placed on the surface of their ipsilateral chest wall for the purpose of dose buildup.[4] OARs included lungs, whole heart, contralateral breast, esophagus, trachea, and spinal cord.

Treatment planning

All plans used a prescribed dose of 50 Gy in 25 fractions. The following criteria were met for each treatment plan to be considered clinically acceptable: the volume of the PTV receiving at least 95% of the prescribed dose is greater than or equal to 95%; the volume of total lungs receiving at least 20 Gy is less than 20%;[20] the volume of heart receiving at least 22.5 Gy is less than 20%[21].

Fixed-beam IMRT plan was generated in a commercial treatment planning system (TPS) (Pinnacle³ v9.8, Philips Medical Systems, Fitchburg, WI, USA) using the direct machine parameter optimization (DMPO) optimization algorithm. Four or five co-planar 6 MV IMRT beams ranging from 150 °to 315 °were used to give enough PTV coverage. Each beam angle was individualized arranged for every patient in order to limit dose to the surrounding organs. Both NC-VMAT and MA-VMAT plans used 6 MV photon beams and were generated in Pinnacle using

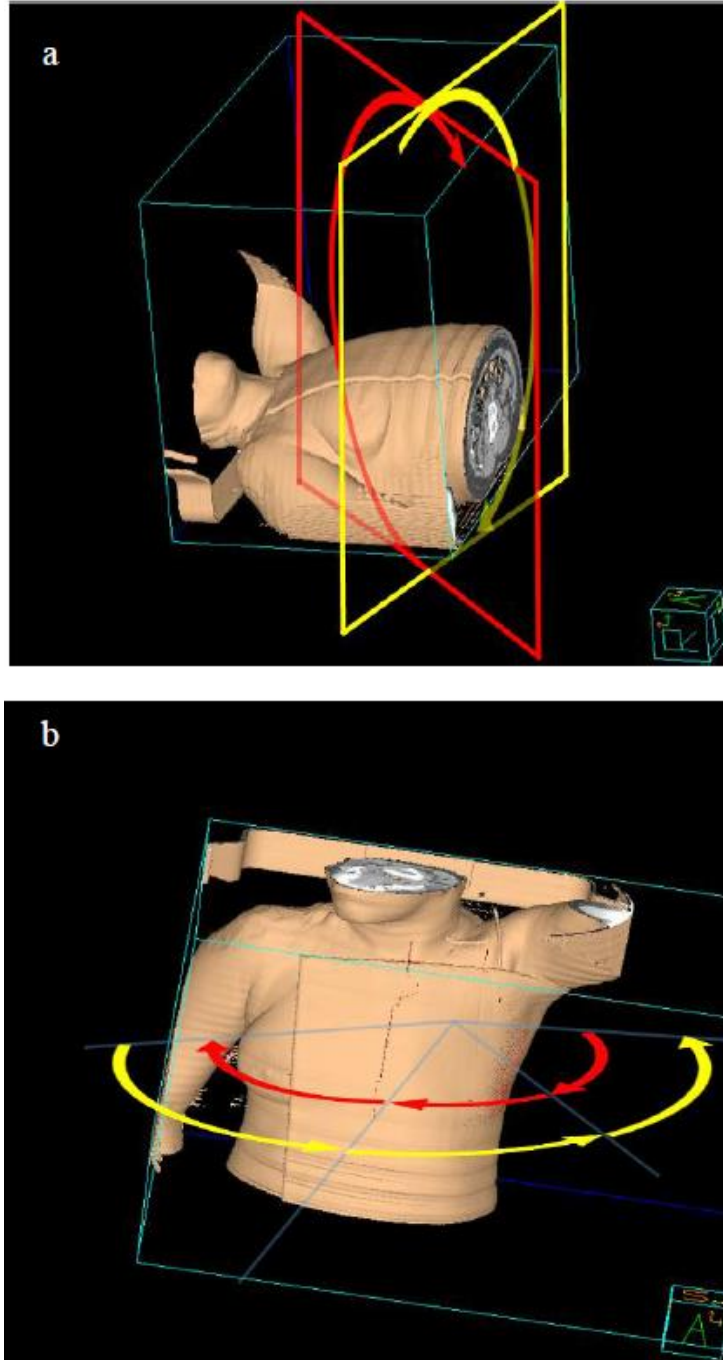


Figure 2.1. Three-dimensional display of (a) two non-coplanar partial arcs for NC-VMAT. Red plane represents gantry plane at 15° couch angle and the yellow plane represents gantry plane at 345° couch angle; (b) six partial arcs for MA-VMAT. The CW arcs display in yellow curvature and CCW arcs in red curvature.

the SmartArc optimization algorithm. NC-VMAT plans utilized two partial arcs (Figure. 2.1 (a)): the first arc was planned to be delivered counterclockwise (CCW) with starting gantry angles between 170° to 180° and stopping gantry angles between 305° to 320° (same as standard VMAT plans that were previously reported by our group[6]) and with 15° couch angle, the second arc was planned to be delivered clockwise (CW) to over the same range of gantry angle and with 345° couch angle. The collimator was rotated to align with the long axis of PTV in both arcs. MA-VMAT plans consisted of six partial arcs (ARC01 to ARC06), each with 60° or 70° gantry rotations (Figure. 2.1 (b)). ARC01 to ARC03 were delivered CW and ARC04 to ARC06 were delivered CCW. The ARC01 started between 170° to 180° and ARC03 stopped between 305° to 320° . The ARC04 started between 305° to 320° and ARC06 stopped between 170° to 180° . The starting angle of ARC01 and stopping angle of ARC03 were the same as the standard VMAT plans. The collimator was always rotated to align with the long axis of PTV in each arc. For TOMO planning, the CT images and contours in Pinnacle were imported into TomoTherapy® Hi-Art TPS (Accuray, Madison, WI) for plan optimization. Parameters for TOMO plan optimization included a pitch of 0.287, a modulation factor of 2.8 and a field width of 5.02 cm. The final TOMO dose distributions were transferred back to Pinnacle for comparison with other plans. The details of standard VMAT and mixed beam therapy treatment planning can be found in our previous publication.[6]

Plan comparison metrics

Dose-volume histograms (DVHs) and dose-volume metrics were calculated for target volume, total lungs, heart and contralateral breast. Dose homogeneity index (DHI)[22] and conformity index (CI)[23] were calculated for the target coverage. Risks of developing of

radiogenic side effects were calculated including lifetime attributable risk (LAR) of secondary lung and contralateral breast cancer, normal tissue complication probability (NTCP) for pneumonitis, and radiation-induced risk of coronary events (RCE).

LAR was calculated as the integration of excess absolute risk (EAR) using BEIR VII model [24]:

$$LAR(D, e) = \int_{a=e+L}^{a_{max}} EAR * \frac{s(a)}{s(e)} da$$

where e is age at exposure, a is attained age, L is a risk-free latent period, $\frac{s(a)}{s(e)}$ is the probability of surviving to age a conditional on survival to age e . [25] EAR is calculated using following equations:

$$EAR = \beta * \mu * OED$$

$$OED = \frac{1}{V_T} \sum_i (v_i * D_i)$$

where OED is organ equivalent dose, β is dose response initial slope ($\beta_{Lung} = 7.5, \beta_{Breast} = 9.2$) [26], μ is age correction factor, V_T is the total organ volume, and v_i is the volume receiving dose D_i . μ was calculated for each patient according to Schneider *et al.* [26] as follows:

$$\mu = \exp \left(\gamma_e * (e - 30) + \gamma_a * \ln \left(\frac{a}{70} \right) \right)$$

where the age modifying factor γ_e and γ_a ($\gamma_{e,Lung} = 0.002, \gamma_{a,Lung} = 4.23, \gamma_{e,Breast} = -0.037, \gamma_{a,Breast} = 1.7$) were taken from by Schneider *et al.* [26]

The Lyman-Kutcher-Burman (LKB) model [27-29] was used to calculate NTCP for pneumonitis using the following equations:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t \exp\left(\frac{-t^2}{2}\right) dt$$

$$t = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)}$$

$$TD_{50}(v) = \frac{TD_{50}}{v^n}$$

where TD_{50} is the uniform dose given to the entire lung that results in 50% complication risk ($TD_{50} = 30.8$ Gy), m is a measure of the slope of the dose-response curve ($m = 0.37$), n is the volume effect parameter ($n = 0.99$), and v is the fractional volume irradiation to the uniform dose D . [29]

RCE was estimated using the dose-response model reported by Darby *et al.* [30]:

$$RCE = 1.074 * D * R_{baseline}$$

where D (Gy) is the mean heart dose, $R_{baseline}$ is the baseline risk of coronary events and was calculated using Reynolds risk model [31] assuming medium risk type.

Statistical analysis

The *post hoc* Tukey test was used to determine the statistical significance of the differences between two PMRT techniques. All statistical analyses were conducted with R software (version 3.2.3) and the differences were considered significant when $p < 0.05$.

2.3. Results

The dose distributions and DVHs for a representative patient are shown in Figure. 2.2 and Figure 2.3, respectively. Table 2.1 lists the total average number of monitor units (MU), PTV and OARs evaluation metrics for various advanced PMRT techniques. The results of *post hoc* Tukey tests and p values are shown in Table 2.2.

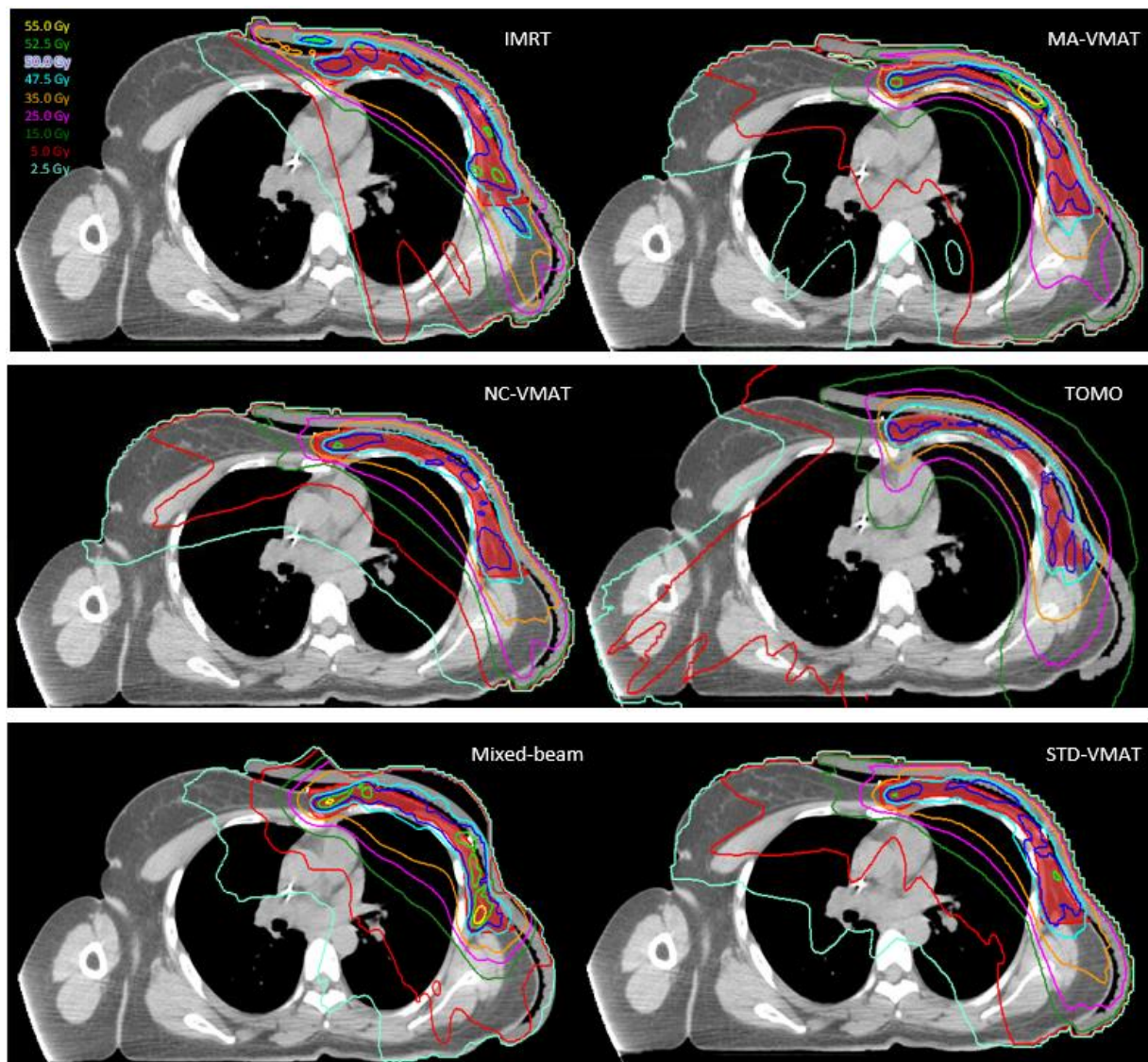


Figure 2.2. Axial view of isodose distribution for fixed-beam IMRT, MA-VMAT, NC-VMAT, TOMO, mixed-beam therapy and standard VMAT plans for a typical PMRT patient. The red color wash represents the PTV.

The four PMRT techniques evaluated in this study as well as two techniques studied previously all meet clinical requirement of PTV coverage. Overall, TOMO plans exhibit the most optimal PTV coverage by showing the lowest D_{max} in PTV, but deliver relatively higher dose to OARs than other plans: significantly higher D_{mean} , V_5 , V_{10} and NTCP for lung, significantly higher

V_{10} for heart, the highest LAR for lung, the highest D_{mean} , V_5 for heart. Fixed-beam IMRT plans induce the lowest D_{mean} , V_5 and LAR for contralateral breast, but induce the highest V_{30} for heart and the highest D_{max} for lung, and yield the significantly higher D_{max} for heart and contralateral breast than other techniques.

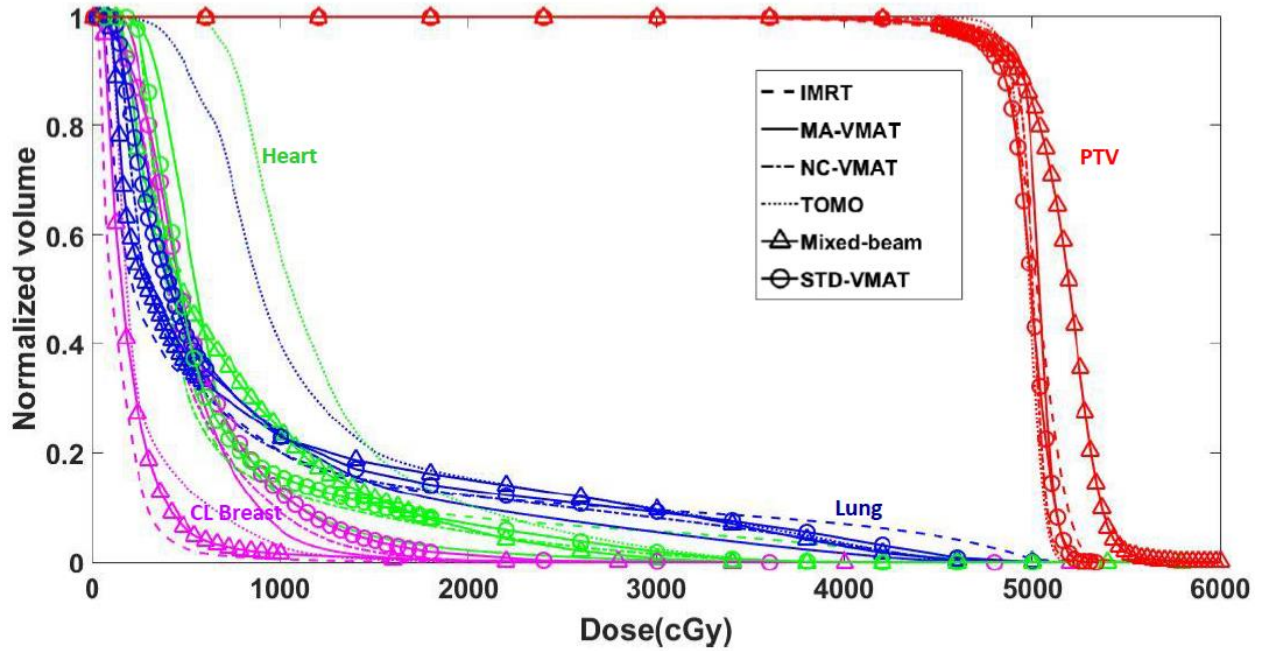


Figure 2.3. DVHs for fixed-beam IMRT, MA-VMAT, NC-VMAT, TOMO, mixed-beam therapy and standard VMAT plans for a typical PMRT patient.

Compared with standard VMAT, both NC-VMAT and MA-VMAT significantly reduce D_{mean} for lungs, heart and contralateral breast, and also significantly reduce V_5 and RCE for heart. NC-VMAT plans exhibit the minimum D_{mean} , V_5 , V_{10} , V_{20} , NTCP and LAR values for lungs and the minimum V_{10} for the heart compared with other plans. Mixed-beam therapy plans show significantly higher D_{max} , DHI and $V_{107\%}$ for PTV than other techniques, and the highest V_{20} for

lungs, but provide the lowest D_{mean} , V_5 , $V_{22.5}$, V_{30} and RCE for heart, the lowest V_5 and the second lowest D_{mean} and LAR for contralateral breast compared with other techniques.

Table 2.1. MU, PTV and OAR evaluation metrics (mean \pm standard deviation) for nine PMRT patients. NC-VMAT: non-coplanar VMAT; MA-VMAT: multiple-arc VMAT; TOMO: Tomotherapy; Mixed: mixed beam therapy; MU: monitor unit; PTV: planning target volume; CL breast: contralateral breast. LAR: lifetime attributable risk; RCE: risk of coronary events.

	NC- VMAT	MA- VMAT	Fixed-beam IMRT	TOMO	Standard VMAT ^a	Mixed ^a
Average total MU	13000.0 ± 1725	14108.3 ± 1839	18130.6 ± 2155	97347.2 ± 8824	11833.3 ± 792	16916.7 ± 3949
PTV						
D_{mean} (Gy)	49.7 \pm 0.2	49.8 \pm 0.3	50.0 \pm 0.3	49.8 \pm 0.4	49.7 \pm 0.3	51.6 \pm 0.4
D_{max} (Gy)	54.1 \pm 1.1	54.9 \pm 2.3	55.9 \pm 2.7	52.4 \pm 0.6	53.5 \pm 0.7	59.9 \pm 3.6
$V_{107\%}$ (%)	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.1	15.0 \pm 8.6
CI	0.7 \pm 0.0	0.6 \pm 0.1	0.5 \pm 0.1	0.6 \pm 0.1	0.7 \pm 0.0	0.5 \pm 0.1
DHI	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.2 \pm 0.0
Lungs						
D_{mean} (Gy)	7.5 \pm 0.8	7.7 \pm 0.9	7.9 \pm 0.6	10.6 \pm 1.5	8.7 \pm 0.6	8.4 \pm 0.9
D_{max} (Gy)	47.7 \pm 1.9	48.5 \pm 2.6	52.8 \pm 1.7	47.0 \pm 1.7	51.1 \pm 1.6	52.0 \pm 2.2
V_5	33.3 \pm 4.9	35.7 \pm 4.9	34.4 \pm 3.1	69.5 \pm 20.3	43.5 \pm 5.8	33.5 \pm 2.6
V_{10}	20.0 \pm 2.2	21.3 \pm 3.6	24.9 \pm 4.0	31.2 \pm 7.9	24.3 \pm 2.4	23.4 \pm 2.9
V_{20}	12.3 \pm 1.0	12.3 \pm 1.8	15.2 \pm 5.1	12.9 \pm 2.1	13.0 \pm 1.0	15.5 \pm 2.6
NTCP (%)	2.1 \pm 0.4	2.2 \pm 0.5	2.3 \pm 0.3	3.8 \pm 1.3	2.7 \pm 0.3	2.7 \pm 0.5
LAR (%)	5.4 \pm 2.8	5.5 \pm 2.8	5.7 \pm 2.8	7.2 \pm 3.8	6.3 \pm 3.1	6.3 \pm 3.3
Heart						
D_{mean} (Gy)	7.4 \pm 1.2	7.7 \pm 1.1	8.53 \pm 1.33	10.3 \pm 2.2	9.3 \pm 1.1	7.1 \pm 1.3
D_{max} (Gy)	41.4 \pm 4.7	40.1 \pm 2.7	48.8 \pm 5.4	38.7 \pm 4.3	42.8 \pm 3.6	38.9 \pm 4.6
V_5	44.6 \pm 13.6	48.6 \pm 12.3	54.4 \pm 14.4	84.3 \pm 18.9	66.9 \pm 13.0	44.3 \pm 7.6
V_{10}	20.7 \pm 5.0	21.2 \pm 6.1	23.3 \pm 5.0	39.1 \pm 18.3	25.3 \pm 4.1	21.0 \pm 5.7
$V_{22.5}$	6.5 \pm 2.3	7.2 \pm 3.7	8.8 \pm 2.0	6.3 \pm 3.0	9.8 \pm 1.9	4.5 \pm 3.4
V_{30}	2.6 \pm 2.2	2.9 \pm 2.7	5.3 \pm 2.5	2.0 \pm 1.7	5.0 \pm 2.6	1.3 \pm 1.8
RCE (%)	8.9 \pm 7.3	8.9 \pm 7.3	9.5 \pm 8.0	9.8 \pm 7.7	9.7 \pm 8.0	8.6 \pm 7.1
CL breast						
D_{mean} (Gy)	3.3 \pm 1.0	3.4 \pm 0.9	1.56 \pm 0.4	3.9 \pm 1.7	4.0 \pm 1.1	1.8 \pm 0.6
D_{max} (Gy)	19.6 \pm 9.1	22.1 \pm 5.9	28.3 \pm 7.6	18.5 \pm 10.5	27.1 \pm 8.4	26.6 \pm 7.7
V_5	16.8 \pm 12.5	21.8 \pm 12.9	5.1 \pm 2.4	24.4 \pm 21.8	24.2 \pm 12.1	4.6 \pm 3.2
LAR (%)	1.2 \pm 0.8	1.4 \pm 0.7	0.6 \pm 0.2	1.6 \pm 0.8	1.7 \pm 0.8	1.1 \pm 0.6

^aData taken from our previous work.[6]

Table 2.2. *p* values for statistic comparison of six advanced PMRT techniques using post hoc Tukey test. NC-VMAT: non-coplanar VMAT; MA-VMAT: multiple-arc VMAT; TOMO: Tomotherapy; Mixed: mixed beam therapy; STD VMAT: standard VMAT; PTV: planning target volume; CL breast: contralateral breast. * indicates statistically significant.

Variable	vs NC-VMAT MA-VMAT	vs NC-VMAT Fixed beam IMRT	vs NC-VMAT TOMO	vs NC-VMAT vs STD VMAT	vs NC-VMAT Mixed	vs MA- VMAT vs Fixed beam IMRT	vs MA- VMAT vs TOMO	vs MA- VMAT vs STD VMAT	vs MA- VMAT vs Mixed	vs Fixed-beam IMRT vs TOMO	vs Fixed-beam IMRT vs STD VMAT	vs Fixed-beam IMRT vs Mixed	vs TOMO vs STD VMAT	vs TOMO vs Mixed	vs STD VMAT Mixed
PTV															
D_{mean}	0.999	0.526	1.000	0.997	<0.001*	0.776	1.000	0.953	<0.001*	0.595	0.243	<0.001*	0.992	<0.001*	<0.001*
D_{max}	0.971	0.057	0.487	0.982	<0.001*	0.328	0.111	0.676	<0.001*	<0.001*	0.006*	0.028*	0.895	<0.001*	<0.001*
V_{107%} (%)	1.000	1.000	1.000	1.000	<0.001*	1.000	1.000	1.000	<0.001*	1.000	1.000	<0.001*	1.000	<0.001*	<0.001*
CI	0.0943	<0.001*	<0.001*	1.000	<0.001*	<0.001*	<0.001*	0.124	<0.001*	0.516	<0.001*	1.000	<0.001*	0.734	<0.001*
DHI	1.000	0.158	0.253	0.525	<0.001*	0.202	0.202	0.601	<0.001*	<0.001*	0.984	<0.001*	0.001*	<0.001*	<0.001*
Lung															
D_{mean}	0.990	0.845	<0.001*	0.004*	0.0712	0.993	<0.001*	0.034*	0.286	<0.001*	0.152	0.643	<0.001*	<0.001*	0.952
D_{max}	0.955	<0.001*	0.956	0.636	<0.001*	<0.001*	0.515	0.984	<0.001*	<0.001*	<0.001*	0.938	0.155	<0.001*	0.004*
V₅	0.988	0.999	<0.001*	0.063	1.000	0.999	<0.001*	0.268	0.993	<0.001*	0.127	0.999	<0.001*	<0.001*	0.073
V₁₀	0.981	0.058	<0.001*	0.136	0.369	0.291	<0.001*	0.495	0.814	0.004*	0.999	0.959	<0.001*	<0.001*	0.996
V₂₀	1.000	0.159	0.996	0.989	0.088	0.164	0.996	0.990	0.091	0.411	0.487	0.999	1.000	0.271	0.333
NTCP	0.999	0.942	<0.001*	0.078	0.187	0.995	<0.001*	0.193	0.382	<0.001*	0.486	0.727	<0.001*	<0.001*	0.999
LAR (%)	0.999	0.966	<0.001*	0.096	0.143	0.999	<0.001*	0.235	0.321	<0.001*	0.469	0.580	0.116	0.076	1.000
Heart															
D_{mean}	0.994	0.360	<0.001*	0.008*	0.993	0.711	<0.001*	0.044*	0.876	0.019*	0.686	0.113	0.533	<0.001*	<0.001*
D_{max}	1.000	<0.001*	0.591	0.958	0.682	<0.001*	0.756	0.878	0.831	<0.001*	0.006*	<0.001*	0.137	1.000	0.186
V₅	0.989	0.643	<0.001*	0.006*	1.000	0.947	<0.001*	0.047*	0.984	<0.001*	0.361	0.613	0.068	<0.001*	0.005*
V₁₀	0.999	0.986	<0.001*	0.864	1.000	0.995	<0.001*	0.914	1.000	0.001*	0.997	0.992	0.007*	<0.001*	0.896
V_{22.5}	0.986	0.262	0.999	0.032*	0.425	0.670	0.941	0.177	0.118	0.152	0.957	<0.001*	0.014*	0.598	<0.001*
V₃₀	0.999	0.021*	0.979	0.056	0.639	0.049*	0.917	0.116	0.454	0.002*	0.999	<0.001*	0.006*	0.965	<0.001*
RCE (%)	1.000	0.252	0.009*	0.025*	0.931	0.337	0.015*	0.040*	0.874	0.823	0.943	0.022*	1.000	<0.001*	<0.001*
CL breast															
D_{mean}	0.998	0.001*	0.644	0.596	0.007*	<0.001*	0.878	0.846	0.001*	<0.001*	<0.001*	0.997	1.000	<0.001*	<0.001*
D_{max}	0.905	0.006*	0.005*	0.029*	<0.001*	0.135	0.113	0.342	0.027*	1.000	0.997	0.992	0.995	0.995	0.898
V₅	0.930	0.215	0.688	0.712	0.181	0.017*	0.996	0.997	0.127	0.003*	0.003*	1.000	1.000	0.002*	0.002*
LAR (%)	0.965	0.259	0.760	0.528	0.997	0.035*	0.995	0.949	0.788	0.006*	0.002*	0.548	0.999	0.450	0.245

2.4. Discussion

This study evaluated four advanced radiotherapy techniques for treating post-mastectomy breast cancer patients, and these techniques were compared with another two PMRT techniques in the literature. Dosimetric and radiobiological endpoints were used to assess the dose to the target and normal tissues. All six techniques provide acceptable dose coverage to target region. Fixed-beam IMRT exhibits the best sparing of contralateral breast, but increases dose to lungs and heart. NC- VMAT provides the best sparing of lungs. Mixed beam therapy provides the best sparing of heart and good sparing of contralateral breast at the cost of inducing less homogenous dose to PTV.

Wang *et al.*[1] drew a conclusion that four fields IMRT has the best balance of target coverage and normal tissue sparing compared with conventional tangential beams, tangential IMRT and single arc VMAT. In our study, we used four to five IMRT beams in fixed-beam IMRT plans because the separation between PTV and OARs is small in some patients and four beams will introduce significantly high dose to OARs. Fixed-beam IMRT plans provide the lowest doses to contralateral breast, which is mainly because this technique is characterized by the limited gantry angles and low dose spread to the organs. On the other hand, also due to the limited gantry angles that are used to cover the entire PTV, the edge of some IMRT beams need to transmit through lungs, heart and contralateral breast in some plans. As a result, the fixed beam IMRT plans yield the highest maximum dose to OARs, which is contradictory to what has been reported in Wang *et al.*[1] These results show that fixed-beam IMRT is not the optimal technique for all PMRT patients and its application should be judged based on the complexity of the target and patient geometry.

Both NC-VMAT and MA-VMAT provide superior OAR sparing than standard VMAT and NC- VMAT offers the best sparing of lungs, which indicates OARs can be spared more for PMRT patients by adjusting the couch angle or splitting a single arc into multiple partial ones since these

will provide more degrees of freedom for plan optimizations. Instead of using 50 ° gantry rotation for each arc in MA-VMAT as reported by Tsai *et al.*[2] for whole breast, we chose larger rotation angle (60 ° or 70 °) in this study in order to achieve enough PTV coverage and optimal OAR sparing. For NC-VMAT, non-coplanar geometries are fixed (couch angle and collimator angle are fixed) in this study, while studies have shown that dynamic couch/gantry rotation and dynamic collimator rotation during VMAT delivery can further improve target coverage or normal tissue sparing[3-5] and should be investigated for PMRT in the future.

The mean lung and heart doses from TOMO are the highest among all the PMRT techniques and can be explained by the fact that radiation to these organs is not limited enough due to the characteristic of TOMO (the beam is delivered from 360 degrees around the body). The other group in our institution independently evaluated TOMO and VMAT for PMRT previously[6]. Our study shows lower lung and heart doses than theirs, which can be explained by the fact different planning goals (they were trying to achieve 90% volume of the PTV receiving the prescribed dose) were used in these two studies and only one optimization objective could be specified for a given OAR in their TOMO TPS, i.e., it was not feasible for them to include more dose objectives to further optimize their plans then. In contrast, the latest TOMO planning system used in our study is capable of including multiple objectives for one OAR.

The CT data representation, contouring and dose calculation algorithm may introduce uncertainties to the dosimetric values. Previous studies[7, 8] reported that using thick CT slice thickness may underdose target volume. Slice thickness of 2.5mm is an optimal and standard choice and was used in our study, and effect of CT data uncertainty on dose values should be minimal. Inter-observer variability in contouring is a major contributor to uncertainty in radiation treatment planning[9, 10]. Kirli *et al.*[11] reported variability in intra-observer contouring was

similar to inter-observer variability and can be reduced by following certain contouring atlas. In our study, all the contours were generated by the same physician following the RTOG atlas and were used for the comparison between different techniques. Thus the uncertainty of inter-observer contouring does not exist and the uncertainty of intra-observer contouring should be minimal. For dose calculation algorithm, we did a test and calculated dose distributions for several patients using adaptive algorithm and fast convolution algorithm besides the standard collapsed-cone convolution superposition algorithm in Pinnacle treatment planning system. The dose differences among three different algorithms for PTV and OARs were very small (within 4%). The absolute dose or risk values in our study could vary slightly due to these uncertainties, but we do not expect dramatic changes of relative values, i.e. the rank of alternative RT techniques.

Deep inspiration breath hold has been shown to significantly reduce cardiac exposure in patients receiving PMRT,[12] which translates to the reduction of risk of heart disease. However, free breathing is the standard of care for PMRT patients in our clinic and breath hold was not adopted for the patients used in this study, neither in most of the previous PMRT studies. Acquiring patients' CT images with breath hold and comparing various advanced radiotherapy techniques for breath hold patients will be further investigated in the near future.

We only compared various photon and electron radiotherapy techniques while did not include proton therapy. Actually proton PMRT was also evaluated by our group previously,[13] and the superior dose distribution makes proton PMRT dominant among all PMRT techniques. However, due to the limited availability and much higher cost, proton PMRT is not as popular as photon or electron PMRT. Robust proton treatment planning is more challenging compared with photon treatment due to uncertainties related to imaging, setup, proton range, dose calculation algorithm, biological effectiveness etc.[14], although Hernandez *et al.*[13] reported that relative

plan comparisons between standard VMAT and proton plans were robust to patient setup errors (up to 1 cm), proton range uncertainty (up to 10%) and uncertainty in dose-risk models. Evidence on the effectiveness and safety of proton therapy from clinical trials is lacking and will not be available until years or decades later, and it is controversial if the additional cost of proton therapy is justified by the potential advantages.

2.5. Conclusions

Four advanced PMRT techniques were evaluated in this study and were compared with another two PMRT techniques in the literature. Our analysis shows it is feasible to use NC-VMAT and MA-VMAT for PMRT patients. Among all techniques, fixed-beam IMRT might reduce contralateral breast dose, NC- VMAT could reduce lungs dose, and mixed beam therapy might lower the heart and contralateral breast doses. Based on evaluated target coverage and estimated risks for OARs, fixed-beam IMRT, NC-VMAT, mixed-beam therapy might be the appropriate PMRT techniques for certain patients who are prone to develop radiogenic side effects.

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CHAPTER 3. COST-EFFECTIVENESS ANALYSIS OF ADVANCED RADIOTHERAPY TECHNIQUES FOR POST-MASTECTOMY BREAST CANCER PATIENTS

3.1. Introduction

About 1 in 8 US women will develop invasive breast cancer over the course of her lifetime, and the number of women being diagnosed continues to increase (seer.cancer.gov). A mastectomy is highly recommended for patients with locally advanced primary breast cancer and extensive lymph node involvement, and post-mastectomy radiotherapy (PMRT) has been shown to improve the overall survival for invasive breast cancer patients by reducing the risk of tumor recurrence and cancer mortality [1].

The current standard of care (SOC) PMRT technique in the US is conventional parallel-opposed tangent photon fields to treat the lateral chest wall plus oblique electron fields; for patients with advanced disease, supraclavicular and axillary nodes were treated with additional photon fields [2]. In the past decades, many advanced technologies had been used for PMRT and shown promising results, such as intensity-modulated radiation therapy (IMRT) [3], standard volumetric modulated arc therapy (STD-VMAT) [4], non-coplanar VMAT (NC-VMAT) [5], multiple arc VMAT (MA-VMAT) [5], Tomotherapy (TOMO) [4], bolus electron conformal therapy (BECT) [6], BECT mixed with IMRT and VMAT (MIXED) [7], and proton therapy [8], each with different degrees of sophistication and cost. Target coverage provided by most of these technologies is comparable with SOC PMRT, while the dose to surrounding normal tissues varies greatly. The more advanced ones have the potential to improve treatment quality by constraining therapeutic dose to radiosensitive organs, but they also have drawbacks like increased low-dose volume which could increase the risk of developing side effects [9, 10]. Long term breast cancer survivors could develop acute and chronic treatment-related morbidity and even mortality after PMRT including

pneumonitis, cardiac toxicities, and secondary cancers etc [11-16], which may significantly decrease their quality of life.

Among all cancer sites, expenditures for female breast cancer remain the highest and will continue to rise to \$20 billion by 2020 [17]. It is controversial whether the additional costs of advanced radiotherapy techniques are justified by the potential advantages. Prior cost-effectiveness studies of PMRT only compared conventional radiotherapy versus no radiotherapy and only considered tumor control [18, 19]. The cost-effectiveness of newer radiotherapy techniques including costs of treating acute and late radiogenic side effects has not yet been examined. Given the prevalence of breast cancer and continued growth of health care costs, results from such an analysis will have a positive impact and can help choose the most cost-effective PMRT technique for certain cohort of patients.

The goal of this study was to perform cost-effectiveness analyses of various PMRT techniques including conventional SOC, fixed-beam IMRT, STD-VMAT, NC-VMAT, MA-VMAT, TOMO, MIXED, and intensity-modulated proton therapy (IMPT). SOC PMRT was used as the reference for modality comparisons. Besides tumor coverage, acute (pneumonitis) and late side effects (cardiac toxicity and secondary cancers) after PMRT were also included in the analyses.

3.2. Methods and materials

Decision model

A Markov model (Figure 3.1) was built using an in-house code to simulate the clinical history of one hypothetical cohort of women with breast cancer who received PMRT with a prescribed dose of 50 Gy in 25 fractions. Patient cohort consisted a population of 55-year-old postmenopausal women. Markov simulation allowed these patients to transition between different

health states, including acute radiogenic side effect which is pneumonitis and assumed to exist for only one year [20], no evidence of disease (NED), distant metastasis, local recurrence, late radiogenic side effects, and death, in a fixed increment of time (one year). The primary endpoints of this study included quality-adjusted life years (QALYs) from a payer perspective over a 15-year horizon. Treatment strategies associated with lower costs and higher QALY were considered dominant.

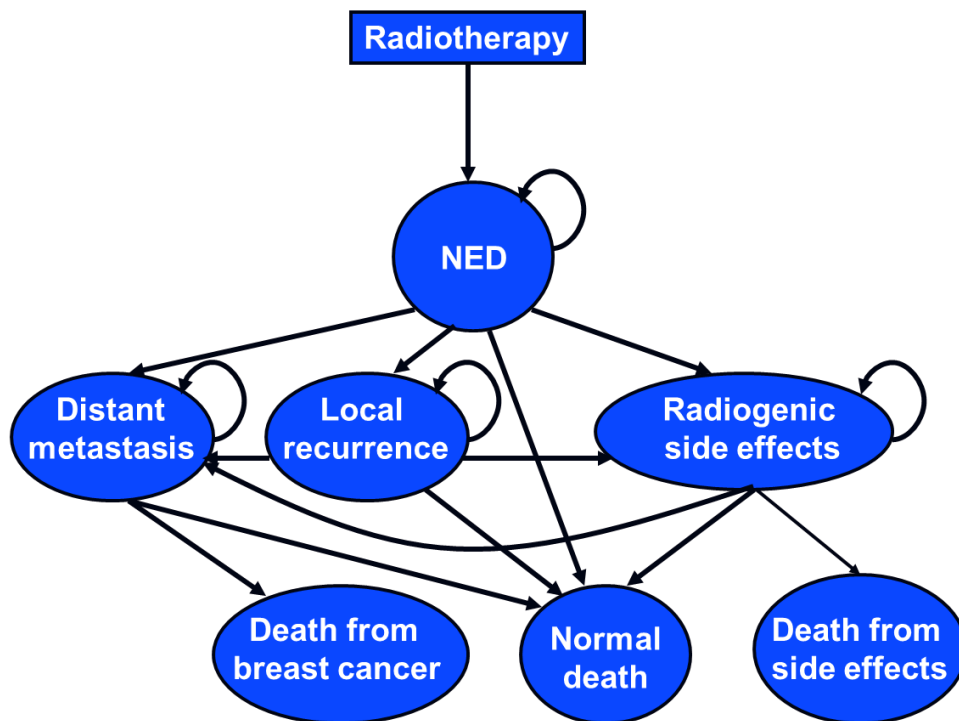


Figure 3.1. Overview of the Markov model. NED = no evidence of disease.

Incremental cost-effectiveness ratios (ICERs), which is defined as the incremental cost divided by the incremental QALY gained, were calculated in scenarios where there was no dominant strategy. We will determine whether a PMRT modality is cost-effective by comparing ICER with common willingness-to-pay (WTP) thresholds of \$50,000/QALY and \$100,000/QALY [21, 22].

Model data input

The transition probabilities for SOC PMRT were taken from literature [12, 18, 20, 23-27]. Table 3.1 shows transition probabilities for 55-year-old PMRT patients receiving SOC PMRT: each baseline value of transition probability was summed over years, and the value divided by the number of years was used in the Markov model.

For advanced PMRT techniques, the transition probabilities were largely lacking in the literature. In this study, the probabilities of tumor coverage, local recurrence, and metastasis after advanced PMRT were assumed to be the same as those after SOC PMRT, while probabilities of radiogenic side effects after advanced PMRT were calculated based on normal tissue complication probability (NTCP) [28], lifetime attributable risk (LAR) of second cancers [29, 30] and risk of coronary events (RCE) [12, 31] models for a 55-year-old cohort as we previously reported [5, 8] (Table 3.3). We assumed that all lung and cardiac events start from year 11 after radiotherapy [12, 32], while contralateral breast events start from year 6 after radiotherapy [26].

The annual mortality rates due to breast cancer were derived from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [1]. The normal death rates were based on the United States life tables [30]. Death from radiogenic side effects were mainly caused by cardiac toxicity and second cancers [25].

Table 3.1. Transition probability and utility for the 55-year-old cohort

Parameters	Years	Value (%) (range)	Reference
Probability			
Local Recurrence	0-5	6.5	[23]
	6-10	1.84	
	11-15	0.325	
NED to metastasis	0-5	18.1	[24]
	6-10	9.2	
	11-15	5.68	
Metastasis to Death	0-5	25.9	[18]
	6-15	15.6	
Normal Death	56-60 (age)	3.2	[30]
	61-65 (age)	4.7	
	66-70 (age)	5.8	
Death due to lung toxicity	11-15	0.49	[25]
Death due to heart toxicity	11-15	2.6	[25]
Death due to CL breast toxicity	11-15	21.7	[23]
SOC PMRT cardiac toxicity	11-15	5.84	[12]
SOC PMRT CL breast cancer	6-15	1.0	[26]
SOC PMRT lung cancer	11-15	4.4	[27]
Utility			
Cardiac toxicity	11-15	0.85 (0.8-0.9)	[33]
CL Breast cancer	11-15	0.803 (0.708-0.816)	[34]
Lung cancer	11-15	0.72 (0.57-0.87)	[34, 35]
Recurrence	0-15	0.85	[18]
NED to metastasis	0-15	0.62	[18]

Table 3.1 also shows the utilities values for each health state in the Markov model. Table 3.2 shows the costs for PMRT patients using different modalities from payer perspective and these

costs were based on local Medicare charges. Costs of treating of acute and late effects are also included in Table 3.2. All costs and utilities will be discounted at 3% per year as recommended by US Panel on Cost-Effectiveness in Health and Medicine [36].

Table 3.2. Treatment costs

Treatment	Cost (range)	Reference
PMRT (SOC)	\$12,140	Based on Medicare charge
PMRT (VMAT/TOMO/IMRT)	\$17,438	Based on Medicare charge
PMRT (MIXED)	\$19,715	Based on Medicare charge
PMRT (IMPT)	\$33,547	Based on Medicare charge
Local recurrence	\$20,879	[37]
Metastasis	\$13,627	[37]
Cardiac toxicity	\$11,570 (8165-14975)	[33, 38]
CL breast cancer	\$14,494 (13295-15693)	[39]
Lung cancer	\$20,577 (17837-23317)	[40-42]

Model calibration & validation

CancerMath is the latest web-based breast cancer prognostic tool that can predict mortality rate in each year for the first 15 years after the current SOC treatment, and the external validity of our model was assessed by comparing 15-year overall survival and breast cancer mortality of patients who received SOC PMRT with the predicted results from CancerMath.

Table 3.3. Calculated probabilities of developing radiogenic side effects for the 55-year-old cohort from previous studies [5, 8]

Side effect	Probability (%)	Range (%)
IMRT cardiac toxicity	0.95	0.05-2.58
IMRT CL breast cancer	0.04	0.02-0.06
IMRT lung cancer	0.57	0.08-0.84
STD-VMAT cardiac toxicity	0.97	0.05-2.54
STD-VMAT CL breast cancer	0.11	0.06-0.23
STD-VMAT lung cancer	0.63	0.08-0.95
NC-VMAT cardiac toxicity	0.89	0.05-2.34
NC-VMAT CL breast cancer	0.08	0.02-0.20
NC-VMAT lung cancer	0.54	0.07-0.89
MA-VMAT cardiac toxicity	0.89	0.05-2.31
MA-VMAT CL breast cancer	0.09	0.04-0.20
MA-VMAT lung cancer	0.55	0.07-0.92
TOMO cardiac toxicity	0.98	0.07-2.39
TOMO CL breast cancer	0.10	0.06-0.22
TOMO lung cancer	0.72	0.11-1.18
MIXED cardiac toxicity	0.86	0.05-2.22
MIXED CL breast cancer	0.07	0.03-0.15
MIXED lung cancer	0.63	0.08-1.01
IMPT cardiac toxicity	0.40	0.04-0.84
IMPT CL breast cancer	0.003	0.00-0.007
IMPT lung cancer	0.22	0.03-0.60

Sensitivity analyses

We performed a series of one-way sensitivity analyses to determine the variability in the ICER as a function of the probabilities, utilities, and treatment costs of contralateral breast cancer, lung cancer and heart toxicities for seven advanced PMRT techniques versus SOC PMRT. Since pneumonitis was assumed to exist for only one year and did not show a significant impact on ICER value, the probability variability of pneumonitis was not included in the sensitivity analysis.

We also performed probability sensitivity analyses (PSA). The probabilities, utilities and costs were varied simultaneously across their distributions using a second-order Monte Carlo simulation. Transition probabilities and utilities were modeled using a beta-distribution and cost was modeled using a gamma distribution as recommended in the literature [43]. The cost effectiveness acceptability curves were plotted based on the result of 100,000 simulations for each PMRT technique at different WTP thresholds.

3.3. Results

For a 55-year-old woman with breast cancer, our model predicted a 15-year overall survival rate of 69.7% and breast cancer mortality rate of 19.2%, whereas CancerMath estimated an overall survival rate of 70.5% and breast cancer mortality rate of 18.0%. These comparisons suggest that our model's predictions are similar to real clinical outcomes.

Table 3.4. Incremental cost-effectiveness ratio for advanced techniques compared to SOC PMRT

Age	IMRT (\$/QALY)	STD- VMAT (\$/QALY)	NC- VMAT (\$/QALY)	MA- VMAT (\$/QALY)	TOMO (\$/QALY)	MIXED (\$/QALY)	IMPT (\$/QALY)
55	27,310	32,617	28,206	34,905	49,487	44,777	74,564

Table 3.4 shows the ICERs for all seven advanced PMRT techniques compared with SOC for 55-year-old patient cohort, and all advanced PMRT techniques are more cost-effective. For the 55-year-old cohort base case, STD-VMAT has the lowest ICER of 27,310 \$/QALY while IMPT still shows the highest ICER of 74,564 \$/QALY. Results of one-way sensitivity analyses indicate

that for 55-year-old cohort, model outcomes are greatly impacted by the probability of cardiac toxicity.

Table 3.5. Probability of being more cost-effective than SOC for advanced techniques

Age	WTP (\$/QALY)	IMRT	STD- VMAT	NC- VMAT	MA- VMAT	TOMO	MIXED	IMPT
55	50,000	30.7%	15.6%	6.1%	1.8%	0.6%	2.4%	0.0%
	100,000	99.8%	96.3%	99.0%	97.4%	88%	97.2%	99.9%

Table 3.5 depicts PSA results which show the probability of being more cost-effective over SOC for the advanced PMRT techniques. At WTP of 50,000 \$/QALY, none of the advanced techniques has an over 31% probability of being more cost-effective. At WTP of 100,000 \$/QALY, all of the advanced techniques are more cost-effective.

3.4. Discussion

To the best of our knowledge, this study evaluated the cost-effectiveness of seven advanced PMRT techniques compared with SOC for the first time. Both tumor coverage and radiogenic side effects were considered in our model. The uncertainty of probabilities, utilities and treatment costs of radiogenic late effects were analyzed using one-way analysis and PSA.

We found most of the advanced techniques would be more cost-effective than SOC PMRT at a WTP of 100,000 \$/QALY. NC-VMAT and fixed beam IMRT exhibit the lowest ICER among all techniques for 55-year-old patients' cohort respectively, which is because NC-VMAT and fixed beam IMRT can significantly reduce lung and contralateral breast doses and lower the probability

of developing secondary cancers in these organs. For age 55-year-old cohort, IMPT has the highest ICER which is mainly due to the high cost of the initial treatment (Table 3.4).

An important strength of our study is the consideration of radiogenic side effects, which was rarely done in the previous cost studies. On average more than 80% breast cancer patients live for 10 years or longer (seer.cancer.gov). Given the favorable oncologic outcomes, it is increasingly paramount to minimize radiogenic side effects and improve survivorship for these patients. Lundkvist *et al.* [33] reported that proton therapy is more cost-effective than conventional radiation therapy if breast cancer patients with high-risk of cardiac disease are treated. Mailhot *et al.* [44] also reported the heart dose and cardiac risk factor are the key factors for cost-effective allocation of proton therapy for breast cancer. Although these two studies were not specifically designed for PMRT, their findings are consistent with ours in that our study also shows the model outcomes are most sensitive to the probability of developing cardiac toxicity. This may be due to the fact the risk value of cardiac toxicity is higher than the risk value of lung cancer or contralateral breast cancer for breast cancer patients [12, 26, 27].

Our study has broad implications. It will provide a quantitative comparison of cost-effectiveness among contemporary PMRT strategies, and enhance the base of evidence upon which clinical decisions can be made, e.g. it has been highly controversial if the additional cost of proton therapy is justified by the potential advantages, and our study shows proton therapy is only cost-effective treatment modality for PMRT patients at a WTP threshold of 100,000 \$/QALY although it confers the lowest risks of radiogenic side effects among all techniques [5, 8]. It may lower the national cost of breast cancer care, and even a small progress in this direction can help relieve patient's burden and national healthcare pressure. The scarce healthcare resources can be saved and used in other aspects of patient care. It can inspire healthcare providers to replace the

current SOC with ones that are more effective and less toxic, and also inspire stakeholders to make stronger cost-containment measures and integrate efficacy and cost-effectiveness into clinical trials in the US, which can potentially bring in enormous savings of time, money, and human resources.

There are several limitations of this study. First, there is a lack of clinical information on late toxicities from advanced PMRT techniques, and the well-defined risk models were used to estimate those risk values in our study. We expect there to be a certain degree of discrepancies in absolute outcome values between our study and future clinical data, but we do not expect dramatic differences in relative values, i.e. the rank of alternative techniques. By taking into account possible uncertainties, we are confident that our model is robust. Further, long-term prospective studies are needed to better explore the probability of late effects and their impact on the cost-effectiveness of various radiotherapy modalities. Second, we did not include the uncertainties of local recurrence and distance metastasis in PSA analyses since we assume that all advanced techniques have the same tumor control probability as conventional SOC. Although there is no clinical evidence currently, it is possible advanced techniques like proton therapy will bring benefits on the survival from the primary cancer and the cost-effectiveness of advanced techniques will improve. Third, we conducted the study only from a payer perspective, while the US Panel on Cost-Effectiveness in Health and Medicine recommended both patient and societal analyses should be presented [45]. The significant capital cost associated with an advanced technique like proton therapy will lower its cost-effectiveness even further. However, as Sher *et al.* [46] pointed out, the cost-effectiveness analysis from the payer perspective is very important because there are already proton facilities in the US and payers only care about the cost per patient and if proton therapy is cost-effective relative to their own reimbursements. Finally, we only performed analyses among a

specific patients' age cohort, while factors such as age difference, smoking history, breast cancer subtype, prior heart diseases, etc. may have significant impacts on the transition probabilities. These personalized factors will be further investigated by us in a future study.

3.5. Conclusions

Advanced PMRT techniques are more cost-effective for breast cancer patients at a WTP threshold of 100,000 \$/QALY. IMRT might be the most cost-effective option for PMRT patients.

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CHAPTER 4. COMPARISON OF CONVENTIONAL AND ADVANCED RADIOTHERAPY TECHNIQUES FOR LEFT-SIDED BREAST CANCER AFTER BREAST CONSERVING SURGERY

4.1. Introduction

Breast cancer has the highest incidence rate among women in the US other than skin cancer (www.cancer.org). Women diagnosed with early-stage breast cancer who have lumpectomy usually underwent whole breast radiation therapy (WBRT) after surgery, which can lower recurrence and metastasis rates and make lumpectomy as effective as mastectomy.[1]

The current standard of care (SOC) for WBRT in the US and in our clinic is using parallel-opposed tangential photon fields to treat the whole ipsilateral breast and chest wall, plus additional photon and electron fields to treat supraclavicular, axillary and internal mammary nodes when necessary.[2] However, significant dose inhomogeneity can occur within the irradiated volume and can cause poor cosmetic outcomes, especially for women with large breasts.[3-5] Field-in-field (FIF) technique is used sometimes to improve dose homogeneity throughout the target volume.[3, 6] Intensity-modulated radiation therapy (IMRT) has been used for WBRT and can improve dose conformity and homogeneity, reduce high dose to heart and lung at the expense of increasing overall low doses,[7] decrease acute skin toxicity.[8] Hybrid IMRT (combination of open tangential and IMRT beams) has been shown to have a good balance of plan complexity and dose coverage/OAR sparing.[9-11] Volumetric modulated arc therapy (VMAT) can achieve similar target coverage as IMRT, spare more normal tissues and can significantly reduce treatment time.[12] Multiple arc VMAT (MA-VMAT) showed good feasibility and OAR sparing for WBRT.[13] Non-coplanar VMAT (NC-VMAT) has been shown to improve OAR dosimetry for post-mastectomy breast cancer,[14] but has not been evaluated for WBRT.

The purpose of this study was to compare target coverage and risks of developing of radiogenic side effects for a sample of WBRT patients using various modalities, including SOC, FIF, hybrid IMRT, IMRT, VMAT, MA-VMAT and NC-VMAT. There have been multiple treatment planning studies of WBRT,[15-24] but most of them did not include hybrid IMRT in the comparison although hybrid IMRT had been recommended as the optimal technique for WBRT[10]; with the advance of inverse planning techniques, the differences in treatment plan outcomes should be evaluated among different VMAT techniques while none of the previous studies did so; in addition, the radiobiological metrics like normal tissue complication probability (NTCP) of pneumonitis, lifetime attributable risk (LAR) of second cancers, and risk of coronary events (RCE) should be evaluated and compared among forward and inverse planning WBRT modalities because it has been shown inclusion of non-dosimetric factors can provide a more robust method of comparing different radiotherapy techniques,[25] while most of the previous studies only performed dosimetric comparisons.

4.2. Methods and materials

Patient selection

Fifteen early stage left-sided breast cancer patients presenting for WBRT without nodal involvement after breast conserving surgery were included in this study. Computed tomography (CT) scans were obtained when patients were immobilized on a breast wing board with the left arm elevated above the head while free-breathing. All CT data were anonymized[26] for this study. The following target definitions were based on the RTOG breast cancer Atlas and were approved by a radiation oncologist: clinical target volume (CTV) was defined as the ipsilateral breast which was limited to 5 mm from the skin and posteriorly to the anterior surface of pectoralis, serratus anterior muscle excluding chest wall, boney thorax and lung; planning target volume (PTV) was

defined as CTV plus 7 mm expansion; PTV-Eval was defined to be limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin, and posteriorly was limited no deeper to the anterior surface of the ribs, and PTV-Eval was used for DVH constraints and analysis. The contours of organs at risk (OARs) for each patient were approved by the same radiation oncologist and included lungs, whole heart and contralateral breast.

Treatment planning

The prescription dose for all patients was 50 Gy in 25 fractions. The following criteria were required for each treatment plan to be clinically acceptable: the volume of the PTV receiving at least 95% of the prescribed dose is greater than or equal to 95%; the volume of left lung receiving at least 20 Gy is less than 20% [27]; the volume of heart receiving at least 22.5 Gy is less than 20%.[28] Maximum and mean dose for heart, lung and contralateral breast were constrained. All plans were generated in a commercial treatment planning system (TPS) (Pinnacle3 v9.8, Philips Medical Systems, Fitchburg, WI, USA).

The SOC plans included two opposed tangential beams of 6, 10 or 15 MV energies depending on patient's anatomy, and the tangential beam angles were determined by the BBs placed on the skin and were usually around anterior midsternum and ipsilateral lower axilla. The collimator was rotated to shield the heart and lung, and dynamic wedges were used to minimize hotspots within the PTV-Eval. FIF plans utilized the same beam angles and energies as the SOC plans. Two to three subfields per beam were manually added using multi-leaf collimators (MLCs) to eliminate hotspots after the open field plan was created.[6] Hybrid IMRT plans included a pair of open tangent fields and a pair of dynamic IMRT tangent fields, where 80% of prescription dose was delivered from open tangent beams and 20% of the prescription dose was delivered from

IMRT beams. [11] IMRT plans were generated in Pinnacle using the direct machine parameter optimization (DMPO) algorithm, and included seven beam equidistantly distributed in a sector of 180 ° that avoided direct exposure to the contralateral breast. All STD-VMAT, NC-VMAT and MA-VMAT plans used 6 MV photon beams and were generated in Pinnacle using the SmartArc optimization algorithm. STD-VMAT plans utilized two coplanar partial arcs: the first arc was planned to be delivered counterclockwise (CCW) with starting and stopping gantry angles at the same as the tangent fields, the second arc was planned to be delivered clockwise (CW) over the same range of gantry angle. NC-VMAT plans utilized two partial arcs: the first arc was planned to be delivered CCW with starting and stopping gantry angles same as tangent fields and with 20 ° couch angle, the second arc was planned to be delivered CW over the same range of gantry angle and with 340 ° couch angle. The collimator was rotated to align with the long axis of PTV in both arcs. MA-VMAT plans consisted of six partial arcs (ARC01 to ARC06), each with 50 ° gantry rotations.[13] ARC01 to ARC03 were delivered clockwise and ARC04 to ARC06 were delivered counterclockwise. The starting angle of ARC01 and stopping angle of ARC03 were the same as SOC technique. The collimator was always rotated to align with the long axis of PTV in each arc.

Plan comparison metrics

Dosimetric parameters were evaluated for the target, lungs, heart, and contralateral breast. The dose homogeneity index (DHI)[29] and conformity index (CI) [30] were evaluated for PTV-Eval. The risk of radiogenic side effects was assessed: LAR was computed for secondary lung and contralateral breast cancers using BEIR VII model [31]:

$$LAR(D, e) = \int_{a=e+L}^{a_{max}} EAR * \frac{s(a)}{s(e)} da$$

where e represents age at exposure, a represents attained age, L is a risk-free latent period, $\frac{s(a)}{s(e)}$ means the probability of surviving to age a conditional on survival to age e , [32] excess absolute risk (EAR) can be calculated using the product of organ equivalent dose (OED) as follows:

$$EAR = \beta * \mu * OED$$

where β represents dose response initial slope [33], μ is age correction factor and was computed for each patient [33]:

$$\mu = \exp\left(\gamma_e * (e - 30) + \gamma_a * \ln\left(\frac{a}{70}\right)\right)$$

where the age modifying factor γ_e and γ_a were recommended by Schneider *et al.* [33] OED is given by:

$$OED = \frac{1}{V_T} \sum_i (v_i * D_i)$$

where V_T is the total organ volume, and v_i is the volume receiving dose D_i .

NTCP for pneumonitis was evaluated using Lyman-Kutcher-Burman (LKB) model [34-36]:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t \exp\left(\frac{-t^2}{2}\right) dt$$

$$t = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)}$$

$$TD_{50}(v) = \frac{TD_{50}}{v^n}$$

where TD_{50} represents the uniform dose given to the entire lung that results in 50% complication risk ($TD_{50} = 30.8$ Gy), m is a measure of the slope of the dose-response curve ($m =$

0.37), n is the volume effect parameter ($n = 0.99$), and v is the fractional volume irradiation to the uniform dose D . [36]

Dose-response model published by Darby *et al.* [37] was used to evaluate RCE for each patient:

$$RCE = 1.074 * D * R_{baseline}$$

where D (Gy) is the mean heart dose, $R_{baseline}$ is the baseline risk of coronary events and was calculated using Reynolds risk model [38] assuming medium risk type.

Statistical analysis

The post hoc Tukey test was used to determine the statistical significance of the differences between two WBRT techniques. All statistical analyses were conducted with R software (version 3.2.3) and the differences were considered significant when $p < 0.05$.

4.3. Results

The dose distributions and DVHs for a typical WBRT patient are shown in Figs. 4.1 and 4.2. Table 4.1 lists PTV and OARs evaluation metrics for various WBRT techniques. The results of post hoc Tukey tests and statistical significances are shown in Table 4.2.

All seven WBRT techniques analyzed in this study meet the clinical requirement of PTV coverage. SOC plans introduce significantly larger hot spots in the PTV by showing the highest V107%, and deliver relatively higher dose to OARs than inverse planning techniques (IMRT,

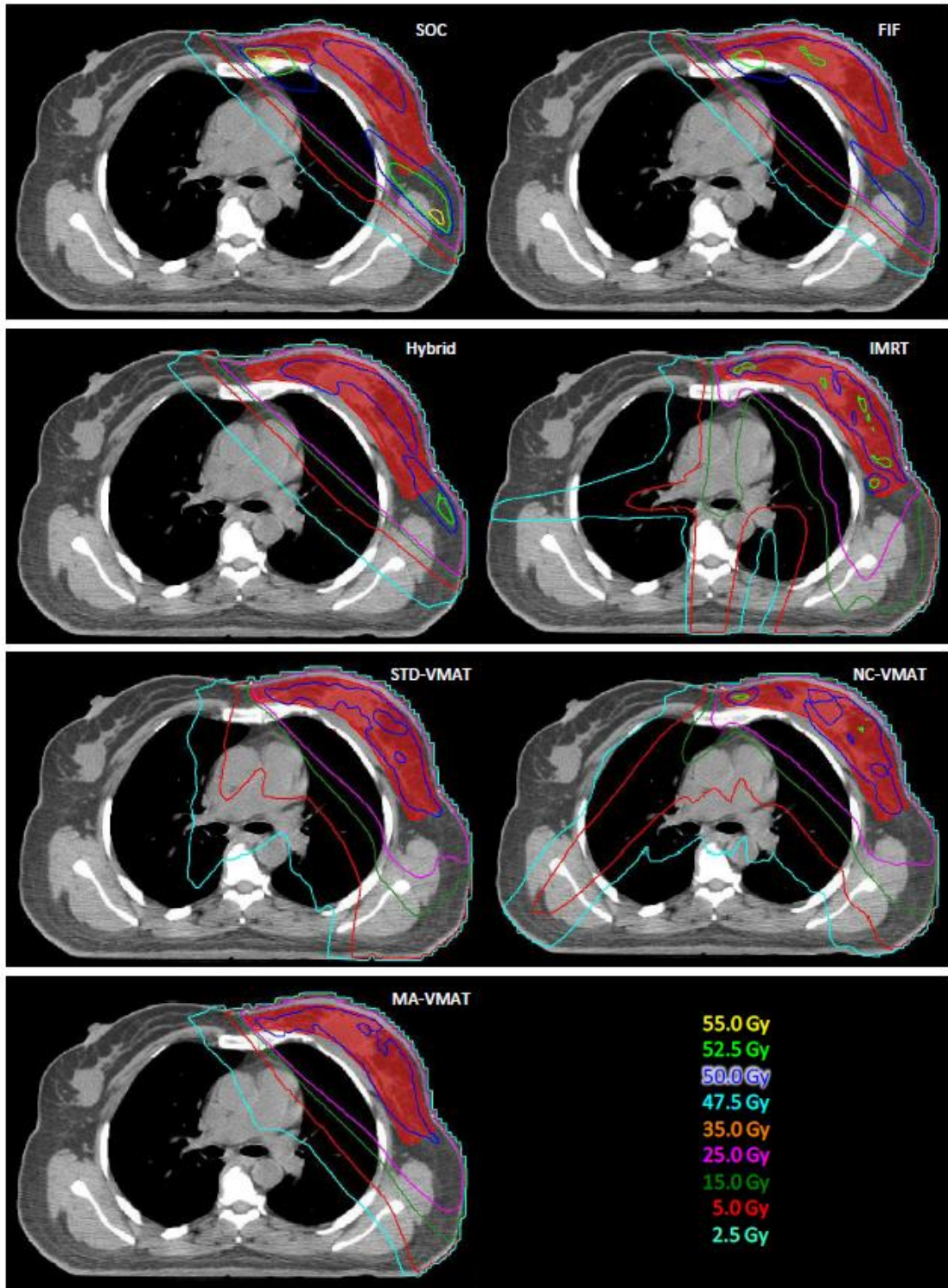


Figure 4.1. Axial view of isodose distribution for SOC, FIF, Hybrid IMRT, IMRT, standard VMAT, NC-VMAT and MA-VMAT plans for a typical WBRT patient. The red color wash represents the PTV-Eval.

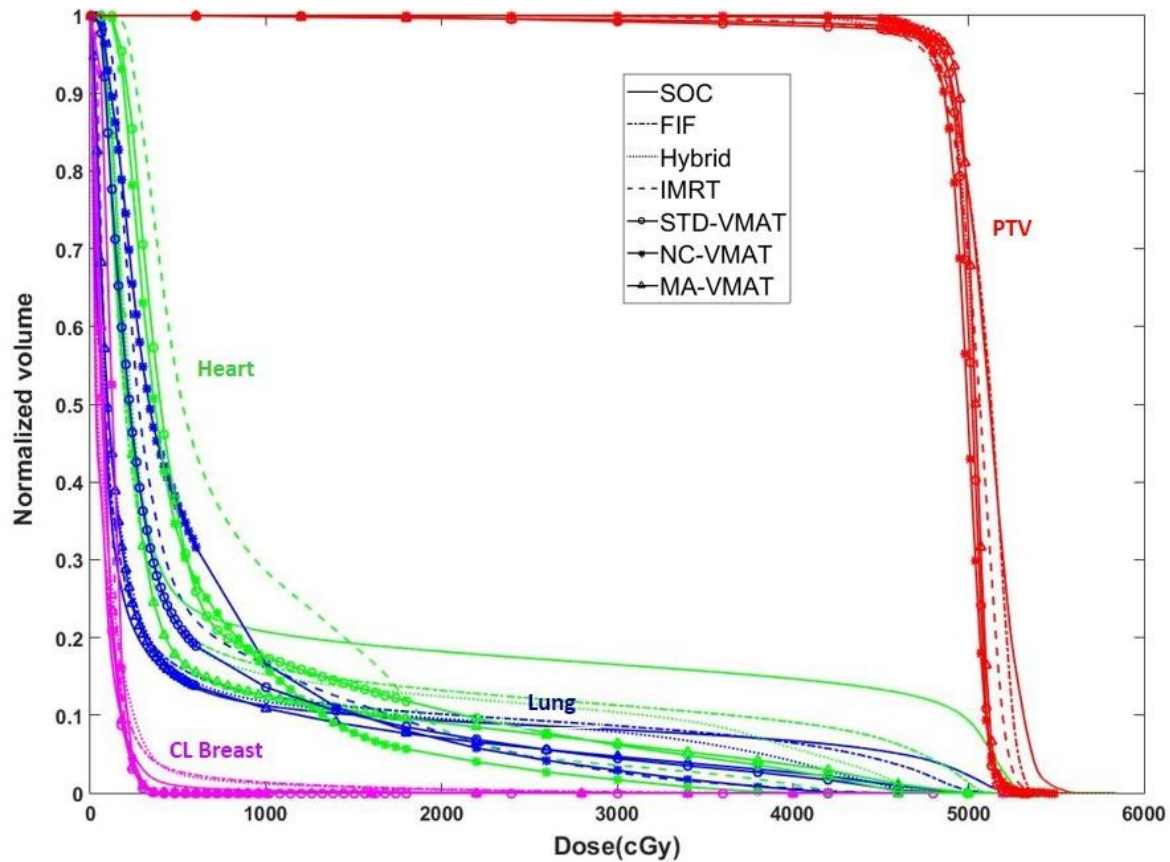


Figure 4.2. DVHs for SOC, FIF, Hybrid IMRT, IMRT, standard VMAT, NC-VMAT and MA-VMAT plans for a typical PMRT patient.

STD-VMAT, NC-VMAT and MA-VMAT): significantly higher Dmean, Dmax, V20 and NTCP for lung, significantly higher V22.5 and V30 for heart, significantly higher Dmean and V5 for contralateral breast. FIF and hybrid IMRT plans exhibit better PTV coverage than SOC by showing significantly lower Dmax and V107% for PTV, deliver relatively lower dose to OARs than SOC, and both show relatively better dose homogeneity than other five techniques. STD-VMAT plans provide the lowest Dmean and Dmax for contralateral breast, and the second lowest LAR ($4.1 \pm 1.4\%$) of secondary cancer in contralateral breast, but significantly increase low dose cloud like V5 for lung and heart. MA-VMAT plans show the lowest Dmean, V10, NTCP and LAR for lung,

the lowest V5 and LAR for contralateral breast, and the lowest Dmean, V5, V10, and RCE for heart. NC-VMAT plans provide the most conformal target coverage, the lowest Dmax, V20 and the second lowest NTCP and LAR for lung, the lowest Dmax, V22.5, V30 and the second lowest RCE for heart compared with other techniques.

Table 4.1. MU, PTV and OAR evaluation metrics (mean \pm standard deviation) for fifteen WBRT patients

	SOC	FIF	Hybrid	IMRT	STD- VMAT	NC- VMAT	MA- VMAT
Average total MU	7343 \pm 962	5647 \pm 227	8673 \pm 1506	19300 \pm 2471	10263 \pm 1049	10397 \pm 1549	11523 \pm 1167
PTV							
D _{mean} (Gy)	50.7 \pm 0.7	50.6 \pm 0.5	50.4 \pm 0.6	50.1 \pm 0.3	50.0 \pm 0.4	49.9 \pm 0.4	50.0 \pm 0.4
D _{max} (Gy)	55.5 \pm 1.7	53.8 \pm 0.9	53.8 \pm 0.9	56.7 \pm 0.9	54.96 \pm 1.4	54.7 \pm 1.0	55.2 \pm 1.3
V _{107%} (%)	0.1 \pm 0.1	0.0 \pm 0.1	0.0 \pm 0.1	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
CI	0.5 \pm 0.1	0.5 \pm 0.1	0.6 \pm 0.1	0.8 \pm 0.1	0.8 \pm 0.1	0.8 \pm 0.1	0.8 \pm 0.1
DHI	0.2 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.1 \pm 0.0	0.2 \pm 0.1	0.2 \pm 0.1	0.2 \pm 0.1
Total lung							
D _{mean} (Gy)	6.7 \pm 1.0	6.4 \pm 0.8	6.1 \pm 1.0	5.9 \pm 0.9	6.0 \pm 0.9	5.4 \pm 1.1	4.9 \pm 0.9
D _{max} (Gy)	53.3 \pm 1.7	51.4 \pm 1.4	50.3 \pm 1.5	48.3 \pm 1.5	47.9 \pm 2.3	46.2 \pm 4.1	50.8 \pm 2.8
V ₅	18.3 \pm 2.2	18.6 \pm 2.3	17.7 \pm 2.0	26.4 \pm 5.0	27.0 \pm 7.1	24.8 \pm 8.2	19.6 \pm 4.2
V ₁₀	14.8 \pm 2.0	15.0 \pm 2.2	14.4 \pm 2.0	15.1 \pm 3.1	14.3 \pm 2.7	12.8 \pm 3.6	12.5 \pm 3.3
V ₂₀	12.7 \pm 2.0	12.6 \pm 2.1	12.2 \pm 1.9	7.9 \pm 2.6	7.8 \pm 1.6	6.6 \pm 1.9	7.3 \pm 1.6
NTCP (%)	1.8 \pm 0.4	1.7 \pm 0.4	1.6 \pm 0.3	1.5 \pm 0.3	1.5 \pm 0.3	1.3 \pm 0.3	1.2 \pm 0.2
LAR (%)	2.2 \pm 0.4	2.2 \pm 0.4	2.0 \pm 0.3	2.0 \pm 0.3	2.0 \pm 0.4	1.8 \pm 0.4	1.7 \pm 0.3
Heart							
D _{mean} (Gy)	9.6 \pm 3.7	8.1 \pm 3.7	8.1 \pm 2.8	7.4 \pm 1.3	7.8 \pm 1.5	5.8 \pm 1.0	5.5 \pm 1.2
D _{max} (Gy)	51.7 \pm 2.2	50.1 \pm 1.7	49.3 \pm 1.4	43.7 \pm 6.2	44.5 \pm 3.3	41.0 \pm 5.4	45.0 \pm 4.1
V ₅	25.3 \pm 10.1	25.7 \pm 9.4	23.9 \pm 8.7	48.3 \pm 14.0	53.2 \pm 8.5	30.5 \pm 9.0	22.1 \pm 9.0
V ₁₀	19.8 \pm 8.8	19.0 \pm 8.0	18.4 \pm 7.7	20.1 \pm 4.9	18.7 \pm 5.7	11.7 \pm 3.5	9.7 \pm 2.7
V _{22.5}	16.6 \pm 8.0	14.9 \pm 6.9	14.7 \pm 6.6	4.7 \pm 3.2	6.2 \pm 2.7	4.3 \pm 1.9	5.0 \pm 1.8
V ₃₀	15.1 \pm 7.5	13.3 \pm 6.4	12.7 \pm 5.9	2.7 \pm 2.9	3.9 \pm 2.2	2.0 \pm 1.4	3.2 \pm 1.9
RCE (%)	12.4 \pm 3.5	11.5 \pm 3.1	11.6 \pm 3.1	11.4 \pm 3.3	11.6 \pm 3.2	10.5 \pm 2.8	10.3 \pm 2.7
CL breast							
D _{mean} (Gy)	2.8 \pm 2.5	1.9 \pm 1.8	1.6 \pm 1.2	1.4 \pm 0.7	1.1 \pm 0.3	1.2 \pm 0.7	1.2 \pm 0.4
D _{max} (Gy)	48.3 \pm 7.2	45.6 \pm 6.8	42.8 \pm 6.7	17.0 \pm 4.3	7.3 \pm 4.9	10.3 \pm 8.5	12.0 \pm 8.3
V ₅	4.2 \pm 2.6	3.8 \pm 3.0	4.0 \pm 3.0	0.2 \pm 0.3	0.3 \pm 0.7	0.2 \pm 0.5	0.1 \pm 0.1
LAR (%)	5.8 \pm 4.9	5.7 \pm 2.7	5.3 \pm 4.7	4.8 \pm 2.4	4.1 \pm 1.4	4.1 \pm 2.2	3.9 \pm 1.3

Table 4.2. Statistic comparison of seven WBRT techniques using post hoc Tukey test. Grey indicates statistically significant (p values <0.05)

Variable	SOC vs FIF	SOC vs Hybrid	SOC vs IMRT	SOC vs STD-VMAT	SOC vs NC-VMAT	SOC vs MA-VMAT	FIF vs Hybrid	FIF vs IMRT	FIF vs STD-VMAT	FIF vs NC-VMAT	FIF vs MA-VMAT	Hybrid vs IMRT	Hybrid vs STD-VMAT	Hybrid vs NC-VMAT	Hybrid vs MA-VMAT	IMRT vs STD-VMAT	IMRT vs NC-VMAT	IMRT vs MA-VMAT	STD-VMAT vs NC-VMAT	STD-VMAT vs MA-VMAT	NC-VMAT vs MA-VMAT
PTV																					
D _{mean}																					
D _{max}																					
V _{107%} (%)																					
CI																					
DHI																					
Lung																					
D _{mean}																					
D _{max}																					
V ₅																					
V ₁₀																					
V ₂₀																					
NTCP																					
LAR (%)																					
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V _{22.5}																					
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RCE (%)																					
CL breast																					
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LAR (%)																					

Table 4.3. Comparison with previous WBRT studies that have the same PTV definition as ours.

	Num. of patients	Techniques compared	Key findings
Descovich <i>et al.</i> (2010)	15	FIF, hybrid IMRT	Hybrid IMRT is preferred since it can reduce hot spot, better coverage and require less planning time.
Schubert <i>et al.</i> (2011)	10	SOC, FIF, tangential IMRT (2 Fields), TOMO, topotherapy	TOMO, topotherapy and tangential IMRT can reduce high dose to target and normal tissue; TOMO results in increased low doses within normal tissue.
Jin <i>et al.</i> (2013)	20	SOC, FIF, tangential IMRT (2 Fields), IMRT (7 Fields), VMAT (starting and ending angle were the same as tangential beam angles)	Tangential IMRT is recommended since it has improved HI and reduced dose in heart and lung.
Viren <i>et al.</i> (2015)	10	FIF, tangential IMRT (2 Fields), tangential VMAT (two dual arcs of 50 °-60 °), continuous VMAT (dual arc of 240 °)	Both VMAT techniques shown improved HI and better sparing for heart and ipsilateral lung tissues. Continuous VMAT may provide best dose coverage at the cost of significantly increased dose to contralateral breast.
Haciislamoglu <i>et al.</i> (2015)	15	SOC, FIF, 9-field IMRT, TOMO, VMAT (Starting and ending beam angles of the arc were 10 °posterior to tangential fields)	TOMO shown reduced high and mean doses to the heart and lung at the cost of increased low dose cloud which may lead to an increased probability of radiogenic side effects.
Han <i>et al.</i> (2016)	10	SOC, FIF, IMRT (10 to 12 fields), VMAT (3-4 partial arcs spanned from 305 °to 152 °), TOMO	TOMO is recommended since it provides the lowest LAR for all surrounding OARs.
Zhang <i>et al.</i> (2018)	50	5-field IMRT, 6-field IMRT, FIF-DMPO-IMRT	FIF-DMPO-IMRT is recommended due to reduced heart and lung doses and treatment time.
Our study	15	SOC, FIF, hybrid, IMRT, VMAT(starting and ending angle were the same as tangential beam angles) , MA-VMAT, NC-VMAT	MA-VMAT and NC-VMAT are recommended due to reduced heart, lung and contralateral breast doses.

4.4. Discussion

We evaluated seven WBRT techniques for treating left-sided lumpectomy breast cancer patients. All seven techniques provide clinical acceptable dose coverage to the target volume. For the two forward planning techniques, FIF plans not only show better PTV coverage but also provide superior OAR sparing than SOC. Five inverse planning techniques show superior OAR sparing than two forward planning techniques. STD-VMAT provides good sparing of contralateral breast at the cost of larger low dose cloud for lung and heart. MA-VMAT plans show the most optimal OARs sparing and minimum risk of developing late side effects among all inverse planning techniques. NC-VMAT provides the most conformal PTV coverage and good sparing of lung and heart.

There are plenty of WBRT planning studies in the literature. Considering it is difficult to compare studies with different target definitions, we compared our study with previous work that had the same PTV delineation based on RTOG as ours (Table 4.3): Descovich *et al.*[1] concluded that hybrid IMRT can reduce the hot spot within PTV compared to FIF for left-sided breast cancer patients and can provide better coverage, which is consistent with our results; Jin *et al.*[2] reported that tangential IMRT has the best balance of target coverage and normal tissue sparing compared with conventional tangential beams, FIF, multi-beam IMRT and VMAT for small breast size, while IMRT provides inferior target coverage or OAR sparing than VMAT especially the advanced VMAT techniques in our study, which is mainly because the mean PTV volume in our study (910.2 ± 439.8 cc) is much larger than theirs (360.8 ± 149.1 cc). These results show that tangential IMRT may not be the optimal technique for all WBRT patients, and its application should be assessed based on planning target and patient's anatomy; Schubert *et al.* [3] and Hacıislamoglu *et al.*[4] both concluded that TOMO may reduce high doses to the heart and lung at the cost of increased low dose cloud which may lead to an increased probability of radiogenic

side effects, and Han *et al.*[5] illustrated that TOMO is recommended compared to SOC, FIF, IMRT and VMAT since it exhibits lowest total LAR to surrounding organs. Our study didn't evaluate TOMO, but NC-VMAT and MA-VMAT have shown better sparing in lung (mean dose of 5.4 ± 1.1 Gy and 4.9 ± 0.9 Gy respectively) and contralateral breast (mean dose of 1.2 ± 0.7 Gy and 1.2 ± 0.4 Gy respectively) than TOMO, e.g. Hacıislamoglu *et al.*[4] reported mean lung dose of 9.6 ± 2.0 Gy and mean contralateral breast dose of 3.1 ± 0.4 Gy for TOMO, which suggests that NC-VMAT and MA-VMAT could be used to substitute TOMO when TOMO System is not available; Zhang *et al.*[6] evaluated different IMRT techniques and recommended FIF- DMPO-IMRT because it can reduce doses to lungs and heart and decrease treatment time. Their FIF-DMPO-IMRT consists of 70~80% FIF and 20%~30% IMRT, although it is similar to our hybrid IMRT technique that has 80% open tangent beams and 20% IMRT, they required 95% volume of PTV to receive 100% of prescription dose which causes their dosimetric results not comparable to ours; Viren *et al.*[7] concluded that both tangential VMAT with two dual arcs of 50° - 60° and continuous VMAT (cVMAT) with a dual arc of 240° have improved HI within PTV and better sparing for heart and ipsilateral lung tissues compare to FIF and tangential IMRT, and cVMAT provided best target coverage at the cost of significantly increased dose to contralateral breast. STD-VMAT (dual arc of approximately 180°) in our study also has improved HI within PTV and better sparing for heart and lung tissues compare to FIF, and STD-VMAT has much better contralateral breast sparing compare to their cVMAT (mean dose of 1.1 Gy using STD-VMAT vs. 2.6 Gy using cVMAT), which suggests that smaller arcs of VMAT may lower the risk of developing contralateral breast cancer.

Jeulink *et al.*[8] illustrated that hybrid IMRT is most optimal WBRT technique among full IMRT, STD-VMAT and MA-VMAT for providing best mean and low dose OARs sparing, while

it is not the most optimal choice in our study. This is possibly because only two tangential IMRT fields were used for hybrid IMRT in our study whereas four tangential IMRT fields were used in theirs. Moreover, the left anterior descending coronary artery (LAD) was contoured as an OAR which may further limited dose to the heart in their study but may create significantly increased workload for physicians and dosimetrists. Additionally, the PTV delineation is different since the boost planning target volume was included in their analysis. These results suggest that hybrid IMRT may not be suitable for all WBRT patients and its application should be determined by all clinical factors.

Among all WBRT techniques in our study, MA-VMAT and NC-VMAT have shown superior OAR sparing. Tsai *et al.*[9] reported a mean heart dose of 7.6 ± 1.4 Gy and lung dose of 5.6 ± 0.4 Gy for MA-VMAT, which were slightly higher than our mean heart dose (5.5 ± 1.2 Gy) and lung dose (4.9 ± 0.9 Gy). This can be explained by the fact that a slightly higher prescription dose (50.4 Gy delivered in 28 fractions) was used in their study, and different dose constraints were used, e.g. our mean heart dose limit is 7 Gy where their mean heart dose limit was 9 Gy. When multiple arcs were used and collimator angle was adjusted for each arc, treatment plans could be further optimized since more degrees of freedom were provided for MA-VMAT. Our study utilizes NC-VMAT for WBRT for the first time and shows it can provide excellent sparing for lung and heart compared to other WBRT techniques, which demonstrates that OARs can be spared more by adjusting the couch angle in order to minimize direct irradiation.

There is a lack of clinical outcome data of radiogenic late effects for advanced WBRT techniques, but our calculated RCE and LARs for SOC WBRT show good agreement with clinical data for breast cancer patients who went through SOC WBRT: Taylor *et al.*[10] reported the annual risk of developing radiogenic lung cancer and contralateral breast cancer was 0.2% and 0.36%,

respectively, and our calculated annual risk is 0.22% and 0.38% for SOC; Hooning *et al.*[11] reported the annual cardiac toxicity was 1.19% whereas our estimation is 1.23%. Based on these good agreements, we expect our estimated radiogenic risks values for advanced WBRT techniques to be reasonable. Prospective clinical studies can validate our calculations and further illustrate the benefit of advanced WBRT techniques.

Heart toxicity such as ischemic heart disease and coronary disease is a major concern for breast cancer patients who received radiotherapy, especially for left-sided breast cancer patients.[12] Our study shows comparable mean heart dose using FIF, IMRT and VMAT as those reported by Viren *et al.*[7]. However, our study shows higher mean heart dose for conventional SOC, FIF, multi-beam IMRT and VMAT than those in Jin *et al.* [2], which is possibly because their extra dose constraints on coronary artery have further limited heart dose. The larger breast size in our study could inevitably lead to larger fields that will induce higher heart dose in order to provide enough PTV coverage. Furthermore, all patients were treated in the supine position in our study, while literature[13, 14] has shown that breast irradiation in prone position may result in lower risk of cardiac toxicity and improve dose homogeneity within PTV compared to standard irradiation in supine position. Further studies are needed to evaluate advanced WBRT techniques in prone treatment position.

In order to further reduce heart irradiation, deep inspiration breath hold (DIBH) has been implemented for WBRT and studies have shown that DIBH can minimize irradiation of heart without compromise target coverage for most left-sided breast cancer patient[15-21]. However, not all patients could benefit from it, e.g. Dell'Oro *et al.*[22] recently reported that DIBH may not be recommended for some patients due to little dosimetric benefit. Several studies[20, 22, 23] reported criteria of selecting breast cancer patients for DIBH, including the patient's age, ability

to hold breath for a fixed time, total lung volume, in-field heart volume, sternal excursion etc. In our study, the fifteen patients were not selected for DIBH in our clinic mainly due to the limited dosimetric benefit for them. The benefit of various WBRT techniques for DIBH patients will be investigated by our group in the near future.

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CHAPTER 5. COST-EFFECTIVENESS ANALYSIS OF RADIOTHERAPY TECHNIQUES FOR WHOLE BREAST IRRADIATION

5.1. Introduction

Breast cancer is estimated to have the highest incidence rate among women in the United States besides skin cancer (www.cancer.org). Lumpectomy is commonly performed for patients with early-stage breast cancer, and whole breast radiotherapy (WBRT) after lumpectomy has been shown to have lower recurrence and is as effective as mastectomy. [1]

The current standard of care (SOC) for whole breast radiation therapy (WBRT) in the US and in our clinic is conventional tangential photon fields.[2] Other advanced technologies had been proposed for WBRT and shown auspicious results, such as field-in-field (FIF) technique,[3, 4] hybrid Intensity modulated radiation therapy (IMRT),[5-7] fixed beam IMRT,[8, 9] standard volumetric modulated arc therapy (STD-VMAT),[10] multiple arc VMAT (MA-VMAT).[11] Non-coplanar VMAT (NC-VMAT) has been shown to improve OAR dosimetry for post-mastectomy breast cancer,[12] but has not been investigated for WBRT. These advanced technologies are superior to SOC in improving the dose homogeneity within the target volume and reduce the dose to radiosensitive organs, but they may increase the low-dose cloud which could cause a higher risk of radiogenic side effects. [13, 14]

It has been reported that breast cancer treatments cost around \$16.5 billion in the United States in 2010, which is higher than any other type of cancer. And annual breast cancer treatment expenditure is projected to reach \$20 billion by 2020.[15] Although more advanced radiotherapy technologies may improve dosimetric outcomes under certain circumstances, their much higher cost may not justify their advantages. There have been some cost-effectiveness studies comparing partial breast irradiation and WBRT, [16-18] but the comprehensive cost-effectiveness comparison among advanced WBRT techniques including costs for radiogenic side effects is still lacking.

The aim of this study is to analyze the cost-effectiveness of various WBRT techniques including conventional SOC, FIF, hybrid IMRT, IMRT, STD-VMAT, MA-VMAT and NC-VMAT. The conventional SOC was set as the reference for modality comparisons. Both tumor coverage and late side effects (cardiac toxicity and secondary cancers) after WBRT were included in the analyses.

5.2. Methods

Decision model

A Markov model (Figure 5.1) was designed using an in-house code to simulate the clinical history of postmenopausal women mean aged 65-year-old (between 60 and 70-year-old) with Stage I breast cancer (pT1N0) who received lumpectomy and subsequent WBRT with a prescribed dose of 50 Gy in 25 fractions. All patients start with no evidence of disease (NED) after WBRT, and transition afterwards to one of the four states (distant metastasis, local recurrence, late radiogenic side effects, and normal death). The patients could also die from breast cancer which is mainly caused by distance metastasis, and die from radiogenic side effects.

A 15- year horizon after radiotherapy was used for the model since study has shown the improvement in local control and survival due to radiotherapy during this time period.[19] The incremental cost effectiveness ratio (ICER) was expressed in terms of cost per life-year gained, according to the following formula:

$$ICER = \frac{C_1 - C_0}{E_1 - E_0}$$

where C_0 and E_0 are the cost and quality adjusted life year (QALY) for SOC technique, and C_1 and E_1 are the cost and QALY for other WBRT techniques. Willingness-to-pay (WTP)

thresholds of \$50,000/ QALY and \$100,000/QALY [20, 21] were used to determine whether a WBRT technique is cost-effective.

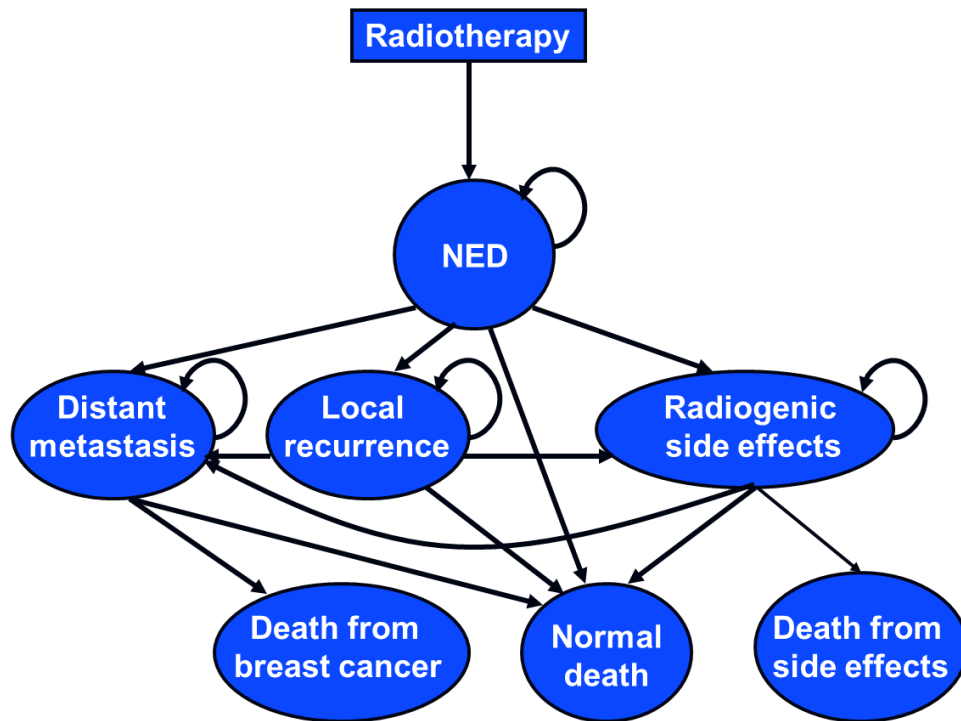


Figure 5.1. Overview of the Markov model. NED = no evidence of disease.

Model data input

All transition probabilities and utilities for SOC were extracted from the published literature [22-27] and are shown in Table 5.1. The utility weights for different states were abstracted from literature and are also shown in Table 5.1. The costs of different WBRT techniques from payer perspective were based on local hospital Medicare charges and are shown in Table 5.2, and the

Table 5.1. Transition probability and utility for the 65-year-old cohort.

Parameters	Years	Value (%) (range)	Reference
Probability			
Local Recurrence	0-5	1.46	[22]
	6-10	0.54	
	11-15	0.06	
NED to metastasis	0-5	12.25	[23]
	6-10	7.75	
	11-15	7.75	
Metastasis to Death	0-5	23.2	[24]
	6-15	14.0	
Normal Death	65-70 (age)	1.46	[25]
	71-75 (age)	1.71	
	76-80 (age)	3.53	
Death due to lung toxicity	11-15	0.078	[26]
Death due to heart toxicity	11-15	0.53	[27]
Death due to CL breast toxicity	6-15	2.12	[22]
Utility			
Cardiac toxicity	11-15	0.57(0.54-0.61)	[28]
CL Breast cancer	6-15	0.54(0.48-0.55)	[29]
Lung cancer	11-15	0.50 (0.39-0.56)	[29], [30]
Recurrence	0-5	0.66	[31]
	6-10	0.65	
	11-15	0.61	
Metastasis	0-5	0.44	[31]
	6-10	0.43	
	11-15	0.41	

costs of treating 3 radiogenic late side effects are also included in Table 5.2. Costs and utilities were discounted at an annual rate of 3%.[32]

Since the clinical data of tumor control or radiogenic late effects after advanced WBRT techniques were largely incomplete, we assumed probabilities of local recurrence and distant metastasis for advanced WBRT to be the same as those after SOC WBRT, and calculated probabilities of radiogenic late effects for those techniques using well-defined risk models including lifetime attributable risk (LAR) for second cancers [33] and risk for coronary events (RCE) [34, 35] as shown in Table 5.3.

The model validity was assessed by comparing 15-year model survival results with predicted results from the latest web-based prognostic tool Cancer-Math.

Table 5.2. Treatment cost

Treatment	Cost (range)	Reference
WBRT (SOC/FIF)	\$12,140	Based on Medicare charge
WBRT (Hybrid IMRT)	\$15,293	Based on Medicare charge
WBRT (VMAT/ IMRT)	\$17,438	Based on Medicare charge
Cardiac toxicity	\$11,570±3405	[28, 36]
CL breast cancer	\$14,494±1199	[37]
Lung cancer	\$20,577±2740	[38], [39], [40]
local recurrence	\$20,879	[41]
Metastasis	\$13,627	[41]

Table 5.3. Calculated probabilities of developing radiogenic side effects for the 65-year-old cohort from a previous study.[42]

Side effect	Probability (%)	Range (%)
SOC cardiac toxicity	1.24	0.80-2.03
SOC CL breast cancer	0.38	0.13-1.39
SOC lung cancer	0.22	0.18-0.28
FIF cardiac toxicity	1.15	0.80-1.97
FIF CL breast cancer	0.38	0.18-0.71
FIF lung cancer	0.22	0.18-0.31
Hybrid IMRT cardiac toxicity	1.16	0.77-1.88
Hybrid IMRT CL breast cancer	0.35	0.12-1.33
Hybrid IMRT lung cancer	0.20	0.16-0.27
IMRT cardiac toxicity	1.14	0.74-1.78
IMRT CL breast cancer	0.32	0.71-0.71
IMRT lung cancer	0.20	0.14-0.27
STD-VMAT cardiac toxicity	1.16	0.69-1.77
STD-VMAT CL breast cancer	0.27	0.17-0.54
STD-VMAT lung cancer	0.20	0.18-0.29
NC-VMAT cardiac toxicity	1.05	0.65-1.51
NC-VMAT CL breast cancer	0.27	0.17-0.78
NC-VMAT lung cancer	0.18	0.13-0.25
MA-VMAT cardiac toxicity	1.03	0.65-1.52
MA-VMAT CL breast cancer	0.26	0.15-0.39
MA-VMAT lung cancer	0.17	0.10-0.24

Sensitivity analyses

A series of one-way sensitivity analyses were performed over a wide range of assumptions for probabilities, utilities, and treatment costs of radiogenic side effects for six advanced WBRT techniques versus SOC.

Probability sensitivity analyses (PSA) were also performed to assess the uncertainty and robustness of the model by assigning specific distributions for model parameters, where the probabilities, utilities, and costs of radiogenic side effects were varied simultaneously across their

distributions using Monte Carlo simulation. Recommended by Briggs *et al.*,[43] we used beta distribution for transition probabilities and utilities estimates, and used gamma distributions for cost parameters. The cost-effectiveness acceptability curves were plotted based on the result of 100,000 simulations for each WBRT technique at different WTP thresholds.

5.3. Results

The external validation of our model was assessed for 65-year-old women with breast cancer. Our model predicted a 15-year overall survival rate of 53.3% and breast cancer mortality rate of 21.7%, and CancerMath estimated an overall survival rate of 55.0% and breast cancer mortality rate of 19.5%. This outcome suggests that our model's prediction is similar to real clinical outcomes, the model's overestimation of breast cancer mortality may be due to the death of contralateral breast cancer were included in the analysis.

Table 5.4. Incremental cost-effectiveness ratio for advanced techniques compared to SOC WBRT (\$/QALY)

Age	FIF	Hybrid	IMRT	Std-VMAT	NC-VMAT	MA-VMAT
65	1,511	86,316	121,087	99,315	97,759	91,872

Table 5.5. Probability of being more cost-effective than SOC for advanced techniques

Age	WTP (\$/QALY)	FIF	Hybrid	IMRT	Std-VMAT	NC-VMAT	MA-VMAT
65	50,000	58.9%	2.0%	0.0%	0.5%	0.5%	0.0%
	100,000	59.2%	72.3%	12.9%	44.9%	56.6%	72.6%

Table 5.4 shows ICERs for all six WBRT techniques compared with SOC, and all WBRT techniques except for IMRT are more cost-effective than SOC for the base case with WTP threshold of 100,000 \$/QALY. Among six techniques that were analyzed, FIF shows the lowest ICER of 1,511 \$/QALY while IMRT shows highest ICER of 121,087 \$/QALY.

The one-way analyses show that the cost-effectiveness of all six advanced WBRT techniques is sensitive to the probability of developing contralateral breast cancer. The probabilities of being more cost-effective than SOC for six WBRT techniques are shown in Table 5.5. At WTP of 50,000 \$/QALY, except FIF which has a 58.9% probability of being more cost effective, none of the other five WBRT techniques has an over 2.0% probability of being more cost-effective. At WTP of 100,000 \$/QALY, hybrid IMRT and MA-VMAT are more likely to be cost-effective than SOC with a probability of 72.3% and 72.6%, respectively.

5.4. Discussion

This study presents the most comprehensive cost-effectiveness analysis of seven WBRT techniques. Not only tumor control but also radiogenic side effects were included in the study. IMRT shows the highest ICER which may be due to its higher initial treatment cost and limited improvement of normal tissue sparing. FIF has the lowest ICER which is mainly due to its low initial treatment cost and relatively lower probability of inducing cardiac toxicity compared with SOC. As shown in the PSA, FIF, hybrid IMRT and MA-VMAT are more likely to be more cost effective than SOC and other WBRT techniques at a WTP of 100,000\$/QALY, while SOC WBRT appeared to be more cost effective than advanced WBRT techniques except for FIF at WTP of 50,000\$/QALY. FIF has shown to be the most cost effective option for WBRT patients which is robust under a wide range of clinical and economic parameters. For all WBRT techniques, hybrid IMRT and MA-VMAT are less cost effective for the base case, however, they are more cost

effective at WTP of 100,000\$/QALY based on the PSA results. This is mainly due to a higher probability of developing contralateral breast cancer, which was used as the base case and a wide range of its uncertainty was studied, which lead to different results in PSA.

Given the prevalence of breast cancer and continued growth of health care costs, results from this analysis will have a positive impact. Prior study has shown that up to 30% of the medical care dispensed in the US is unnecessary or inappropriate because too much of health care spending goes toward services that have little value in terms of improved quality of life.[44] Moreover, study on Medicare patients found that higher cost was associated with more care but not better health outcomes.[45] The results from our analysis may benefit the insurance companies and health care professionals to adjust the reimbursement rate for different WBRT techniques, and help choose the most cost-effective health intervention for breast cancer patients.

Radiation therapy is a crucial component of breast cancer treatment, and several studies have compared cost effectiveness between different WBRT and accelerated partial breast irradiation (APBI) techniques. Shah *et al.* [17] reported that APBI cost less and is more effective than hypofractionated WBRT after 3 month of the initial treatment. Another study published by their group[46] showed that APBI is a more cost-effective approach compared to WBRT using 3D conformal therapy and WBRT using IMRT. Sher *et al.*[16] compared the cost effectiveness between WBRT, external beam (EB)- and MammoSite (MS) PBI, they also conclude that EB-PBI is most cost effective strategy for early stage breast cancer patient. However, not all lumpectomy patients are eligible for PBI, and the cost-effectiveness analysis of different advanced WBRT techniques is largely lacking. Sen *et al.*[47] compared no radiotherapy, conventional external beam WBRT and IMRT WBRT for women older than 70 and only considered tumor control, and they reported that IMRT would have to be substantially more effective in improving quality of life than

conventional external beam therapy to be cost effective. Because they did not include short-term or long-term side effects in their study, they used the increase of utility of baseline state to be a vague representation of improvement in quality of life. Our study shows that the risk of developing contralateral breast cancer may significantly affect the cost effectiveness estimation for advanced WBRT techniques, and contralateral breast cancer is directly related to quality of life for WBRT patients. Our study is therefore consistent with Sen *et al.*[47] and clearly suggests reducing irradiation of contralateral breast could be a key to making advanced WBRT technique more cost effective.

A previous study from our group evaluated the cost effectiveness of current SOC post-mastectomy radiotherapy (PMRT) and seven advanced PMRT techniques over 15 years. It used a similar Markov model and showed that the model outcomes are most sensitive to the probability of developing cardiac toxicity for PMRT patients. As shown in the one-way analysis in this study, the cost effectiveness for all WBRT techniques is most sensitive to the risk of developing contralateral breast cancer. The possible reason is that the treatment target is much closer to the heart for PMRT patients compared to WBRT patients, which significantly increases the risks of heart toxicity and makes it a contributing factor to the cost-effectiveness of radiotherapy techniques for PMRT patients. On the other hand, the risk of developing contralateral breast cancer for WBRT patients is much higher for PMRT patients, which is mainly due to the relatively large field size used in WBRT to cover the whole ipsilateral breast and increased irradiation of the contralateral breast. Additionally, treating contralateral breast cancer will cost almost \$3000 more than treating heart toxicity (Table 2). Therefore, providing better sparing of contralateral breast is essential for advanced WBRT technique to be cost effective.

For SOC WBRT, considerable volumes of the heart and ipsilateral lung are likely to receive high doses which may lead to radiation-related toxicity such as secondary lung cancer[48] and heart disease[34, 49]. The radiogenic side effects will not only affect patients' quality of life, but also add further economic burden for WBRT patients. Advanced radiotherapy techniques could avoid high dose exposure to surrounding and underlying healthy tissues in order to improve the quality of life for the patients. We used well-defined dose-risk models to calculate probabilities of developing radiogenic late effects for advanced WBRT techniques because there is a lack of clinical outcome data. However, as shown in another study from our group,[42] the calculated risks of cardiac toxicity and second cancers after SOC WBRT are in good agreement with the clinical outcome, so we expect our calculated risks values for advanced WBRT techniques in this study are reasonable. Long-term clinical trial outcomes will be needed to validate the benefits and cost-effectiveness of advanced WBRT techniques compared to SOC.

Proton therapy was not included in this study. Although proton therapy has been shown as a promising WBRT technique to reduce heart and lung dose, [50, 51] it did not gain popularity due to its limited availability and significantly higher cost. In addition, the multiple uncertainties [52, 53] and possible skin toxicity [54, 55] make proton WBRT challenging. Another effective method to limit radiation dose to the heart and lung is the use of deep inspiration breath-hold (DIBH), which is particularly useful for treating patients with left-sided breast cancer.[56, 57] Macrie *et al.* [58] reported a DIBH program that is inexpensive to implement and has minimum influence on patient throughput. Chatterjee *et al.* [59] concluded that although DIBH requires significant resource commitments regarding person-hours, it is still more cost effective due to the reductions in cardiac mortality. The study that compares the cost-effectiveness of various WBRT techniques for patients with DIBH is still lacking, and will be investigated by our group in the near future.

5.5. Conclusions

In this study, we evaluated the cost-effectiveness of seven WBRT techniques. Based on calculated ICER values and comprehensive uncertainty analyses, FIF appears to be the most cost-effective approach for WBRT patients. Hybrid IMRT and MA-VMAT would have to be substantially more effective than SOC in improving sparing of contralateral breast to be cost-effective. Providing better sparing of contralateral breast might be essential for advanced WBRT techniques to be cost effective.

5.6. References

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CHAPTER 6. CONCLUSION

6.1. Significance

This work reports comprehensive treatment planning comparison analyses for both PMRT and WBRT patients using various radiotherapy techniques, followed by comprehensive cost-effectiveness analyses which included radiogenic side effects, where the probabilities of developing radiogenic side effects are quantified using well-defined risk models. In chapter 2, the predicted treatment outcomes comparison among standard VMAT, MA-VMAT, NC-VMAT, IMRT, Tomotherapy, mixed beam therapy and proton therapy for patients who underwent radiotherapy after mastectomy was performed. The cost-effectiveness evaluation of these advanced radiotherapy techniques was further analyzed in chapter 3. For early stage breast cancer patients who underwent lumpectomy, chapter 4 compared seven WBRT techniques including 3D conventional RT, field-in-field, hybrid IMRT, full IMRT, standard VMAT, MA-VMAT and NC-VMAT, where the investigation of cost-effectiveness of these seven techniques for WBRT patients with 15 years follow-up was exhibited in chapter 5.

6.2. Implications

The results from this work affect physicians' decision to choose the most optimal radiotherapy technique for breast cancer patients among all available treatment modalities. This study may also help to determine the most cost-effective radiotherapy technique for breast cancer patients with different stages.

The works presented in this dissertation suggest that fixed-beam IMRT, NC-VMAT, and mixed beam therapy could be the optimal radiation technique for certain post- mastectomy breast cancer patients, and IMRT might be the most cost-effective option for PMRT patients. And for early stage breast cancer patients who underwent lumpectomy, MA-VMAT and NC-VMAT could

be the optimal radiation technique for their superior sparing of OARs. Moreover, FIF is more likely to be cost-effective for WBRT patients.

6.3. Future Work

The long-term goal of this study is to improve radiotherapy outcomes for breast cancer patients by providing comprehensive treatment options to reduce the risk of radiogenic side effects, and choose the most cost-effective radiotherapy technique for an individual patient. This study has built a workflow to compare and analyze cost-effectiveness of different radiotherapy techniques for breast cancer patients. Although the calculated RCE and LARs for advanced WBRT radiotherapy techniques have shown a good agreement with clinical outcome data of radiogenic late effects in chapter 4, some additional prospective clinical researches are required to confirm that these calculated risk values are matched with the clinical outcome data of different stages of breast cancer patients using various advanced radiotherapy techniques, which may further illustrate the advantages of advanced radiotherapy techniques and make choosing the most cost effective radiotherapy technique more authentic.

This dissertation compared various advanced radiotherapy techniques for left-sided free-breathing PMRT and WBRT patients. Studies have shown that deep inspiration breath hold (DIBH) can reduce cardiac exposure without compromising the planning target coverage for left-sided breast cancer patients [1-6], which may significantly reduce the risk of developing radiation induced heart disease. It is necessary to investigate the benefit of DIBH for different advanced radiotherapy techniques. Comparing the efficacy and cost-effectiveness of various advanced radiotherapy techniques for breath hold patients will be further investigated by our group in the near future.

Additionally, there has been an increasing interest in using flattening filter-free (FFF) beams recently. Unflattened photon beams exhibit many benefits over traditional flattened beams, including reduced penumbra, reduced head scatter and lower out-of-field dose[7]. Another benefit of FFF beams is an increase in delivery efficiency due to the increased dose rates [8, 9], which can reduce the delivery time of treatments. In addition, studies have shown that increased dose rates will have no influence over treatment outcomes compared to lower dose rates seen with flattened beams[10]. The treatment planning investigation of using FFF radiotherapy techniques will be performed by our group for PMRT, WBRT and partial breast irradiation (PBI) patients.

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APPENDIX A

SCATTER PLOTS FOR PSA

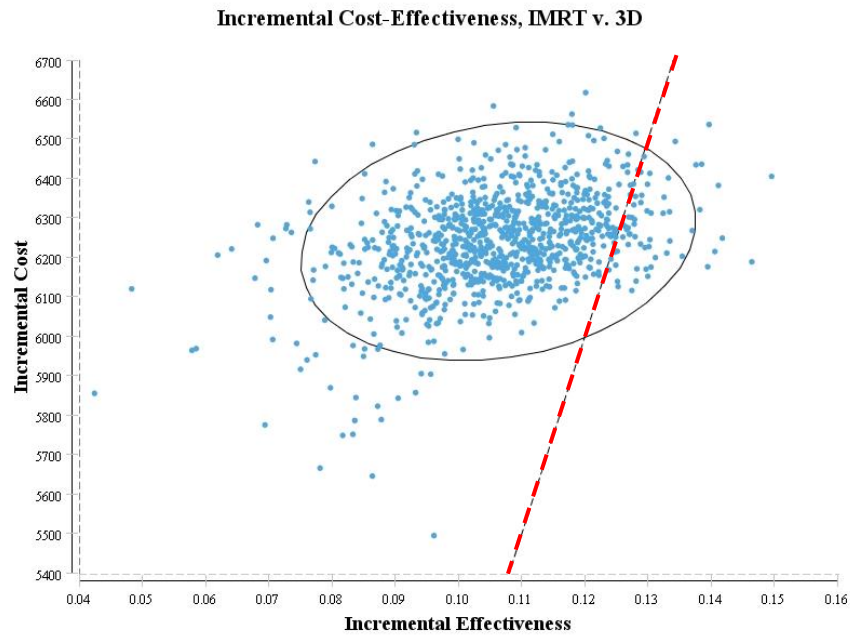


Figure A.1. Scatter plot of PSA that comparing the cost-effectiveness of IMRT to SOC at WTP of 50,000 \$/QALY for PMRT patients

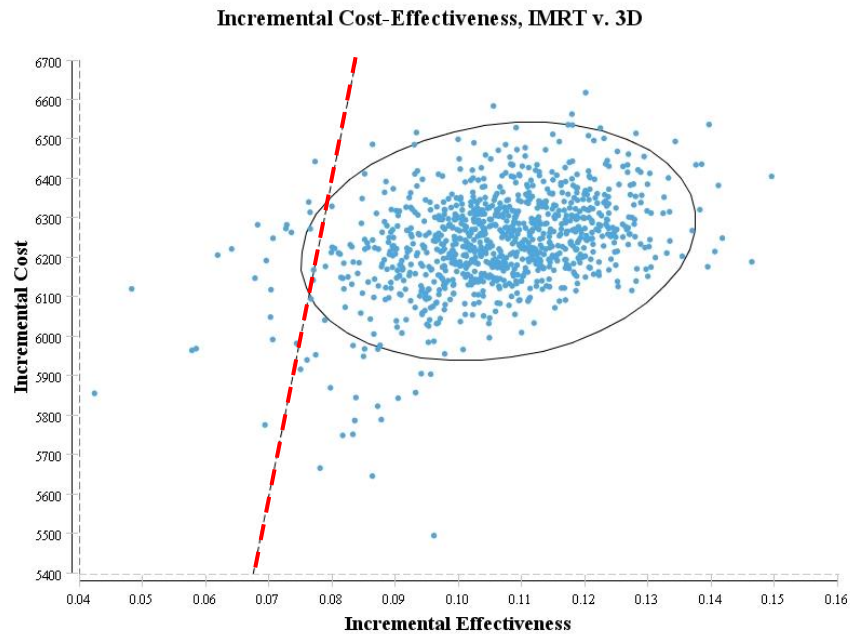


Figure A.2. Scatter plot of PSA that comparing the cost-effectiveness of IMRT to SOC at WTP of 100,000 \$/QALY for PMRT patients

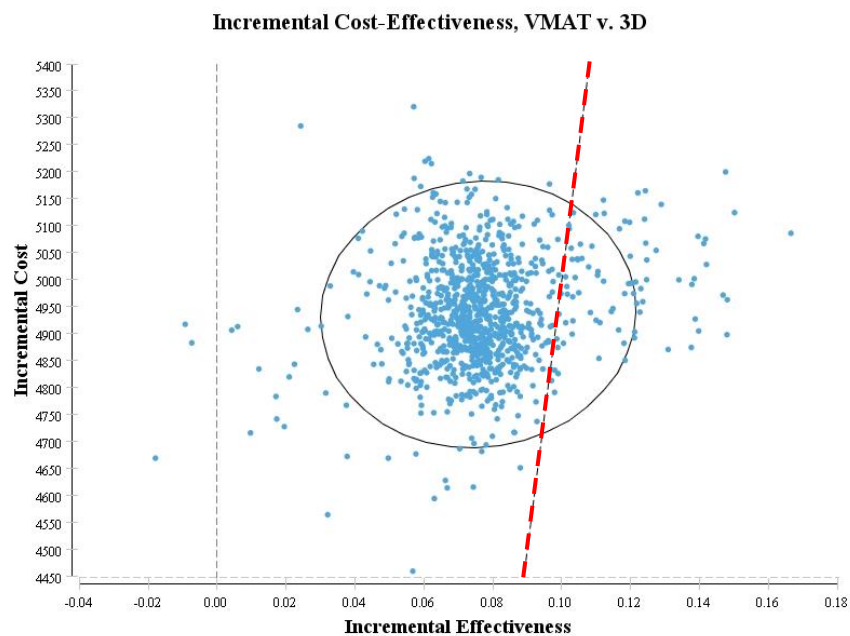


Figure A.3. Scatter plot of PSA that comparing the cost-effectiveness of STD-VMAT to SOC at WTP of 50,000 \$/QALY for PMRT patients

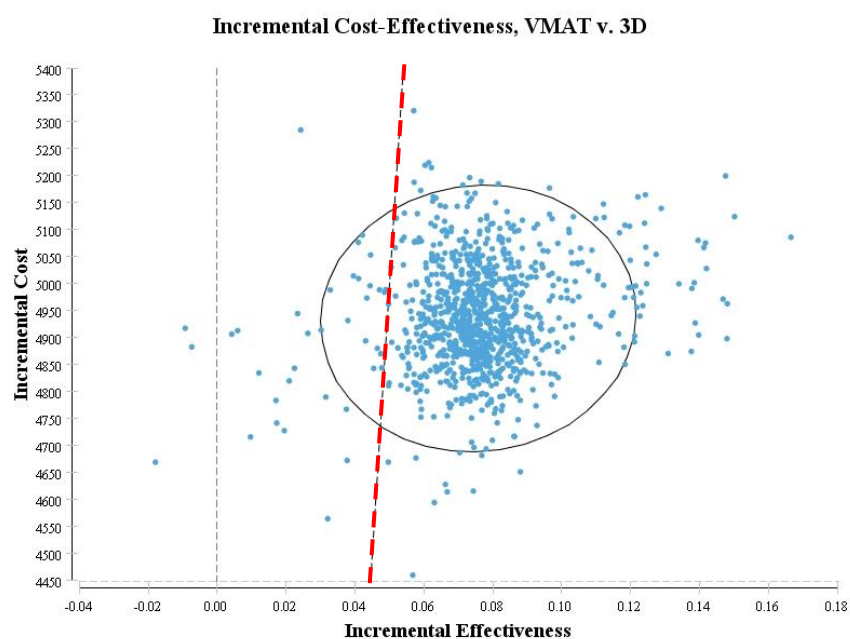


Figure A.4. Scatter plot of PSA that comparing the cost-effectiveness of STD-VMAT to SOC at WTP of 100,000 \$/QALY for PMRT patients

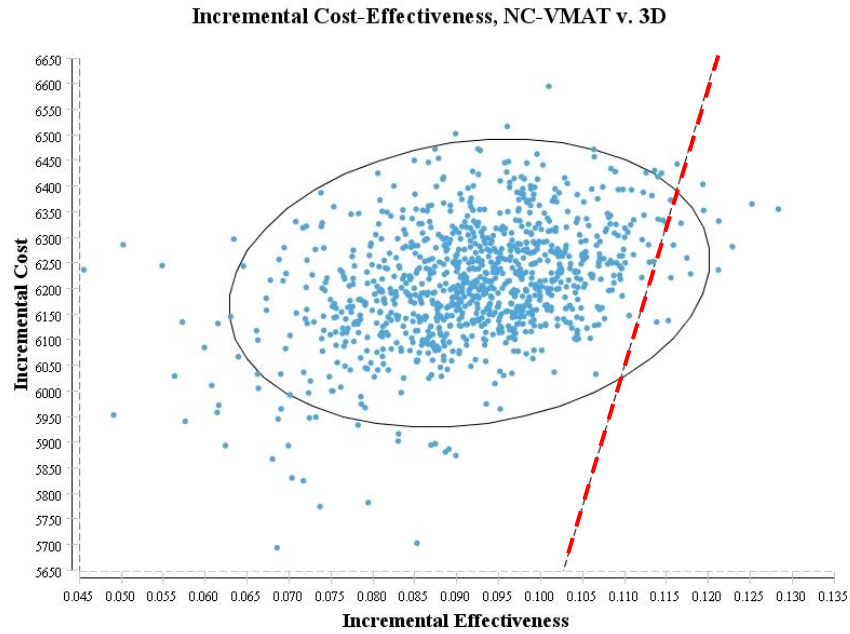


Figure A.5. Scatter plot of PSA that comparing the cost-effectiveness of NC-VMAT to SOC at WTP of 50,000 \$/QALY for PMRT patients

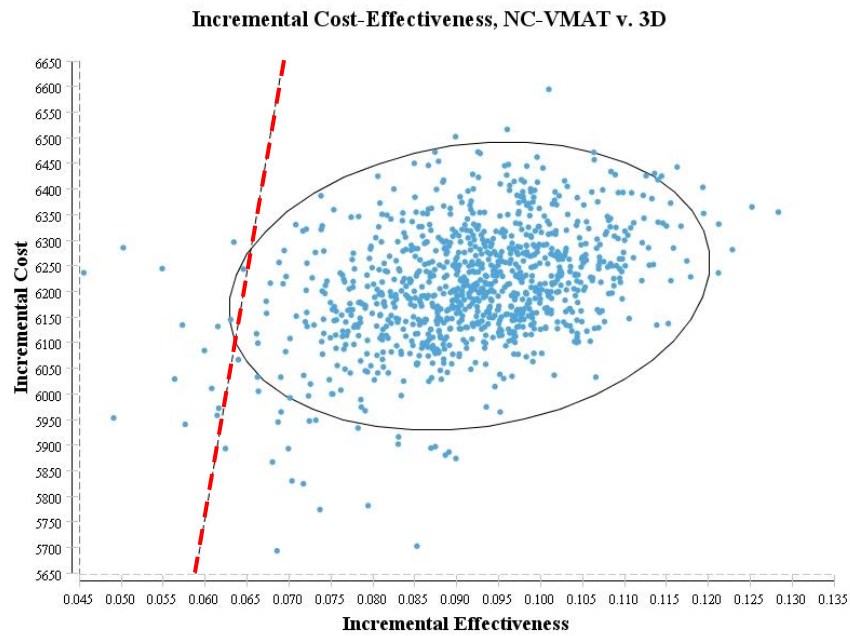


Figure A.6. Scatter plot of PSA that comparing the cost-effectiveness of NC-VMAT to SOC at WTP of 100,000 \$/QALY for PMRT patients

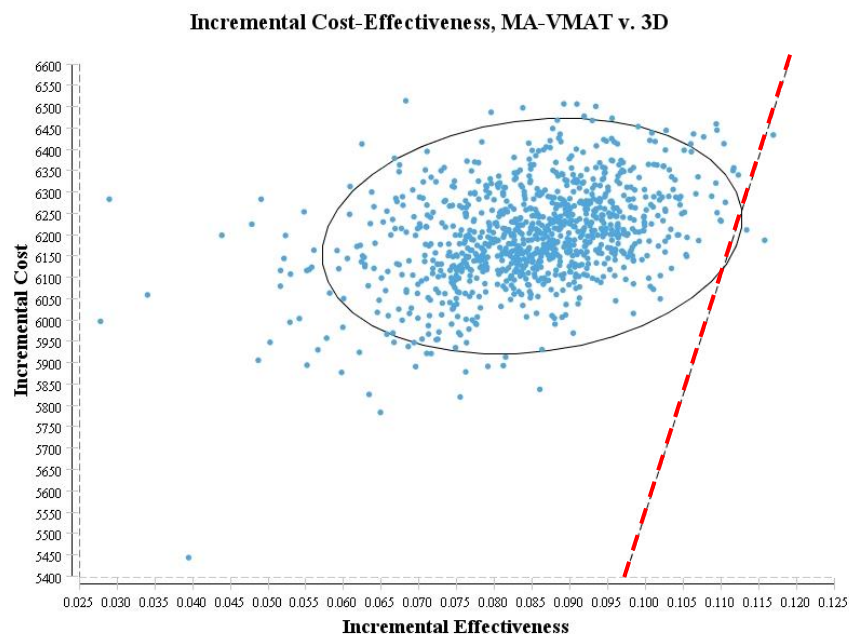


Figure A.7. Scatter plot of PSA that comparing the cost-effectiveness of MA-VMAT to SOC at WTP of 50,000 \$/QALY for PMRT patients

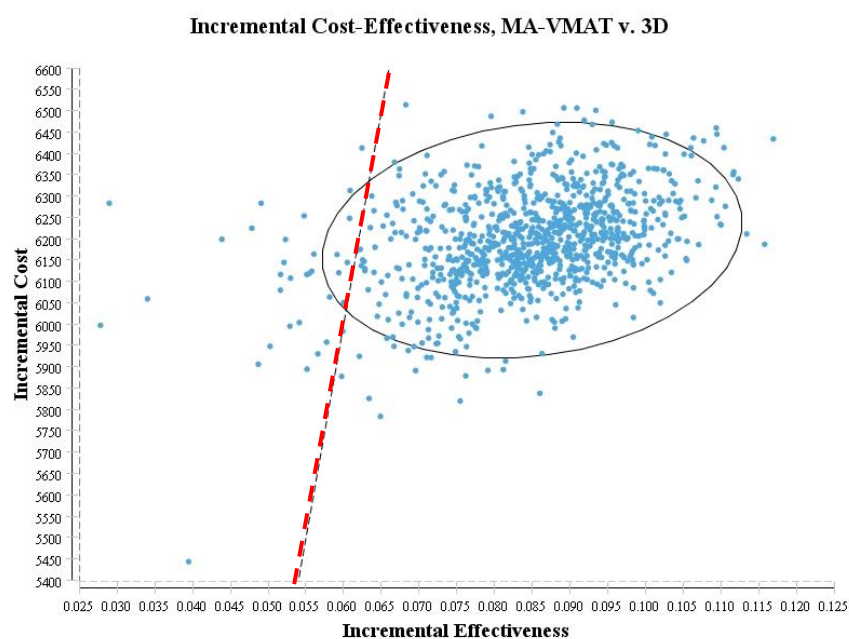


Figure A.8. Scatter plot of PSA that comparing the cost-effectiveness of MA-VMAT to SOC at WTP of 100,000 \$/QALY for PMRT patients

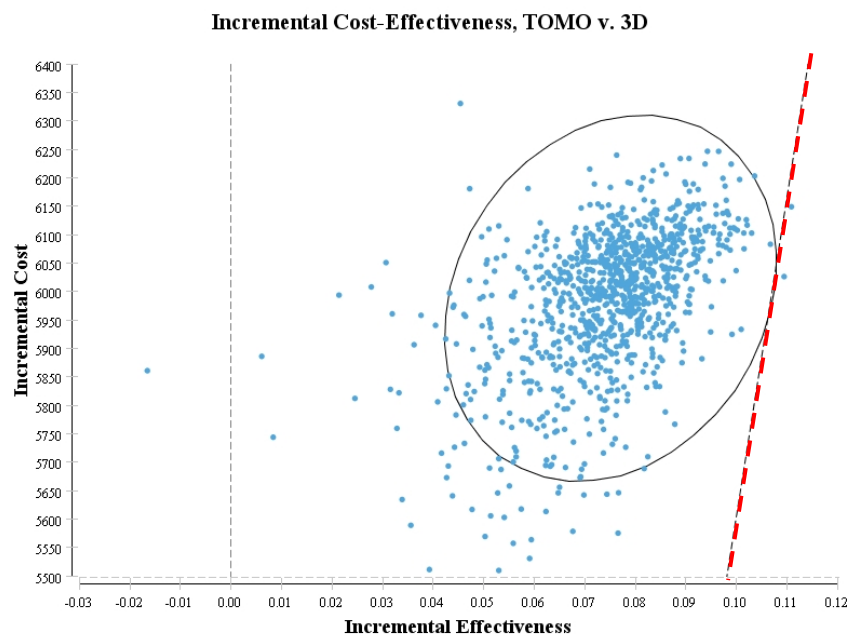


Figure A.9. Scatter plot of PSA that comparing the cost-effectiveness of TOMO to SOC at WTP of 50,000 \$/QALY for PMRT patients

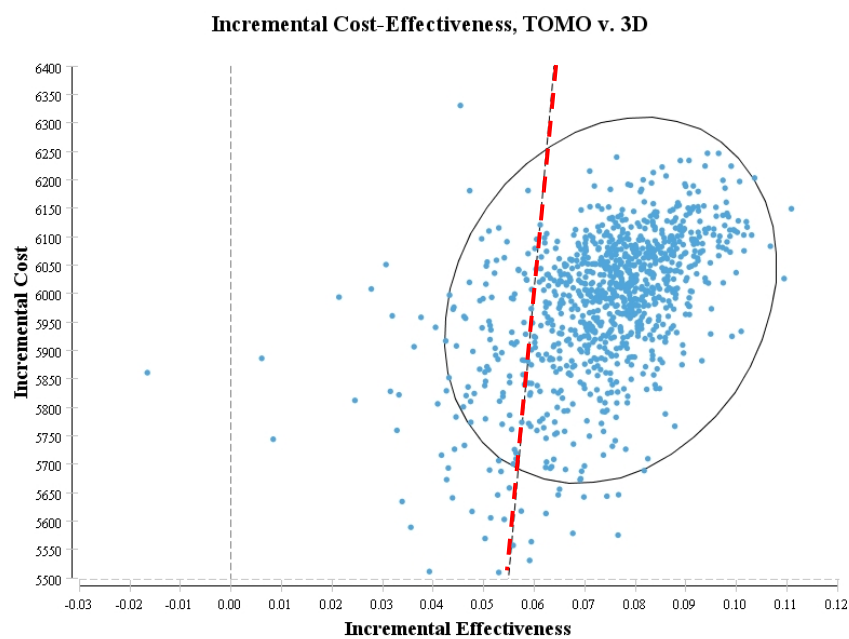


Figure A.10. Scatter plot of PSA that comparing the cost-effectiveness of TOMO to SOC at WTP of 100,000 \$/QALY for PMRT patients

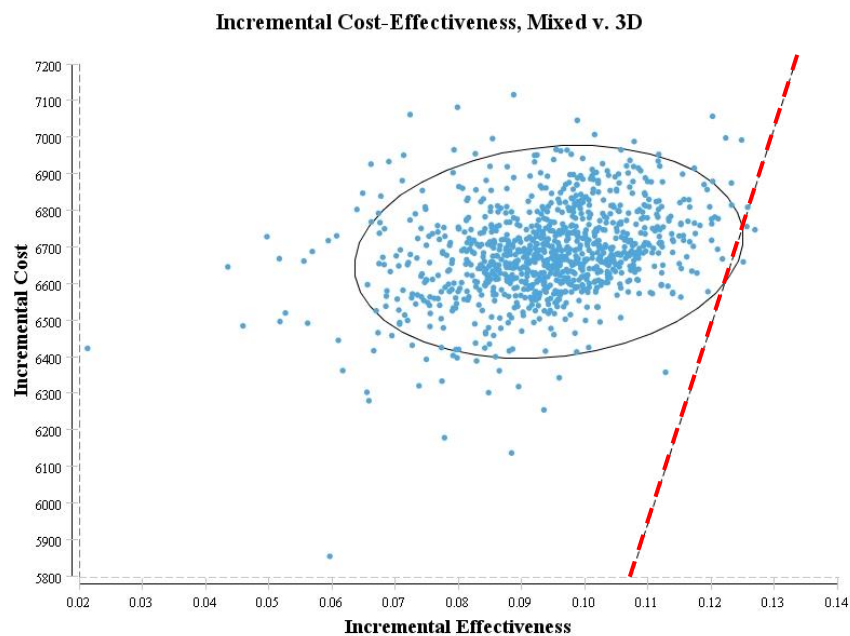


Figure A.1. Scatter plot of PSA that comparing the cost-effectiveness of Mixed beam to SOC at WTP of 50,000 \$/QALY for PMRT patients

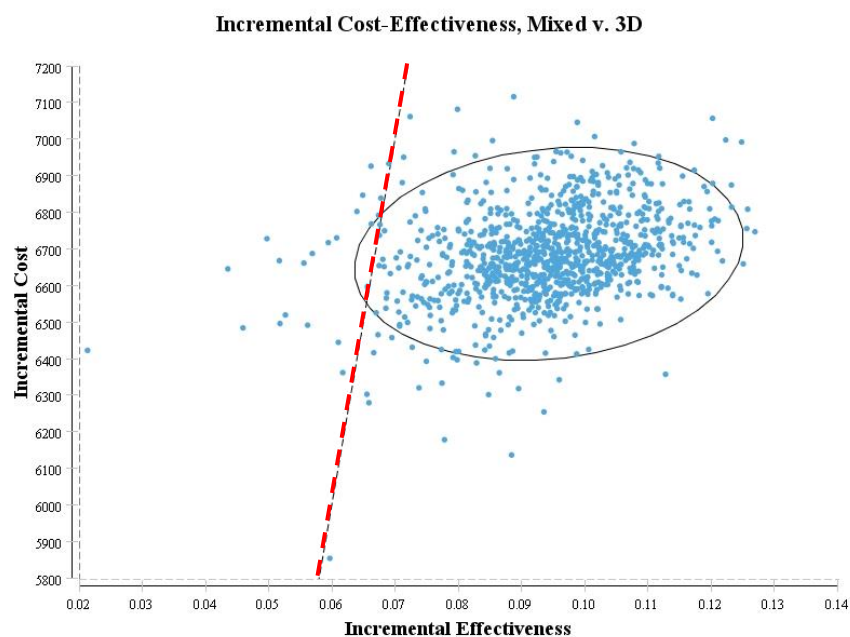


Figure A.2. Scatter plot of PSA that comparing the cost-effectiveness of Mixed beam to SOC at WTP of 100,000 \$/QALY for PMRT patients

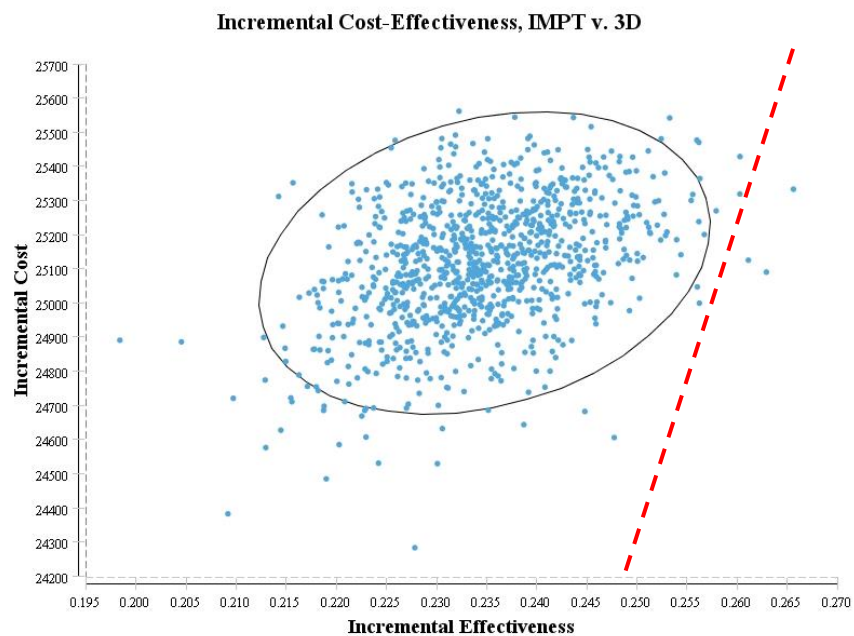


Figure A.3. Scatter plot of PSA that comparing the cost-effectiveness of IMPT to SOC at WTP of 50,000 \$/QALY for PMRT patients

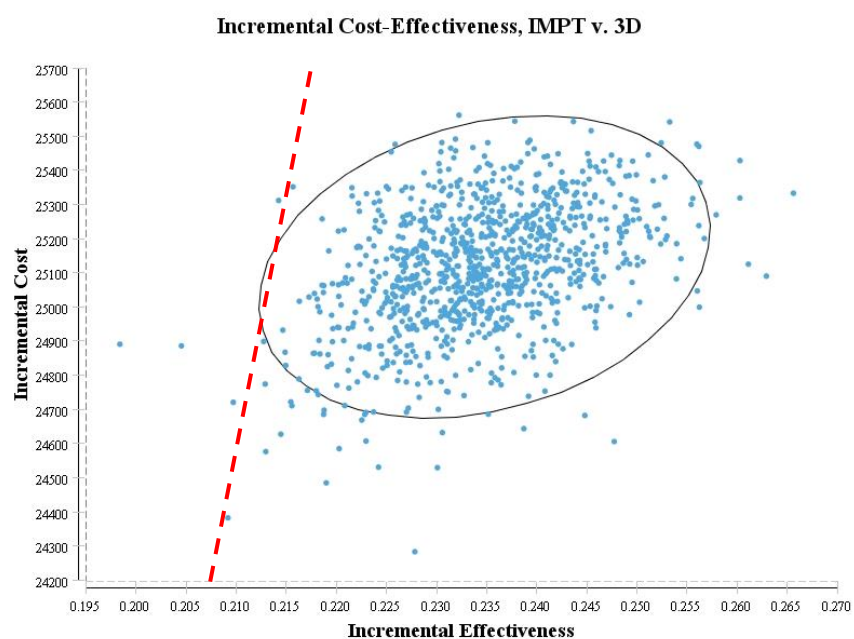


Figure A.4. Scatter plot of PSA that comparing the cost-effectiveness of IMPT to SOC at WTP of 100,000 \$/QALY for PMRT patients

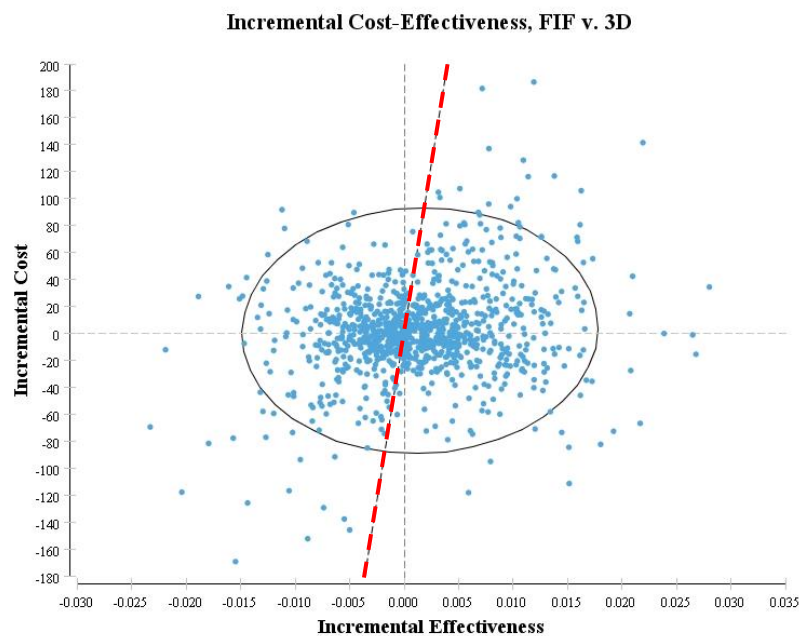


Figure A.5. Scatter plot of PSA that comparing the cost-effectiveness of FIF to SOC at WTP of 50,000 \$/QALY for WBRT patients

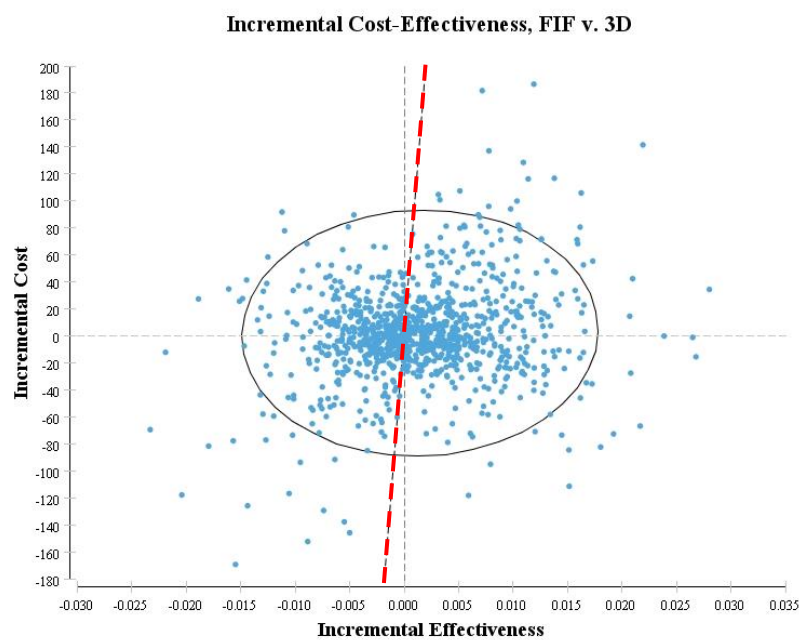


Figure A.6. Scatter plot of PSA that comparing the cost-effectiveness of FIF to SOC at WTP of 100,000 \$/QALY for WBRT patients

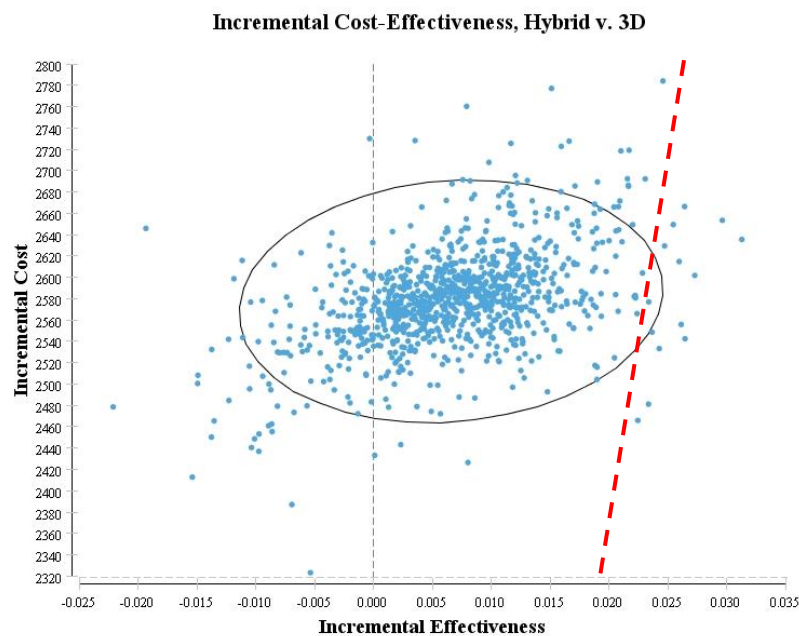


Figure A.7. Scatter plot of PSA that comparing the cost-effectiveness of Hybrid IMRT to SOC at WTP of 50,000 \$/QALY for WBRT patients

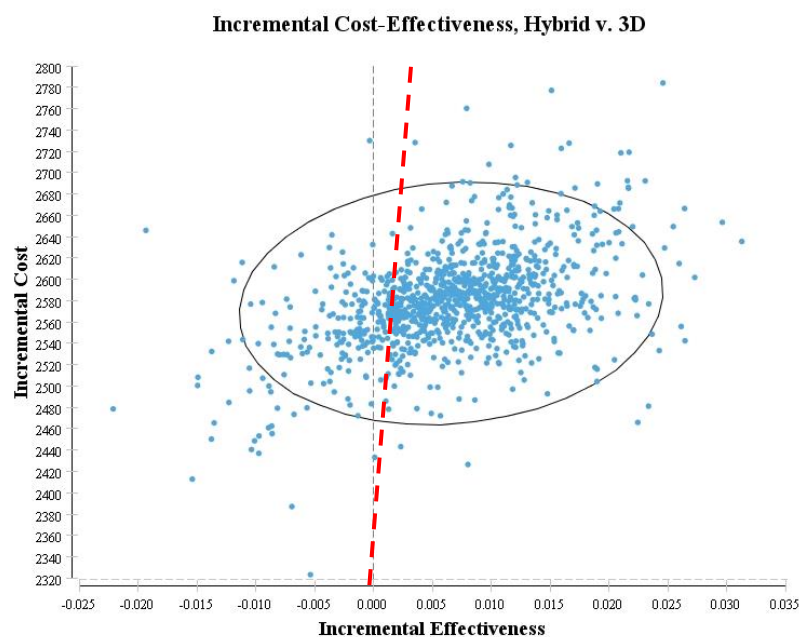


Figure A.8. Scatter plot of PSA that comparing the cost-effectiveness of Hybrid IMRT to SOC at WTP of 100,000 \$/QALY for WBRT patients

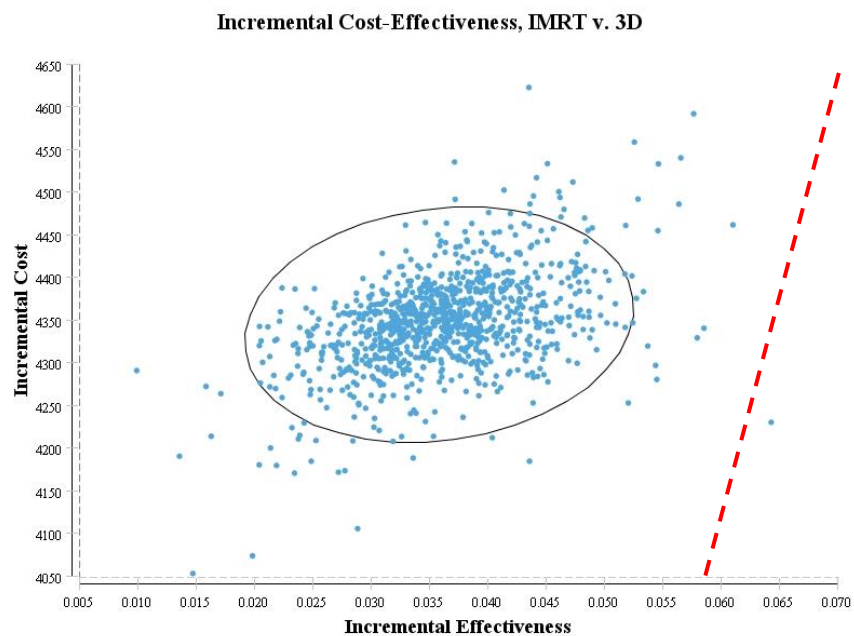


Figure A.9 Scatter plot of PSA that comparing the cost-effectiveness of IMRT to SOC at WTP of 50,000 \$/QALY for WBRT patients

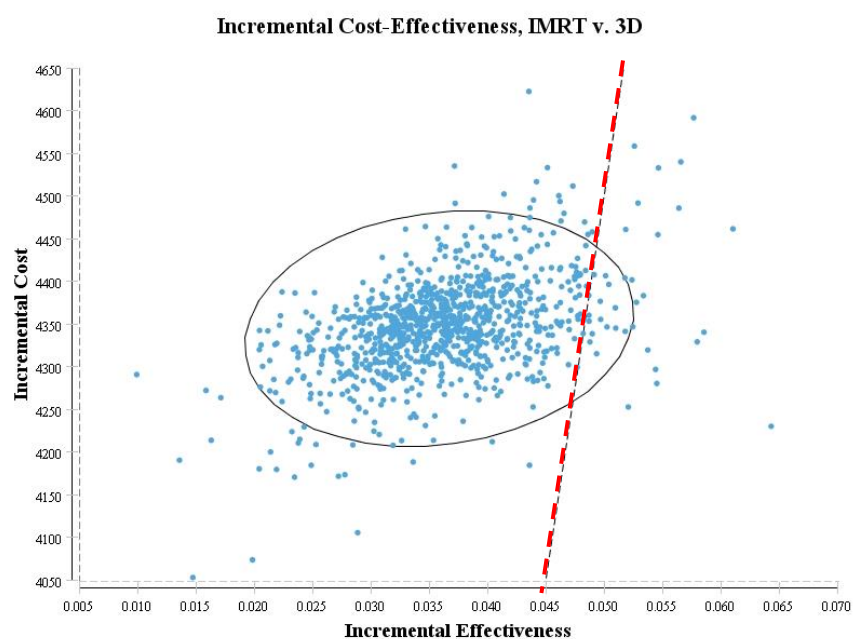


Figure A.10. Scatter plot of PSA that comparing the cost-effectiveness of IMRT to SOC at WTP of 100,000 \$/QALY for WBRT patients

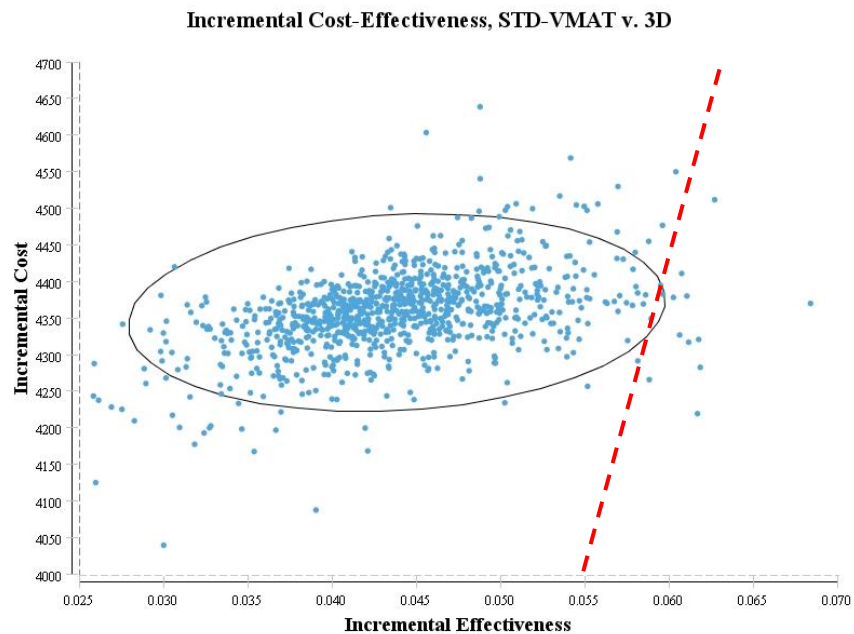


Figure A.11. Scatter plot of PSA that comparing the cost-effectiveness of STD-VMAT to SOC at WTP of 50,000 \$/QALY for WBRT patients

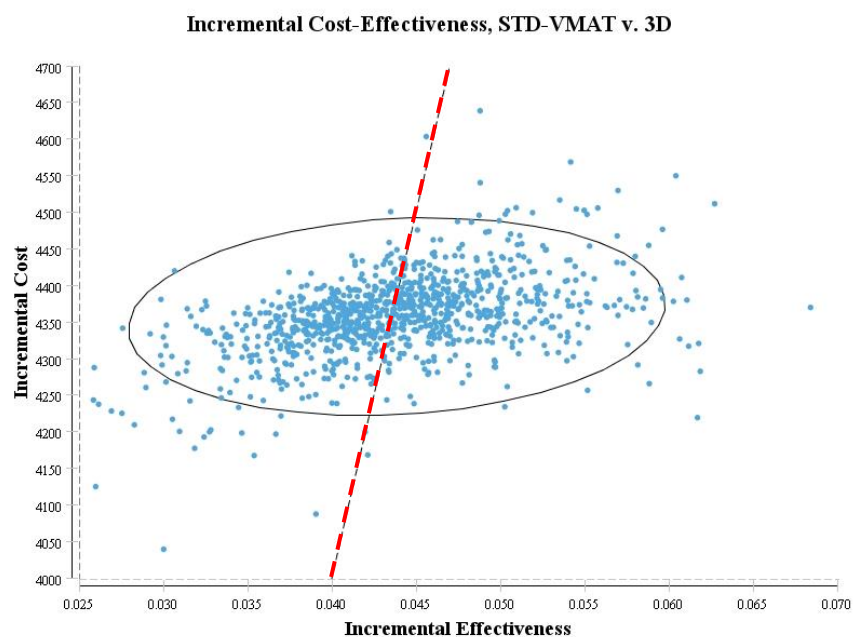


Figure A.12. Scatter plot of PSA that comparing the cost-effectiveness of STD-VMAT to SOC at WTP of 100,000 \$/QALY for WBRT patients

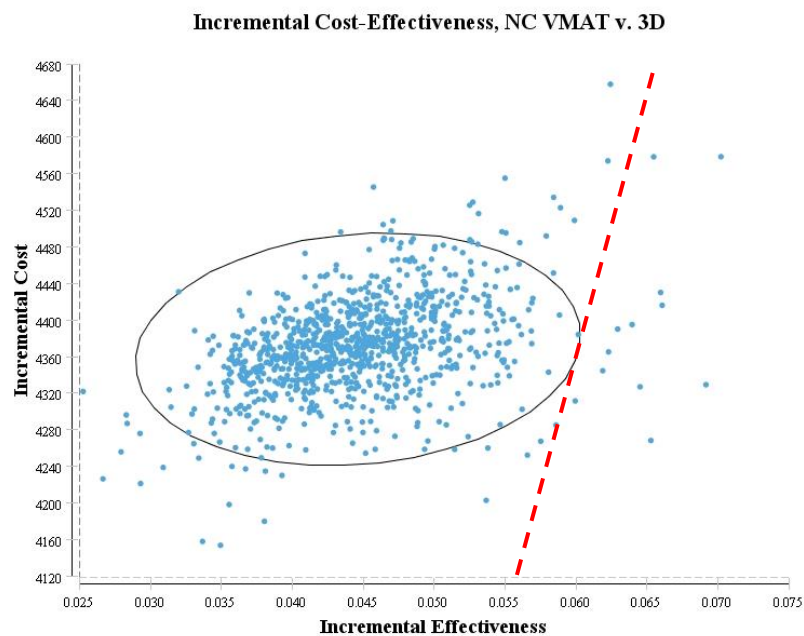


Figure A.13. Scatter plot of PSA that comparing the cost-effectiveness of NC-VMAT to SOC at WTP of 50,000 \$/QALY for WBRT patients

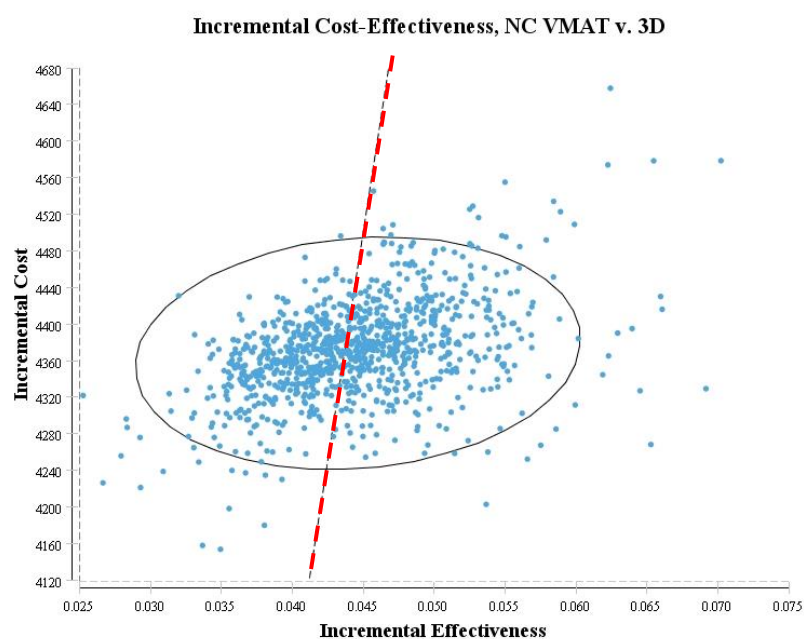


Figure A.14. Scatter plot of PSA that comparing the cost-effectiveness of NC-VMAT to SOC at WTP of 100,000 \$/QALY for WBRT patients

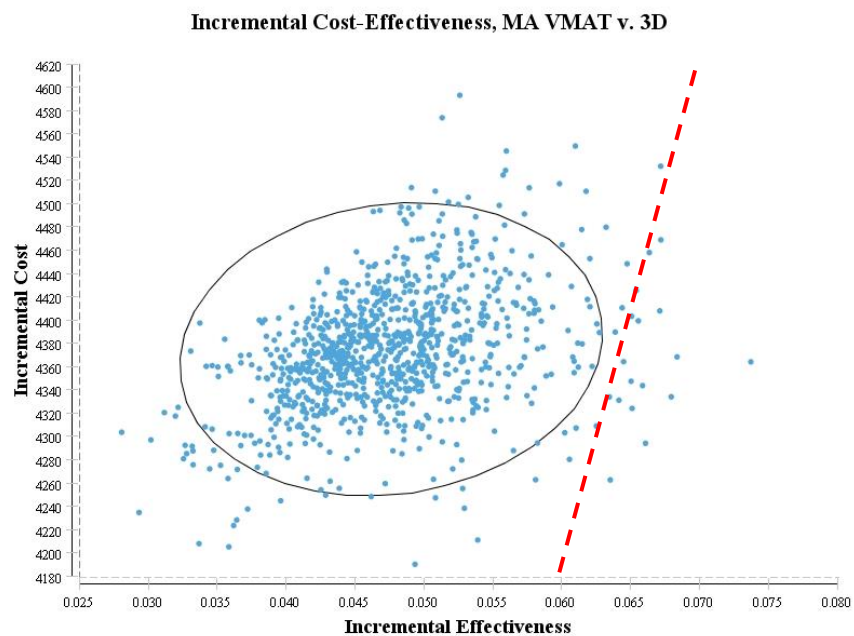


Figure A.15. Scatter plot of PSA that comparing the cost-effectiveness of MA-VMAT to SOC at WTP of 50,000 \$/QALY for WBRT patients

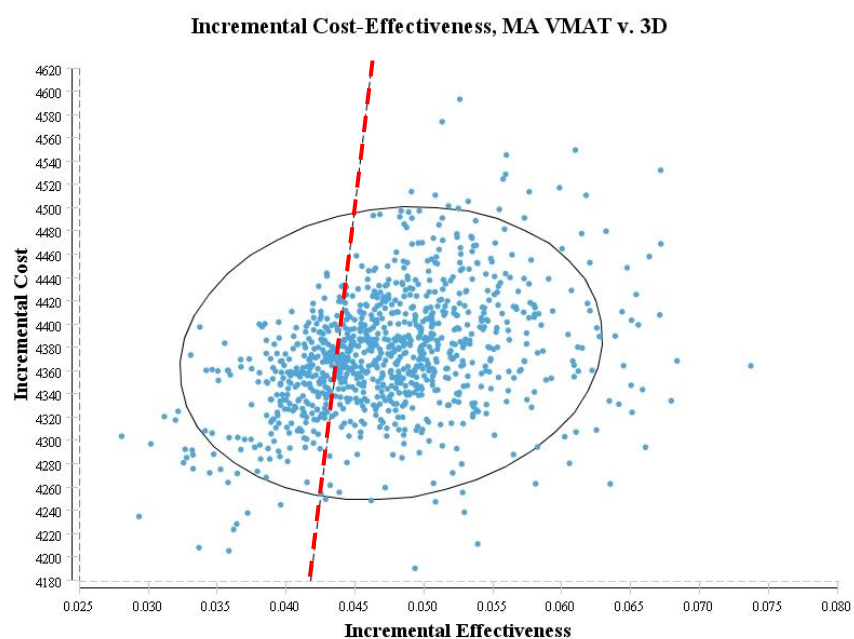


Figure A.16. Scatter plot of PSA that comparing the cost-effectiveness of MA-VMAT to SOC at WTP of 100,000 \$/QALY for WBRT patients

APPENDIX B

PUBLICATION AGREEMENTS AND PERMISSIONS



Postmastectomy radiotherapy for left-sided breast cancer patients: Comparison of advanced techniques

Author: Yibo Xie, Daniel Bourgeois, Beibei Guo, Rui Zhang

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