Dose to non-routinely delineated risk organs in left postconservative surgery conformal breast irradiation

A thesis submitted in the partial fulfillment of master degree in Clinical Oncology

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ABSTRACT

***Background*:** Radiotherapy following Breast-conservative surgery is a standard treatment for breast cancer, Techniques developed to obtain better target definition, dose homogeneity and coverage, however, studies of radiation toxicity in the treatment of breast cancer showed that the effects on normal tissues can constitute a significant clinical problem and increased cardiac mortality in particular may offset survival benefit of treatment

Objectives: This a cross section planning study aiming at evaluation of brachial plexus, coronary artery & thyroid gland doses in previously treated breast cancer cases at Kasr Alaini Center of Clinical Oncology & Nuclear Medicine (NEMROCK) for post-operative loco-regional conformal irradiation after left Breast Conservative Surgery (BCS) with no previous care about brachial plexus, coronary artery or thyroid gland as our technique does not involve their routine delineation. And to identify the patients group in need for routine delineation of these ROs to avoid toxic doses to these ROs.

Methods: 25 patients previously treated at NEMROCK for post-operative loco-regional conformal irradiation after left BCS will be included in the study . Delineation of coronaries of the heart was done using the steps provided by University of Michigan Medical Center ,While the brachial plexus was delineated according to the RTOG & Thyroid gland was delineated manually by its gross appearance.

Results: Mid beam cut separation ranged from 16.3 cm to 28.7 cm with mean value ± SD (20.5 ± 3.0) while Central lung distance ranged from 1.1cm to 4.0 cm with mean value ± SD (2.4 ± 0.7) . Maximum heart distance mean value ± SD was 2.9 cm ± 1.1 cm.Conformity index mean value was 1.71 with 0.12 SD. The mean value of breast V_{45} was 82.12 % with 21.3 % SD. While the mean value of the heart V_{30} was 3.44 % with 3.59 % SD. And the mean value of the heart D_{mean} was 3.92 Gy ± 2.02 Gy SD. The mean value of the CA D_{max} was 41.9 Gy with 6.60 Gy SD. The mean value of the CA D_{mean} was 23.4 Gy with 10.9 Gy SD. The mean value of thyroid V_{40} was 32.7 % with 4.1 % SD while the mean value of thyroid D_{mean} was 20.6 Gy with 5.3 Gy SD. The brachial plexus D_{max} was 46.7 Gy with 3.0 Gy SD while the mean value of the brachial plexus D_{mean} was 33.7 Gy with 6.4 Gy SD. The maximum heart distance when it was less than 3 cm, the mean of the D_{mean} of the anterior descending coronary artery was 18.5 Gy with SD 10.9 Gy while when more than 3 cm the mean of the Dmean of the anterior descending coronary artery was 27.9 Gy with SD 9.1 Gy with a P-value 0.030 which is statistically significant. The heart V_{30} when it was less than 2% the mean of the D_{mean} of the anterior descending coronary artery was 16.9 Gy with SD 10.5 Gy while when more than 2% it was 29.5 Gy with SD 7.3 Gy with a P-value 0.005 which is statistically significant.

Conclusion: A significant dose may be received by non-routinely delineated organs at risk (of brachial plexus, coronary artery & thyroid gland) in post-operative loco regional radiotherapy of patients with left breast cancer after BCS. A significantly higher dose was received by left ADCA in cases with high MHD & heart V30 & borderline significance in obese cases where obesity is a known risk factor for developing coronary artery diseases.

Keywords: *Breast cancer, Radiotherapy, coronaries of the heart, brachial plexus .*

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List of Abbreviations

ADCA	**Anterior descending coronary artery**
APBI	accelerated partial breast irradiation
ASTRO	American Society of Radiation Oncology
BCS	Breast conserving surgery
BCT	Breast conserving therapy
CALGB	Cancer and Leukaemia Group B
CI	Conformity index
CIS	carcinoma in situ
CLD	Central lung distance
Co	Cobalt
COM	centre of mass
CT	computed tomography
CTV	Clinical Target Volume
CVS	Cavity visualization score
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DRRs	Digitally reconstructed radiographs
DVH	Dose volume histogram
EB-APBI	External beam - accelerated partial breast irradiation
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECG	Electrocardiogram
EIC	Extensive intraductal carcinoma
EORTC	European Organisation for Research and Treatment of Cancer
EPBI	External Partial Breast Irradiation
EPID	Electronic portal imaging devices
ER	Estrogen receptor
ESTRO	European Society of Radiation Oncology
GBT	Glandular breast tissue
GMI	Geographical miss index
GTV	Gross tumour volume
HDR	High dose rate
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio

ICRU	International Commission on Radiation Units
IDC	Invasive ductal carcinomas
ILC	Invasive lobular carcinoma
IMN	Internal Mammary Nodes
IMRT	Intensity modulated radiotherapy
IMs	Internal margins
IMV	Internal mammary vessels
IORT	Intraoperative radiotherapy
ITV	Internal target volume
JCRT	Joint Center for Radiation Therapy
LC	lumpectomy cavity
LCIS	lobular carcinoma in situ
LDR	Low Dose rate
LFR	Limited field radiation
LR	Local recurrence
LRR	Local recurrence rate
MBC	Mid beam cut separation
MHD	Maximum heart distance
MLC	Multi leaf collimator
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National cancer institute
NCT	Neoadjuvant chemotherapy
NSABP	National Surgical Adjuvant Breast and Bowel Project Experience
NTI	Normal tissue index
OAR	Organ at risk
PBI	Partial breast irradiation
PBT	Proton beam therapy
PD	Prescribed dose
PET	Positron emission tomography
PMRT	Post mastectomy radiation therapy
PRV	Planning at risk volume
PTV	Planning Target Volume
RT	radiotherapy

RTOG	Radiation Therapy Oncology Group
SCLN	Supraclavicular Lymph nodes
SIB	Simultaneous Integrated Boost
SLNB	Sentinel lymph node biopsy
SM	Setup margin
SPECT	Single photon emission computed tomography
SPSS	Statistical Package for the Social Science
TC	Technetium
Uk	United kingdom
UV	Ultraviolet
VBV	Visible boost volume
VEGF	Vascular endothelial growth factor
WBI	Whole breast irradiation
3DCRT	three dimensional conformal radiotherapy
4D	four-dimensional

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among females **(Jemal et al, 2011).**One of the very important factors in reducing the impact of breast cancer is effective loco regional therapy **(Donovan et al, 2006**)

However, studies of radiation toxicity in the treatment of breast cancer showed that the effects on normal tissues can constitute a significant clinical problem and increased cardiac mortality in particular may offset survival benefit of treatment **(*Gagliardi et al., 1992*)**.

The development of 3Dimensional Radiation Therapy Planning (DRTP) systems especially, the commercial availability of 3DRTP systems, led to widespread adoption of 3D planning. ***(Smith et al 1991 and Zink et al 1995)*** which makes accurate delineation of organs at risk and target volume(s) an essential step in modern radiation therapy. The organs at risk and target volume(s) were well defined in the International commission on radiation Units and Measurements ***(ICRU Report 50).***

From the year 2000, Oxford overview of radiotherapy trials confirmed that standard mortality ratio for heart disease was 1.62 times higher for irradiated patients than for the non-irradiated patients ***(Early Breast Cancer Trialists Collabrative Group 2000).***The same result continued to be evident in 2005 & 2010 analyses.

Lesions to the brachial plexus have to be considered a highly relevant late morbidity after radiotherapy of the supraclavicular lymph nodes in breast cancer patients**.** After an aggressive postoperative telecobalt therapy using high doses per fraction, serious morbidities increased progressively over the whole 34-year follow-up period. The incidence of brachial plexus lesions in patients irradiated for breast cancer was shown to increase with total radiation dose and dose per fraction ***(Johansson et al., 2002)***

As brachial plexus & coronary artery are considered radio-biologically serial organs, proper care about junction technique between the 2 tangential chest wall\breast fields with the supraclvicular portal and proper avoidance of coronary artery inclusion in field of irradiation are crucial.

In a small trial evaluating absorbed dose of thyroid gland during breast cancer irradiation ‘with supraclaviculor field”. The distal thyroid lobe and the isthmus received 2.9 ± 0.7 Gy (6.55± 1.56% of prescribed dose) and 3.69 ± 0.77 Gy (8.39± 1.76% of prescribed dose) respectively **(*Daoud J,et al 2004a*).**In another small trial included 37 breast cancer patients showed evidence of biological & may even clinical hypothyroidism ***(Daoud J,et al 2004b)***.

The three risk organs (ROs) namely brachial plexus, coronary artery & thyroid gland delineation did not gain much popularity in routine breast irradiation in spite of being of relevant clinical value regarding morbidity and even mortality.

AIM OF THE WORK

This a cross section planning study aiming at:-

- Evaluation of brachial plexus, coronary artery & thyroid gland doses in previously treated breast cancer cases at Kasr Alaini Center of Clinical Oncology & Nuclear Medicine (NEMROCK) for post-operative loco-regional conformal irradiation after left Breast Conservative Surgery (BCS) with no previous care about brachial plexus, coronary artery or thyroid gland as our technique does not involve their routine delineation.
- Identify the patients group in need for routine delineation of these ROs to avoid toxic doses to these ROs.

Patients and Methods:

Twenty five patients previously treated at NEMROCK for post-operative loco-regional conformal irradiation after left BCS will be included in the study fulfilling the following criteria:

1. Female gender.
2. Age 18-70 years.
3. Pathologically proven breast carcinoma after left BCS.
4. WHO performance status between 0 and 2.
5. Planning included supraclavicular nodal irradiation.

➢ ***Exclusion Criteria:***

1. Thin flat chest wall treated with electron beam.
2. Previously delineated brachial plexus, coronary artery or thyroid gland.
3. Axillary irradiation for any reason (e.g.: inadequate dissection).

Brachial plexus, coronary artery & thyroid gland will be delineated according to RTOG guidelines. After delineation, the following measures will be documented:

- Height, weight, surface area and body mass index
- Depth of supraclavicular nodes, depth of brachial plexus

Outcome parameters from Dose Volume Histogram (DVH) will be analyzed specially D_{max} & D_{mean} for both coronary artery & bracial plexus and Dmean & V40Gy to thyroid gland. A trial of co-relation between worse plan outcome regarding risk organs (ROs) and previously mentioned body measures will be conducted aiming to reach the patients group in need for routine delineation of these non routinely delineated ROs.

General outlines in Management of Breast Cancer

Introduction:

Statistics estimated almost 230,480 new cases of the invasive breast cancer occurring among women during 2011 and about 2,140 new cases in men. For the year 2012, almost 39,970 deaths due to breast cancer are expected along with 226,870 new cases **(Cancer Facts & Figures, 2011).**

Local Treatment options

A: Surgery

Breast cancer surgery has changed dramatically over the past 20 years. With the emergence of breast conserving surgery (BCS), many women now have the option of preserving a cosmetically acceptable breast without sacrificing survival **(Veronesi et al, 2002).**

BCS refers to surgical removal of the tumor without removing excessive amounts of normal breast tissue. The aim of BCS is to provide a cancer operation equivalent to mastectomy and a cosmetically acceptable breast, with a low rate of recurrence in the treated breast **(Fisher et al, 2002)**

All of the available data, including six randomized trials directly comparing BCS with mastectomy and an overview of completed trials, show equivalent survival with BCS as compared to mastectomy **(Early Breast Cancer Trialists' Collaborative Group, 2000).**

Breast conservation should be executed with caution in the following settings: very young women (<35 years), or extensive ductal carcinoma in situ (heralded by extensive micro calcifications) mounting up to one-quarter of the breast, particularly in women under 40 years of age. Prof WC Wood from Atlanta, GA, USA, addressed the impact of close/positive margins on breast cancer recurrence. The margin of normal tissue beyond the primary tumor that significantly reduces the risk of local recurrence remains undefined. Sufficient data are available to say that in the era of systemic therapy, excellent radiation therapy techniques, and boost doses when indicating no margin of normal breast tissue beyond the tumor has been shown to be clearly superior to a layer of cells between the ink and the tumor. However, a larger tumor size and aggressive biology are reason to be less confident that a single layer of cells at the point of histological study accurately represents a clear margin. As in all medical decisions, wise judgment must integrate all the known factors to reach the best recommendation. (**Highlights from the 13th St Gallen international breast conference 2013)**

Two different operations of the axilla can be preformed. Traditional axillary lymph node dissection or sentinel lymph node biopsy, the former has been the standard procedure for a long time with additional side effects such as sensory disturbances, lymphedema, pain, seroma formation, poorer cosmetics and infections **(Blanchard et al, 2003; Reitsamer et al, 2003)**. The sentinel node biopsy is by definition the first lymph node to receive lymphatic drainage from a tumor, the technique is considered to be standard procedure **(Bergqvist et al, 2008)**

Figure (1): Sentinel lymph node biopsy (SLNB) is standard care for patients with early-stage breast cancer.

B: Radiation therapy

Over the past 5 decades, radiotherapy (RT) has become an integral part of the combined modality management of breast cancer. Although its effect on local control has been long demonstrated, only recently has adjuvant RT been shown to have a significant effect on breast cancer mortality and overall survival .With a better understanding of the parameters predicting for local failure, such as tumor margins, the