Post-mastectomy radiotherapy in pT1-T2 N1breast cancer versus observation: Interim analysis results of pro-spective randomized study at NCI

Thesis

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Introduction

Post-mastectomy radiotherapy (PMRT) has been shown to improve loco-regional control &survival in breast cancer patients

Two prospective, randomized clinical trials have shown that when radiation therapy is appropriately utilized in patients with a high risk of persistent local-regional disease, the resulting improvement in loco-regional control contributes to improved survival **(Overgaard et al., 1997, 1999).**

This benefit however, was more evident in patients with stage III breast cancer, but impact on patients with stage II disease remained debatable, due to many criticisms to the above mentioned studies.

A retro-spective analysis of 238 patients with stage II (1-3 positive axillary nodes) were treated in the period from 1990-2004 at Massachusetts General Hospital with mastectomy was done.

Among those patients, 73 patients were treated by PMRT, while 165 patients were kept under observation.

Loco-regional recurrence (LRR) & disease free survival (DFS) were significantly improved by PMRT with LRR rates 0% at both 5 & 10 years versus 6% & 11% at 5 & 10 years respectively for those kept under follow up (P= 0.02). **(Shannon M. et al, 2009).**

High level evidence is awaited from results of SUPREMO trial to verify the real value of PMRT in stage II patients & until these results are available, we believe that all patients should be encouraged to participate in clinical trials.

Aim of the work

This is an interim analysis of a randomized prospective study included 99 patients with primary breast cancer stage II, treated at NCI in the period from 2004-2010, aiming at:

1-Evaluation of impact of PMRT in stages II breast cancer on overall survival, metastasis-free survival & recurrence-free survival.

2-Study of different prognostic factors which may affect outcome.

Epidemiology & Risk factors

The American Cancer Society estimates that 234,580 Americans are diagnosed with breast cancer with 40,030 deaths from disease in the year 2013 in the United States (***American Cancer Society, 2013***).Breast cancer is the most common malignancy in women in the United States and the second leading cause of cancer death after lung cancer.

The incidence of breast cancer is steadily rising in the United States over the past few decades, but breast cancer mortality appears to be declining (***Siegel R., et al, 2011***), suggesting a benefit from early detection & more effective treatment.

In Egypt, Breast cancer came as number 1 in ranking of malignant tumors constituting 30% of all female malignancies (***El Bolkainy N. et al, 2013***)

Risk factors for breast cancer can be divided into those that are modifiable and those that are not. Non-modifiable risk factors include gender, age, family history, age at menarche, age at menopause, race, and history of prior benign breast biopsy. Modifiable factors include parity, age at first live birth, mammographic density, breast-feeding, obesity and weight gain, exogenous hormones, radiation, alcohol consumption, and diet.

Aside from being female, age is the single most important breast cancer risk factor. According to the National Cancer Institute, the risk between ages 30 and 39 is 0.43% (1 in 233), 40 and 49 is 1.44% (1 in 69), 50 and 59 is 2.63% (1 in 38), and between 60 and 69 is 3.65% (1 in 27) based on probabilities for the whole population and not individual risk factors ***(Ries L. et al, 2008).***

A family history of breast cancer particularly in a first-degree relative is a significant risk factor, and the risk escalates with the number of relatives affected

and younger age at diagnosis. This pattern suggests an inherited genetic mutation that predisposes to the development of breast cancer. Approximately 5% to 10% of breast cancer patients have a familial form of the disease ***(Garber & Offit, 2005)***.Many of these cases contain an alteration in the breast cancer genes, *BRAC1* and *BRAC2*. More than 100 distinct mutations have been identified in high-risk families and it is not clear if all carry an equal cancer risk. Some populations have a higher likelihood of carrying germline mutations such as family members of Ashkenazi Jewish (Eastern European) heritage and families with multiple cases of breast and/or ovarian cancers. The estimated lifetime risk of developing a breast cancer is up to 80% (36% to 85%), with a near 40% risk of developing a contralateral breast cancer. The risk of developing an ovarian cancer is 40% in *BRCA1* carriers and 20% for *BRAC2* carriers ***(Ford D. et al, 1994 & Malone KE. et al., 1998)***. Genetic counseling should be offered to these patients including those of young age at diagnosis, two primary breast cancers (ipsilateral or contralateral) or with breast and ovarian cancer and male breast cancer ***(Gulati AP& Domchek SM., 2008)*** There are other rare familial genetic syndromes that display a predisposition to breast cancer, the most well-known are Li-Fraumeni syndrome with germline mutations in *TP53* and Cowden and Bannayan-Riley-Ruvalcaba syndrome due to *PTEN* mutations***(Davison TS et al,1998).***

The absolute risk of a contralateral breast cancer in women with a personal history is 0.5% to 1% per year or up to 10% during the 10 years following diagnosis ***(Fowble B et al.,2001 & Clarke M et al. , 2005)***.Biopsy-proven atypical proliferative disorders, including atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), and atypical ductal hyperplasia (ADH), may increase the risk by a range of fourfold to tenfold with a further increase in a patient with a family history ***(Smart CR et al., 1997 & Hartmann LC et al., 2005).***

Mammographic density is a strong independent risk factor with a fourfold to sixfold increase for postmenopausal women with high breast density compared with those with least dense breasts ***(Chen J et al., 2006)***. Breast density refers to the amount of white area (fibrous and glandular tissue) on a black (primarily fat tissue) mammogram. While methods of measurement and definitions of breast density vary among studies, women with breast densities of more than 60% to 75% have been found to have an increased risk of breast cancer ***(McCormack VA et al., 2006).*** Higher breast density is more common in Caucasian women and younger women and decreases during menopause. Hereditary factors may account for the majority of highly dense breasts. Several studies have identified genes that influence mammographic density ***(Vachon CM. et al, 2007.)*** Tamoxifen has been shown to decrease breast density especially during the first 18 months of treatment ***(Cuzick J. et al., 2004).***

The risk of developing breast cancer after exposure to ionizing radiation is dose and age dependent and has been demonstrated from data collected from the Japanese atomic bomb survivors and patients exposed to radiation for nonmalignant conditions, such as thymus enlargement, multiple chest fluoroscopies for tuberculosis, and mastitis examinations ***(Land CE, 1995)***. Particularly susceptible are adolescents who demonstrate the greatest risk of breast carcinogenesis over a lifetime. Secondary breast cancer has been described in young women who underwent mantle irradiation for Hodgkin disease with doses ranging from 20 to 44 Gy ***(Hoppe RT, 1997).*** In a multi-institutional review of 1380 adolescents treated before age 16 years old, a cumulative probability of breast cancer at age 40 years was 35%. This cohort of survivors had a risk of breast cancer 75 times higher than that of the general population ***(Bhatia S. et al., 1996).*** The risk of breast cancer significantly increases 15 to 30 years after treatment for

those women exposed between the ages of 10 to 30 years; however, relative risk begins to increase several years following radiation exposure ***(Travis LB. et sl., 2005)*** Current practice using lower doses of radiation and limited fields for Hodgkin disease may decrease the risk of breast cancer for these patients ***(Tinger A. et al., 1997).***

A moderate relative risk is associated with factors which affect circulating hormone levels such as delayed childbirth, nulliparity, early or late menarche and exogenous hormones. Body mass index (BMI) or postmenopausal obesity, has clearly been associated with breast cancer risk likely due to higher estradiol levels associated with aromatase in adipose tissue, which converts androgens to estradiol. A pooled analysis of prospective studies demonstrated a 30% higher risk in postmenopausal woman with a BMI more than 31 kg/m^2 compared with a BMI of less or equal to 20 kg/m^2 ***(Van den Brandt PA. et al., 2000).*** Weight gain at menopause is associated with increased risk; however, weight loss with maintenance is associated with a substantial lowering of breast cancer risk ***(Eliassen AH. et al., 2006).***

The use of combined estrogen and progestin hormone replacement therapy (HRT) also increases breast cancer risk. In the Women's Health Initiative (WHI), 16,688 postmenopausal women aged 50 to 79 years with an intact uterus were randomly assigned to receive conjugated equine estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) daily or placebo. When compared to placebo, the use of HRT was associated with a hazard ratio of 1.24 ($P < .001$) for breast cancer development ***(Chlebowski RT et al, 2003).*** The effects of HRT were noted after a relatively short duration of use. An excess of abnormal mammograms was observed after 1 year of HRT use and persisted throughout the study, and an increase in breast cancer incidence was noted after 2 years. The cancers occurring

in HRT users were larger and more likely to have nodal or distant metastases than those occurring in the placebo group (25.4% vs. 16%; P = .04), although they were of similar histology and grade. The findings of the WHI are supported by the results of the Million Women Study, an observational study of 1,084,110 women in the United Kingdom. In this study, current use of HRT was associated with a relative risk of breast cancer development of 1.66 (P <.001) and a relative risk of breast cancer death of 1.22 (P = .05) ***(Beral V., 2003).***

Alcohol consumption increases the risk of breast cancer. In the Oxford meta-analysis of 53 epidemiologic studies, 58,515 patients with breast cancer and 95,067 women without breast cancer demonstrated that two drinks a day (defined as 24 g of alcohol) can increase breast cancer risk by 21% ***(Hamajima N. et al.,2002)***. The relative risk of breast cancer was dose-dependent and increased with daily amount. Another analysis of 184,418 postmenopausal women showed that moderate intake of one to two drinks a day can increase risk by about 32% and three or more by 51% ***(Lew J. et al., 2008)***.

Environmental factors, pollutants, tobacco, nutrition and physical activity have not clearly been linked with breast cancer risk to date. Diet, nutrition, and physical activity are clearly interrelated with obesity and BMI but are difficult to dissect apart. Environmental pollutants and other environmental factors are an ongoing topic of investigation.

Two commonly used models to estimate an individual's breast cancer risk are the Gail and Claus models which heavily weigh family history with a combination of other risk factors ***(Claus EB. et al., 1994)***. A breast cancer risk assessment tool is available on the National Cancer Institute website based on the Gail model (cancer.gov/bcrisktool). Other decision models have been developed to estimate

the likelihood of a BRCA mutation include the BRCAPRO ***(Parmigiani et al.,1998)*** and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) ***(Antoniou AC. et al., 2004)***

Pathology

Infiltrating ductal carcinoma is the most common type of invasive breast cancer, accounting for 70 to 80 percent of invasive lesions. It is also termed infiltrating carcinoma of no special type or infiltrating carcinoma not otherwise specified (NOS).

Infiltrating ductal carcinomas are divided into three grades based upon a combination of architectural and cytological features, usually assessed utilizing a scoring system based on three parameters ***(Elston CW& Ellis IO 1991).***

Infiltrating lobular carcinomas are the second most common type of invasive breast cancer, accounting for about 5 to 10 percent of invasive lesions.

Incidence rates of lobular cancer are rising faster than the rates of ductal carcinoma in the United States, and postmenopausal hormone therapy may be more strongly related to lobular cancer risk than to ductal cancer risk.

- Infiltrating lobular carcinomas have a higher frequency of bilaterality and multicentricity than infiltrating ductal carcinomas ***(Orvieto E et al, 2008).***
- Infiltrating lobular carcinomas arise in older women and are larger and better differentiated tumors ***(Orvieto E et al, 2008)***. As a rule, invasive lobular carcinomas are ER-positive, with variant lesions showing occasional variable expression.
- While older series report a similar prognosis for infiltrating lobular cancers and invasive ductal lesions, more recent reports suggest that outcomes (at least in the short-term) may be more favorable for lobular cancers and improving over time ***(Cristofanilli M et al,2005).*** However, variants of

infiltrating lobular carcinoma exist, some of which have a poorer prognosis ***(Orvieto E et al, 2008).***

- As a group, invasive lobular carcinomas tend to metastasize later than invasive duct carcinomas and spread to unusual locations such as peritoneum, meninges, and the gastrointestinal tract ***(Ferlicot S et al, 2004).***

A number of other histologic types account for the remaining invasive breast cancers. These include tubular carcinoma, mucinous carcinoma, medullary carcinoma, invasive micropapillary carcinoma, metaplastic carcinoma, adenoid cystic carcinoma, and others.

Staging:

Table (1): American joint committee on cancer (AJCC) TNM staging system, 2010

Primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis(DCIS)	DCIS
Tis(LCIS)	LCIS
Tis(Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor $\leq$ 2 cm in diameter
T1mic	Tumor $\leq$ 1 mm in diameter
T1a	Tumor > 1 mm but $\leq$ 5 mm in greatest dimension
T1b	Tumor > 5mm but $\leq$ 1 cm in greatest dimension
T1c	Tumor > 1cm but $\leq$ 2 cm in greatest dimension
T2	Tumor > 2 cm but $\leq$ 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

T4a	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory breast cancer

Regional LN (N) –Clinical-	
Nx	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s), with or without level I, II axillary node involvement, or in clinically detected * ipsilateral internal mammary lymph node(s) and in the presence of clinically evident level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Pathologic (pN)	
pNx	Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically. *Note:* Isolated tumor cell clusters (ITCs) are defined as small clusters of cells ≤ 0.2 mm, or single tumor cells, or a cluster of < 200 cells in

	a single histologic cross-section; ITCs may be detected by routine histology or by immunohistochemical (IHC) methods; nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated
pN0 (i-)	No regional lymph node metastases histologically, negative IHC
pN0 (i+)	Malignant cells in regional lymph node(s) ≤ 0.2 mm (detected by hematoxylin-eosin [H&E] stain or IHC, including ITC)
pN0 (mol-)	No regional lymph node metastases histologically, negative molecular findings (reverse transcriptase polymerase chain reaction [RT-PCR])
pN0 (mol+)	Positive molecular findings (RT-PCR) but no regional lymph node metastases detected by histology or IHC
pN1 mic	Micrometastases (> 0.2 mm and/or > 200 cells, but none > 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes (at least 1 metastasis > 2.0 mm)
pN1b	Metastases in internal mammary nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4-9 axillary lymph nodes or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥ 10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected‡ ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive level I, II axillary lymph nodes; or in > 3 axillary lymph nodes and in internal mammary lymph nodes, with micrometastases or macrometastases detected by sentinel lymph