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ORIGINAL RESEARCH

Assessment of the Risk of Second Malignancies Following Radiotherapy in Patients of Breast Carcinoma at a Tertiary Care Hospital

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ABSTRACT

Background: Chemotherapy and radiation playa very crucial role in the treatment of breast cancers but also associated with risk for development of second primaries. Hence, the present study was conducted to assess the risk of second malignancies following radiotherapy in patients of breast carcinoma at a tertiary care hospital.

Materials &Methods:A total of 50 patients of locally advanced breast cancer (LABC) or metastatic cases(MBC)were taken. LABC were treated with neoadjuvant chemotherapy followed by radical surgery followed by radiation to loco-regional area with or without hormonal treatment and targeted therapy. Ovarian ablation therapywas also considered when required. MBC were treated with palliative radiation as per requirement to site either painful or prone to fracture and also with systemic chemotherapy alone or hormonal therapy alone depending on tumor burden. All patients were followed with a median time of 23 months. Complete demographic and clinical details of all the patients were recorded. Follow-up for second malignancies was mainly conducted through direct contact with the patients at regular visits at out-patient clinics. Follow-up was done and occurrence of second malignancies was recorded.

Results: A total of 50 patients were evaluated. The mean age of the patients was 51.5 years. Out of them 31 were locally advanced breast cancer (LABC)while 19 were metastatic cases(MBC). radiotherapy along was done in all 31 of the LABC patients and 16 patients of MBC, while chemotherapy received by all 46 patients at any part of treatment and hormonal therapy alone was done in4 patients. The median follow up post treatment was approximately 23 months. On follow up 5 cases in LABC category and one case in MBC category developed second primary malignancy. Amongst sites of second malignancies 4 have developed in contralateral breast and 2 in lung as large solitary mass.

Conclusion: The advancement of newer imaging techniques and facilities had led to early detection of breast cancer. And adjuvant therapy had increased the number of breast cancer survivors. However, further studies are recommended for better exploration of results. Although the absolute risk of development of second malignancies is low, we should consider that the benefits of breast cancer treatment significantly outweigh the risk of adverse effects.

Key words: Malignancies, Breast Cancer, Radiotherapy.

INTRODUCTION

Breast cancer ranks among the most frequently diagnosed cancers and is the fifth leading cause of cancer-related mortality, with an estimated 2.3 million new cases globally, as reported by GLOBOCAN 2020. The incidence of breast cancer fatalities is significantly higher—approximately 88%—in transitioning countries such as Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean, in contrast to transitioned regions including Australia/New Zealand,

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Western Europe, Northern America, and Northern Europe.[1]The effectiveness of screening programs is influenced by a variety of factors, including the availability of comprehensive guidance manuals, the creation and application of suitable diagnostic instruments, and the proper execution of the program alongside sufficient human resources. Additionally, the reliability of the screening test in minimizing the occurrence of false positives, as well as the avoidance of unnecessary biopsies and surgical procedures, is a critical consideration.[2- 4]

Radiation therapy is advised following lumpectomy to mitigate the likelihood of local recurrence. Whole breast radiotherapy encompasses the entire breast tissue, administering a standard dose ranging from 45 Gy to 50 Gy. This is typically succeeded by a boost of an additional 10 Gy to 16 Gy directed at the lumpectomy site. The conventional fractionation schedule is generally spread over a period of six weeks. In cases where the risk of recurrence is elevated, radiation therapy may also be applied to regional lymph nodes, with doses similarly ranging from 45 Gy to 50 Gy. This nodal irradiation may involve the supraclavicular, axillary, and internal mammary regions, contingent upon clinical indications. For patients who are 50 years or older, node-negative, and not undergoing chemotherapy, hypofractionation may be an option, particularly if the separation is 25 cm or less.[5- 7] Hence; the present study was conducted to assess risk of second malignancies following radiotherapy in patients of breast carcinoma at a tertiary care hospital.

MATERIALS & METHODS

A total of 50 patients of locally advanced breast cancer (LABC) or metastatic cases (MBC)were taken. LABC were treated with neoadjuvant chemotherapy followed by radical surgery followed by radiation to loco-regional area with or without hormonal treatment and targeted therapy. Ovarian ablation therapywas also considered when required. MBC were treated with palliative radiation as per requirement to site either painful or prone to fracture and also with systemic chemotherapy alone or hormonal therapy alone depending on tumor burden.

Radiation was planned with conventional or 3DCRT. in post operative setting 50 Gy in 25 fractions were given with 2 Gy per fraction, 5 days per week. In palliative cases, a dose of 30 Gy in 10 fractions was given to the respective site.Neoadjuvant chemotherapy schedule was followed for four cycles of Adriamycin and cyclophosphamide and 4 cycles of Taxane.In case of her2neu positivity, docetaxel, carboplatin and Herceptin based chemotherapy was planned.

As hormonal therapy tab tamoxifen or tab anastrozole was given depending upon the menopausal status.

All patients were followed with a median time of 24 months.Complete demographic and clinical details of all the patients were recorded. Follow-up for second malignancies was mainly conducted through direct contact with the patients at regular visits at out-patient clinics. On some visits information on health status was also verified by accompanying relatives. Follow-up was done and occurrence of second malignancies was recorded. All the results were recorded in Microsoft excel sheet and were subjected to statistical analysis using SPSS software.

RESULTS

A total of 50 patients were evaluated. The mean age of the patients was 51.5 years. Out of them 31 were locally advanced breast cancer (LABC)while 19 were metastatic cases(MBC). radiotherapy along was done in all 31 patients of the LABC patients and 16 patients of MBC, while chemotherapy received by all 46 patients at any part of treatment and hormonal therapy alone was done in 4 patients.

The median follow up post treatment was approximately 23 months. On follow up 5 cases in LABC category and one case in MBC category developed second primary malignancy. Amongst sites of second malignancies 4 have developed in contralateral breast and 2 in lung as large solitary mass.

Table 1: Distribution of patients according to TNM staging in LABC category

T/N/M	Number	Percentage
Stage IIIB/IIIC	31	62
Stage IV	19	38
Total	50	100

Table 2: Distribution of patients according to type of therapy

Type of therapy	Number	Percentage
Post op Radiotherapy	31	62
Palliative RT	16	32
Palliative chemotherapy	15	30
Adjuvant chemotherapy	31	62
Hormonal therapy in MBC	4	8

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Table 3: Incidence of second malignancies

Type of therapy	Second malignancies	
	Number	Percentage
LABC	5	10
MBC	1	2
Total	6	12

DISCUSSION

Breast cancer represents the most prevalent form of cancer and is the leading cause of cancer-related deaths among women globally. Each year, a significant number of patients receive this diagnosis and typically undergo surgical intervention, often followed by adjuvant radiation therapy. The adoption of radiation therapy has surged since randomized trials conducted in the 1980s demonstrated comparable outcomes for patients who underwent breast-conserving surgery combined with radiation therapy and those who received modified radical mastectomy. With improvements in early detection and treatment modalities, breast cancer is increasingly viewed as a manageable disease, resulting in a growing cohort of long-term survivors. Recent clinical trials have indicated a notable survival advantage associated with adjuvant radiotherapy for breast cancer. However, substantial evidence exists linking radiation exposure to the development of secondary cancers, particularly highlighted by epidemiological studies of atomic bomb survivors in Japan, as well as various investigations involving medically-exposed populations. Specifically, the irradiation of adjacent tissues during breast radiotherapy has been implicated in the emergence of second malignancies within those tissues. A second malignancy is defined as a new primary cancer occurring in an individual who has previously survived another cancer.[8-10]Most common second malignancy is contralateral breast followed by lung and esophagus.[11-12] Zhang W et al evaluated the effect that radiotherapy may have had on the subsequent risk of second malignancies, including the possible influences of age at treatment and menopausal status.This study indicated an increased relative risk of all second cancers combined following radiotherapy. The increased relative risk appeared five or more years after radiotherapy and appeared to be highest amongst women treated after the menopause. Increased relative risks were observed specifically for leukaemia and other solid cancers, excluding contralateral breast cancer. For contralateral breast cancer, no raised relative risk was observed during the period more than five years after radiotherapy. The study indicated a raised risk of second malignancies associated with radiotherapy for breast cancer, particularly for women treated after the menopause.[13]

Burt LM et al, in another previous study, assessed risks of second malignancies in breast cancer patients who received radiation therapy compared to patients who did not. There were 374,993 patients meeting the inclusion criteria, with 154,697 who received radiation therapy. With a median follow-up of 8.9 years, 13% of patients (49,867) developed a second malignancy. The rate of second malignancies was significantly greater than the endemic rate in breast cancer patients treated without radiation therapy, and with radiation therapy. Approximately 3.4% of second malignancies were attributable to radiation therapy. The increased risk of second malignancies in breast cancer patients treated with radiation therapy compared to those without was significant regardless of age at breast cancer diagnosis and more pronounced with longer latency periods. There was an increased risk of second malignancies for breast cancer patients both with and without radiation therapy compared to the general population.[14]The likelihood of developing second cancers is notably elevated in individuals who have previously undergone treatment for primary breast cancer. Specifically, the association between prior radiation therapy for breast cancer and the incidence of second radiation-induced malignancies has been well-documented across various studies. These malignancies include contralateral breast cancer, lung cancer, thyroid cancer, and leukemia. A meta-analysis encompassing 13 studies with a total of 762,468 breast cancer patients revealed that radiotherapy for breast cancer correlates with an increased risk of developing a second non-breast cancer more than five years post-radiation, with a relative risk (RR) of 1.12. The relative risks for lung cancer, esophageal cancer, and second sarcoma following radiotherapy were found to be 1.39, 1.53, and 2.53, respectively. Notably, the risk of second cancers escalates over time, peaking at 15 years or more following the initial diagnosis. Furthermore, a linear relationship has been established between the radiation dose administered to lung tissue and the subsequent risk of developing secondary lung cancer after breast cancer treatment. Consequently, the potential for the emergence of additional malignancies represents a significant concern for breast cancer survivors, necessitating the implementation of strategies to reduce radiation exposure to adjacent tissues.[15-16]

Many studieshave shown that tamoxifen causes endometrial cancers with significantly high risk for development of uterine sarcoma.[17-19] In case control study, tamoxifen was associated with an increased risk of endometrial cancer (OP=2.4;95% CI: 1.8-3.0).[20,21]The present study shows very early onset of

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second malignancy in comparison to other metanalysis and studies.[22] It may be due to by chance and need a more reliable sample size with longer follow up of at least more than 5 years to validate the data. Furthermore, BRCA study may be done in such kind of early presentation of second malignancies.

CONCLUSION

The advancement of newer imaging techniques and facilities had led to early detection of breast cancer. And adjuvant therapy had increased the number of breast cancer survivors.However, further studies are recommended for better exploration of results. Although the absolute risk of development of second malignancies is low, we should consider that the benefits of breast cancer treatment significantly outweigh the risk of adverse effects. Furthermore, the adverse effect of treatment in form of second malignancies may also reflect not only effect of treatment but also the effect of other multifactorial reasons such as etiological factors, environmental factors and lifestyle factors.

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