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COMPARATIVE EVALUATION OF SEQUENCIAL CHEMORADIATION VERSUS SANDWICH CHEMORADIATION IN LOCOREGIONALLY ADVANCED CARCINOMA BREAST POST MASTECTOMY

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ABSTRACT

BACKGROUND: Combination of chemotherapy and radiotherapy are well established in the treatment of carcinoma breast. Chemotherapy is generally recommended prior to radiotherapy but decisive data on the optimal sequence of these two modalities are sparse. This retrospective analysis aimed to assess the role of sequencing of chemoradiation in patients after mastectomy because of advanced locoregional breast cancer. **METHOD:** A total of 579 histopathologically proven eligible patients included in the study in the period of 2012 to 2017 and had locoregionally advanced breast cancer and received adjuvant chemotherapy and radiotherapy after modified radical mastectomy and axillary dissection. Out of these patients, 394 patients were treated sequentially i.e. chemotherapy followed by radiotherapy (SQ group), and 185 patients had a sandwich treatment i.e. radiotherapy sandwiched between chemotherapy (SW group). Radiotherapy was administered with dose of 50 Gy to thoracic wall and regional lymph nodes. Anthracycline and taxanes based chemotherapy were given to all patients. **RESULT:** The baseline parameters like age, grading, stage and hormonal receptor status were distributed homogeneously among the two groups. The parameter significantly imbalanced was nodal involvement among the two treatment groups. The 5 year overall survival (OS) and disease free survival (DFS) were 65.3% vs 52.8% (p=0.02, significant), and 58.3% vs 46.6% (p=0.08, NS), respectively for the SQ and SW group. There was no significant difference seen with respect to the 5 year locoregional or distant recurrence free survival among the two groups. On multivariate analyses, the sequence of chemoradiation had no significant impact on overall survival or disease free survival. Also, the acute and late toxicities showed no significant differences among the two groups. The grade III acute side effects were seen in 3.8% and 6.5% for the SQ and SW group, respectively with no significant difference. **CONCLUSION:** To conclude, no significant advantage can be stated for chemotherapy and radiation sequence in breast cancer treatment. This was confirmed in our retrospective study also in high risk breast cancer patients after modified radical mastectomy. However, the sequential chemoradiation approach is better and recommended according to the current treatment guidelines considering a lower toxicity.

KEYWORDS: Chemotherapy, radiotherapy, sequential, sandwich, breast, mastectomy.

BACKGROUND

Adjuvant radiation treatment and chemotherapy are gold standard established treatment in multidisciplinary management of carcinoma breast. As chemotherapy is systemic treatment and radiation treatment is localized treatment, so radiotherapy is used after adjuvant chemotherapy completion. Though, concluding study for a scientifically based decision on the current sequencing of the chemotherapy and radiotherapy is not very well established. The most of the published literature is related to early stage (stage 1 and 2) carcinoma breast. The various trials focusing on the sequencing of chemo-radiation in early stage carcinoma breast found no statistically significant difference in loco-regional recurrence and/or distant recurrence among the two groups.[1,2,3] However, in locoregionally advanced carcinoma breast (stage 3), who have been treated surgically with mastectomy and axillary clearance or modified radical mastectomy (MRM); very little data is available regarding sequencing of radiation and chemotherapy.[4] The objective of this retrospective study is to comparatively evaluate sequencing of radiation and chemotherapy in locoregionally advanced breast cancer patients post mastectomy / MRM.

MATERIAL AND METHODS

In this retrospective study, 579 locoregionally advanced carcinoma breast patients were treated with MRM and axillary dissection followed by adjuvant radiation and chemotherapy, during 2012 to 2017. Inclusion criteria were locoregionally advanced carcinoma breast treated with MRM and adjuvant radiation and chemotherapy. The patients were characterized by a pT3/pT4 tumor in 53%, involvement of axillary lymph nodes in 73.9% and multicentric carcinoma breast in 38.2% of patients. All patients underwent MRM and axillary clearance. Post MRM, all the patients were treated with adjuvant chemotherapy and radiotherapy.

The range of age of patients was 22 to 77 years with the median age of 51 years. The patients were allocated into two groups on the basis of the sequence of chemotherapy and radiation. Out of these, 394 patients (68%) were treated sequentially (SQ group) in which patients received chemotherapy first, then followed by radiation. In sandwich (SW) group, 185 patients (32%) received radiation in between chemotherapy. In SW group, patients received four cycles of anthracycline based chemotherapy followed by radiation, and then received four cycles of taxane based chemotherapy. In this study, 439 patients (75.8%) were positive for estrogen and / or progesterone receptors and they received hormonal therapy.

All the patients received radiation on Cobalt-60 machine with conventional tangential medial and lateral opposed fields to chest wall and locoregional nodal area. Radiation dose was 50 Gray (Gy) in 2 Gy per day fraction and 5 days a week. Written informed consent was taken from all the patients. The radiation induced acute and late toxicity included skin hyperpigmentation, skin erythema, telangiectasia, skin ulcers, subcutaneous fibrosis and arm edema. These were recorded as per RTOG (Radiation Therapy Oncology Group) toxicity criteria. The mean follow-up in the study was 43.6 months with range of 24-79 months. Table 1 summarizes the distribution of the categorical variables in the present study.

Table 1: Summary of the distribution of various categorical variables in the present study.

		All patients N=579	SQ group N=394	SW group N= 185	P value
Age n(%)	age≤50 age>50	220 (38%) 359 (62%)	158 (40.1%) 236 (59.9%)	62 (33.5%) 123 (66.5%)	0.1
pT n(%)	pT1/2 pT3/4	213 (36.8%) 366 (63.2%)	149 (37.8%) 245 (62.2%)	64 (34.6%) 121 (65.4%)	0.45
pN n(%)	pN0 pN1 pN2 pN3	78 (13.5%) 105 (18.1%) 267 (46.1%) 129 (22.3%)	59 (15%) 75 (19%) 187 (47.5%) 73 (18.5%)	19 (10.3%) 30 (16.2%) 80 (43.2%) 56 (30.3%)	0.03*
LVI n(%)	Yes No	180 (31.1%) 399 (68.9%)	126 (32%) 268 (68%)	54 (29.1%) 131 (70.9%)	0.5
G n(%)	G1 G2 G3	18 (3.1%) 234 (40.4%) 327 (56.5%)	11 (2.8%) 161 (40.9%) 222 (56.3%)	7 (3.8%) 73 (39.5%) 105 (56.7%)	0.4
ER and/or PR n(%)	Positive Negative	403 (69.6%) 176 (30.4%)	283 (71.8%) 111 (28.2%)	120 (64.9%) 65 (35.1%)	0.3

Statistical analysis

The continuous variables in the study were summarized with mean, maximum, minimum and standard deviation. Categorical data in the study were summarized with absolute and relative values. Cross tabulations were used to analyze the frequency distributions. The Pearson Chi Square test was used to assess the associations demonstrated by cross tabulations. The observation period was calculated from the day of surgery. Kaplan-Meier survival curves were used for overall survival (OS) and disease free survival (DFS). The log-rank test was used to compare DFS and OS curves between the groups. Multivariate Cox regression test was used to establish the independent prognostic factors with respect to OS and DFS. The statistically significant result was considered for p-value ≤ 0.05. All statistical analyses were carried out using the recent version SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

The baseline characteristics amongst the two groups were matched as shown in table 1. The two treatment groups were significantly imbalanced with respect to nodal involvement (pN). The 5 year overall survival (OS) and disease free survival (DFS) rate was 61.4% and 53.4% for all patients, respectively (table 2).

Table 2: Summary of 5 year overall survival and 5 year disease free survival in the two treatment Groups and With respect to various parameters also.

		5 year OS	p value	5 year DFS	p value
All patients		61.4%		53.4 %	
Chemoradiation	SQ SW	65.3% 52.8%	0.02*	58.3% 46.6%	0.08
Age (%)	age≤50 age>50	65.8% 53.3%	0.06	68.7% 56.3%	0.08
pT (%)	pT1/2 pT3/4	76.2% 57.7%	0.004*	71.8% 53.3%	0.008*
pN (%)	pN0 pN1 pN2-3	88.7% 71.6% 51.2%	0.2	81.3% 68.8% 46.7%	0.3
LVI (%)	Yes No	54.2% 72.7%	0.008*	52.3% 74.1%	0.001*
G (%)	G1 G2 G3	78.7% 67.8% 51.7%	0.4	76.9% 59.7% 49.5%	0.7
ER and/or PR (%)	Positive Negative	71.9% 58.6%	0.3	71.7% 60.1%	0.6

The 5-year OS and DFS rates were 65.3% and 58.3% in SQ group, and, 52.8% and 46.6% in SW group respectively (table 2). Although, the difference in 5 year OS was statistically signigicant (p=0.02) and 5 year DFS rates were not statistically significant in the two groups, in the univariate analysis, log-rank test (table 2, figure 1).

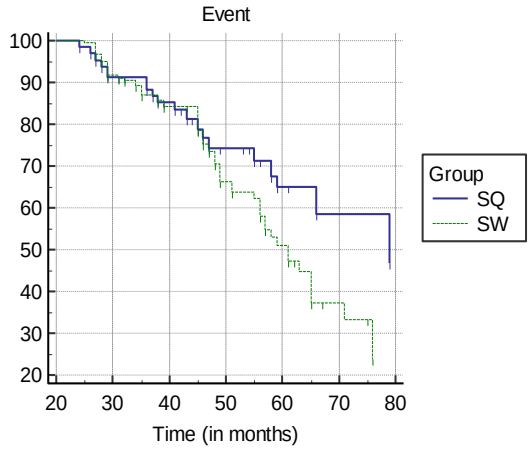

Figure 1: Kaplan-Meier survival curve depicting 5 year OS in Sequential group (SQ) and Sandwich group (SW).

The 5 year rates of LRFS (locoregional recurrence free survival) and DRFS (distant recurrence free survival) were 79.2% and 56.3% in SQ group, and 63.6% and 44.3% in SW group respectively, which were statistically significantly better in SQ group.

Statistically significant difference was visible in 5 year OS (p=0.004) and 5 year DFS (p=0.008) in the favour of early pT1/2 involement. Additionally, positive lymphovascular invasion was associated with decreased 5 year rates of OS and DFS with p=0.008 and p=0.001 respectively on univariate analysis. Moreover, the different variables like age, pN, grading and ER/PR receptor status had no significant effect on overall survival in univariate analyses (table 2). The grade III acute toxicity was seen in 3.8% and 6.5% for the SQ and SW group, respectively with no significant difference. On multivariate Cox regression analyses, the sequencing of radiation and chemotherapy in SQ and SW groups, depicted no statistically significant effect on 5 year OS (p = 0.06) and 5 year DFS (p = 0.08). Although SQ group had 5 year OS of 65.3% as compared to 52.8% in SW group, which was better in the SQ group.

DISCUSSION

The mainstay of treatment of post mastectomy patients of breast cancer is adjuvant chemotherapy and radiation. However, the optimal sequencing of adjuvant radiation and chemotherapy in carcinoma breast cancer patients remains unclear inspite of various studies.[5] Some retrospective studies demonstrate an increase in rates of local recurrence when radiation treatment was delayed. So this fact is in favour of sandwich group.[6-9] While, on the other hand, when radiation was given first, an increase in the rate of distant recurrence was reported. This was in favour of sequential chemoradiation.[10-12] A prospective, randomized trial by Recht et al in 1996 showed whether the chemotherapy followed by radiation or radiation followed by chemotherapy sequence is better.[2] The rates of local recurrence were 5% vs. 14% in favour of radiation first arm and a statistically significant higher 5 year locoregional or distant recurrence of 32% vs. 20% in chemotherapy first arm and radiation first arm respectively. The 5 year DRFS was 36% vs. 25% in the radiation first arm in comparison to the chemotherapy first arm, which was statistically significant.

Bellon et al in 2005 depicted results with a median follow up of 135 months and demonstrated no statistically significant difference in locoregional or

distant recurrence rates among two groups.[1] Although this trial was underpowered. Various other studies showed no statistically significant difference in survival rate or recurrence rate depending on the sequence of radiation and chemotherapy.[10,11,13] A loophole in assessment of role of sequencing of radiation and chemotherapy may be the use of some old regimen of chemotherapy like CMF, and this is not optimal in recent systemic treatment strategies.[14] Most of the studies refer to only early carcinoma breast which underwent organ sparing breast conserving surgery inspite of mastectomy. Hence, data demonstrating chemoradiation sequencing in high risk locoregionally advanced breast cancer patients post mastectomy are limited. The aim of this study was to evaluate the effect of sequencing of chemoradiation in locoregionally advanced breast cancer. In this retrospective study, 579 patients were included. All the patients were treated with mastectomy and axillary nodal dissection followed by adjuvant chemotherapy and radiation from 2012 to 2017.[15,16]

Anthracycline based or anthracyclines followed by taxane based chemotherapy regimens was administered according to the established literature.[17,18] The chemotherapy was administered either sequentially or as sandwich with radiation. In patients with positive lymphovascular invasion or close surgical margin, a sandwich regimen was preferred. Chemotherapy consisted of 6 courses of FEC (5-fluorouracil, epirubicin and cyclophosphamide) or 4 courses of AC (doxorubicin and cyclophosphamide) followed by 4 courses of taxane (paclitaxel).[19,20]

The rates of 5 year OS and 5 year DFS in all the patients were 61.4% and 53.4%, respectively. The corresponding 5 year LRFS and DRFS rates were 71.3% and 59.7% respectively in all patients. The prognostic factors of paramount importance for OS and DFS are the total number of positive axillary lymph nodes[21-24] and lymphovascular invasion (LVI).[25,26] In this study, 68.4 % patients were found to have ≥ 4 axillary lymph node involvement and LVI in 31.1% of patients. The OS and DFS regarding these prognostic factors in this study was comparable to that of the published literature. Ragaz et al showed 5 year rates of OS and DFS as 60% and 47% respectively in patients with 4 or more axillary lymph node involvement, which is comparable to this study.[27] However, Overgaard et al revealed better 5 year rates of OS and DFS as 72% and 61% respectively, but they had only 29.1% patients with ≥ 4 axillary lymph node involvement.[28] On univariate analysis, 5 year OS rates were 65.3% vs 52.8% and 5 year DFS rates were 58.3% vs 46.6%, in sequential and sandwich group respectively, which was worse in sandwich group.

In the multivariate analysis, no statistically significant effect on OS and DFS was seen. The 5 year rates of LRFS and DRFS were statistically significant in favour of sequential group ($p = 0.0005$ and $p = 0.02$, log-rank test). The 4 or more axillary lymph node involvement was seen in 66% and 73.5 % patients in SQ and SW group respectively. The acute and late toxicities in this study are in line with Markiewicz et al.[29] They analysed data of 1053 breast cancer patients regarding effects of sequencing of chemoradiation on cosmetic outcome and post surgical complications and they depicted no statistically significant difference. In the current modern era, anthracyclines and taxanes are gold standard in breast cancer treatment, especially in the patients with locoregionally advanced disease.[14,30,31] The concurrent anthracyclines have radiosensitizing property, but not recommended.[14,32-35]

Because of the variability in distribution of parameters, the results of any retrospective study must be analyzed very cautiously, specially in interpreting the prognostic importance of different parameters. The current study consolidates the use of sequential chemoradiation regimen as state of the art treatment in locoregionally advanced carcinoma breast.[36-38]

CONCLUSION

To conclude, sequential chemoradiation is associated with better five year overall survival and disease free survival in locoregionally advanced carcinoma breast. On further subgroup analysis, better five year rates of overall survival and disease free survival were noted in early tumor grouping and negative lymphovascular invasion, which establish these two parameters as prognostic factors in breast cancer treatment. Nodal involvement with 4 or more lymph nodes was also a bad prognostic factor. Sequential approach was associated with lower toxicity also. Based on these findings, radiotherapy should follow chemotherapy as a sequential approach.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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