

EARLY SURGICAL OUTCOMES OF OPERABLE BREAST CANCER PATIENTS BASED ON MOLECULAR SUBTYPING – A SINGLE-CENTRE STUDYVISHAL VERMA¹, RAVISHEKAR N HIREMATH², SHARANJIT SINGH BASRA¹, PRANAV CHANDRAKANT KULKARNI¹, SANDHYA GHODKE³¹Department of Surgery, AFMS, New Delhi, India. ²Department of Community Medicine, AFMS, New Delhi, India. ³Department of Anaesthesiology, Rainbow Children's Hospital, Bengaluru, Karnataka, India. Email: wishmamc@yahoo.com

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ABSTRACT

Objectives: The aim of the study was to assess patients belonging to four main molecular subtypes (Luminal A, Luminal B, HER2 neu positive and Triple negative) and their treatment plans with a view to compare their early surgical complications and the final outcomes specific to the surgical procedure adopted and molecular subtype.

Methods: A Cross-sectional observational study was carried out in central UP for a two-year period. Data Collection was carried out from the patients, and diagnostic confirmation was done to rule out any exclusion criteria. Clinical staging was done using the standard TNM criteria. All the specimens were subjected to immune-histochemical evaluation for surrogate molecular subtyping to see later the early surgical outcomes.

Results: Mean age ranged from 47.57±9.57 (Group III) to 50.67±8.08 (Group II) years and BMI ranged from 23.71 (Group IV) to 26.38 kg/m² (Group II). Neoadjuvant chemotherapy use was reported in 15.6% of Luminal A group, 33.3% of Luminal B group, 40% of Her2 negative and 52.2% of Triple negative group cases. Statistically, there was a significant difference among groups with respect to use of neoadjuvant chemotherapy. Breast conservation therapy was the preferred surgical intervention in majority of cases with Luminal A (60%) and Luminal B subtype (66.7%) whereas MRM was preferred in 54.3% of Her2 negative and 65.2% of Triple negative cases. MRM was performed in 36% of Luminal A cases. Primary surgical intervention failure (BCS) was seen in 1 (4%) case with Luminal A subtype. In this patient, mastectomy was performed as the corrective measure. Surgical site infection was noted in 1 (4%) case in Luminal A group only. Seroma formation was noted in 4 (16%) of Luminal A, 8 (22.9%) of Her2 negative and 2 (8.7%) of Triple negative patients. No case of flap necrosis was noted. Follow-up duration ranged from 15 days to 36 months. Median duration of follow-up was 6 months. No mortality was noticed in any group.

Conclusion: Different surgical management strategies suggested that breast conservative surgery was more feasible in Luminal A cases whereas MRM was the preferred mode of surgery in other molecular subtypes. Within the limitations of short duration of follow-up, there was no significant difference among different molecular subtypes with respect to late complications and survival. Further studies with longer duration of follow-up and larger sample size are recommended.

Keywords: Surgical outcomes, Operable breast cancer, Molecular subtyping.

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INTRODUCTION

Cancer of the breast in women is a major universal health burden. It is the most common malignancy among women in both developed and developing countries. In 2018, out of the total global annual malignancy burden, 25.4% of cancers are of breast [1]. As per the GLOBOCAN 2020 estimates, in 2020, there were 2.3 million women diagnosed with breast cancer and 68500 deaths globally, and by the end of 2020, total number of women alive who were diagnosed with breast cancer in the past 5 year was estimated to be 7.8 million and hence made breast cancer, the world's most prevalent cancer; however, age standardized breast cancer mortality in high income countries dropped by 40% from 1980s till 2020 [2]. Breast cancer is not only the commonest malignancy but also the second leading cause of cancer related death among women [2]. However, overall survival rate of breast cancer is estimated to be above 90% for all stages. As per the SEER 13 (Surveillance Epidemiology End results), data on US Population estimated new breast cancer cases and deaths by the end of 2021 would be 2,81,550 and 43,600, respectively [3]. No special type (NST) formerly known as invasive ductal carcinoma not otherwise specified or invasive ductal carcinoma of no special type) which comprises of the 75% of breast cancers in which no specific histological types identified and rather it is diagnosis of exclusion [4]. Clinical decision-making

based on the histological typing is having limited value so in due course of time, additional standards such as tumor grade, tumor size, lymph node status, and vascular invasion were added which have been shown to be required for breast cancer prognostication and treatment decision-making [5-7]; however, the predictive and prognostic power of these parameters is also inadequate, and the clinical course of breast cancer patients varies immensely even when tumors of the same histologic grade are considered. Recent advancement in the diagnostic armamentarium like immunohistochemistry and *in situ* hybridization has identified the breast cancers with variable estrogen and progesterone receptor expression and her 2 neu expression which have proven to be useful predictive markers for the management of breast cancer patients. Keeping this background in mind, in our single institution study, patients belonging to four main molecular subtypes (Luminal A, Luminal B, HER2 neu positive, and Triple negative) and their treatment plans were studied with a view to compare their early surgical complications and the final outcomes specific to the surgical procedure adopted and molecular subtype.

METHODS**Study type**

A Cross-sectional observational study

Study Place

Tertiary care center in central UP.

Study Duration

Two-year period

Inclusion Criteria

Early and locally advanced breast cancer with age bracket between 18-75 years and willing to participate in the study.

Exclusion Criteria

Metastatic cancer, Inoperable tumor and who are medically unfit

Data Collection

After obtaining informed consent from the patients, diagnostic confirmation to rule out any exclusion criteria was performed. Patient's age, gender and duration of disease was noted. Anthropometric measurements were taken, and BMI was calculated. Clinical staging was done using the standard TNM criteria. All the specimen were subjected to immune-histochemical evaluation for surrogate molecular subtyping to see later the early surgical outcomes.

Data Analysis

Data was entered in excel sheet and statistical analysis was done using SPSS version 15.0 or above.

RESULTS

Group I to IV constituted four different molecular profile to which study participants belonged (Table 1). Majority cases belonged to Luminal A variety (32 cases) and HER2 positive (35) with mean age ranging from 47.57±9.57 (Group III) to 50.67±8.08 (Group II) years, BMI ranged from 23.71 (Group IV) to 26.38 kg/m² (Group II). Clinical Nodal involvement was seen in 21.9% of Group I (6 N1, 1 N3), 54.3% of Group III (all N1) and 52.2% of Group IV (all N1) cases (Table 1). None of the cases in

Group II had nodal involvement. Pathological Nodal involvement was seen in 16.1% of Group I (4 PN1, 1 PN3), 42.4% of Group III (13 PN1, 1 PN2) and 50% of Group IV (9 PN1, 1 PN2, 1 PN3) cases.

Neoadjuvant chemotherapy use was reported in 15.6% of Group I, 33.3% of Group II, 40% of Group III, and 52.2% of Group IV cases. Statistically, there was a significant difference among groups with respect to use of neoadjuvant chemotherapy (Table 2).

Breast conservation surgery (CS) was the preferred treatment modality in Groups I and II whereas modified radical mastectomy (MRM) was the preferred modality in majority of patients in Groups III and IV. In Group I, details of surgical intervention were available in 25 patients, of these 15 (60%) underwent breast conservation surgery (BCS) and 9 (36%) underwent MRM. In 1 (4%) patient, breast conservation surgery was attempted as preferred modality but later on mastectomy had to be performed. Similarly, the details of surgical intervention of Group II, III, and IV are shown in Table 2. Statistically, there was a significant difference among groups with respect to mode of surgical intervention ($p < 0.001$).

With regards to complications, surgical site infection was noted in 1 (4%) case in Group I only. Seroma formation was noted in 4 (16%) of Group I, 8 (22.9%) of Group III, and 2 (8.7%) of Group IV patients. No case of flap necrosis was noticed in any group. Statistically, there was no significant difference among groups with respect to complications ($p > 0.05$) (Table 2).

All the patients were alive till last followup. Duration of follow-up ranged from 15 days to 36 months. Median duration of follow-up was 6 months. Mean duration of follow-up ranged from 5.67±1.53 months (Group II) to 8.13±5.50 months (Group IV) (Fig. 1). Statistically, there was no significant difference among different groups with respect to duration of follow-up. None of the case expired during the entire period of follow-up. Recurrence/primary intervention failure was noticed in 1 (4%) case of Group I in whom the primary surgical intervention was BCS; however, mastectomy had to be performed as rescue. Statistically, no significant difference among groups was observed with respect to outcome (Table 2).

DISCUSSION

In the present study, the proportion of patients who had received neoadjuvant chemotherapy was significantly higher in Her2/neu positive and Triple negative subtypes as compared to those in Luminal

Table 1: Distribution of cases according to molecular profile

Serial number	Group	Molecular profile	Number of cases (%)
1	I	Luminal A	32 (34.4)
2	II	Luminal B	3 (3.2)
3	III	HER2 positive	35 (37.6)
4	IV	Triple negative	23 (24.7)

HER2: Human epidermal growth factor receptor 2

Table 2: Comparison of use of neoadjuvant chemotherapy, surgical intervention, complications, and outcome

Neoadjuvant chemotherapy	Group I (n=32), n (%)	Group II (n=3), n (%)	Group III (n=35), n (%)	Group IV (n=23), n (%)	Statistical significance
Yes	5 (15.6)	1 (33.3)	14 (40.0)	12 (52.2)	$\chi^2=8.71$ (df=3); $p=0.033$
No	27 (84.4)	2 (66.7)	21 (60.0)	11 (47.8)	
Type of surgical intervention	Group I (n=25), n (%)	Group II (n=3), n (%)	Group III (n=35), n (%)	Group IV (n=23), n (%)	Statistical significance
BCS	15 (60.0)	2 (66.7)	16 (45.7)	8 (34.8)	$\chi^2=26.9$ (df=6); $p < 0.001$
MRM	9 (36.0)	1 (33.3)	19 (54.3)	15 (65.2)	
BCS f/b mastectomy	1 (4.0)	0	0	0	
Complications	Group I (n=25), n (%)	Group II (n=3), n (%)	Group III (n=35), n (%)	Group IV (n=23), n (%)	Statistical significance
Surgical site infection	1 (4)	0	0	0	$\chi^2=2.94$ $p=0.496$
Seroma formation	4 (16)	0	8 (22.9)	2 (8.7)	$\chi^2=3.02$ $p=0.388$
Outcome	Group I (n=25), n (%)	Group II (n=3), n (%)	Group III (n=35), n (%)	Group IV (n=23), n (%)	Statistical significance
Mortality	0	0	0	0	-
Recurrence/primary intervention failure	1 (4)	0	0	0	$\chi^2=2.94$ $p=0.496$

BCS: Breast conservation surgery, MRM: Modified radical mastectomy

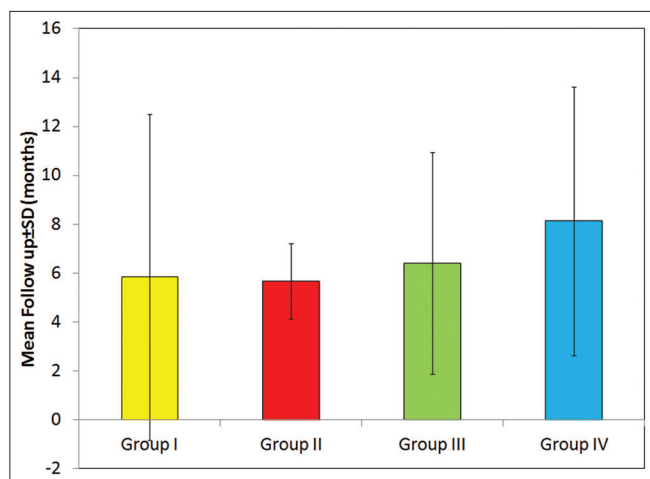


Fig. 1: Mean duration of follow-up (months) among different groups

A subtype. This could be probably owing to the fact that being in larger grades, neoadjuvant chemotherapy was used in larger proportion of patients of Her2/neu positive and Triple negative subtypes to downgrade the patient before surgery. This finding emphasizes the fact that had this neoadjuvant chemotherapy not been received by the patients, then probably the differences in clinical grade of patients in different molecular subtypes might have been more vocal and pronounced.

In the present study, a significant association between molecular subtyping and surgical management strategy was observed. Significantly higher proportion of patients with luminal A and luminal B subtypes underwent conservative and less radical intervention as compared to those with her2/neu positive and triple negative cancer. This decision was in accordance with the clinical and histopathological profile of the patients and as per the existing practice guidelines [8,9]. Findings in the literature have also shown that after mastectomy, luminal B, luminal-HER2, HER2-enriched, and basal subtypes were all associated with an increased risk of local, regional relapse, and poor outcomes [10-13], and hence, it is not a suitable choice for this purpose. In the present study, the management strategy, primarily based on clinical profile itself, was selective and its impact was further noticed.

In the present study, complications like surgical site infection were rare and observed in only one patient with luminal A subtype. One of the reasons for this low incidence of SSI in present study could be a high degree of sanitation, compulsory sanitation, and maintenance of discipline in sterilizing the hospital environment at regular intervals. As a matter of fact, the surgical site infection rates are dependent more on the hospital environment and factors other than choice of type of procedure and molecular subtypes. In the present study as a whole, the SSI rate was 1.1%. In the literature, these rates have been reported to vary substantially and range from 0.8% to 26% [14,15].

Other complications like seroma formation were also noticed in 0–22.9% patients in different groups but did not vary significantly for different molecular subtypes. Considering the fact that for different molecular subtypes, the surgical management strategy varied significantly coupled with state-of-the-art infrastructure and quality of care, it might be inferred that use of appropriate intervention averted the complication rate and as such ensured a better outcome. As a matter of fact, a better health-care environment can limit the generally encountered complications like flap necrosis too. In the present study, no case of flap necrosis was noted.

In the present study, the follow-up period ranged from 6 months to 36 months. Mean follow-up time was 6.62±5.54 months. Mean

follow-up time ranged from 5.67±4.53 months to 8.13±5.50 months. This follow-up time is relatively a much shorter period to evaluate the outcome. Comparative evaluation of outcome in terms of survival requires a much longer time. There are series that have a median follow-up duration of more than 10 years [10] that have commented on the survival and recurrence rate among different molecular subtypes. From that point of view in present study, the follow-up period was much shorter and as such no case of recurrence or mortality was noted. Although studies with shorter duration of follow-up [11] have also been able to differentiate among different molecular subtypes for the purpose of survival and recurrence rate; however, even those studies have a much longer median follow-up period (33 months) than the present study. As such we did not come across any study with such shorter period of follow-up commenting on the outcome in terms of survival and recurrence among different molecular subtypes.

Thus, within the limitations of the present study, as such we found that clinical and pathological profile of different molecular subtypes varied substantially and based on this profile, the choice of surgical intervention was almost appropriate and did not result in any untoward complication or outcome difference for different molecular subtypes. Considering the short duration of follow-up, it is difficult to come at a conclusion regarding relationship between molecular subtype, surgical intervention approach, and outcome in terms of survival and recurrence. Nonetheless, the present study at least showed that choice of surgical management approach generally based on clinicopathological profile of patient corresponds with the molecular subtypes; however, given the fact that management approach is not directly in agreement with molecular subtyping, it would be interesting to note whether a management approach based on luminal subtyping can help in improving the outcome. For this purpose, a larger study with longer duration of follow-up is recommended.

CONCLUSION

Neoadjuvant chemotherapy use was reported in 15.6% of Luminal A group, 33.3% of Luminal B group, 40% of Her2 negative and 52.2% of Triple negative group cases. Statistically, there was a significant difference among groups with respect to use of neoadjuvant chemotherapy. Breast conservation therapy was the preferred surgical intervention in majority of cases with Luminal A (60%) and Luminal B subtype (66.7%) whereas MRM was preferred in 54.3% of Her2 negative and 65.2% of Triple negative cases. MRM was performed in 36% of Luminal A cases. Different surgical management strategies suggested that breast conservative surgery was more feasible in Luminal A cases whereas MRM was the preferred mode of surgery in other molecular subtypes. Within the limitations of short duration of follow-up, there was no significant difference among different molecular subtypes with respect to late complications and survival. Further studies with longer duration of follow-up and larger sample size are recommended.

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AUTHORS CONTRIBUTION

All authors have contributed to preparation of manuscript.

CONFLICTS OF INTEREST

Nil.

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