GENERAL SIR JOHN KOTELAWALA DEFENCE UNIVERSITY (KDU)

8th INTERNATIONAL RESEARCH CONFERENCE

Inculcating Professionalism for National Development

27 – 28 August 2015

Proceedings

Medicine

General Sir John Kotelawala Defence University
Ratmalana 10390
Sri Lanka
www.kdu.ac.lk

Predictive Factors of Breast Cancer Specific Survival of Patients Who Received Neoadjuvant Chemotherapy

HH Peiris[1#], LKB Mudduwa[2], NI Thalagala[3], KAPW Jayatilake[4],
U Ekanayake[5] and J Horadugoda[5]

[1]*Allied Health Sciences Degree Programme, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka*
[2]*Department of Pathology, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka*
[3]*Family Health Bureau, Ministry of Health, Colombo, Sri Lanka*
[4] *Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka*
[5]*Oncology Unit, Teaching Hospital Karapitiya, Galle, Sri Lanka*
[#]bbharshi@yahoo.com

Abstract— *Neoadjuvant Chemotherapy (NAC) is a safe and effective therapeutic approach for larger primary and locally advanced breast cancer. The objective of this study was to determine the factors predicting the survival of breast cancer patients who received NAC and underwent surgical treatment.This retrospective study included all breast cancer patients who received NAC and had sought the services of the Immunohistochemistry Laboratory in the Faculty of Medicine, Galle from May 2006 to December 2012. Data was collected through follow up visits, clinic and laboratory records. Degree of down staging was estimated using clinical and pathological stage of the tumour. Breast Cancer Specific Survival (BCSS) and Recurrence Free Survival (RFS) rates were estimated using Kaplan-Meier model. Cox-regression model was used for multivariate analysis. This study comprised of 164 patients. Five year BCSS of patients who received NAC was 63% and RFS was 59%. Only 2% had pathological complete response following NAC. Nodal down-staging (19%) was less prevalent than tumour down-staging (80%). Down-staging by overall TNM group was seen in 71.4%. There was no statistically significant difference in RFS or BCSS in terms of degree of down-staging. In the multivariate analysis, the presence of lympho-vascular invasion(LVI), negative progesterone receptor(PR) status and pathological stage following NAC were found to affect the BCSS ($p<0.05$) while the initial clinical stage did not have an effect ($p>0.05$).This study indicates that degree of down-staging by NAC does not influence the RFS or BCSS. The presence of LVI, expression of PR and the final pathological stage predict the BCSS of patients who received NAC but not the initial clinical stage.*

Keywords— Neoadjuvant Chemotherapy, Down Staging, Survival of Breast Cancer

I. INTRODUCTION

Breast cancer is the commonest cancer among females in Sri Lanka. It is a heterogeneous disease and treated using three principal treatment modalities; surgery, systemic therapy and radiation therapy. Traditionally, systemic therapy is administered to breast cancer patients after surgery. However, the breast cancer patients with advanced disease receive systemic chemotherapy prior to the surgery. It is known as neoadjuvant chemotherapy (NAC).

NAC is a safe and effective therapeutic approach for larger primary and locally advanced breast cancer. The purpose of NAC is to down-stage the tumour reducing the extent of subsequent surgery and to treat at the earliest possible moment for micro-metastases (Nagao et al., 2012; Schott and Hayes, 2012). However, the effect of NAC on the tumour burden and hence the survival following the surgical treatment is controversial. Hence, the objective of this study was to determine the factors predicting the survival of breast cancer patients who received NAC and underwent surgical treatment.

II. METHODOLOGY

A. Study design

This was a retrospective study which included all breast cancer patients who received NAC and had sought the services of the Immunohistochemistry laboratory in the Department of Pathology, Faculty of Medicine, University of Ruhuna, Galle, from May 2006 to December 2012.

B. Data collection

Histopathological data were retrieved from the laboratory records available at the Department of Pathology. The patients' clinic files were perused to collect data on treatment and radiological investigations. The study subjects have been staged by the clinician before any form of treatment was started based on the physical examination. The clinical staging details were retrieved from the clinic files. The pathological TNM staging was done based on the findings in the histopathology report.

The degree of down staging by tumour size (Table 1), lymph-node stage (Table 2) and overall TNM stage (Table 3) were defined separately using the difference between the pre treatment clinical findings and final pathological findings.

The complete down stage of invasive tumour in breast and axillary lymph nodes was considered pathologic complete response (pCR) (Carey et al, 2005).

C. Follow up and outcomes

After enrolling, the study subjects were followed up for recurrence or death at six months intervals. The study ended on 31st December 2013. The actual minimum follow up period was 12 months. Ninety three percent of patients were followed up for 24 months, 65.8% for 36 months, 44.5% for 48 months and 32.9% for five or more years.

Table 1. Degree of down staging by tumour size

Clinical tumour stage	Pathological tumour stage	Degree of down staging
T4	T0	4
	T1	3
	T2	2
	T3	1
	T4	0
T3	T0	3
	T1	2
	T2	1
	T3	0
T2	T0	2
	T1	1
	T2	0

T1=Tumour size ≤20mm, T2= Tumour size 20-50mm, T3=Tumour size >50mm, T4=tumour of any size with distinct extension to the chest wall/skin

Breast cancer specific survival (BCSS) of all NAC received patients were calculated from the date of diagnosis of breast cancer to the last follow up date or the event; death due to breast cancer. Deaths from other causes or from unknown causes were censored to the date of death.

Recurrence free survival (RFS) was calculated from the date of the first NAC cycle received to the radiological / histopathological confirmation of the development of recurrence (loco-regional or distant metastasis whichever occurred first). Patients who had died without any recurrence were censored to the date of death.

The five year BCSS and RFS were estimated using the Kaplan-Meier model and the survival curves were compared with the log-rank test. A Cox proportional hazard model with backward stepwise exclusion of factors was performed to identify the factors influencing the survival.

Table 2. Degree of down staging by lymph-node stage

Clinical LN stage	Pathological LN stage	Degree of down staging
3	0	3
	1	2
	2	1
	3	0
2	0	2
	1	1
	2	0
1	0	1
	1	0

0=No positive lymph nodes, 1=1-3 positive lymph nodes, 2=4-9 positive lymph nodes, 3= ≥10 positive lymph nodes

III. RESULTS

This study comprised 164 female patients. The mean age was 52.5 (SD±10.8). The median follow up time was 32.4 months. Out of the total, 29% developed recurrences, 1% had contra-lateral breast cancer and 27% died due to breast cancer. The five year BCSS of patients who received NAC was 63% and RFS was 59%.

The NAC regimens given to the study subjects were AC (Adriamycin + Cyclophosphamide -19 patients), FEC (5-fluorouracil + Epirubicin + Cyclophosphamide -37), CMF (Cyclophosphamide + Methotrexate + 5-fluorouracil – 6), taxol (5) and combinations of taxol with AC (45) or FEC (34). There were 18 patients who had not received recommended complete NAC regimen. There was no statistically significant difference between the BCSS curves of taxol received and not received groups (p=0.56).

Only 2% (3/138) had pathologic complete response (2 patients $-T_0N_0$; 1 patient $-T_{(DCIS)2}N_0$) . They did not have recurrences and survived beyond 5 years following NAC.

A 13.5% of patients (16/118) had complete axillary down staging and only 2.5% (3/118) had complete invasive tumour down staging. None had complete tumour down staging with partial axillary down staging. Out of all patients who had complete axillary down staging, three patients had recurrences and died within the five years following NAC; one patient had a recurrence within the

five years following NAC and died after five years (at 64 months).

Table 3. Degree of down staging by TNM stage

Clinical stage	Pathological stage	Degree of down staging
Stage IV	Stage 0	7
	Stage I	6
	Stage IIA	5
	Stage IIB	4
	Stage IIIA	3
	Stage IIIB	2
	Stage IIIC	1
	Stage IV	0
Stage IIIC	Stage 0	6
	Stage I	5
	Stage IIA	4
	Stage IIB	3
	Stage IIIA	2
	Stage IIIB	1
	Stage IIIC	0
Stage IIIB	Stage 0	5
	Stage I	4
	Stage IIA	3
	Stage IIB	2
	Stage IIIA	1
	Stage IIIB	0
Stage IIIA	Stage 0	4
	Stage I	3
	Stage IIA	2
	Stage IIB	1
	Stage IIIA	0
Stage IIB	Stage 0	3
	Stage I	2
	Stage IIA	1
	Stage IIB	0

Nineteen per cent of patients (22/118) had nodal down staging (degree of down staging; 1=16%, 2=2%, 3= 1%) while 80% (94/118) had tumour down staging (degree of down staging; 1=10%, 2=40%, 3=28%, 4=2%). Nodal down staging was less prevalent than tumour down staging.

Down-staging by overall TNM group was seen in 71.4% (85/119) of the patients (degree of down staging; 1=18%, 2=16%, 3=17%, 4=3%, 5=16%, 6=1%).

There was no statistically significant difference in RFS or BCSS in terms of degree of down-staging.

The univariate analysis revealed that Nottingham grade *(p=0.039)*, lympho-vascular invasion (LVI) *(p=0.014)*, lymph-node stage *(p=0.008)*, Nottingham Prognostic Index *(p=0.012)*, pathological stage *(p=.0.001)*, clinical stage *(p=0.001)*, expression of oestrogen receptors (ER) *(p=.042)*, progesterone receptors (PR) *(p=0.001)* and Her2 *(p=.0.019)* and triple negative status*(p=0.041)* significantly affected the BCSS of patients who received NAC. All the said factors were used for multivariate analysis.

The presence of LVI, negative PR status and pathological stage following NAC were found to affect the BCSS ($p<0.05$) while initial clinical stage did not have an effect ($p>0.05$).

IV. DISCUSSION

The aim of this study was to determine the factors predicting the survival of breast cancer patients who received NAC and underwent surgical treatment. NAC is given to breast cancer patients mainly for the purpose of reducing the tumour size (down-staging the tumour) facilitating the subsequent conservative surgery (Schott and Hayes, 2012).

In the current study 13.5% of patients had complete axillary down staging, 2.5% had complete tumour down staging. Although the prevalence of some degree of nodal down staging is less, complete nodal down staging was more prevalent than complete tumour down staging. Rouzier and colleagues found that 23% had complete axillary down staging after the NAC in their study population. However, in our study cohort the prevalence of complete axillary down staging was less compared to the data published by Rouzier (Rouzier et al, 2002). Four patients (out of 16) had recurrences within the five years following NAC although they had complete axillary down stage, probably because they had residual tumour in the breast.

Apart from the potential clinical benefits that are achieved by down staging, NAC allows direct and early observation of the response to treatment, which could lead to modifications of the treatment plan in the event of poor response (Schott and Hayes, 2012). The present study cohort shows some resistance to tumour clearance but when it occurred, it has given a survival benefit. The low prevalence of pathological complete response (pCR) can be due to the type of treatment modalities used for NAC. As an example, the patients who had received taxol drugs in the NAC regimen, had no survival benefit compared to those who did not receive taxol. Although some degree of down staging has occurred in a substantial percentage of patients the degree of down

staging by NAC did not have an association with the RFS or BCSS.

The most important parameter for treatment success and improved survival is the achievement of pCR. However pCR is a relatively uncommon phenomenon (Carey et al, 2005). In our cohort of patient, only 2% of patients had pCR. There were 10.9% (18/164) of patients who could not have the full neoadjuvant chemotherapy regimen and may have contributed to the poor prevalence of pCR.

Even after receiving the NAC, the poor prognostic features remain with the residual tumour of the breast. The effect of these affects the prognosis. It is unclear whether the initial clinical stage or the final pathological stage is more meaningful in terms of prognosis and further treatment decisions. However, the multivariate analysis of our study revealed that the final pathological stage independently affects the BCSS. Consistently, Carey and colleagues found that prognosis of patients treated with neoadjuvant chemotherapy was best determined using the final pathological stage defined by the 2003 AJCC TNM system (Carey et al, 2005). In addition LVI and expression of PR also independently affected the prognosis of our cohort of patients.

The heterogeneity of the NAC regimens that had been used for this cohort of patients limited the evaluation as the therapeutic groups became smaller when divided according to the drug regimens. There was no statistically significant difference between the survival curves according to the NAC regimens used and the statistical power of this finding is doubtful due to the smaller size of the subgroups. The present cohort of patients had been treated at a single institution based on recommended guidelines giving some consistency to the treatment provided to the setoff patients included in the study.

For patients those who had received NAC, pCR is recognized as the best prognostic endpoint (Schott and Hayes, 2012). But prognostic ability of pCR is limited in the present study due to the small number of patients who achieved this endpoint.

V. CONCLUSION

Degree of down-staging by NAC does not influence the RFS or BCSS. The presence of LVI, expression of PR and the final pathological stage predict the BCSS of patients who received NAC but not the initial clinical stage.

ACKNOWLEDGEMENT

The authors wish to acknowledge the staff of the Department of Pathology, Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka for the technical assistance. Funds for the research were provided by the University Grants Commission-Research grants and University of Ruhuna, Research Grants, Sri Lanka.

REFERENCES

Carey LA, Metzger R, Dees EC et al (2005). American Joint committee on cancer tumour-node-metastasis stage after neoadjuvant chemotherapy and breast cancer outcome. Journal of National Cancer Institute, 97(15), 1137-1142.

NagaoT, Kinoshita T, Hojo T, et al (2012). The difference in the histological types of breast cancer and the response to neoadjuvant chemotherapy: The relationship between the outcome and the clinicopathological characteristics. *The Breast*, 21, 289-295.

Rouzier R, Extra JM, Klijanienko J et al (2002).Incidence and prognostic significance of complete axillary down staging after primary chemotherapy in breast cancer patients with T1 to T3 tumours and cytologically proven axillary metastatic lymph nodes. Journal of Clinical Oncology, 20, 1304-1310.

Schott AF and Hayes DF (2012).Defining the benefits of neoadjuvant chemotherapy for breast cancer.*Journal of Clinical Oncology*, 30(15), 1747-1749.

BIOGRAPHY OF AUTHORS

Ms. H Harshini Peiris is a Lecturer attached to the Medical Laboratory Science degree programme in the Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka. At present, she is engaged in a research in the field of breast cancer survival as her PhD research project. Her research interests are cancer survival and applications of immunohistochemistry for detection of tumour markers.