RESEARCH ARTICLE

Clinical, Histopathological and Molecular Characteristics of Metastatic Breast Cancer in North-Eastern Kazakhstan: a 10 Year Retrospective Study

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Abstract

Background: Breast cancer (BC) is the top cancer among women worldwide and has been the most frequent malignancy among Kazakhstan women over the past few decades. Information on clinical and histopathological features of metastatic breast cancer (MBC), as well as the distribution of molecular subtypes is limited for Kazakh people. **Materials and Methods:** The present observational retrospective study was carried out at Regional Oncologic Dispensaries in the North-East Region of Kazakhstan (in Semey and Pavlodar cities). Clinical and histopathological data were obtained for a total of 570 MBC patients in the 10 year period from 2004-2013, for whom data on molecular subtype were available for 253. Data from hospital charts were entered into SPSS 20 for analysis by one-way ANOVA analysis of associations of different variables with 1-5 year survival. Pearson correlation and linear regression models were used to examine the relation between parameters with a p-value < 0.05 considered statistically significant. **Results:** No significant relationships were evident between molecular subtype and survival, site of metastases, stage or ethnicity. Young females below the age of 44 were slightly more likely to have triple negative lesions. While the ductal type greatly predomonated, luminal A and B cases had a higher percentage with lobular morphology. **Conclusions:** In this select group of metastatice breast cancer, no links were noted for survival with molecular subtype, in contrast to much of the literature.

Keywords: Breast cancer- molecular subtypes- mortality- metastasis- North-East Kazakhstan

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Introduction

Breast cancer is of great importance throughout Asia (Forman et al., 2014; Ferlay et al., 2015) including Central Asia, the incidence rate for example being recently found to be increasing in Kazakhstan (Bilyalova et al., 2011; Igissinov et al., 2011; 2012; Beysebayev et al., 2015). According to the oncology service of the Kazakhstan for 2013, breast cancer (BC) took first place in the structure of cancer among women, accounting for 11.7% of the total cancers. Reports for neighbouring parts of Russia also emphasize the importance of breast cancer (Poddubnaya et al., 2007; Kutikhin et al., 2012; Dudarev et al., 2013). The situation in Central Asia may be complicated by higher rates in Russians than Turkic inhabitants (Igisinov et al., 2005).

In Kazakhstan the absolute number of new cases in 2012 was 6,252 patients (GLOBOCAN, IARC 2012). Incidence in Kazakhstan amounted to 22.7/100,000. The death rate from breast cancer was 8.1% 000 (after lung cancer and stomach). In general, the incidence and mortality of breast cancer continues to grow steadily in Kazakhstan (Beysebayev et al., 2015). While incidence rates appear to be increasing across the country at around 1.9% per year, and mortality rates are decreasing at 0.8%, there is considerable regional variation within the country.

Survival of breast cancer varies widely depending on a number of factors. Generally the major cause of short survival in breast cancer is formation of metastases (Rezaienzadeh et al., 2012). High mortality in late stages is due to the "incurable" nature of metastatic breast cancer (MBC) at the current time. It is estimated that 6% of patients have metastatic disease at the time of diagnosis and 20% to 50% patients first diagnosed with primary breast cancer will eventually develop metastatic disease. Even with the remarkable advances in research and clinical management, the current treatment strategies for breast cancer metastasis still largely rely on the use of systemic cytotoxic agents, which frequently deteriorate the patient's life quality due to severe side effects and, in many cases, have limited long-term success.

The prognosis for MBC patients is poor, with

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an estimated 5-year survival of only 26% (Lu et al., 2009). Numerous studies have been done worldwide to estimate survival of breast cancer patients with regard to demographics and clinicopathological features for example shows that tumor characteristics and molecular subtypes of breast cancer metastases significantly influence post-relapse patient survival, emphasizing that molecular investigations at relapse provide prognostic and clinically relevant information. Zaha et al., (2010) demonstrated that molecular differences have been shown to correlate very well with clinical features and survival, even better than traditional histopathological parameters. The discovery of certain molecular characteristics of breast cancers has helped to understand better the pathophysiology of disease and to develop more direct therapeutic strategies. But no such study has been done in Kazahstan, where there are different ethnic groups.

This study was carried out to find out the impact of age, ethnicity, stage, histological type and molecular subtype dependent on estrogen and progesterone receptor status, and Her 2 neu positivity, on survival of a breast cancer cohort from North East Region of Kazakhstan, registered at the Oncology Department of ROD, Semey and Pavlodar cities. According to the immunohistochemical (IHC) test of ER, PR and HER-2, breast cancer can be divided into 4 different molecular subtypes: Luminal A subtype (ER or PR positive and HER-2 negative), Luminal B subtype (ER or PR positive and HER-2 positive), HER-2 subtype (ER and PR negative, HER -2 positive) and basal-like (triple negative) subtype (ER, PR and HER-2 negative) and also important Ki67 overexpression of activity of proliferation of tumour (REF). The present study was to analyze the clinical features of different breast cancer subtypes, and try to find the predictive factors depending on age and other characteristics for patients with metastatic breast cancer.

Materials and Methods

The present study was carried out at Regional Oncologic Dispensary of the North East Region of Kazakhstan (Semey and Pavlodar cities). We selected patients based upon the following criteria: having histologically proven MBC; all types of metastases, stage at the time of registration, no previous or concomitant malignancy.

This observational retrospective study covered a total of 570 patients with histopathologically proven MBC from 2004-2013. Of these, 253 had findings for molecular subtype, clinical and histopathological data, ethnicity and sites of metastasis. were obtained and studied between different age groups in a 10 year retrospective study. For the molecular subtyping, Luminal B (HER2 negative)– ER positive, HER2 negative, and either Ki-67 high or PR low, while Luminal B-like (HER2 positive) – ER positive, HER2 overexpressed or amplified, any Ki-67, and any PR. The cutoff for HER2 of Luminal B was done by Allerd score between 0-8 in which 0-2 is negative, 3-4-intermediate,5-6-positive, 7-8 strong.

Data from hospital charts were entered into SPSS 20 for analysis by one-way ANOVA analysis of associations of different variables, especially molecular subtype and with 1-5 years survival.

Age (years), and the presence or absence of nodal involvement and distant metastasis, 1, 2,3,4,5 year survival was estimated for all patients from the date of diagnosis (date of histopathology verification) to the date of death.

The association of age, stage, molecular subtype (ER, PR, and Her 2 Neu status and Ki67 with molecular subtype was sought employing by ANOVA analysis, also Fisher's exact test and Tau-Kendall was done to find out percentage of patients for overall survival in relation to molecular subtype. A p-value of less than 0.05 was considered statistically significant.

Results

The total number of cases of MBC analyzed was 570 with molecular subtype data available for 253. Findings

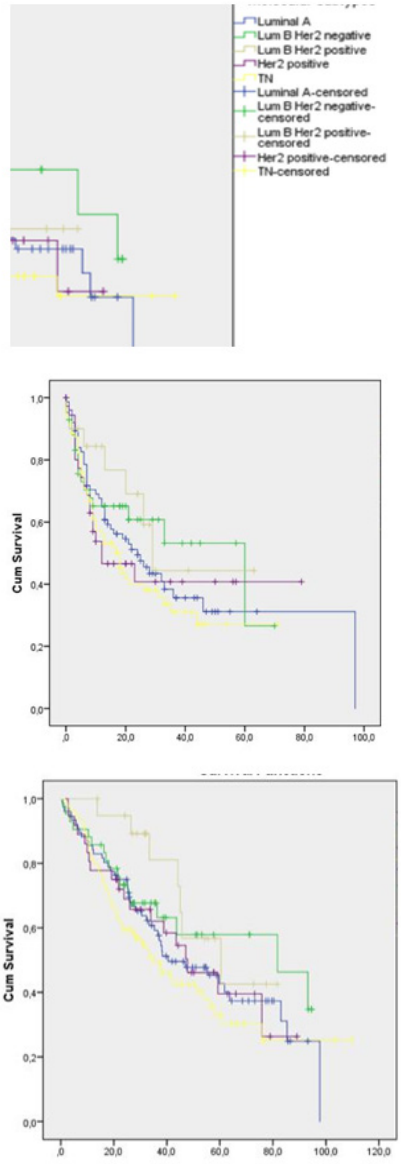

Figure 1. Kaplan-Mayer Survival Curves Depending on the Molecular Type,. Total Number=253. a) Time from diagnosis to metastasis; b) Time from metastasis to death; c) Time from diagnosis to death

Table 1. Demographic and Tumour Findings for Molecular Subtypes of Breast Cancer, 253 Cases

Subtypes		Luminal A		Lum B Her 2-		Lum B Her 2+		Her 2+		TN		All		p value
		N	%	N	%	N	%	N	%	N	%	N	%	
Age Mean (SD)		57.2	(11.3)	56.2	(9.7)	55.1	(8.9)	51.1	(12.6)	51.7	(10.0)	53.2	(10.8)	0.088
Distribution		76	30	42	16.6	21	8.3	36	14.2	79	31.2	253	100	
Age group														0.02
< 44		11	14.5	3	7.1	7	35	8	22.2	21	26.6	50	19.8	
45-59		36	47.4	23	54.8	11	55	21	58.3	39	49.4	130	51.4	
≥60		29	38.2	16	38.1	2	10	7	19.4	19	24.1	73	28.9	
Ethnicity														0.529
Kazakh		19	25	17	40.5	5	25	14	38.9	27	34.2	82	32.4	
Russian		50	65.8	20	47.6	14	70	20	55.6	43	54.4	147	58.1	
Other		7	9.2	5	11.9	1	5	2	5.6	9	11.4	24	9.5	
Stage														0.596
I-II		41	53.9	20	47.6	10	50	16	44.4	45	57	132	52.2	
III		28	36.8	16	38.1	8	40	18	50	31	39.2	101	39.9	
IV		7	9.2	6	14.3	2	10	2	5.6	3	3.8	20	7.9	
Histologic type														0.029
Lobular*		12	15.8	11	26.2	4	20	1	2.8	6	7.6	34	13.4	
Ductal*		55	72.4	27	64.3	15	75	29	80.6	58	73.4	184	72.7	
Others		9	11.8	4	9.5	1	5	6	16.7	15	19	35	13.8	
Metastases location														0.33
Lung		9	11.8	4	9.5	3	15	2	5.6	6	7.6	24	9.5	
Bone		21	27.6	15	35.7	6	30	9	25	20	25.3	71	28.1	
Liver		1	1.3	4	9.5	2	10	3	8.3	2	2.5	12	4.7	
CNS		4	5.3	0	0	1	5	2	5.6	7	8.9	14	5.5	
Lymph nodes		25	32.9	7	16.7	3	15	10	27.8	20	25.3	65	25.7	
Pleura		2	2.6	2	4.8	0	0	0	0	2	2.5	6	2.4	
Skin+scar +perit		6	7.9	1	2.4	0	0	0	0	6	7.6	13	5.1	
Combined		8	10.5	9	21.4	5	25	10	27.8	16	20.3	48	19	
Mortality														
1 year	alive	64	84.2	36	85.7	20	100	28	77.8	64	81	212	83.5	0.083
	dead	12	15.8	6	14.3	0	0	8	22.2	15	19	41	16.2	
2 years	alive	56	73.7	27	64.3	18	90	22	61.1	47	59.5	170	67.2	0.06
	dead	20	26.3	15	35.7	2	10	14	38.9	32	40.5	83	32.8	
3 years	alive	38	50	15	35.7	10	50	17	47.2	32	40.5	112	44.3	0.54
	dead	38	50	27	64.3	10	50	19	52.8	47	59.5	141	57.7	
4 years	alive	25	32.9	11	26.2	7	35	11	30.6	21	26.6	75	29.6	0.866
	dead	51	67.1	31	73.8	13	65	25	69.4	58	73.4	178	70.4	
5 years	alive	16	21.1	7	16.7	4	20	6	16.7	13	16.5	46	18.2	0.947
	dead	60	78.9	35	83.3	16	80	30	83.3	66	83.5	207	81.8	

*infiltrative

for these are summarized in Table 1 with details for age, stage, histology, ethnicity. Regarding the distribution of molecular subtypes, triple negative (TN) was most common with 31%, followed by luminal A 30%, luminal B 25% and Her2+ 14%.

No significant relationships were evident between molecular subtype and survival (see Figure 1 for Kaplan-Mayer cureves regarding time from diagnosis to metastasis, time from metastasis to death and time from diagnosis to death), site of metastases (see Figure 2), stage

Table 2. Proportions of Various Molecular Subtypes of BC as Reported in Selected Recent Medical Literature

Study	Year	Country	Luminal A (%)	Luminal B (%)	HER2 (%)	TN/Basal (%)	
Ihemelandu et al	2007	USA (African)	55	12	12	21	
Shibuta et al	<35	Japan	25	14	4	57	
	2011		71	8	9	12	+6*
Tamaki et al	2013	Japan	65	9	13	8	
Wei et al	2013	China	45	17	17	21	
	<35	China	24	32	22	27	
Chuangsuwanich et al	≥35	China	47	16	17	20	
	2014	Thailand	39	18	18	25	
Guo et al	2014	China (Han)	38	27	15	20	
Hashmi et al	2014	China (Uygur)	33	20	25	21	
	2014	Pakistan	46	18	18	19	
Jia et al	2014	China (Guangzhou)	41	28	11	21	
Song et al	2014	Korea	56	14	14	17	
Elkablawy et al	2015	KSA	47	28	7	18	
Liu et al	2015	China	24	37	18	21	
Alnegheimish	2016	Saudi Arabia	58	15	12	15	
Kaplan et al	2016	Turkey	33	35	12	20	
Zavyalova et al	2016	Russia Tomsk	62	14	15	9	
Present paper	2016	Kazakhstan	30	25 (17/8)	14	31	

* Unclassified

or ethnicity. Main sites were bone and lymph nodes.

Young females below the age of 44 were slightly more likely to have triple negative lesions. While the ductal histopathology greatly predominated in all molecular subtypes, luminal A and B cases had higher percentages with lobular morphology than their TN and Her2+ counterparts.

Discussion

Overview, the present study revealed that in our highly selective population of MBC cases a ductal subtype and late stage were predictive of poor survival at both 1 year and 5 year. Although a number of studies have been done worldwide to estimate survival of cancer patients with regard to demographics and clinicopathological features no such study has been conducted previously in Kasakhstan. Contrary to Europe and America, in Kazakhstan more than 48% of cancer patients present at an advanced stage of the disease.

The lack of any significant influence of molecular

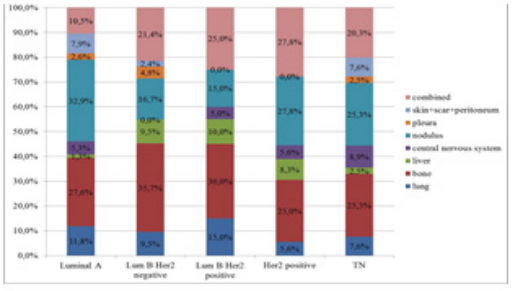

Figure 2. Distribution of Metastases Depending on the Molecular Type

subtype is not in agreement with the literature. The distribution of subtypes reflected the elatively low average age, with a greater preponderance of TN/Basal types (see Table 2), even more exteme results being reported by Ihemelandu et al (2007) for young African -Americans.

In the present study there was no statistically significant variation in subtype with the ethnicity, although as expected being Russian was associated with a higher incidence, in line with earlier findings (Igisinov, 2005).

This contrasted with a report that percentage of luminal A type breast cancer in Uygur patients was significantly lower when compared with the Han patients, whereas the percentages of basal-like and Her-2 overexpression types were significantly higher (Guo et al., 2014)

In China, luminal A tumors had the most favorable prognosis, Conversely, HER-2-enriched tumors exhibited the highest rate of locoregional recurrence (Jia et al., 2014)In Indonesia breast cancer molecular subtypes in regard to age, histological grade, lymph node status and staging Her-2+ subtype breast cancer was more commonly diagnosed with large size, positive lymph node metastasis and poor grade (Widodo et al., 2014).Compared with all other subtypes except nonluminal HER2 positive, triple negative tumors had the highest rate of tumor recurrence ($p<0.01$) (Shim et al., 2014). In Pakistan, triple negative and Her2neu cancers more frequent in younger age group, triple negative cancers being associated with higher grade and proliferation index (Hashmi et al., 2014) Disease free survival rate in the HER-2 positive groups (luminal B and HER-2 enriched) was worse than the HER-2 negative groups (luminal A and triple negative) *+Najafi et al., 2013)Oman, higher stage at presentation (Stage III and

IV) was observed in Her2+ tumours (59%), and a

higher (22.4%) mortality was detected in basal like/TN tumours +Mehdi et al., 2014a). In Iran, Vascular invasion was more prevalent in HER-2 subtype (Kadivar et al., 2014)

In Tomsk, various molecular subtypes of breast cancer differ in the morphological structure, the expression characteristics of the primary tumor and the rate of lymphogenous and hematogenous metastasis, luminal

A very predominant, TN least prevalent, HER2 + most aggressive, largest' although hematogenous dissemination and N2-3 node status higher in TN (*+Zavyalova et al., 2016) Complicated by intratumoral morphological heterogeneity, phenotypic drift Zavyalova et al., 2013, exerts an effect on multidrug resistance (Denisov et al., 2014). Human epidermal growth factor receptor 2-positive and triple negative tumors had a higher histologic grade and a larger tumor size at diagnosis, and they were more common in women under 50 years (Alnegheimish et al., 2016). In Thailand, TNs demonstrated significantly higher tumor grade, mitotic count, Ki-67 index, p53 and vimentin and decreased overall survival compared with nonTN (Chuangsuwanich et al., 2014).

In Nepal, the proportion of histological grade II or III was found to be higher in younger patients, lymphatic and vascular invasion being more common, with a higher proportion of triple negative tumors (Thapa et al., 2013).

In general, the majority of breast cancers in young women presents with more aggressive tumor biology than in older women (Tichy et al., 2013) but in our study we did not find any statistically significant links between age and stage, or age and histological type.

In Saudi Arabia,luminal A was predominantly found in the old age group,with low tumor grade ($p< 0.001$) and small tumor size,whereas HER-2 and basal-like subtypes were significantlyassociated with young age, high tumor grade, lymph nodemetastasis and lymphovascular invasion (Elkablawy et al., 2015). In another study, HR- HER2- patients were youngerand more obese, compared to HR+ HER2- patients, the other subtype patients having more children and lower frequencies of earlier menarche, later FFTP and longer endogenous estrogen exposure (Song et al., 2014)

Regarding site of metastasis, we did not find any significant variation with the molecular subtype, although the high rates for bone and lymph nodes were typical. Earlier differences among subgroups were higher bone incidences (66.2% and 53.9%) in luminal A and B thanin HER2 -overexpressing (38.9%) and triple negative (45.1%) and the opposite in brain (25.3% in HER2-overexpressing and 23.1% in triple negative vs. 10.1% and 15.1% in luminal A and B) (Kaplan et al., 2016). Breast cancer subtype has been suggested to not be a statistically

significant predictor of LN positivity, but higher grade and larger tumor size (Liu et al., 2015). Shibuta et al. (2011) and Tamaki et al (2013) found no significant differences between the subtypes regarding age, menopausal status, disease stage, lymphatic invasion, blood vessel invasion and lymph node metastasis, despite links to histological type and grade. The present study showed that survival of metastatic cancer patients was relatively low in Kazakhstan, In future, more emphasis is needed on early detection and screening (Chukmaitov et al., 2008; Beysebayev et al., 2015b).

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