İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi,2014;18:41-51

ARAŞTIRMA MAKALESİ

HORMONE RECEPTOR STATUS DEFINES SURVIVAL AND METASTASIS RATE IN BREAST CANCER

MEME KANSERINDE HORMON RESEPTÖRÜ SAĞKALIM VE METASTAZ ÜZERINDE BELIRLEYICIDIR

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ABSTRACT

Triple Negative (TN) breast cancer has few treatment alternatives. The chance for cure is poor, prognosis is bad and it is more aggressive than other types of breast cancers. Axillary involvement and early solid organ metastasis especially internal organs are more frequent. TN breast cancer with less treatment alternative was compared to divulge the differences with Luminal B (LB) which showed better outcomes with new treatment protocols. Comparison of these two groups may help us to produce promising treatment and follow up protocols. In Ege University General Surgery Department 91 TN (estrogen negative, progesterone negative and human epidermal growth factor negative) and 183 LB (estrogen positive, progesterone positive and human epidermal growth factor positive) patients operated between 1998 and 2007 were included in this study

Survival without metastasis were lower than in TN group than LB group at 12th and 24th months but these were statistically indifferent. At 36th and 60th months however differences were significant (Log Rank p=0.021 and p=0.041 respectively) TN phenotype has negative prognosis due to the effect of early high internal organ metastasis rate. This finding has a strategic importance in treatment and follow up approach

Key Words: Breast cancer, Triple negative breast cancer, Luminal type breast cancer

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ÖZET

Triple Negatif (TN) meme kanseri sınırlı tedavi alternatiflerine sahiptir. Bu grupta tedavinin fayda şansı azdır. Prognoz kötüdür ve diğer tiplere nazaran daha saldırgan seyirlidir. Daha fazla aksiller lenf nodu tutulumu, erken dönemde ve özellikle iç organlara erken metastaz karakteristiktir. Az sayıda tedavi alternatifine sahip TN meme kanseri aralarındaki farklılıkların da ortaya konulabilmesi için yeni tedavi protokollerinden fayda gören Luminal B (LB) meme kanseri ile kıyaslanmıştır. Bu iki grup arasındaki farklılıkların ortaya konması ümit vadeden tedavilerin oluşturulabilmesi ve takip stratejilerinin geliştirilebilmesine yardımcı olabilir. Bu çalışmaya Ege üniversitesi Genel Cerrahi Servisinde 1998 ile 2007 yılları arasında bilinen metastazı olmayan 91 TN (östrojen reseptör negatif, progesteron reseptör negatif ve insan epidermal büyüme faktör reseptörü 2 negatif)ve 183 Luminal B (östrojen reseptör pozitif, progesteron reseptör pozitif ve insan epidermal büyüme faktör reseptörü 2 pozitif) hasta dâhil edilmiştir TN grubunda metastazsız sağkalım oranları 12 ve 24. aylarda LB gruba nazaran daha düşük olmasına rağmen istatistiksel olarak anlamlı değildi. Bununla birlikte 36 (Log Rank p=0.021) ve 60. (Log Rank p=0.041) aylarda anlamlı bir fark bulundu. TN fenotipi erken zamanda artmış iç organ metastaz riski nedeni ile prognozda negatif etki göstermektedir. Bu bulgu takip ve tedaviye yaklaşımda stratejik bir değere sahiptir.

Anahtar Sözcükler: Meme kanseri, Üçlü negatif meme kanseri, Luminal tip meme kanseri

INTRODUCTION

Understanding the immunohistochemical properties is playing crucial role in order to construct new treatment strategies in breast cancer. A kind of breast cancer cluster named as "triple negative subgroup" has the worst prognosis type. Limited treatment alternatives are available in this subgroup due to either hormone receptor negativity or HER-2 negativity. Tumor behavior and specificities should be understood better for constructing new treatment strategies.

Understanding the relationship between TN breast cancer together with axillary involvement and early phase distant organ metastasis is the aim of this study. Tumor behavior, axillary involvement, prognostic factors are analyzed and conducted to early period distant organ metastasis affair.

Patients in triple negative breast cancer subgroup having few treatment choices are compared with luminal B (LB) subgroup patients who have benefit from new treatment protocols in order to put forth the dissimilarity. Determining the differences in between these two groups if any may help us to establish promising management and follow-up strategies in clinical practice.

Feature	Luminal B	Triple Negative	*p*-value
	No. (%)	No. (%)	
Patient number	183	91	
Age (yr)[1]	51.4 (30-82)	51.1 (30-82)	NS
Tumor size			
T1	68 (37.2)	13 (14.2)	NS
T2	102 (55.7)	71 (78.0)	
T3	13 (7.1)	7 (7.8)	
Multifocality			
Yes	156 (85.2)	84 (92.3)	NS
No	27 (14.8)	7 (7.7)	
Histologic grade[2]			
1	13 (7.8)	2 (3.3)	$p<0.05$
2	108 (65.1)	21 (34.4)	
3	45 (27.1)	38 (62.3)	
Nuclear grade[2]			
1	12 (7.2)	6 (9.5)	NS
2	135 (80.8)	43 (68.3)	
3	20 (12.0)	14 (22.2)	
p53			
Yes	116 (63.4)	50 (55)	NS
No	67 (36.6)	41 (45)	

Table1. Clinicopathological characteristics of LB and TN patients.

[1] mean (range)
[2] some data not obtainable
NS: Not significant

Feature	Luminal B	Triple Negative	*p*-value
	No. (%)	No. (%)	
Ki-67			
Yes	4 (2.2)	2 (2.2)	NS
No	179 (97.8)	89 (97.8)	
Lymphovascular invasion			
Yes	31 (16.9)	12 (13.2)	NS
No	152 (83.1)	79 (86.8)	
Axillary lymph node metastasis			
pNo	71 (38.8)	52 (57.1)	NS
pN1	70 (38.3)	21 (23.1)	
pN2	22 (12.0)	12 (13.2)	
pN3	20 (10.9)	6 (6.6)	
Axillary lymph node surrounding soft tissue involvement[2]			
Yes	61 (54.5)	21 (53.8)	NS
No	51 (45.5)	18 (46.2)	
Adjuvant Chemotherapy			
Yes	161 (88.0)	87 (95.6)	NS
No	22 (12.0)	4 (4.4)	
Adjuvant Radiotherapy			
Yes	131 (71.6)	55 (60.4)	NS
No	52 (28.4)	36 (39.6)	

Table 1. Clinicopathological characteristics of LB and TN patients. (continued)

	Hormone receptor status	Metastasis		Total (%)	*p*-value
		None (%)	Exist (%)		
12th month	LB	178(97.3)	5 (2.7)	183 (100)	NS
	TN	84 (92.3)	7 (7.7)	91 (100)	
24th month	LB	149 (93.7)	10 (6.3)	159 (100)	NS
	TN	75 (87.2)	11 (12.8)	86 (100)	
36th month	LB	130 (90.9)	13 (9.1)	143 (100)	*p*<0.05
	TN	64 (80.0)	16 (20.0)	80 (100)	

Table 2. Hormone receptor status and distant organ metastasis analysis at the 12th, 24th, 36th months of follow-up NS: Not significant LB=Luminal B; TN=triple negative

Hormone receptor status		Site of metastasis							
		Bone	Liver	Brain	Cervical LAP	Lung	Supraclavicular LAP	Ovary	Total
LB	No. in LB group	6	7	2	1	2	0	0	18
	% in LB group	33.3	38.9	11.1	5.6	11.1	0	0	100
	% in LB+TN	60	70	50	100	25	0	0	50
TN	No. in TN group	4	3	2	0	6	2	1	18
	% in TN group	22.2	16.7	11.1	0	33.3	11.1	5.6	100
	% in LB+TN	40	30	50	0	75	100	100	50
Total	No. in LB + TN	10	10	4	1	8	2	1	36
	% in LB + TN	27.8	27.8	11.1	2.8	22.2	5.6	2.8	100
	% in site	100	100	100	100	100	100	100	100

LB=Luminal B; TN=triple negative; LAP=lymphadenopathy

Table 3. Patients characteristics based on hormone receptor status and the site of metastasis.

Hormone receptor status	Average time of metastasis detection (month)	Minimum (month)	Maximum (month)	*p*-value
Luminal B	28.05	3.0	68.0	*p*<0.05
TN	23.0	7.0	54.0	

Table 4. Comparison of hormone receptor status and time of distant organ metastasis onset. LB=Luminal B; TN=triple negative

METHODS

Patients with breast cancer without documented metastasis at the time of administration and undergone operation between 1998 –2007 are included in this study. Of them, 91 were TN (ER, PR and HER-2 negative) and 183 were LB (ER, PR, HER-2 positive). Retrospective 12th, 24th, 36th month's disease statuses including distant organ metastasis were analyzed. ER and PR status are recorded according to the pathologist's interpretation of the assays. ER and PR are considered negative if immuno peroxidase staining of tumor cell nuclei is less than 5%. HER-2 was assessed through immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). IHC is scored on a qualitative scale from 0 to 3+, based on interpretation of staining intensity, with 0 and 1+ classified as negative, 2+ as borderline, and 3+ as positive. FISH is scored on a quantitative scale with less than 2 copies of the HER-2 gene classified as negative. Log Rank test or chi-square tests were used to analyze statistical significance of variables. Reported *p* values are two-sided and *p*-value of less than 0.05 was considered to indicate statistical significance. All statistical analysis were performed using the SPSS 12.0 statistical package (Chicago, USA).

RESULTS

The mean follow-up time was 58.6 months in TN group and 49.4 months in LB group. Mean age of TN and LB groups were 51.1 and 51.4 years respectively. Adjuvant chemotherapy regime had applied 95.6% of TN patients and 88% in LB patients. In the same way, adjuvant radiotherapy séances had applied 60.4% of TN group and 71.6% in LB group. Breast-conserving surgery had performed in 18.7% patients whereas 81.3% had undergone mastectomy in TN group. On the other hand, breast-conserving surgery had performed 33.3% patients and mastectomy was the choice of therapy in 66.7% in LB group. These two groups of breast cancer series were statistically similar for tumor size, multifocality, histologic grade, nuclear grade, p53 gene mutation, Ki-67 gene expression, lymphovascular and peri neural invasion. Pathologic metastatic lymph node involvement in TN and LB groups was 42.9% and 61.2% respectively (Table 1).

Distant organ metastasis rates until 12th month are 7.7 % (7) in TN group, 2.7% (5) in LB group. Until 24th months, distant organ metastasis rates are 12.8% (11) in TN group and 6.3% (10) in LB group. At the 36th month of follow-up distant organ metastasis rates for TN and LB groups are 20% (16) and 9.1% (13) respectively (Table 2). Percent of metastasis detected in TN group at 12th, 24th and 36th months of follow-up are 38.9% (7) 61.1% (11) and 88.9% (16) respectively. Only 2 (11.1%) cases of relapse were encountered after 36th month. On the other hand in LB group, metastasis rates at 12th, 24th, 36th month follow-up are 27.8% (5), 55.6% (10) and 72.2% (13) respectively. After 36th month there are 5 (27.8%) metastasis cases exit. The only relapse detected after 60th moths is one LB patient at 68th

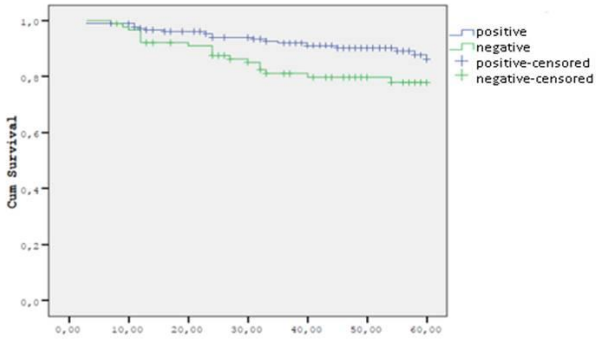

Figure 1.Overall metastasis free survival time curve

month of follow-up at all. No relapse detected in TN group after 60th month of follow-up. The mostly involved organs in TN group are lung (33.3%), bone (22.2%) and liver (16.7%) whereas liver (38.9%) and bone (33.3%) are the most frequent organs of metastasis detected in LB group (Table 3). Average time of metastasis detection in our study were 23 (7-54) and 28 (3-36) months for TN and LB groups respectively (Table 4). Follow-up of 12 months discloses average of 11.8 months survival time without metastasis for both group whereas there were %92.3 and 97.3% metastasis free survival rate for TN and LB groups. These figures for 24 months are 22.8 and 23.3 months for TN and LB groups for average survival time without metastasis whereas there were %87.2 and 93.7% metastasis free survival rate for TN and LB groups respectively. The average survival time without metastasis for 36 months follow-up is 32.8 for TN group and 34.3 months for LB group and metastasis free survival rate for TN and LB group is 80% and 90.9%. The average survival time without metastasis for 60 months follow-up is 52.1 for TN group and 56.3 months for LB group and metastasis free survival rate for TN and LB group is 80.2% and 90.2% respectively (Figure 1) (Table 5).

DISCUSSION

Breast cancer is the most abundant cancer in female population and incidence is increasing while screening and diagnosis methods are developing. However breast cancer mortality rates are decreasing in developed countries with the help of screening programs, early detection and improvement in treatment success. Immunohisto chemical markers are more and more noticed in recent years while their relationship with breast cancer subgroups, prognosis, survival and potential to guide treatment protocols are pronounced. A special subgroup named as "Triple Negative" had appeared with all ER, PR and HER-2 receptor negative characteristic (1). Proceedings in targeted cancer treatment manners are getting more and more place in breast cancer subgroup treatment as well. Targeted treatment modalities are fastening on cell surface and nuclear receptor molecules important in growth and progression of the tumor (for example tamoxifen and trastuzumab). Targeted breast cancer treatment modalities such as hormonal therapy or trastuzumab have been somehow unsuccessful in triple negative breast cancer subgroup because of specific target absence (2). In contrast to hormone receptor positive types, this kind of breast cancer which shows poor prognosis has few treatment alternatives (3).As there is no additional therapy protocol available in TN patients (for example tamoxifen and trastuzumab) T2 tumors in this group had had more liberal chemotherapy with regard to their age, physical performance, histologic grade, lymphovascular invasion and nuclear grade. Triple negative breast cancer type constitutes 10-15% of all kind of breast cancers (4, 5). Poor prognosis and aggressive progression are main characteristic of this kind of breast cancer (1, 6). Younger females are more prone to develop TN breast cancer. Likewise metastasis happens in earlier periods of the disease and mainly attracts to visceral organs (7). Distant organ metastasis risk is much more possible for first 5 years in TN breast cancer insomuch that it makes a peak in 3rd year where as other kind of breast cancers have flat slope for distant organ metastasis risk rate in whole period of disease (3,8).

70% of female having proven breast cancer are over 50 years of age. Females over 50 years of age are 3-4 time more prone to develop breast cancer compared to younger than 50. On the

other hand, lots of studies stated that TN breast cancer type is more frequent in younger ages (2,9-11). TN breast cancer patients are average age of 51.1(30-82) years and 52.7% of them are under the age of 50 whereas LB patients average age was 51.4(30-82) and 37.7% of them are under the age 50. Our patient series discloses the similar findings with literature.

TN breast cancer shows more aggressive phenotype and poor prognosis. There are multiple studies revealing much higher and earlier distant organ metastasis and recurrence rates for TN breast cancer (1,12-14). Ihemelandu et al. (15) reported a case series of 372 breast cancer patients (TN:79, LB:49) in which %42.9 of all metastasis were seen in TN group after 36 months of follow-up whereas distant organ metastasis were seen in %18.9 of TN and %6.8 of LB groups. They speculated that TN breast cancer subgroup is a predictor of distant organ metastasis. Node positive 835 patients series of Wang et al. (16) disclosed %24.1 and % 17.8 distant organ metastasis for TN and LB groups respectively after 47 months of follow-up. Sachdev et al. (17) reported %16.1 metastasis rate in 124 TN breast cancer patients after 23 months of follow-up. Similar results were gained in Kurada et al. (18) series including 202 patients as follows: 23% and 4.5% metastasis in TN and non-TN patients respectively. There are some studies discloses much more distant organ metastasis rates in the literature. Dent et al. (19) reported a 1608 patients series in which distant organ metastasis rates for TN and non-TN cases are %33.9 and %20.7 respectively after 8 years of follow-up and they stated that metastasis were happening in early periods especially in first five years. On the other hand, Lin et al. (20) with 1048 breast cancer patients series in which 167 were TN had found that distant organ metastasis rates were %3.2 and %2.2 in TN and non-TN patients after 40 months of follow-up.

Although metastasis rates for TN group after 12, 24 and 36 months of follow-up were higher than LB group, there were no statistically significant difference for first and second period (p=0.112 for 12 mo and p=0.970 for 24 mo) but after 36 months of follow-up we reached the statistically significant difference (p=0.024).

TN patient group discloses the metastasis rate for definite time interval as; 7 (38.9%) in 12 month, 11 (61.1%) in 24 month and 16 (88.9%) of metastasis occur in 36 month. Only 2 (11.1%) patient show metastasis after 36 month in this group. LB patients on the other hand show as follows; 5 (27.8%) in 12 month, 10 (55.6%) in 24 month and 13 (72%) in 36 month. However 5 (27.8%) patients showed metastasis after 36 month in LB group. Metastasis after 60 month of follow-up is seen in 1 patient in LB group and none in TN group.

Distant organ metastasis rate in our study is found to be higher and earlier in TN group than LB group. Most of the metastasis occurs in first 36 months resembling the literature.

The site of distant organ metastasis in TN breast cancer is more prominent for visceral organs (lung liver) and central nervous system (21-24). There are some studies saying bone metastasis is less likely in TN patient than others (25, 26). Dent et al. reported a 1608 breast cancer series including 180 TN patients in which metastasis sites are 63.9% visceral organs and 16.4% bone whereas non TN patients discloses 41.5% visceral organs and 39.5% bone metastasis (19). Parallel results were obtained in a study of Luck et al. (25) as; 52% lung and 18% central nervous system metastasis.

The most abundant distant metastasis we figured out are 33.3% lung, 22.2% bone and 16.7% liver in TN group whereas 38.9% liver and 33.3% bone metastasis in LB group.

The greater probability of distant organ

metastasis in TN breast cancer for first five year after diagnosis is meaningful. Beside of this while the distant organ metastasis probability curve makes a peak in 3rd year in TN group, it rather draws a horizontal line in any other types of breast cancers (3,8). Linderholm et al. (27) in their study showed that the mean metastasis time for TN group is 19 month whereas it is 33.9 months in non-TN patients. Sachdev et al. (17) reported that the mean time for metastasis in TN breast cancer is 23 months.

The mean times of metastasis in our study are 23 and 28 month for TN and LB group patients respectively. As what we figured out in our study and told in the literature, TN breast cancer has more tendency to metastasize earlier especially in first 2 to 3 years than any other types of breast cancers. Literature and our figures are matching for the mean time of metastasis onset.

It is reported that metastasis free survival time is shorter than the others in the literature. Sachdev et al. (17) reported in their 124 TN case series that 3 year local or distant metastasis free survival rate is 68%. Haffty et al. (13) with their 117 TN cases included series reported 79% metastasis free survival rate in TN group whereas 88% in non-TN group. Solin et al. (28) reported in TN patients undergone nipple preserving surgery reveals 85% metastasis free survival rate while it is 95% in non-TN patients.

Even metastasis free survival rate for TN group after 12 and 24 months are low with respect to LB group, they are found to be statistically insignificant. However this is just the opposite in 36 months follow-up (Log Rank p=0.021) as what we found statistical significance after 60 months (Log Rank p=0.041).Our study and literature suggests that TN subgroup is tending to metastasize more frequent and earlier than non-TN breast cancer. Metastasis risk makes a peak at 2-3 years. Metastasis free survival rate is approximately 70-80% in the literature and in most of the studies, local recurrences are included in to the metastasis number while some studies has been done in worse prognosis groups such as node positive patients. Although metastasis free survival rate is little bit higher in our study, it resembles with the literature.

We found that distant organ metastasis is more frequent in triple negative breast cancer than LB subtype and particularly important in 36 months after diagnosis. Visceral organs are more likely sites to metastasize.TN breast cancer's aggressiveness is best translated by the fact that the peak risk of recurrence is between the 1st and 3rd years and mortality occurs in the first 5 years following therapy. On the other hand, the differences in outcome among the subtypes are reduced at 10 years of follow up.

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Yazının alınma tarihi:24.01.2014
Kabül tarihi:15.02.2014
Online basım:15.02.2014