الاختلاف في الإنذارية بين النقائل المتواقتة واللاحقة في سرطان الثدي

محمد محمد * **ماهر سيفو ****

الملخص

خلفية وهدف البحث: يوجد العديد من الأبحاث السابقة التي درست علاقة العوامل الإنذارية مع سرطان الثدي الانتقالي، حيث زودتنا بمعلومات مهمة عن عوامل تتعلق بطبيعة الورم بحد ذاته، وأخرى تتعلق بالمريض. كما أكدت الأبحاث اختلاف العوامل الإنذارية باختلاف طبيعة النقائل وتوقيت حدوثها. تهدف هذه الدراسة لتبيان الاختلاف بالإنذارية بين النقائل التي تشخص عند بداية المرض (النقائل المتواقتة) وبين النقائل التي تشخص عند النكس (النقائل اللاحقة).

مواد وطرائق البحث: ضمت الدراسة مريضات سرطان ثدي انتقالي راجعن مشفى البيروني الجامعي بين عامي 2008 و2010، تم حساب الزمن اللازم للتطور الأول للورم للنقائل المتواقتة واللاحقة. حددت نسب البقيا ووسطي الزمن اللازم للتطور الأول للورم باستخدام طريقة كابلان مايير. كما تم تحديد العوامل الإنذارية باستخدام طريقة كوكس لعوامل الخطورة.

النتائج: ضمت الدراسة 350 مريضة، كان وسطي الزمن اللازم للتطور الأول للورم أطول عند المريضات ذوات النقائل المتواقتة بالمقارنة مع النقائل اللاحقة (14 شهر مقابل 8 شهور P=0.0001). في مجموعة النقائل المتواقتة، كان الزمن اللازم للتطور الأول للورم أطول عند إيجابية المستقبلات الهرمونية HR = 0.63 (0.4 – 0.99)(P=0.046)، وأقصر في الأورام عالية الدرجة HR=3.83 (1.12– 13.03) (P=0.032). أما بالنسبة لمجموعة النقائل اللاحقة فقد تأثر الزمن السابق بشكل كبير بالحالة العامة للمريضات HR=3.6 (1.38 – 9.34) (P=0.009) وبالأورام عالية الدرجة HR=2.3 (1.03–5.11) (P=0.042) وتعدد أماكن النقائل HR=7.12 (0.9– 56.3) (P=0.063).

الاستنتاج: إن الزمن اللازم للتطور الأول للورم عند مريضات سرطان الثدي الانتقالي المتواقت أطول مقارنة مع مريضات سرطان الثدي الانتقالي اللاحق ، كما أن العوامل الإنذارية المؤثرة في المجموعة الأولى تختلف عن العوامل في المجموعة الثانية ، وهذا يدل على أن المجموعتين مستقلتين عن بعضهما ، مما يستدعي مقاربة خاصة لكل منها من حيث الإنذار والمعالجة.

الكلمات المفتاحية: سرطان الثدي الانتقالي، العوامل الإنذارية، زمن حدوث تطور المرض، النقائل المتواقتة، النقائل اللاحقة

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Differences in Prognosis between Synchronous and Metachronous Metastatic Breast Cancer

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Abstract

Background and aim: There are many previous articles that studied the relationship of prognostic factors with metastatic breast cancer, as they provided us with important information on factors related to the nature of the tumor itself, and others related to the patient. Also, the prognostic factors differ with the nature of the metastasis and its time of occurrence. We aim to identify the differences in prognosis between synchronous and metachronous metastatic breast cancer.

Patients and Methods: We identified women in Al-Bairouni-University Hospital with metastatic breast cancer (MBC) diagnosed between January 2008 and December 2010. 1st time to progression (TTP) was calculated for metachronous versus synchronous patients. Survival rates and median TTP After metastasis diagnosis were determined using the Kaplan-Meier method and prognostic factors were determined in a Cox Proportional Hazard model.

Results: We identified 350 patients, median TTP (mTTP) was longer for synchronous versus metachronous MBC (14 months for SMBC versus 8 months for MMBC) (P=0.0001). While TTP for patients with synchronous MBC is longer in positive hormonal receptor HR= 0.63 (0.40-0.99) (P = 0, 046) and was affected negatively by high grade of tumor HR= 3.83 (1.12-13.03) (P = 0.032). Otherwise, TTP for patient with metachronous MBC is to a larger extent associated with factors intrinsic to the patients and tumor such as performance status HR=3.6 (1.38-9.34) (P =0.009), high grade of tumor HR=2.30 (1.03-5.11) (P = 0.042) and high number of metastatic site HR=7.12(0.90-56.30) (P =0.063).

Conclusion: TTP with synchronous metastases is longer than with metachronous metastases and the prognostic factors affect differently between two groups which requires special approach to each of them in terms of prognosis and treatment.

Keywords: metastatic breast cancer, first time to progression, prognostic factors, metachronous metastasis, synchronous metastasis.

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Background:

Breast cancer is the most common malignancy and the second leading cause of cancer mortality among women in the United States[1,5], with estimated 231.840 new cases and 40.290 deaths in 2015, respectively[1,2].

Despite the recent improvement in early detection and wide application of systemic adjuvant therapy, approximately (5-10%) of patients are diagnosed with metastatic breast cancer at initial presentation (de novo metastatic breast cancer or synchronous metastatic breast cancer) while (20-30%) eventually develop metastatic recurrence at some time in the future (metachronous metastatic breast cancer)[1,3,4,6,9]. Prior lines of systemic treatment and active follow-up of patients after primary breast cancer treatment could modify the course of metachronic disease[10]. So synchronous and metachronous metastases may represent distinct entities with respect to their biological behavior. Indeed, optimal clinical management may require different strategies for synchronous and metachronous metastases.

Over the last decade, significant achievements have been made in first-line treatment for metastatic breast cancer (MBC). Although there maybe clinical remission or disease stabilization in many MBC patients with first-line treatment. Most of them will ultimately experience disease progression and be candidates for further treatment[11]. So in clinical trials we applied an effective endpoints like time to progression (TTP) to make a decision about treatment. Additionally clinical trials with application of a valid short- term surrogate endpoint would shorten developmental cycles and save research costs. In previous review, the correlation between time to progression (TTP) and overall survival (OS) has been estimated for patients with MBC who have undergone first-line treatment[11,12] .

One meta-analyzed trial declared that using TTP alone as a primary trial endpoint in the 1st-line setting is not recommended[11], so we decided to study this period of time with redundancy to determine the relation between previous phase and usual prognostic factors associated with clinical outcomes. These factors may influence the choice of treatment and include (age of the patient, performance status PS, sites of metastatic disease, number of disease sites, hormone receptor status, Her-2 status, tumor subtype histology, tumor grade).

Methods:

Patient selection:

A comprehensive database is maintained for all breast cancer patients undergoing treatment in our institution (Al-Bairouni University Hospital).This database was examined for all female patients who developed metastatic breast cancer with a known biological subtype between January 2008 and December 2010.The patients were divided to two major groups based on the type of breast cancer metastasis: 1) synchronous metastatic breast cancer (SMBC) 2) metachronous metastatic breast cancer (MMBC).Patients from the metachronous metastases group were reclassified as synchronous if they had been detected within three months following the primary breast cancer diagnosis.

We should mention that the majority of standard systemic anti-cancer therapies (hormonal therapy, chemotherapy, anti-Her2 treatment) are paid for by the Syrian Ministry of Health and distributed by our hospital.

Data collection:

Retrospective review of medical records according to study protocol was utilized, chart abstraction form was summarized at the monthly patient visit. Age, tumor subtype histology, tumor grade, Estrogen Receptor (ER) Status, Progesterone Receptor (PR) status, Human Epidermal Receptor 2 (HER2) status, performance status (PS), number of metastatic sites, metastatic location, date at diagnosis, date at relapse and date at 1st progression were assessed at diagnosis of MBC using the chart abstraction form. 16 Cases with incomplete clinical data were excluded.

Independent variables:

Determination of ER / PR and HER2 status used the pathologic report following the first metastatic site biopsy if available and the initial breast cancer site biopsy, otherwise. HER2 status was only identified by immunohistochemistry[5].

Metastatic locations were categorized in to eight groups: bone, liver, local, lung, pleural effusion, node, skin, brain and other sites were combined and termed “Other” due to a small sample size or

non- significant effect on TTP according to uni-variate and multi-variate analysis.

Outcome variable:

The primary endpoint of the study was time to progression (TTP), it was calculated by two different ways according to our major subdivides: first, in SMBC patients, TTP calculated from the date of diagnosis of MBC until first disease progression after the initiation of treatment. Second, in MMBC patients, TTP estimated from the date of relapse with metastasis until first disease progression after the initiation of treatment.

The first disease progression was defined as local recurrence and/or distant metastasis.

We summarize the data collected from the patients in (Table1) and display them in (Figure1).

Statistical analysis:

Descriptive statistics were applied to describe patient and tumor characteristics and the chi-square test was used to evaluate differences between patients with synchronous and those with metachronous metastases. We estimated crude TTP probabilities separately for synchronous and metachronous metastases using the Kaplan –Meier method (Figure 2) and applied log-rank tests to assess differences in TTP rates for each factor (Table 2). In addition, we develop cox proportional hazards models to identify independent prognostic factors for TTP (Table 3), with factors being selected on the basis of both clinical plausibility and significance in uni-variate analysis (P-value < 0.005)[10].

Data were manipulated and analyzed using the Sata version (6.0).

Results:

Patients' characteristics:

During the study period, 350 MBC were recorded. The majority of cases were relapsed tumors (MMBC) n=255 (72.8%). The demographic, clinical, and pathologic characteristics of the study population are presented in (Table 1).

Table (1): Characteristics of the patients with MBC.

	All patients (n=350)%	MMBC (n=255)%	SMBC (n=95)%	P-value
Age at diagnosis				
Median (interquartile range) years	46(39-53)	45 (38-52)	49(42-55)	
Age <50	223(63.71%)	174(68.24%)	49(51.58%)	0.004
Age ≥50	127(36.28%)	81 (31.76%)	46(48.42%)	
Performance status(PS)*				0.012
0	66(18.85%)	57(22.35%)	9 (9.47%)	
1	128(36.57%)	95(37.25%)	33(34.74%)	
2	118(33.71%)	77(30.2%)	41(43.16%)	
3	33(9.42%)	21(8.24%)	12(12.63%)	
4	5(1.42%)	5 (1.96%)	0	
Estrogen Receptor(ER)				0.363
Negative	186(53.14%)	139(56.05%)	47(50.54%)	
Positive	155(44.28%)	109(43.95%)	46(49.46%)	
Unknown	9 (2.57%)	8 (3.13%)	1 (1.05%)	
Progesterone Receptor(PR)				0.202
Negative	160(45.71%)	111(44.94%)	49(52.69%)	
Positive	180(51.42%)	136(55.06%)	44(47.31%)	
Unknown	10 (2.68%)	9 (3.53%)	1(1.05%)	
Human-epidermal receptor(HER2)**				0.124
-	111(31.71%)	86(36.44%)	25(28.09%)	
+	45(12.85%)	32(13.56%)	13(14.61%)	
++	68(19.42%)	42(17.8%)	26(29.21%)	
+++	101(28.85%)	76(32.2%)	25(28.09%)	
Unknown	25 (7.14%)	20(7.84%)	5(5.26%)	
Tumor subtype histology				0.833
Ductal	301(86%)	221(86.67%)	80(84.21%)	
Lobular	32(9.14%)	22(8.63%)	10(10.53%)	
Other	17(4.85%)	12(4.71%)	5 (5.26%)	
Tumor grade				0.166

G1	10(2.85%)	7(2.75%)	3(3.16%)	
G2	180(51.42%)	139(54.51%)	41(43.16%)	
G3	160(45.71%)	109(42.75%)	51(53.68%)	
Multifocality of metastatic site				0.03
Single	251(61.42%)	191(74.9%)	60(63.16%)	
Multiple	99(28.28%)	64(25.1%)	35(36.84%)	
Metastatic sites				0.007
Bone	79(22.57%)	48(18.82%)	31(32.63%)	
Liver	42(12%)	33(12.94%)	9 (9.47%)	
Local	43(12.28%)	33(12.94%)	10(10.53%)	
Lung	34(9.71%)	29(11.37%)	5(5.26%)	
Pleural effusion	12(3.42%)	12(4.71%)	0	
Node	12(3.42%)	11(4.31%)	1(1.05%)	
Skin	10(2.85%)	10(3.92%)	0	
Brain	5(1.42%)	4(1.57%)	1(1.05%)	
Other	6(1.71%)	4(1.57%)	2(2.11%)	
Number of metastatic site				0.111
1	251(71.71%)	191(74.9%)	60(63.16%)	
2	74(21.14%)	50(19.61%)	24(25.26%)	
3	23(6.57%)	13(5.1%)	10(10.53%)	
4	2(0.57%)	1(0.39%)	1(1.05%)	
Time to progression(TTP)				
Median (interquartile range) months	8.5(5.3-15.1)	8(5-12)	14(7-23)	0.0001
* Apply ECOG score, ** By immunohistochemistry				

The patients with SMBC were significantly associated with an older median age when compared to those without metastasis at presentation MMBC (49 versus 45) with more patients being premenopausal in two groups (51.58%, 68.24% respectively) (P =0.004).
SMBC patients also had a worse ECOG performance status than patients with MMBC at diagnosis (ECOG $\geq$ 2 was recorded for 55.79 % versus 40.4% of patient respectively, P= 0.012).

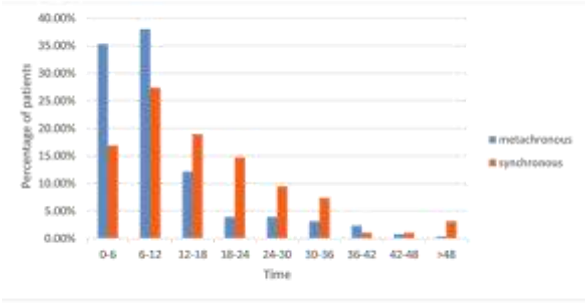

Figure 1: Histogram represent persentage of MMBC , SMBC patients through time.

The most common histologic subtype was Invasive Ductal Carcinoma (IDC) (86% in general population; 84.21% in SMBC; 86.67% in MMBC) followed by Invasive Lobular carcinoma (ILC) (9.14%; 10.53%; 8.63% respectively) followed by other (P =0.833) [13].
Most of the patients (63.16% in SMBC; 74.9% in MMBC) had single metastasis at diagnosis (P=0.03)[14].
Bone was the most common site for metastasis in two subgroups (32.63% in SMBC, 18.82% in MMBC), liver metastasis was in 9.47% versus 12.94% of cases, local recurrence was presented in 10.53% versus 12.94% of cases and lung metastasis was presented in 5.26% versus 11.37% of cases, respectively (P =0.007) (Table1).

Table (2) Median time to progression (months) estimated in general population, metachronous and synchronous patients

	All patients		MMBC		SMBC	
Performance Status(PS)*	Median(Q1,Q3)	P-value	Median(Q1,Q3)	P-value	Median(Q1,Q3)	P-value
0	10(6-20)	0.1658	9(6-19)	0.0485	14(12-29)	0.4669
1	8(6-15)		7(5-13)		14(7-21)	
2	8(5-15)		8(5-10)		15(7-25)	
3	7(4-13)		5(5-10)		11(7-18)	
4	5(1-10)		5(2-7)		-	
Age						
<50	8(5-14)	0.2519	8(5-12)	0.5654	15(8-22)	0.8659
≥50	9(5-18)		8(5-13)		14(6-23)	
Estrogen receptor (ER)						
Negative	8(5-15)	0.1714	8(5-12)	0.6632	14(8-21)	0.2201
Positive	9(5-17)		8(5-13)		15(7-28)	
Progesterone receptor(PR)						
Negative	8(5-14)	0.0194	7(5-11)	0.1514	12(7-18)	0.0035
Positive	9(6-18)		8(5-13)		18(8-29)	
ER or PR Negative positive	8(5-14) 9(6-18)	0.016	7(5-10) 8(5-13)	0.1051	12(7-19) 15(7-28)	0.0375
Human epidermal receptor (HER2)**						
-	10(5-17)	0.7221	8(5-14)	0.6235	15(11-22)	0.4719
+	9(6-15)		7(5-9)		18(11-22)	
++	8(5-16)		7(5-12)		16(7-27)	
+++	8(5-15)		7(5-13)		15(7-23)	
Tumor subtype histology						
Ductal	9(5-14)	0.412	8(5-12)	0.2795	14(7-23)	0.7089
Lobular	7(5-25)		7(5-12)		18(11-27)	
Other	11(6-22)		13(7-23)		11(7-22)	
Tumor grade						
G1	26(8-31)	0.0013	21(6-30)	0.006	30(28-35)	0.0324
G2	9(5-17)		8(5-13)		16(10-24)	
G3	8(5-12)		7(5-10)		11(7-19)	
Multifocality of metastases						
Single	8(5-15)	0.8646	8(5-13)	0.6677	15(10-22)	0.377
Multiple	9(5-16)		8(5-12)		10(5-25)	
Metastatic sites						
Bone	12(6-23)	0.0069	8(5-14)	0.1047	18(12-27)	0.4752
Liver	7(5-10)		6(5-8)		11(7-15)	
Local	8(5-15)		7(5-14)		11(7-19)	
Lung	9(5-14)		9(5-12)		11(11-21)	
Pleural effusion	8(4-14)		8(4-14)		-	
Node	9(4-17)		8(4-16)		-	
Skin	7(5-11)		8(5-11)		-	
Brain	6(2-14)		2(2-6)		-	
Other	9(8-16)		8(6-16)		4(4-11)	
Number of metastatic site						
1	8(5-15)	0.9966	8(5-13)	0.0388	15(10-22)	0.7764
2	8(5-16)		8(5-11)		10(5-25)	
3	11(7-14)		12(7-13)		7(7-28)	
4	13(3-24)		-		-	

*Apply ECOG score, **By immunohistochemistry

The median time to progression (mTTP)of patients with SMBC was 14 months (IR 7-23 months) compared with 8 months (IR 5-12 months) for patients with MMBC (P = 0.0001) (Figure 2). During the follow up period 6,12,18,24 months patients` percentages were 16.84%; 27.37%; 18.95%; 14.74% respectively for SMBC patients, compared with35.29%; 38.04%; 12.16%; 3.92% respectively for MMBC patients (P =0.0001) (Figure 1). Figure 2: Kaplan-Meier curve in MMBC, SMBC patients and in general populations

Table 2 shows the result of multi-variate analysis, the median TTP for each tumor grade subtype was as follow: 1) In SMBC patients G1:30 months, G2:16 months, G3:11 months (P=0.0324) 2) In MMBC patients G1:21 months, G2: 8 Months, G3:7 months (P =0.006) (Figure 3). Patients with bone metastasis in SMBC group had a significantly better median TTP (18 months) than patients with bone metastasis in MMBC group (8 months), also we find this observation in other sites such as liver (11versus6) Local (11versus 7), lung (11versus 9) but not in other (4versus8) (P =0.4752 versus 0.1047).

101 patients with Her2 receptor (+++) who certainly received anti-Her2 therapy in general population, there was no significant difference in median TTP between Her2 receptor (-) and Her2 receptor (+++) subgroups .we notice that in MMBC subgroups (8 versus 7 respectively) (P =0.6235) and in SMBC subgroups (15 months in two groups) (P =0.4719).

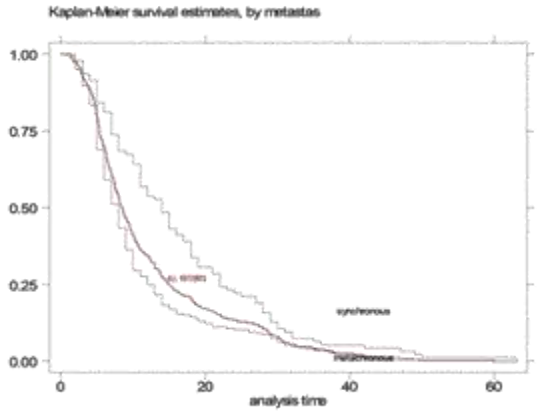

Figure 2: Kaplan-Meier curve in MMBC, SMBC patients and in general populations

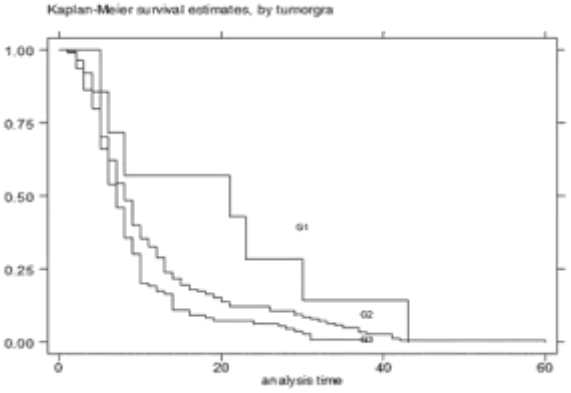

Figure 3: Kaplan-Meier curve in MMBC patients according to grade.

Table (3) Muti-variate Cox Analysis for prognostic factors related to TTP in MBC patient

	All patients		MMBC		SMBC	
Performance Status(PS)	Hazard ratio (HR) 95%Confidance Interval (CI)	P-value	Hazard ratio (HR) 95%Confidance interval (CI)	P-value	Hazard ratio (HR) 95%Confidance interval (CI)	P-value
Greater stage versus Others(4 in MMBC, 3 in SMBC)	3.49 (1.38-8.82)	0.008	3.6 (1.38-9.34)	0.009	1.43 (0.55-3.73)	0.461
Age						
<50	1	0.283	1	0.176	1	0.747
≥50	0.88 (0.70-1.11)		0.82 (0.62-1.09)		0.93 (0.61-1.43)	
ER or PR						
Negative	1		1		1	
Positive	0.83 (0.66-1.04)	0.103	0.85 (0.66-1.11)	0.244	0.63 (0.40-0.99)	0.046
Grade						
G3 versus G1&G2	2.39 (1.25-4.56)	0.009	2.30 (1.03-5.11)	0.042	3.83 (1.12-13.03)	0.032
Number of metastatic site						
4 versus 1&2&3 sites	-	Non-significant	7.12 (0.90-56.30)	0.063	1.13 (0.14-8.81)	0.908
Synchronous versus Metachronous	0.52 (0.41-0.67)	<0.0001	-		-	

Uni-variate and Multi-varite analysis:

Potential prognostic factors for 350 patients with metastasis (MBC) were analyzed by uni-variate and multi-variate Cox Proportional Hazard Regression .In (Table 2) Uni-variate Hazard Regression analysis identified the following prognostic factors for SMBC patients: HR status(especially PR), tumor grade (P =0.0035 & 0.0324) respectively. Other prognostic factors for MMBC patients were found: performance status, tumor grade, number of metastatic site (P =0.0485 & 0, 006 & 0.0388) respectively. Those significant factors were selected for further multivariate Cox Proportional Hazard analysis. In (Table 3) we find for SMBC patients: Hormonal Receptor positivity (ER or PR) is a favorable independent prognostic factor HR =0.63 (0.40-0.99); P =0.046 (Figure 4) and high grade of the tumor is an unfavorable independent prognostic factor HR=3.83 (1.12-13.03); P =0.032. In addition, we find for MMBC patients: greater stage of PS is an unfavorable independent prognostic factor HR=3.6 (1.38-9.34); P =0.009, high grade of tumor is an unfavorable independent prognostic factor HR=2.30 (1.03-5.11); P =0.042 and high number of metastatic site is an unfavorable independent prognostic factor HR=7.12 (0.90-56.30) P =0.063 with reservation to the previous result.

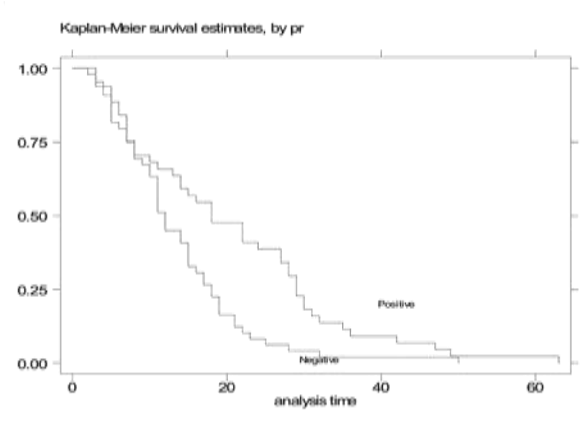

Figure 4: Kaplan –Meier curve in SMBC according to PR status

Discussion:.

In keeping with previous studies, our data provide useful survival estimates for patients with MBC of the two major subgroups (SMBC&MMBC), these estimates can form the basis for realistic discussions about prognosis with individual patients based on the biomarker expression pattern of their diseases (grade, histologic subtype, ER status, PR status, HER2 status) and the type of metastatic presentation (place, number of metastatic site)[6]. So this study supports the hypothesis which says that early events in the primary tumor determine the intrinsic aggressiveness of the disease and are capable of predicting outcome at the time when patients with metastatic breast carcinoma develop recurrent disease [15].

Among these factors, the site of metastasis seems to be the most significant independent prognostic factor in general population (P =0.0069), patients with metastatic bone disease were associated with a relatively better mTTP (12 months) and bone is the most frequently reported site of metastasis (22.57% in MBC patients) in our study [15,16], as previously reported, the association between brain or liver metastasis and low survival was observed[5,8] mTTP was 6 months, 7 months respectively in MBC patients.

The number of metastatic sites was a major prognostic factor for TTP in uni-variate and multivariate analysis especially in MMBC patients (HR=7.12) .this finding validates previous work that found more metastatic sites at diagnosis a poor prognosis[5].

As expected, we found a favorable impact of HR-positive breast cancer, with a (HR=0.63) compared with HR negative breast cancer in SMBC patients.

Overexpression of PR is associated with the best mTTP 18 months (P =0.0035) especially in SMBC patients [1] (figure 4).

Amplification of HER2 in breast cancer was demonstrated to be strong unfavorable prognostic factor, However with the availability of anti-HER2 therapy this unfavorable prognostic factor has also become a favorable predictive factor for response to anti-HER2 therapy [17].

The present study also showed that ECOG performance status >2 was unfavorable prognostic factor especially in MMBC patients (HR=3.6) consistent with previous studies[18].

Proportion of aggressive subtypes and grade3 were further more significantly higher among patients with SMBC compared to MMBC in

accordance with data from previous studies (53.68% in SMBC; 42.75% in MMBC) [8].

In our study women with age≥50 and postmenopausal status do not affect TTP significantly (HR=0.88) in general population (P =0.283).

The most important thing we should mention that patients with SMBC have longer average time to progression than patient experiencing a metastatic relapse. One theory said that most of the patients with MMBC will eventually develop drug resistance and lost their therapeutic targets like hormone receptors or HER2. The potential mechanisms behind this phenomenon are becoming better understood. There are some theories trying to explain that such as selection pressure, altered gene expression profile or mutations which have been increasingly reported [7].

On the other hand, another study declare that women with MMBC may probably benefit from a better surveillance than SMBC and metastasis in MMBC may be diagnosed at an earlier stage which will allow an increase in their survival [8] .The same study suggested that there is some kind of bias. So we need more laboratory experiments and studies in trying to understand previous results.

This study has several limitations .First of all, it is a single center study with a relatively small number of patients .Secondly; we only use immunohistochemistry to describe HER2 status. Finally most of all profiled samples come from primary tumors rather than metastatic tumors, the reality is that metastatic tissues are not always available in clinical practice.

Conclusion:

Our study shows that prognostic factors appear to affect TTP in different ways. While TTP for patient with synchronous metastases is prolonged by positive hormonal receptor and low grade primary tumor. TTP for metachronous metastases is to a larger extent associated with factors intrinsic to the patient and tumor such as performance status PS, grade of tumor and number of metastatic site.Overall, patients` time to progression is slightly longer when metastases are detected synchronously versus metachronously.

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