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Biological subtypes of breast cancer and their impact on recurrence and survival rates: Alexandria surgical oncology unit experience

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ABSTRACT

The effect of breast cancer molecular subtypes and treatment on survival, loco regional and distant recurrences were analyzed. Aiming to decrease the incidence of recurrence, continuous urgue exists about the optimal surgical decision (BCS or mastectomy) to breast cancer subtypes (Triple negative breast cancer and her2 enriched. Alexandria Surgical Oncology Unit Data base was used to identify eligible breast cancer patient. Female patients who were diagnosed and/or treated from January 2000 to December 2010 with primary, invasive, unilateral breast cancer at our hospital were included. A total of 664 patients made up the study population. Kaplan Meier curves and log rank tests were used to estimate 5 year Loco regional and distant recurrence and to compare them across strata. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals to fit the effect of conservative surgery, mastectomy and other independent variables. After a median follow up of 5 year (range 1 10), 16 (6.72%) patients in the BCS groups had Loco regional recurrence (LRR) versus 10(2.34%) patients in the mastectomy group. For distant recurrence, 37(8.68%) patients had distant recurrence in the mastectomy group versus 10(4.2%) patients in the BCS group. Lymphovascular invasion (HR 2.55; 95% CI, 076 to 8.49) and an extensive intraductal component (HR, 2.22; 95% CI, 0.69 to 7.15) are risk factors for (LRR) after BCT, however nodal status represents a risk factor for (LRR) after both BCS & MRM. Tumor size, nodal status, high histologic grade & breast cancer diagnosed at a young age (≤ 35 years) are correlated with higher distant recurrence rates after BCT, whereas lymphovascular invasion & triple negative breast cancer and Her 2 enriched breast cancer are predictive of the risk of distant recurrence after MRM. One of the main predictors of breast cancer survival is molecular subtypes. Luminal A subtype is associated with low risk of recurrence. Women with Her2 enriched, triple negative breast cancer, luminal B subtypes have the poorest survival. For TNBC patients breast conservative therapy is more beneficial than mastectomy. Putting in mind that TNBC subtype predicts a poorer prognosis than non TNBC breast cancer which make the need for newer innovation adjuvant therapy.

Keywords: Biological subtypes, breast conservative surgery, modified radical mastectomy..

Introduction

Breast cancer affecting women is the commonest malignancy worldwide. It is the leading cause of cancer related deaths (458.000 deaths/year). In Egypt, breast cancer represent the most common cancer in females constituting 37% of women's cancer with incidence of 49.6/100,000.[1,2]

Based on the estrogen, progesterone receptor status and Her-2 over expression; four main

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biological subtypes are identified: luminal A, luminal B, triple negative and Her-2 enriched.[3,4]

Breast cancer subtypes are now introduced in treatment decision making besides the considered traditional factors such as tumor size, grade, lymph node involvement and surgical margins.

However, knowledge is still lacking about the impact of biological subtypes on the effect of received adjuvant treatment as well as on long term prognosis.[5-7] Moreover, variations in laboratory methods have made it difficult to make meaningful conclusions.

Therefore, the goal of the current study was to examine the impact of breast cancer subtypes on long-term survival after surgical treatment.[8-12]

Material and Methods

Patients selection and analysis

The data of 664 breast cancer patients admitted to the surgical oncology unit, Alexandria University were retrospectively evaluated. The data were collected during the period from 2000 through 2010 with a median follow up of 5 years. Data abstracted from the patients included detailed clinical history, physical examination, routine laboratory tests (liver function tests, renal function tests, fasting blood glucose), and mammography. The preoperative diagnosis of breast cancer was made on basis of FNA and/or core biopsy. All patient were subjected to metastatic work up including chest X-ray (CXR) or CT and abdominal ultra-sound in addition to bone scintigraphy if bone metastasis is suspected.

According to the preoperative evaluation of each patient, the suitable surgery was chosen; either BCS or modified radical mastectomy (MRM). After completion of the operation, local radiotherapy, hormonal therapy or the suitable comination of adjuvant chemotherapy were administered as indicated according to the international guidelines to the determined stage, grade, lymph node status and different receptor expression (ER, PR and HER2/neu). Clinical follow-up included physical check-up, laboratory tests, and imaging tests (CXR and/or CT chest, ultrasound abdomen and pelvis) every 6-12 months for detection of relapse. Loco-regional recurrence, distant metastases or death were considered as end point for the follow up.

Loco-regional was defined as the reappearance of cancer in the treated remnant breast skin, chest wall, ipsilateral axillary, internal mammary or supraclavicular lymph nodes. Any relapse at a distant site including the contralateral axillary or supraclavicular lymph nodes was considered as distant metastasis.

The resected specimens were pathologically evaluated the following parameters were determined as: tumor size, grade, lymph node status, lymphovascular invasion, histopathological type, intraductal component and margin status in cases of breast conservative surgery.

Immunohistochemistry was performed on paraffin-embedded samples fixed by formalin. Immunostaining was done using specific antibodies against ER, PR and Her2/neu. For hormonal receptors, tumors were considered positive if nuclear staining was observed in at least 1% of tumor cells. Tumors were considered positive for Her2/neu if a score 3+ was given (strongly positive).

Definition of biological subtypes

According to IHC results, the sample was divided based on ER, PR, and HER2/neu into four subytpes: luminal A (ER+ and/or PR+ and HER2/neu-); luminal B (ER+ and/or PR+ and HER2/neu-; HER2-enriched (ER-, PR-, HER2/neu+); and triple negative breast cancer (basal-like) (ER-, PR- and HER2/neu).[13]

Statistical analysis

Loco-regional recurrence free survival of patients who underwent (BCS) and those who underwent (MRM) was estimated using the Kaplan-Meier method and compared among different categories using log-rank tests. (Univariable analysis of risk factors for loco regional recurrence in both groups).

Distant recurrence free survival for both groups will be analyzed using the same test (Univariable analysis of risk factors for distal recurrence in both groups).

Associations with local and distant recurrence after BCS and MRM were further evaluated using multivariable COX proportional hazards regression model and summarized with hazard ratios 95% confidence intervals (CIs).

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Results and Discussion

Total number of included patients was 664.238 pa tients underwent breast conservative surgery representing 36% of the included patients 426 patients underwent modified radical mastectomy representing 64% of the included patients.

Clinicopathological features

The mean age of all women at the time of diagnosis was 52 years with range from 24 to 80 years. The majority of patients were above 35 years old (91.3%). Stage II was the most encountered stage at diagnosis (48.8%) while (58.6%) of patients had positive lymph node metastasis. Most carcinomas were intermediate grade (82.5%), followed by high grade (15.5%). (Table 1,2)

Immmunohistochemical profile

Immunohistochemcial analysis showed that 89% of cases were ER positive, 84.9% were PR positive and 16.86% positive for HER2/neu. (Table 3)

Table-1. Histopathological types and grade.

Histology	No	%
▪ IDC	617	92.9
▪ ILC	38	5.7
▪ Mixed	9	1.4
Grade		
▪ I	13	2.0
▪ II	548	82.5
▪ III	103	15.5

Table-2. Tumour characteristics.

Tumour characteristics	No	%
Size		
▪ T1	222	33.4
▪ T2	348	52.4
▪ T3	88	13.3
LNs		
▪ N0	275	41.4
▪ N1	204	30.7

Table-3. Hormone receptors

Hormone receptors	No	%
Estrogen		
▪ -ve	73	11.0
▪ +	71	10.7
▪ ++	340	51.2
▪ +++	180	27.1
Progesterone		
▪ -ve	100	15.1
▪ +	156	23.5
▪ ++	280	42.2
▪ +++	128	19.3
Her2		
▪ -ve	552	83.1
▪ +	54	8.1
▪ ++	4	0.6
▪ +++	54	8.1

Distribution and behavior of the different hormonal subtypes

Of the 664 patients included in the study, 579 patients (87.2%) were luminal A, 43 patients (6.4%) were triple negative breast cancer, only 21 (3.2%) and 21 (3.2) patients were luminal B and HER2 enriched respectively (Table 4).

Characteristics of each biological subtype are summarized in Table-5. Triple negative breast cancer (TNBC) had the highest percentage among young age (<35years) compared to the other subtypes.
A pathological tumor of 2.1-5 cm was the commonest presentation among all subtypes.

Luminal B had the highest percentage among stage III (57.1%) followed by TNBC (51.2%) while HER2 enriched had the highest percentage among stage II (76.2%), lastly luminal A had the highest percentage among stage I (19.3%) those differences were statistically significant.

Table-4. Biological subtypes

Type	No	%
▪ Luminal A	579	87.2
▪ Luminal B	21	3.2
▪ Triple negative	43	6.4
▪ Her2 enriched	21	3.2

Luminal B had the highest percentage among P(N3) (14.3%), followed by TNBC (11.6%). However, this was statistically not significant. MRM was the commest procedure done among different subtypes espically, HER2 enriched, TNBC, luminal B and luminal A with the following percentage respectively 85.7%, 81.4%, 81% and 61.5% which was statistically significant.

All luminal B and TNBC cases were given post-operative chemotherapy.

Post-operative radiotherapy was given to 95.2%, 90.7%, 85.7% and 84.3% with HER2 enriched, TNBC, luminal B and luminal A cases respectively.
Finally, hormonal treatment was given only to luminal A and luminal B patients.

Regarding the recurrence, HER2 enriched had the highest percentage among recurrence followed by TNBC compared to other subtypes. On the other hand, luminal A had the lowest percentage of recurrence which was statistically significant.

Study participants were followed a maximum of 10 years (median of 5 years, range 1-10 years). 16 (6.72%) patients in the BCS group had loco-regional recurrence versus 10 (2.34%) patients in the mastectomy group. Using the Kaplan-Meier method to determine the loco-regional recurrence free survival in both groups, It was 97.1% for mastectomy group & 92.7% for BCS group, which was statistically significant indicating that BCS is a significant risk for LRR p=0.001. (Figure 1) For distant recurrence, 37 (8.68%) patients had distant recurrence in the mastectomy group versus 10 (4.2%) patients had distant recurrence in BCS group, Appling Kaplan Meier method to determine the distant recurrence free survival in both group, it reveals that 91.4% of patients in mastectomy group achieved 5 years distant recurrence free survival, versus, 96.4% of patients in BCS group but it was statistically not significant. (Figure 1,2)

Using the Kaplan Meier method and univariate analysis for loco-regional recurrence of MRM, triple-negative and Here2 enriched breast cancer had the highest percentage of LRR and therefore affecting the 5 years survival rate. On the other hand, no recurrence occurred to HER2 enriched and TNBC

Table-5. Distribution of clinicopathological characteristics among the different biological subtypes.

		Biological subtypes								P
		Luminal A		Luminal B		Triple negative		Her2 enriched		
		No	%	No	%	No	%	No	%	
Age										
	<35	37	6.4	2	9.5	6	14.0	1	4.8	0.270
	>35	542	93.6	19	90.5	37	86.0	20	95.2	
Size										
	T1	209	36.1	2	9.5	6	14.0	5	23.8	
	T2	293	50.6	14	66.7	26	60.5	15	71.4	0.012*
	T3	72	12.4	5	23.8	10	23.3	1	4.8	
	T4	5	0.9	0	0.0	1	2.3	0	0.0	
PLNs										
	PN0	245	42.3	7	33.3	15	34.9	8	38.1	
	PN1	179	30.9	5	23.8	9	20.9	11	52.4	0.067
	PN2	98	16.9	6	28.6	14	32.6	2	9.5	
	PN3	57	9.8	3	14.3	5	11.6	0	0.0	
Stage										
	I	112	19.3	1	4.8	3	7.0	3	14.3	0.002*
	II	282	48.7	8	38.1	18	41.9	16	76.2	
	III	185	32.0	12	57.1	22	51.2	2	9.5	
Pre operative neo adjuvant										
	No	552	95.3	21	100.0	43	100.0	21	100.0	0.248
	Yes	27	4.7	0	0.0	0	0.0	0	0.0	
Operation. type										
	MRM	356	61.5	17	81.0	35	81.4	18	85.7	0.003*
	BCT	223	38.5	4	19.0	8	18.6	3	14.3	
Histology										
	IDC	537	92.1	21	100.0	42	97.7	21	100.0	0.940
	ILC	33	5.7	0	0.0	1	2.3	0	0.0	
	Mixed	9	1.6	0	0.0	0	0.0	0	0.0	
Grade										
	I	13	2.2	0	0.0	0	0.0	0	0.0	<0.001*
	II	498	86.0	13	61.9	26	60.5	11	52.4	
	III	68	11.7	8	38.1	17	39.5	10	47.6	
Intra ductal component										
	No	479	82.7	16	76.2	33	76.7	16	76.2	0.580
	Yes	100	17.3	5	23.8	10	23.3	5	23.8	
Lympho-vascular invasion										
	No	383	66.1	15	71.4	28	65.1	15	71.4	0.914
	Yes	196	33.9	6	28.6	15	34.9	6	28.6	
Post operative chemotherapy										
	No	80	13.8	0	0.0	0	0.0	1	4.8	0.010*
	Yes	499	86.2	21	100.0	43	100.0	20	95.2	
Post operative radiotherapy										
	No	91	15.7	3	14.3	4	9.3	1	4.8	0.380
	Yes	488	84.3	18	85.7	39	90.7	20	95.2	
Hormonal therapy										
	No	33	5.7	12	57.1	43	100	21	100	<0.001*
	Yes	546	94.3	9	42.9	0	0	0	0	
Recurrence										
	No	524	90.5	18	85.7	33	76.7	16	76.2	0.009*
	Yes	55	9.5	3	14.3	10	23.3	5	23.8	

P value < 0.05 is significant

patient subjected to breast conservative therapy (Tables 6,7, Figures 3,4).

Figure-1. The Kaplan-meier method for LRR free survival in both groups.

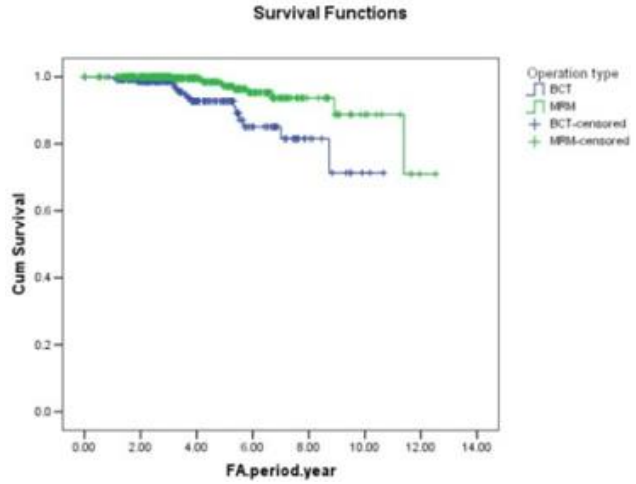


Figure-2. The Kaplan-Meier method for distant free survival in both groups.

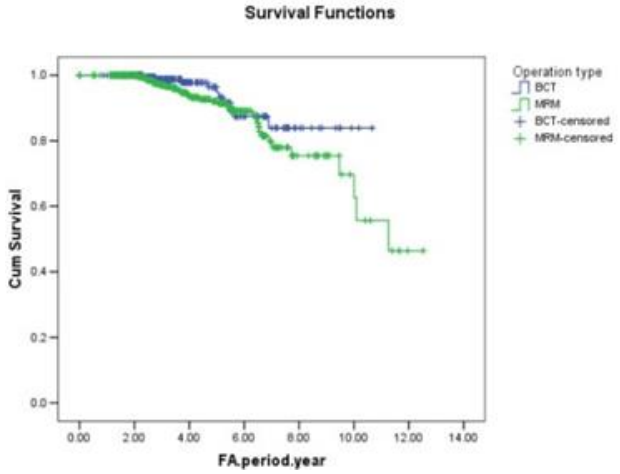
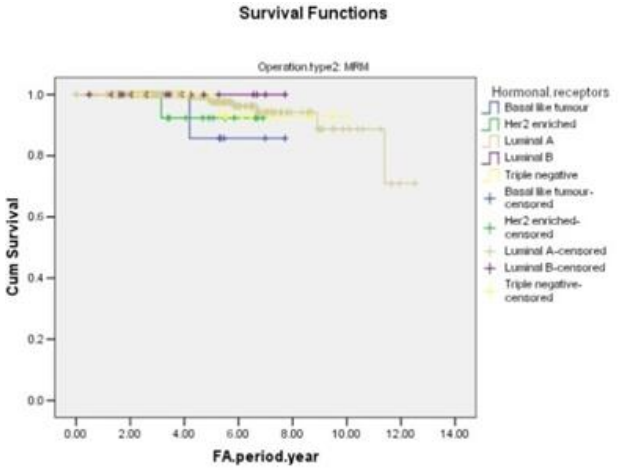


Figure-3. A Kaplan-Meier plot showing LRR free survival by hormonal subtypes in MRM group.



Upon applying Kaplan Meier and univariate analysis for distant recurrence after MRM the 5-year free survival of distant recurrence after MRM was 83.3% for patients with triple negative breast cancer & versus 87.5% for luminal B patient & 91.5% for luminal A and 88.2% for Her 2 enriched patients which was statistically significant upon univariate analysis, p value = 0.012.

As regard univariate analysis for distant recurrence of BCS patient by hormonal subtypes BCT benefits patient with Her-2 enriched and TNBC than mastectomy. (Tables 8,9, Figure 5)

As 87.2% of the included patients were luminal A, the risk of recurrence among luminal A patients was assisted.

According to the results of the multivariate cox proportional hazards survival analysis, nodal status, & stage were all highly predictors factor of recurrence among luminal A patients. Thus, hormonal therapy plays a protecting factor against recurrence with (HR=0.154; CI=0.081-0.292). (Table 10).

Following the introduction of different biological subtypes: luminal A, luminal B, her2 enriched and triple negative breast cancer. A great revolution has been experienced in the available number of targeted therapies as regards hormones receptor-positive (Er or PR) and human epidermal growth factor receptor (erb-B2 (Her2)) positive, while targeted therapy for TNBC remains empirical thus increasing their adverse effect without significant impact of survival rates.[14]

The present study found that 5-year free survival of distant recurrence after MRM is great affected by molecular classification of breast cancer. Luminal A to be the most frequent subtype encountered it is associated with lowest rate of recurrence. Whereas TNBC and HER2 enriched subtypes had bad outcome and they were reported to be significant risk for relapse.

This result is concordant with the repeated observation made by Miller et al and Voduc et al that luminal A subtype has a best prognosis and impact on survival. Whereas TNBC and HER2 enriched as associated with increased risk of recurrence.[15,16]

In addition, a significant rate of distant recurrence was encountered among triple negative breast cancer patients who underwent MRM versus those who underwent BCS. Among 35 triple negative breast cancer patients who underwent MRM, 8 (22.8%) patients experienced distant recurrence versus none of 8 patients who underwent BCS.

Due to the aggressive nature of TNBCs, there is a belief that a more aggressive surgical treatment (i.e., mastectomy) should be done.[2] To investigate the impact of BCT in reducing locoregional recurrences for TNBC, several studies had been done, in agreement with other and Wang et al (2013) BCT helps in reducing both loco-regional and distant recurrences in patients with TNBC compared to

Table-6. Univariate analysis of LRR after MRM by hormonal subtypes

Hormonal receptors	MRM				MCP
	Loco-regional recurrence				
	No		Yes		
	No	%	No	%	
Luminal A	349	98.0	7	2.0	0.445
Luminal B	17	100.0	0	0.0	
Triple negative	33	93.7	2	6.3	
Her2 enriched	17	94.4	1	5.6	

MCP: p value based on Mont Carlo exact probability.
P value < 0.05 is significant

Table-7. Univariate analysis of LRR after BCS by hormonal subtypes

Hormonal receptors	BCT				MCP
	Loco-regional recurrence				
	No		Yes		
	No	%	No	%	
Luminal A	207	92.8	16	7.2	0.886
Luminal B	4	100.0	0	0.0	
Triple negative	8	100.0	0	0.0	
Her2 enriched	3	100.0	0	0.0	

MCP: p value based on Mont Carlo exact probability.
P value < 0.05 is significant

Table-8. Univariate analysis of distant recurrence after MRM by hormonal subtypes.

Hormonal receptors	MRM				MCP
	Distal recurrence				
	No		Yes		
	No	%	No	%	
Luminal A	333	93.5%	23	6.5%	0.000*
Luminal B	15	88.2%	2	11.8%	
Triple negative	27	80.65%	8	19.35%	
Her2 enriched	14	77.8%	4	22.2%	

MCP: p value based on Mont Carlo exact probability.
P value < 0.05 is significant

Table-9. Univariate analysis of distant recurrence after BCS by hormonal subtypes.

Hormonal receptors	BCT				MCP
	Distal recurrence				
	No		Yes		
	No	%	No	%	
Luminal A	214	96.0%	9	4.0%	0.309
Luminal B	3	75.0%	1	25.0%	
Triple negative	8	100.0%	0	0.0%	
Her2 enriched	3	100.0%	0	0.0%	

MCP: p value based on Mont Carlo exact probability.
P value < 0.05 is significant

Table-10. Multivariate analysis of risk factor for recurrence among luminal A subtype

		B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for exp (B) Lower	Upper
Luminal A	Stage	-.816	.341	5.739	1	.017	.442	.227	.862
	Horm	-1.870	.326	32.902	1	.000	.154	.081	.292
	LNs	.737	.228	10.438	1	.001	2.090	1.336	3.267

mastectomy especially in early stage. The great result brought by BCT might be due to post operative radiotherapy, which also changes the previous view that TNBCs are radio resistant.[14,17-19]

Figure-4. A Kaplan-Meier plot showing LRR free survival by hormonal subtypes in BCS group.

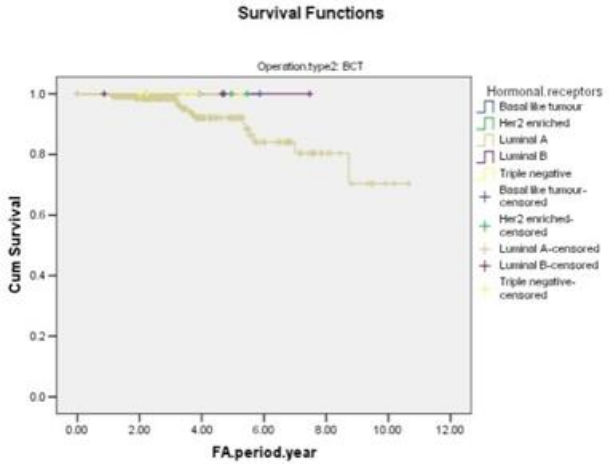
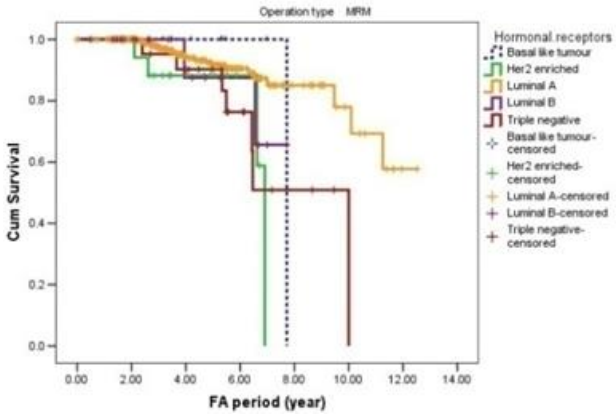


Figure-5. A Kaplan-Meier plot showing distant recurrence free survival by hormonal subtype in MRM group.



In conclusion, given the aggressive nature of TNBC, triple-negative subtype predicts a worse outcome than the luminal subtype for patients under grouping BCT. However, BCT still provides a better prognosis for TNBC in decreasing the risks of both local and distant recurrences, as compared to mastectomy. To adjust the prognosis and optimize the treatment patients with TNBC, the value of adjuvant radiotherapy should be further evaluated in prospective studies, as well as the alternative forms of systemic therapy including the use of targeted molecular therapies.

Conclusion

- 5-year free survival of distant recurrence after MRM is great affected by molecular classification of breast cancer.
- Luminal A subtype is associated with low risk of recurrence while TNBC and Her2 enriched are associated with increased risk of relapse.
- BCT is an effective method for treatment of TNBC.

Conflict of Interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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