ORIGINAL ARTICLE

SURVIVAL OF PREMENOPAUSAL BREAST CANCER PATIENTS IN RELATION TO MENSTRUAL TIMING OF SURGERY WITH PERITUMORAL ESTROGEN RECEPTOR STATUS AND ANGIOGENESIS

By

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Aim: *to define the prognostic significance of menstrual timing of breast cancer (BRCA) surgery, its interaction with estrogen receptor (ER) and angiogenesis.*

Methods: *Prospective randomized involving 40 premenopausal BRCA patents with accurate triangulation of surgery (no multistage) in objectively defined menstrual cycle side (transvaginal ultrasound-serum progesterone), immunocytochemical stain for estrogen receptors and factor VIII, 5 years follow up with well proved finite end points.{ disease free survival (DFS)and disease free time (DFT)}.*

Results: *Resected Tumors in the follicular phase had more angiogenic score (P, 0.001) plus higher micro vessel count (P, 0.001). Patients who underwent surgery in the luteal phase had better (DFS) (P, 0.02). On univariant analysis the menstrual timing (P, 0.01) and angiogenic score (P, 0.01) predicted the DFS, their bivariant analysis found luteal phase subset with low angiogenic score had the best prognosis (P, 0.04), but on multivariate analysis the menstrual timing was the discriminant factor (P, 0.04), the predictors for DFT were menstrual timing (P, 0.02), and ER status (P, 0.04) with insignificant difference on subset analysis.*

Conclusion: *Menstrual timing represented grade II prognostic factor, with better DFS, DFT for patients operated in the luteal phase. It acts through angiogenesis modulation*

Keywords: *unopposed estrogen, prognosis, vascular.*

INTRODUCTION

World wide breast cancer (BRCA) is the most common cause of cancer death among women.(1) In the United States 180.000 new cases are diagnosed annually (45% premenopausal).(2) In United Kingdom 41.000 women had BRCA each year "one in every three below 55 years"(3) and in Egypt data indicated BRCA is number one (29.9%) among females,(4) but 60.5% premenopausal.(5) So, premenopausal BRCA is a critical topic that even modest advantages in outcome should be exploited.(6)

Recently, the potential effects of cyclic hormones on BRCA has become a focus of research(7) and studies found menstrual cycle had robust nature despite the stress of

BRCA diagnosis and surgery.[8] The fluctuation in sex hormones during the cycle might affect the immunologic characters of the host and tumor cells, also the biologic characters including angiogenesis,[9] sex hormone receptor concentrations[10] cancer cell dissemination and dormant micro metastasis escape.[11,12]

Notwithstanding tumor growth and metastasis are dependent on angiogenesis[13,14] and similarly estrogen in important in breast tumorogenesis that mediates its effects through its receptors.[15]

There's some evidence that breast surgery during luteal phase had better outcome,[16,17] others favored follicular[18] and others disputed that association,[19] its suggested mechanisms unopposed estrogen through estrogen receptors[20] and angiogenesis.[21]

The inconsistency on the correlation of timing of surgery in relation to the menstrual cycle and outcome of premenopausal BRCA patients are both methodological (cut off points) and sample size.[22,23] That variability of reports made its prognostic significance uncertain.

Recently the multistate model offers the appropriate way to study the prognostic markers,[24] and here we study the prognostic significance of menstrual timing of surgery and its interaction with estrogen receptor (ER) status and angiogenesis in a well designed prospective randomized study (level of evidence "LOE II") on pathologically proved (fine needle aspiration cytology) 40 premenopausal BRCA patients with accurate triangulation of surgery (only modified radical mastectomy-neither open biopsy nor reconstruction to avoid multistage procedures).

Twenty patients were operated in each menstrual cycle side (objectively defined through transvaginal ultrasound and serum progesterone level). The follow up period was 5 years with well proved finite end points {disease free survival(DFS), and disease free time (DFT)}.

MATERIALS AND METHODS

Patients Cohort: Forty premenopausal BRCA patients were recruited in a prospective randomized study from February 2003 to April 2007 in Mansoura University Hospital (General Surgery Department "Sector 8").

The inclusion criteria were premenopausal (amenorrhea < 6 months), regular menstrual cycles that did not vary > 5 days each month, below 48 years, operable unilateral pathologically confirmed BRCA. The exclusion criteria were previous cancer, concomitant cancer, bilateral BRCA, BRCA during pregnancy or lactation, BRCA histologic types other than carcinoma and BRCA patients on hormonal contraception.

Local ethical committee was approved and patients informed consent were signed.

Ascertainment of pathologic status: The patients were examined clinical, laboratory and radiological (mammography& chest x ray &abdominal ultrasound).

Pathologic detection was done by fine needle aspiration cytology (FNAC) as it is the only procedure not worsen the prognosis whether luteal or follicular[25] to avoid the bias of multiple procedures and tumor staged according to TNM staging.[26]

Ascertainment of menstrual status: Twenty four hours on either side of surgery a transvaginal US (6.5 MH prope) to detect ovulatory status "Corpus luteum" (CL) (the cycle is centered on ovulation not menstruation as the biologic effects of hormones not reflect their serum levels,[27]) together with serum progesterone level on the day of surgery using radio immunoassay kits (CIS, Gif Sur Yvette, France) and considered luteal if (PG) level > 2.5 ng/ml {transvaginal US, CL + serum PG > 2.5 ng/ml considered luteal& transvaginal US, no CL + serum PG < 2.5 ng/ml considered follicular& transvaginal US, no CL + serum PG > 2.5 ng/ml excluded from study& transvaginal US, CL + serum PG < 2.5 ng/ml considered luteal (Presence of corpus luteum is confirmed by US while its functioning is confirmed by PG level) (Stricker & Eberhart, 2006).[28]

Chart Review: The patients received general anesthesia and underwent modified radical mastectomy without reconstruction. The resected specimens were formalin embedded &paraffin fixed, stained with Haematoxylin & Eosin and examined microscopic to detect tumor type, grade (Scraff, Bloom and Richardson "SBR" 1957)[29] and lymph nodes status.

The patients received their adjuvant therapy "CMF" (cyclophosphomide- methotrexate – 5-floro uracil) ± "Tam" (tamoxifen) as Node +ve, ER +ve → TAM + CMF&Node +ve, ER –ve → CMF & Node –ve, ER –ve → CMF when T > 3 cm or higher grades in Mansoura Radiotherapy, Nuclear Medicine Unit.

Ascertainment of estrogen receptor status: The immunocytochemical technique was used (ICC) (to avoid the cyclic variation of estrogen levels that affect intratissular ER).[30] On paraffin-embedded tissue. The primary antibody was ABID5 (Dako Co, Carpinteria, CA), streptovidinbiotin complex method was used and diamino benzidine for visualization as chromogen (Sigma Chemical Co, St Louis, MO) to detect (a) numerical grading, (0 negative, 1 ≤ 25% positive, 2 ≤ 50%, 3 ≤ 75% and 4 > 75%) and (b) intensity grading, (1 weak, 2 moderate, 3 strong) and (c) scoring i.e. numerical and intensity together if > 3 considered positive.[31]

Ascertainment of angiogenic status the tumor specimens slides (formalin fixed) were used, stained with immunoperoxidase (streptovidin and biotinylated horse radishperoxidase) technique using monoclonal polyvalent mouse antibody against factor VIII (Universal Detection Kits, Dako Company) to detect. (a) Angiogenesis grade (microvessel density grade "MVDG"), under low power detection of hot spot number VL (1), low,[2] high,[3] very high.[4] (Fig. 1) (b) Angiogenesis score, under high power to count the microvessels in the intense hot spot, i.e. microvessel count (MVC) to detect score I, (1-9 MVC), II, (10-19 MVC), III ≥ (20 MVC) (Fig. 2).[32] Other breast quadrant slides were used as a control. All steps for accurate examination are followed after.[33]

Follow up: The patients were checked clinically every 6 months, with annual mammography, chest x-ray, bone scan and abdominal US for 5 years

Recurrences were confirmed clinical, radiological and/or pathologic and the disease free time was calculated as months from tumor resection to the first recurrence (Local ± systemic).

Statistical Methods: The mathematical theory of cyclic covariate as menstrual cycle for an analogous correction is not available, the sample size (satiation view) had not influenced the type I error (false +ve) as the cut off points were exactly ascertained) objective data for menstrual timing and end points) and type II error (false –ve) as all patients had operable (BRCA).

The significance of differences in the frequency of events among groups was determined by χ 2 test. Kaplan and Meier estimates of disease-free survival were obtained and the differences between survival curves tested using Mantel-Cox statistics. The relationship of potential prognostic factors to disease-free survival (DFS) was evaluated using Cox proportional hazards regression models. Multivariate results were obtained by allowing for stepwise entry of the potential factors into a proportional hazards model.[34,35]

RESULTS

Patients characteristics were insignificant between both groups except the angiogenic score and the mean MVC were significantly higher in the follicular phase group (P, 0.01 & P, 0.001 respectively) Table 1.

The 5 year DFS was 50% {local recurrences in 2 (5%), distant metastasis in18 (45%)-bony in10 (25%) & visceral in 8 (20%)}, with significant recurrences in the follicular group 14 (70%) compared to luteal group 6 (30%) (P, 0.02).

Overall recurrences tended to have high tumor grading (P, 0.02) and more angiogenic score (P, 0.04) Table 2-A. For follicular group recurrences they had larger tumor size (P, 0.001) and advanced staging (P, 0.02), but the luteal phase recurrences characteristic was positive vascular invasion (P, 0.02) Table 2-B, C.

The univariant Cox (DFS) predictors were menstrual timing (P = 0.01, B = 0.30, 95% CI 0.11 – 0.80) and angiogenic score (P = 0.01) Table 3A, their subset bivariant analysis of menstrual timing time with the angiogenic score defined the luteal phase patients having low angiogenic score (P = 0.02, B = 0.09 95% CI 0.01 – 0.69) Table 3-c, and the multivariate Cox proportional hazard Table 3B defined menstrual timing as the discriminant factor (P = 0.04, B = 0.32 95% CI 0.11 – 0.99). Since a large standard error was present thus implying multicolinearity, so the model is statistically unstable to detect the relative risk.

The cumulative disease free time (DFT) (5 years) using Kaplan-Meier curve was 45.6 ± 2.7 months, (Fig. 3), when prepared for menstrual timing, ER status, lymph and vascular invasion and analyzed by Log Rank test, the significant predictors for (DFT) were menstrual timing {39.10±4.17 months "follicular" & 51.50±3.34 months "luteal" (P = 0.02), (Fig. 4)}, ER status {47.53±3.5 months" ER +ve" & 40.2±7.5 months "ER -ve "((P, 0.04)}, their subset analysis were neither significant in the follicular phase{40.4± 4.8 months "ER +ve"&38.4± 5.9 months "ER -ve "(P, 0. 7) (Fig. 5)}, nor in the luteal phase {54.67± 2.9 months "ER +ve" & 42.0± 8.7 months "ER –ve" (P, 0.07)} (Fig. 6).

Table 1. Patients pathologic characteristics.

		Luteal phase	Follicular phase	P value
Tumor	T1	4 (20%)	5 (25%)	0.81+
	T2	7 (35%)	8 (40%)	
	T3	9 (45%)	7 (35%)	
Node	N0	4 (20%)	1 (5%)	0.33+
	N1	12 (60%)	13 (65%)	
	N2	4 (20%)	6 (30%)	
Grade	G1	6 (30%)	1 (5%)	0.12+
	G2	8 (40%)	11 (55%)	
	G3	6 (30%)	8 (40%)	
Stage	I	3 (15%)	1 (5%)	0.22+
	II	8 (40%)	7 (35%)	
	IIIA	9 (45%)	12 (60%)	
Angiogenesis grade	1	2 (10%)	1 (5%)	0.87+
	2	6 (30%)	5 (25%)	
	3	6 (30%)	8 (40%)	
	4	6 (30%)	6 (30%)	
Angiogenesis score	1	10 (50%)	2 (10%)	0.017+*
	2	6 (30%)	8 (40%)	
	3	4 (20%)	10 (50%)	
Microvessel count (MVC)	10.650±8.222	19.00±6.316	0.001‡*	
Lymph vessel invasion (+ve)	3 (15%)	5 (25%)	0.43+	
Blood vessel invasion(+ve)	4 (20%)	9 (45%)	0.091+	
Estrogen receptors (+ve)	14 (70%)	11 (55%)	0.33+	

* $P < 0.05$ is significant
+ $\chi 2$ is used.
‡ Student t-test is used

Table 2. Recurrent patients according to pathologic characteristics.

		All (A)	Follicular (B)	Luteal (C)
Tumor	T1	2/9	1/5	1/4
	T2	8/15	6/8	2/7
	T3	10/16	7/7 (S3)*	3/9
Node	N0	0/5	0/1	0/4
Grade	N1	12/25	9/13	3/12
	N2	8/10	5/6	3/4
	G1	1/7	0/1	1/6
	G2	9/19	7/11	2/8
Stage	G3	10/14(S1)*	7/8	3/4
	I	0/4	0/1	0/3
	II	7/15	3/7	3/8
	IIIA	13/19	11/12 (S4)*	2/7
Angiogenesis grade	1	0/3	0/1	0/2
	2	4/11	3/5	1/6
	3	9/14	6/8	3/6
	4	7/12	4/6	2/6
Angiogenesis score	1	2/12	1/2	1/10
	2	7/14	3/8	4/6
	3	11/14 (S2)*	9/10	2/4
Lymph vessel invasion	–ve	14/32	10/15	4/17
	+ve	6/8	4/5	2/3
Blood vessel invasion	–ve	10/27	7/11	3/16
	+ve	10/13	7/9	¾(S5)*
Estrogen receptor	–ve	11/18	8/13	3/5
	+ve	9/22	6/7	3/15

$\chi 2$ test is used * $P < 0.05$ is significant(S)
P = (S1),0.02& (S2), 0.007& (S3), 0.01&(S4), 0.02&(S5), 0.02.

Table 3. Cox analysis of disease free survival.

		B	SE	Wald	Df	Sig.	Exp(B)	95% CI for Exp (B)	
								Lower	Upper
(A)	Group	-1.182	0.491	5.797	1	0.016*	0.307	0.117	0.803
	Stage			4.279	3	0.233			
	Stage1	-13.588	453.213	0.001	1	0.976	0.000	0.000	-
	Stage2	-0.781	1.081	0.523	1	0.470	0.458	0.055	3.807
	Stage3	0.249	1.041	0.057	1	0.811	1.283	0.167	9.878
	Ang.sc			8.926	2	0.012*			
	Ang.sc1	-2.181	0.772	7.981	1	0.005	0.113	0.025	0.513
	Ang.sc2	-0.796	0.485	2.696	1	0.101	0.541	0.174	1.167
	ER	0.742	0.451	2.706	1	0.100	2.100	0.868	5.082
(B)	Group	-1.135	0.573	3.917	1	0.048*	0.322	0.105	0.989
	Stage			5.954	3	0.114			
	Stage1	-13.287	447.595	0.001	1	0.976	0.000	0.000	-
	Stage2	-1.424	1.221	1.361	1	0.243	0.241	0.022	2.635
	Stage3	0.004	1.195	0.000	1	0.997	1.004	0.096	10.443
	Ang.sc			4.657	2	0.097			
	Ang.sc1	-1.680	0.790	4.519	1	0.034	0.186	0.40	0.877
	Ang.sc2	-0.410	0.527	0.606	1	0.436	0.664	0.236	1.863
	ER*group	0.267	0.509	0.276	1	0.600	1.306	0.482	3.542
(C)	Ang.sc*group			5.874	2	0.053*			
	Ang.sc1*group	-2.394	1.033	5.373	1	0.020*	0.091	0.012	0.691
	Ang.sc2*group	-0.587	0.630	0.868	1	0.352	0.556	0.162	1.913
	Group*Stage			4.360	3	0.225			
	Group*Stage1	-14.717	850.018	0.000	1	0.986	0.000	0.000	-
	Group*Stage2	-1.015	0.635	2.559	1	0.110	0.362	0.104	1.257
	Group*Stage3	-1.173	0.754	2.421	1	0.120	0.309	0.071	1.356

P < 0.05 is significant
A = Univariant analysis
B = Multivariate analysis
C = Subset analysis

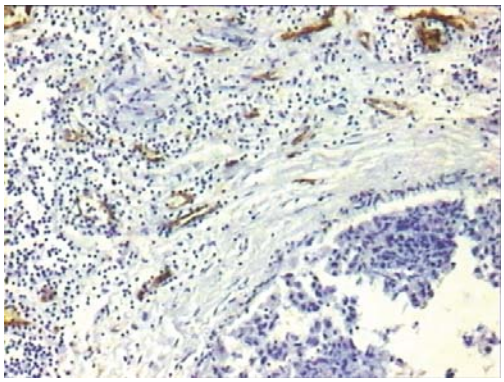

Fig 1. Breast cancer factor VIII Immunocytochemical stain Low power X 40 MVDG (VH).

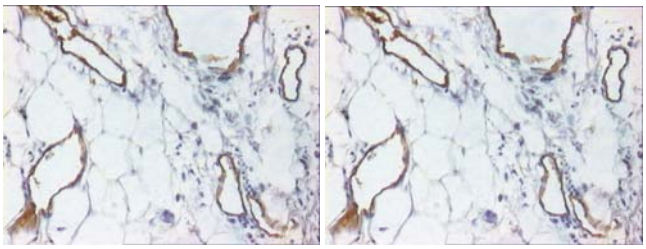

Fig 2. Breast cancer factor VIII Immunocytochemical stain High power X 200 MVC 6 Angiogenic score 1.

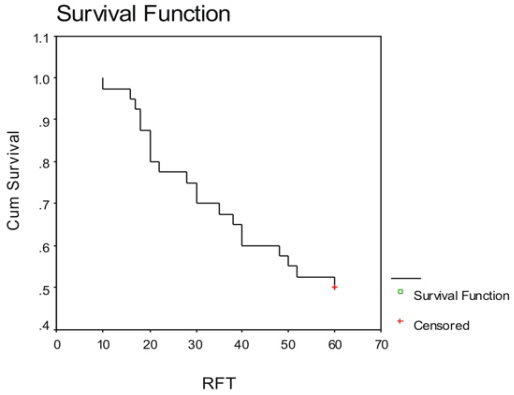

Fig 3. Survival function for all patients.

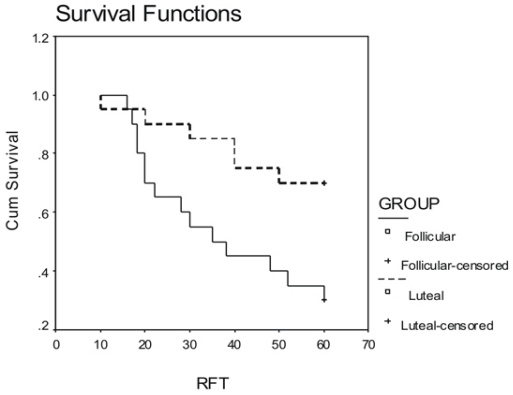

Fig 4. Kaplan Meier Survival curve for follicular and luteal groups.

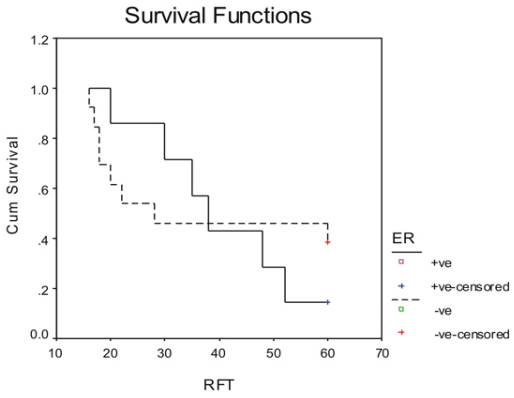

Fig 5. Kaplan Meier Survival curve according to estrogen receptor status in the follicular group.

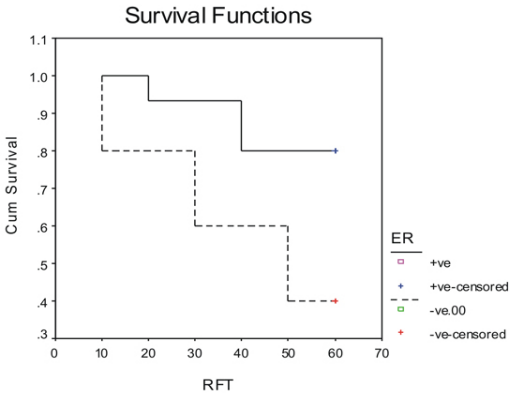

Fig 6. Kaplan Meier Survival curve according to estrogen receptor status in the luteal group.

DISCUSSION

In this study, the microvessel count (MCV) & angiogenic score (ang. score) fluctuated during menstrual cycle, with aggressive pattern (more MVC & ang. score) follicular, as evidenced indirectly by.[36] That's related to vascular endothelial growth factor (VEGF) cyclic changes.[37]

Coinciding with[38] the 5 years DFS was 50%, significantly the tumor recurrences were common in the follicular phase as evidenced in most studies[16,17] contradicting.[18] The low luteal recurrences are mostly related to the protective strait jack effect of progesterone on per operative cancer cell dissemination.

For the study population, tumor recurred with aggressive tumor microenvironment (higher tumor grade as[39] and higher angiogenic score as).[33,40]

But follicular phase recurrences occurred at certain tumor burden i.e. "Rapidly growing fared Worst" (advanced tumor stage and larger tumor size) as.[41,42] and luteal phase recurrences occurred when the tumor cells are discohesive (positive angioinvasion) which represents as a marker for "snap shot" of tumor dissemination as proved by[43] i.e. flawed the strait jack effect of PG

On univariant Cox analysis , this study defined menstrual timing as a predictor of survival (luteal phase protection 0.3 to get 95% CI), as found by[43] but that association was disputed by.[45] That association in mostly related to the unopposed estrogen of Hrushesky[46] & spontaneous dissemination autonomy (SDA).[47]

Similarly the angiogenic score was a predictor of survival as,[40,48] that's speculated to the secreted pro angiogenic factors (facilitate meta static cascade &allow selective growth advantage) and increase the surface area for cancer cell dissemination.

Their bivariant analysis defined luteal phase patients with low angiogenic score had the best prognosis that's related to tumor resection when Estrogen drive is minimal, progesterone derive is maximal in already angiostatics predominance so SDA[47] and microscopic deposits at a chaotic boundary may flaw, that notion open the way for chaotic mathematics in cancer breast modeling and selective criteria for antiangiogenic therapy.

Seeming logic this study on multivariate analysis found TNM staging "chronologic tumor age" was not relevant as,[48] but the menstrual timing was the discriminant factor (overall luteal protection 0.32) as found by[50,51] also[52] found luteal phase mastectomy and oophrectomy as a discriminant factor.

The life table study declared significantly shorter survival time for women took place their surgery in the follicular as most studies[44,45] but[46] found longer follicular phase (DFT)and[19, 54] reported insignificant relation, that could be explained by the nonlinear, chaotic, 3 shoulder model of host tumor interaction and fine perturbation "endocrine status" at time of surgery "menstrual phases" affect the ultimate outcome through SDA,[47] angioswitch of micro metastasis[55] or increased colonagenic fraction.[56]

Also ER +ve group had better relapse free time when compared to ER –ve group as corporated by[19] that's related to its differentiating action (low risky).

When studied together (ER status and menstrual timing of surgery) in relation to DFT, the correlation were insignificant either follicular or luteal as,[57] contradicting[19] who found ER +ve patients in the follicular phase had better DFT.

The lack of correlation corporates the beneficial effect of menstrual timing may be mediated by another mechanisms other than estrogen receptors.

In conclusion: patients operated in the follicular phase had aggressive angiogenic pattern. The breast cancer recurrences occurred frequently with aggressive microenvironment, follicular phase recurrences occurred at certain tumor burden more frequently than luteal phase recurrence that coincided with discohesive pattern. This study reinforce the importance of timing of surgery in the prognosis of premenopausal operable cancer breast (univariant, subset, multivariate), the benefit is pronounced in those with low angiogenic score resected in the luteal phase, also the effect of menstrual timing is angiogenesis dependent but hormonal receptor independent. Furthermore trial conducted on neo-adjuvant endocrine therapy in follicular phase and antiangiogenic therapy for luteal phase patients having low angiogenic score are required. This marker according to Tumor marker Utility Grading System (TUGS) is scored as grade I (investigational) as our data found menstrual timing had an effect on the biologic process of host and tumor, and affect disease outcome (DFS, DFT) but not considered for standard clinical practice as the systemic adjuvant therapy may confound the outcome, and the LOE is II.

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