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Measuring Ovarian Escape in Premenopausal Estrogen Receptor-Positive Breast Cancer Patients on Ovarian Suppression Therapy at Suez Canal University Hospital, Ismailia, Egypt

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Abstract

Background: **Limited studies measured the proportion of persistent ovarian escape (OE) in breast cancer patients on ovarian suppression (OS) therapy.** ***Aim:*** **To investigate persistent OE in premenopausal breast cancer patients on OS therapy and its correlation to clinical data and early clinical outcomes.** ***Methods:*** **This was a retrospective study, evaluating the percentage of persistent OE in premenopausal women on OS therapy within 3, 6, 9, 12, and 18 months of goserelin acetate injections. Demographic data, histopathological, hormonal receptor status, stage, and treatment received were retrieved from files of 143 eligible patients attending the Clinical Oncology and Nuclear Medicine department, Suez Canal University, Hospitals, Ismailia, Egypt. Blood Hormonal levels were assessed quarterly for the first year and then after 6 months.** ***Results:*** **88 (61%) patients showed OE within the first 3 months. The OE group was significantly younger than the OS group (mean age 38.26 and 42.47 years for OE and OS groups, respectively) (p-value <0.001). The mean BMI was higher in the OE group (32.8 kg/m2) compared to the OS group (31.2 kg/m2) and was statistically significant (p-value 0.020). Rates of ovarian escape were significantly higher in women who were receiving aromatase inhibitors versus tamoxifen (94.7% vs. 49.5%) (p-value <0.001). Also, OE group has slightly lower disease-free survival compared to OS group.** ***Conclusions:*** **A significant percentage of patients did not achieve OS after 3 months of OS therapy. That was associated with younger age and higher BMI. OS was slightly better regarding disease-free survival than OE group.**

Keywords: Ovarian Escape; Ovarian suppression; Premenopausal; Breast Cancer

Introduction

Worldwide and in Egypt, breast cancer is the most prevalent type of cancer among women[1]. The estrogen receptor is present in around 70% of breast cancers.[2] Premenopausal women must receive extra attention since they typically have a higher probability of having an advanced condition when they present[3]. The International Breast Cancer Study Group began two randomized trials in 2013: the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT). The treatment of high-risk premenopausal women with estrogen receptor-positive (ER+) and/or progesterone receptor-positive breast cancer has

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changed dramatically because of these two trials. At 8 years, women who took either tamoxifen or an aromatase inhibitor (AI) along with ovarian suppression (OS) had a higher disease-free survival rate than those who just received tamoxifen[4]. The American Society of Clinical Oncology suggested that premenopausal women with estrogen receptor-positive breast cancer will benefit from OS in combination with adjuvant endocrine therapy based on the findings of the SOFT and TEXT trials[5]. According to recent studies, 25% of patients receiving ovarian suppression treatment did not have a sufficient OS at three months. Even at 12 months, almost 17% of patients did not have a satisfactory OS[6]. Although the therapeutic significance of this is still unknown, failing to attain maximally suppressed estradiol levels could theoretically result in worse outcomes for individuals with ER+ breast cancer. The objective of this study is to analyze predisposing factors and their relationships to clinical outcome in premenopausal patients with ER+ breast cancer at Suez Canal University Hospital, Ismailia City, Egypt who did not achieve maximal estradiol (E2) suppression within 3 months.

Patients and Methods

This was a retrospective study evaluating the proportion of persistent OE in premenopausal, estrogen-receptor positive breast cancer patients on OS therapy and its correlation to baseline clinical data and early clinical outcomes. The study was conducted at the Clinical Oncology and Nuclear Medicine department, Suez Canal University Hospital (SCUH), Ismailia city, Egypt. 143 premenopausal breast cancer patients were included with the following criteria: age more than 18 years old, patients defined to be premenopausal by appropriate clinical parameters or laboratory tests if needed, female patients with breast cancer stage I-III, estrogen receptor-positive breast cancer, patients receiving OS therapy with Goserelin Acetate (GnRH agonist) injections in conjunction with Tamoxefen or Aromatase Inhibitor. We excluded patients with metastatic breast cancer and postmenopausal women. Patients were selected by a non-probability convenience sampling method. Patients' clinical, pathological, and treatment-related data were retrieved from medical records from Jan. 2010 to Dec. 2018. Patients' BMI was classified according to WHO classification. Premenopausal, estrogen-receptor positive breast cancer patients receiving gosrelin 3.6mg every 28 days as ovarian suppression therapy were evaluated by estradiol level at 3, 6, 9, 12 and 18 months after starting OS therapy. OE is defined as estradiol level > 2.7 pg/ml if on aromatase inhibitor therapy. This definition is based on the recommended guidelines by Smith et al., which is also employed in the SOFT- EST analysis[6,7]. Although there are no guidelines for determining adequate ovarian suppression for patients on tamoxifen, we will define it as having estradiol lever <21 pg/ml as this is the cutoff accepted by our institution for pre *vs.* post menopause. All laboratory tests were performed in SCUH lab[8]. The study was conducted on 143 premenopausal estrogen-receptor positive breast cancer patients. The patients were divided into two groups. The 1st group contains patients who had achieved ovarian suppression, and the 2nd group contains those who did not achieve ovarian suppression while on OS therapy.

Statistical Analysis

Then we compared baseline clinical data

and early clinical outcomes between the two groups. Patients' data was entered into a Microsoft Excel sheet and then analyzed using the statistical package for social sciences (SPSS) software program version 25.0. Data was presented as tables and graphs, as suitable. For descriptive analysis, numerical data was expressed as mean± standard deviation, whereas categorical data was expressed as frequencies and percentages. Student t-test and ANOVA were used to compare scores between two groups, whereas Chi-square test was used to compare categorical data. Results are considered statistically significant at a p-value less than 0.05 and highly significant at p-value < 0.001.

Ethical Considerations

Ethical approval was obtained from the Research and Ethics Committee at Faculty of Medicine, Suez Canal University and both SCU hospital and the Clin. Oncology Dept. Patients' data was kept confidential and was not used outside this study.

Results

Table 1 summarizes the baseline characteristics of the entire study group, as well as those who developed OS versus OE after 3 months of treatment. The mean age of the total population was 39.88± 6.05 years. The mean BMI of the population was 32.2 ± 5.5 kg/m^2. 73.4% of the patients were on tamoxifen as an oral endocrine drug. There were 88 (61%) patients with OE within the first 3 months. The OE group was significantly younger than the OS group (mean age 38.26 and 42.47 years for OE and OS group, respectively) (p value <0.001). The mean BMI was higher in the OE group (32.8 kg/m^2) compared to the OS group (31.2 kg/m^2) and was statistically significant (p value 0.020). Rate of ovarian escape were significantly higher in women who were receiving aromatase inhibitor versus tamoxifen (94.7% vs. 49.5%) (p value <0.001). Figure 1 shows that there is a gradual decrease in the percentage of ovarian escape. all over the 18 months follow up. Subsequently, there has been a gradual increase in the percentage of ovarian suppression all over the 18 months follow up. At the end of follow up period (18 months), about 13% still had sustained OE. Ultimately, of the 143 women in our analysis, 88 (61%) did not attain OS at 3 months, and 59 women (41%) still had not attained OS after 12 months of goserlin therapy and 20 women (13%) after 18 months, still had OE. At 6 months, 80 women had sustained OE. 67 women had sustained ovarian escape at 9 months.

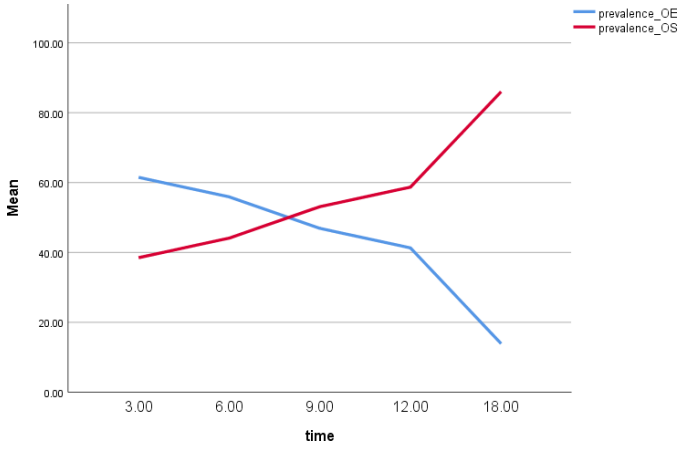

Figure 1: Percentage of OS and OE among the studied sample over time

And after 18 months, 20 women still had OE. Those with persistent ovarian escape tended to be younger and overweight. For those with ovarian escape at 3, 6, 9, 12 and 18 months, their median age was 38.26, 38.48, 38.52, 38.47 and 34.8 years, respectively (Table 2). Mean BMI was 32.8, 32.9, 32.9, 32.6, 32.0 kg/m^2 for OE group at 3, 6, 9, 12, and 18 months of treatment, respectively. On multivariable analysis of age, BMI, and type of hormonal drug, all variables retained statistical significance for achieving OE. Age showed odds ratio of 0.82 with 95% confidence interval 0.75–0.89 (p value 0.000). BMI showed odds ratio of 1.16 with 95% confidence interval 1.06–1.27 (p value 0.001) (Table 3). Although our study was not powered enough to look atthe disease-free survival in both groups, it is interesting to note that OE group has slightly lower disease-free survival compared to OS group, as shown in table 4 and figure 2.

Table 1: Baseline characteristics by OE or OS

Variables	Total (n=143)	OE (n=88)	OS (n=55)	P-value
Age at diagnosis (yrs)	39.88± 6.05	38.26 ± 5.59	42.47 ± 5.90	**<0.001**[*a]
BMI, kg/m2 Mean ± SD	32.2 ± 5.5	32.8 ± 5.4	31.2 ± 5.7	**0.020**[*a]
Comorbid diseases no. (%)				
Absent	123 (86)	79 (89.8)	44 (80)	0.101[b]
Present	20 (14)	9 (10.2)	11 (20)	
Staging no. (%)				
I	17 (11.9)	13 (14.8)	4 (7.3)	0.090[b]
II	60 (42)	31 (35.2)	29 (52.7)	
III	66 (46.2)	44 (50)	22 (40)	
HER2 receptor no. (%)				
Negative	115 (80.4)	72 (81.8)	43 (78.2)	0.594 [b]
Positive	28 (19.6)	16 (18.2)	12 (21.8)	
Surgery no. (%)				
MRM	121 (84.6)	71 (80.7)	50 (90.9)	0.099 [b]
CBS	22 (15.4)	17 (19.3)	5 (9.1)	
Trustuzumab administration				
No	118 (82.5)	74 (84.1)	44 (80)	0.531 [b]
Yes	25 (17.5)	14 (15.9)	11 (20)	
Oral endocrine drug no. (%)				
Aromatase inhibitor	38 (26.6)	36 (40.9)	2 (3.6)	**<0.001**[*b]
Tamoxifen	105 (73.4)	52 (59.1)	53 (96.4)	

Data are presented as number (%) or mean (SD). [a=]p-values are based on independent t- test. Statistical significance at P < 0.05. [b=]p-values are based on Chi square test. MRM; modified radical mastectomy, CBS; conservative breast surgery, BMI; body mass index, HER2; human epidermal growth factor receptor 2, OS; ovarian suppression, OE; ovarian escape.

Discussion

The current study showed a significant percentage of women with OE while on OS therapy. More than half of patients (61%) did not attain OS at 3 months. After 18 months of goserlin therapy, still 13% of women had OE. These findings are quite different from previous literature. For example, a single-centered, retrospective

study on 46 premenopausal patients showed that 24% of patients were not adequately suppressed after 3 months of therapy with 6% persisted in having OE after 1 year[9]. This difference might be related to the type of drug used. We used goserlin in all patients, while Burn's et al used either goserlin or leuprolide. Also, our study population showed higher BMI (32 kg/m^2) compared to BMI of 27.9 kg/m^2 in Burn's et al study[9].

Table 2: characteristics of patients with persistent OE at 3, 6, 9, 12 and 18 months.

Characteristics	3 mon. N (%)	6 mon. N (%)	9 mon. N (%)	12 mon. N (%)	18 mon. N (%)
Patients with sustained OE	88 (61)	80 (55)	67 (46)	59 (41)	20 (13)
Age at diagnosis (yrs) Mean ± SD	38.26 ± 5.59	38.48 ± 5.66	38.52 ± 5.70	38.47 ± 5.562	34.8 ± 4.456
BMI, kg/m^2 Mean ± SD	32.8 ± 5.4	32.9 ± 5.4	32.9 ± 5.6	32.6 ± 5.5	32.0 ± 5.6
Aromatase inhibitor	36(40.9)	34 (42.5)	27 (40.3)	24 (40.7)	6 (30)
Tamoxifen	52(59.1)	46 (57.5)	40 (59.7)	35 (59.3)	14 (70)

Abbreviations: BMI, body mass index (kg/m^2); OE, ovarian escape.

Table 3: Odds ratio for achieving ovarian escape within 3 months from univariable and multivariable logistic regression models.

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.87 (0.81 -0.93)	0.000	0.82 (0.75-0.89)	0.000
BMI	1.08 (1.01-1.15)	0.023	1.16 (1.06-1.27)	0.001
Type of hormonal drug	0.05 (0.01-0.25)	0.000	0.05 (0.01-0.25)	0.000

Abbreviations: BMI, body mass index (kg/m^2); CI, confidence interval; OR, odds ratio.

Similarly, the SOFT-EST prospective study, conducted on 116 patients randomly assigned to triptorelin plus exemestane or triptorelin plus tamoxifen, showed that 25%, 24%, and 17% of patients on exemestane plus triptorelin had suboptimal estradiol suppression at 3, 6, and 12 months, respectively. That suggested a significant ratio of early OE. Again, the different results can be attributed to the type of GnRH agonist used in each study. This needs to be further addressed in future studies to compare each drug efficacy in ovarian suppression. Also, the mean BMI of the current study population is 32 kg/m^2 compared to 24 kg/m^2 in the SOFT-EST trial. That can explain the higher percentage of ovarian escape in the current study[6]. In the current study, younger age was significantly associated with higher rate of OE. The mean age of the current study's population was 39.8 (SD 6.0). After 3 months of OS therapy, the OE group had a mean age of 38.2 (SD 5.5) compared to the OS group who had mean age of 42.4 (SD 5.9). The mean age of OE group was similar at 3 months (38 years). In the study of Burns *et al.*, the whole group of the study had a mean age of 42 years, and the average age of the OE group was 38.5 years compared to 43 years in OS group. Young age was the only statistically significant associated risk factor demonstrated in that study[9]. The SOFT-EST study could not show an association between age and OE as the median age of population was 45 years and

younger population represented small percentage of the study group. However, it was observed that sustained OE was mainly noted in the younger women[6]. That was supported by a study by Guerrero *et al.* showing that age <48 years was a predictor factor for ovarian function recovery overtime[10].

Table 4: 3-year disease free survival in both groups			
Variables	Mean (months)	Standard error	p-value
Ovarian escape	32.455	0.756	0.006
Ovarian suppression	34.836	0.656	

** P values are based on as log-rank test. Statistical significance at P <0.05*

In practice, it is important to consider that younger women with stronger ovarian reserve have higher probability of experiencing ovarian function recovery during treatment and close monitoring should be done[11]. Higher BMI was statistically significantly associated with higher probability of OE. In the current study, the mean BMI of the entire group was 32.2 ± 5.5. At 3 months of follow up, the mean BMI of OE group was higher than that of OS group (32.8 and 31.2 kg/m^2 respectively). Similarly, the SOFT-EST study showed that one of the factors that predicted the odds of OE was higher BMI (p= 0.05)[6]. Burns *et al.* also showed that the mean BMI of the entire group was 27.9. After 3 months of OS therapy, the BMI of the OE group was 29, while the BMI of the OS group was 27.5. However, this difference was not statistically significant. It may be due to the small sample size of the study[9]. That could be attributed to the metabolic changes that occur in obese women. Some investigators observed that excess body weight leads to hormonal alterations including elevation in estradiol plasma levels and production rates.

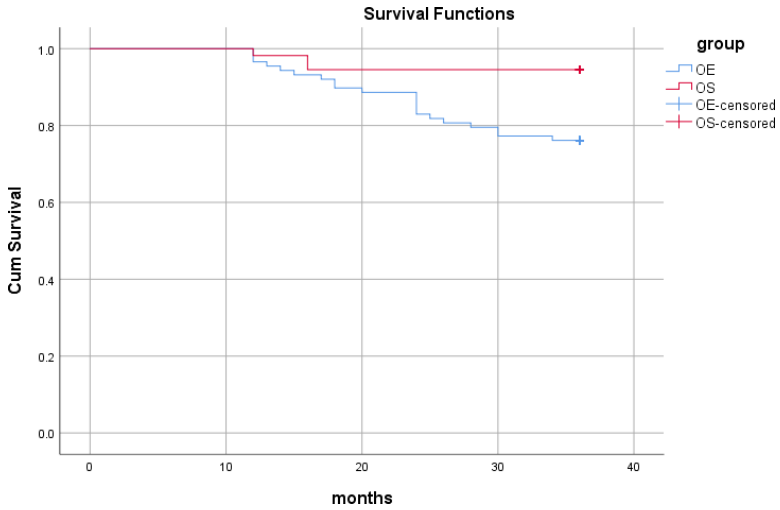

Figure 2: Three-year disease-free survival in both groups

Adipocytes could synthesize and secrete substances called adipocytokines that act like hormones affecting the whole body. Leptin is one of these substances that influences the hypothalamus-pituitary-gonadal axis at multiple levels. Additionally, adipocytes manufacture estrogens through aromatization of androgenic

precursors, and this production rises proportionally to overall body adiposity[12]. Another important factor is the endocrine therapy used in conjunction with OS. In the current study, rates of OE were significantly higher in women who were receiving aromatase inhibitor versus tamoxifen (94.7% vs. 49.5%, p value <0.001). The study of Burns *et al.* showed almost similar rates of OE in both groups receiving aromatase inhibitors and tamoxifen (23% vs 25% respectively). Because of the limited sample size, the study's power to detect a meaningful difference was insufficient[9]. On the other hand, the SOFT-EST study showed that AI plus triptorelin had OE at least once in the follow up time at a rate of 34%. The tamoxifen plus triptorelin group had higher rates of OE. The findings of the SOFT/TEXT trial, which demonstrated higher disease-free survival in the AI group compared to the tamoxifen group, reinforced this. In SOFT, the rates of 8-year disease-free survival with tamoxifen alone, tamoxifen plus OS, and exemestane plus OS were 78.9%, 83.2%, and 85.9%, respectively. Tamoxifen alone had an 8-year overall survival rate of 91.5%, tamoxifen with OS had a rate of 93.3%, and exemestane plus OS had a rate of 92.1%[6] The contradictory results could be explained by ovarian escape. For instance, patients who are overweight and have a larger percentage of fat and, consequently, a higher amount of aromatase, may not receive an adequate dose of aromatase inhibitors. No prior chemotherapy (P =.06) and a higher BMI (P =.05) were related with greater estrogen levels in the SOFT-EST research[13]. The difference between the current study and other studies regarding the effect of endocrine therapy may be due to the fact that the current study used a retrospective approach which limited the patients' selection. Therefore, more than 70% of the study population were on tamoxifen beside the OS. The real comparison between AI and tamoxifen needs further studies with different study designs. Tamoxifen may be fair to consider in younger women as initial therapy until OS is attained and validated by laboratory findings, even though significant trials like SOFT-EST revealed improved outcomes of AI over tamoxifen with concurrent OS. Age, BMI, and the kind of hormonal medication were discovered to be predictors of attaining ovarian escape in the current study's multivariable analysis of characteristics associated with ovarian escape. Age had a 0.82 odds ratio with a 0.75 to 0.89 95% confidence interval (p = 0.000). With a p value of 0.001, the odds ratio for BMI was 1.16, with a 95% confidence interval of 1.06 to 1.27. Burns et al. further demonstrated that age was the sole variable with sustained statistical significance (odds ratio, 0.86; 95% confidence range, 0.76-0.98; p =.024) for obtaining OE after multivariable analysis of age, BMI, and receipt of prior treatment[9]. In the current study, the disease-free survival duration was statistically significantly longer in the OS group than in the OE group (34.8 months and 32.4 months; p-value 0.006 respectively). The clinical outcome of OE in the SOFT-EST trial can only be theorized and was not addressed directly. Another meta-analysis by key *et al.* found that levels of endogenous sex hormones including estradiol were statistically significantly associated with breast cancer risk. However, it was conducted on postmenopausal women [14]. There is currently no level I evidence that suggests clinical outcomes vary according to the degree of ovarian suppression. To address the risk of breast cancer recurrence in premenopausal women with OE despite receiving OS therapy, additional research is required. In conclusion, a large proportion of patients did not

achieve OS following 3 months of OS therapy. Younger age and higher BMI were associated with that. OS had a somewhat higher rate of disease-free survival than the OE group.

Limitations

The brief follow-up period and relatively small sample size. There also might be an institutional bias because this study was performed in a single government hospital. This, in turn, limits generalizability. It is a retrospective study which limits the process of patients' selection and categorization. For example, most of the patients started tamoxifen as initial therapy with OS. Also, due to selection bias, most premenopausal patients who started on AI are high risk patients. Therefore, the real comparison between AI and tamoxifen in the efficacy of OS needs further studies. Some patients did not start OS therapy with the endocrine therapy from the beginning, rather it was added later for unreported reasons. As there was no established cutoff for acceptable OS while using a GnRH agonist and tamoxifen, we used the estradiol cutoff values typically used for postmenopausal women.

Recommendations

Additional research on a larger sample size and a longer follow-up is advised. Multicenter studies are advised to get rid of institutional and selection biases.

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Authors' contributions: All authors participated in the design of work, analysis, and interpretation of data.

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