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RESEARCH ARTICLE

Peri-operative surgical outcome of breast cancer in geriatric age females in Egypt

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ABSTRACT

Background: Nodular thyroid lesions are common among the population, especially there no consensus about the best surgical treatment options for geriatric breast cancer patients due to exclusion from clinical trials. Further, fear of complications due to increased age often plays an important role in the decision making that affect the choice of treatment offered to these patients. **Methods:** This is a clinical multi-institutional retrospective study that included 308 geriatric patients (>65y) with breast cancer, surgically treated at Menoufia University Hospital and Tanta Cancer Center, Egypt from the period between January 2010 to end of December 2019. Data on treatment, surgical complications, and tumor characteristics were collected and analyzed. **Results:** One or more complications were experienced by 41·6 % of the patients, predominantly they were minor wound complications as seroma or minor wound infections. Serious complications occurred in 11% of patients. The main risk factors for complications included age >75years old (p<0.001 *: OR=2.65, CI95%:1.64-4.30), co-morbidity (P=0.029: OR=1.76, CI95%:1.06-2.93)) where two co-morbidities served as a risk factor in comparison to one morbidity (P=0.013: OR=2.17, CI95%: 1.17-4.03)) and More than two (P=0.039: OR=2.45, CI95%:1.03-5.85), and MRM surgery (P=0.029: OR=2.0, CI95%: 1.06-3.76). **Conclusion:** The incidence of serious postoperative complications is not high in elderly breast cancer patients. Aggressive surgical approaches, age more than 75 and multiple co-morbidity, are important factors affecting the incidence of early postoperative complications in these patients.

Keywords: Breast cancer; Complications; Early postoperative; Geriatric

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INTRODUCTION

Elderly cancer patients represent a major public health issue. Indeed, the number of elderly patients living with cancer has increased in the last years, due to a longer life expectancy and to the possibility to diagnose cancer early and treat it accordingly. Breast cancer is the most common type of cancers in females, one of every eight women worldwide has breast cancer through her life. It is estimated that 21% of newly diagnosed patients are over 70 years of age (Markopoulos 2012) It has been extensively reported that breast cancer-related mortality increases with age, regardless of disease stage (Gosain et al., 2016). As increasing age is an important predictive factor for the development of breast cancer, it is expected that the number of older patients diagnosed with breast cancer will rapidly increase concomitantly (McPherson et al., 2000).

In older patients, breast cancer occurs against a background of other diseases as multimorbidity (having two or more chronic diseases) is strongly associated with increasing age (Barnett et al., 2012). In contrast, studies have shown that increasing longevity may be accompanied by an extended period of good health, resulting in a relevant population of older patients with breast cancer and minimal comorbidity (Chatterji et al., 2017). This diversity in health

status in older patients is challenging for clinicians in decision making when balancing the benefits and toxicities of breast cancer treatment. In a practice setting for elderly breast cancer patients, many treatment options are necessary because of their comorbidity, low organ function, and poor performance status. This frailty of elderly patients sometimes means that not enough elderly patients receive treatment and also causes a high rate of adverse events, resulting in a low rate of positive outcomes even though patients have received standard treatment. Moreover, there are few data to suggest guidelines for standard treatments of elderly breast cancer patients (NCCN guidelines 2017), because they have potentially been underrepresented in clinical trials (Clarke et al., 2005).

In this study we considered female patients diagnosed as breast cancer in age of 65 years or older is elderly.

PATIENTS AND METHODS

This study designed to be retrospective study in Tanta Cancer Center and Menoufia University Hospital in the period between January 2010 to end of December 2019 where 308 female patients 65 years old and older diagnosed by triple assessment (clinically, radiologically and pathologically) as breast cancer were collected with their data regarding the tumor size, site, stage, grade, nodal status, type of surgical interference WERE done for every patient and the adjuvant or neoadjuvant treatment together with the co morbid diseases and its effect on surgical decision and outcome of surgery with the pathological results, hormonal receptors ER, PR, Her2/neu and KI67.

Ethical approval was granted for the study by Menoufia University-Faculty of Medicine`s ethics committee according to the Declaration of Helsinki. It was taken for research done on elderly patients diagnosed with cancer breast.

All post-operative complications occurred within 30 days of the last primary surgery were recorded. Patients were classified as having serious complications if they had complications (other than a seroma or primary/minor infection) that warranted readmission, or delayed her discharge. Patients with DM or skin lesion other than the skin cancers excluded from collected data. All data are computerized from medical files and analyzed to get the results.

The main endpoint of this study is analysis of clinicopathological factors of breast cancer in this age group and the second endpoint is factors affecting post-operative complication in these patients.

RESULTS

This study, retrospectively, included 308 female patients 65years old and older diagnosed and treated from breast cancer in Menoufia University Hospital and Tanta Oncology Center from the period from January 2010 to the end of December 2019. The clinical and demographic details of these patients are listed in Table 1, the mean age was (70.5 ± 4.6 years), and 69,9% of them had one or more comorbidity. 59,7% of the tumors were left sided, 49.4% located at upper outer quadrant and 67.5% were T2 (2.1-5 cm.). Only 16 patients (5.2%) had neoadjuvant treatment and most of them (81,8%) surgically treated by modified radical mastectomy.

The histopathological characters of the resected tumors are listed in Table 1; 84.4% of them were invasive ductal carcinoma, grade 2 and 77.9% had positive intra ductal component ranged from 3 to 70%. Only 4 cases (1.3%) had infiltrated positive surgical margin with the least margin in negative cases ranges from 0.4 to 6.0 cm. The median number of harvested axillary lymph nodes was 15 (11-29), 35.1% were positive for lympho-vascular invasion and 5.2% had Perinodal invasion.

As regards the molecular characters of the studied population, data was available for 300 patients (as regard ER, PR and HER2/neu) and for 297 patients (as regards KI67). 78.7% (236/300) were ER +ve, 65.3% (196/300) were PR +ve and only 17.3% (52/300) were HER2 neo +ve. The mean percentage of KI67 expression was 23.8±19.4%. 41.6% (128/308) of the patients in this study developed early postoperative complications and most of these complications 114/128, (89%) were minor complications (grade 1 and 2 according to Clavien –Dindo classification). (Tables 2 and 3).

14.4% (43/304) of these patients developed systemic recurrence, while 4.4% (13/304) had loco-regional recurrence during follow up (Figure 1).

The 30-days postoperative mortality was 1.3% (4/308), of the remaining patients (304pts.), 43.3% had adjuvant chemotherapy, 56.6% had adjuvant radiotherapy and 82.9% received adjuvant hormonal treatment. Age >75 years old was a risk factor for occurrence of complications (p<0.001 *: OR=2.65, CI95%:1.64-4.30). Co-morbidity was a risk factor for occurrence of complications (P=0.029: OR=1.76 (1.06-2.93)), Two co-morbidities served as a risk factor in comparison to one morbidity (P=0.013: OR=2.17 (1.17-4.03)) and More than two (P=0.039: OR=2.45 (1.03-5.85)). Also MRM served as a risk factor for occurrence of complications (P=0.029: OR=2.0 (1.06-3.76)) (Table 4).

Statistical Analysis

Analyses were conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as the mean ± SD or no and %. The significance of the association between the two groups for qualitative variables was determined using Pearson's chi-square ($\chi 2$) test. Odd ratio (OR) was used to detect the risk factors where OR =1 →nil, >1-→ risky and <1-→protective. A p-value was considered significant if <0.05.

DISCUSSION

By the end of the first half of this century, the number of old people (the age group between 65 and 79 years) in western countries will reach 44% of the population, and the number of very old people (≥80 years old) will increase by 180% (Karim-Kos et al., 2008).

Cancer prevalence will increase in this age population to reach 15% with the most frequently sites affected in older women, (representing just over 50% of all cancer cases): breast (18%), colon-rectum (13%), lung (11%), stomach (6%) and uterus (6%) (Ferlay et al., 2006).

Now, 40% of breast cancer patients are older than 65 years of age in developed countries, so the health care system will face increased number of old people suffering from breast cancer with multiple comorbidities and geriatric syndromes (Wildiers et al., 2007). Most of these patients are not treated according to evidence-based guidelines, because of age, comorbid conditions, frailty and patients and physician's preferences. (Van de Water et al., 2012, Land LH et al., 2012).

This study retrospectively evaluates the clinicopathological factors of 308 geriatric patients with breast cancer, surgically treated at two high flow oncology departments in Egypt, and their impact on early postoperative mortality and morbidity from the period from Jan. 2010 to Dec. 2019.

In this study, the mean age was 70.5 ± 4.6, and no upper age limit was considered, but the oldest case was 85 years patient, which had modified radical mastectomy.

As in younger patients, most of the tumors analyzed were invasive ductal carcinoma (84.4%), and located at the upper outer quadrant of the breast (49.4%). FNAC was mostly used for pathological diagnosis in early years of this study (66.2%), and later True-cut biopsy became the standard method in late cases (31.2%).

Breast cancer is often presented with a larger tumor size in elderly women than in younger females, due to lack of screening mammography programs in women older than 70 in most countries (Ecomard et al., 2013), and this is coinciding with this study where only about 22% of the studied patients presented by T1 tumors.

The surgical treatment of these patients should always have radical oncological intent no matter the patient's age (Alderman et al.,2011). The most recent recommendations of the International Society of Geriatric Oncology and the European Society of Breast Cancer Specialists (EUSOMA) state that breast conserving surgery with whole-breast radiotherapy or mastectomy followed by postoperative radiotherapy in selected patients as standard local treatment for elderly breast cancer patients, and in some cases radiotherapy could be omitted specially in hormone positive cases (Biganzoli et al., 2012, NCCN guidelines 2013).

Table 1. Age and tumor characteristics of the studied patients (n=308)

Item	No.	%	Item	No.	%
Age			**Histological Type**		
Range	65 – 85		**IDC**	260	84.4
Mean ± SD.	70.5 ± 4.6		**IDC + ILC**	20	6.5
Side			**Others**	28	9.1
Right	120		Mucoid carcinoma	4	14.3
Left	184		Squamous cell carcinoma	12	42.9
Bilateral	4		Metaplastic carcinoma	4	14.3
Site			Squamous differentiation	4	14.3
UOQ	152	49.4	Papillary carcinoma	4	14.3
UIQ	92	29.9	**Positive intra-duct component**	68 (22.1%)	
LOQ	24	7.8	Min. – Max.	3 – 70	
LIQ	4	1.3	Mean ± SD.	15.8 ± 21	
UOQ & LIQ	8	2.6			
UOQ & UIQ	4	1.3	Positive **HER2 (n = 300)**	52	17.3
Retro areolar	24	7.8			
Pre-operative pathological diagnosis	204	66.2	**ER (n = 300)**	64	21.3
FNAC	96	31.2	Negative	64	21.3
True cut	4	1.3	Mild	24	8.0
Wedge biopsy	4	1.3	Moderate	148	49.3
Lumpectomy			Marked		
Mass size (cm)			**PR (n = 300)**		
1 – 2	68	22.1	Negative	102	34.7
2.1 – 5	208	67.5	Mild	88	29.3
>5	32	10.4	Moderate	52	17.3
			Marked	56	18.7
			Ki67 (n = 296)	2 – 70	
			Min. – Max.	23.8 ± 19.4	
			Mean ± SD.		
Surgery			**Lymph nodes**		
MRM	252	81.8	Min. – Max.	11-29	
CBS	56	18.2	Mean ± SD.	15.6+ 8.2	
Least margin (cm)					
Range	0.4 – 6		**Multicenteric (n = 308)**	12	3.9
Mean ± SD.	2.7 ± 1.1				
Deep Margin infiltration	4		**Neoadjuvant Therapy**	16	5.2
Skin infiltration	60	19.5	**Adjuvant chemotherapy (n = 304)**	132	43.4
PNI(Perinodal infiltration)	16	5.2	**Radiotherapy (n = 304)**	172	56.5
LVSI(lymphovascular invasion)	108	35.1	**Hormonal therapy (n = 304)**	**252**	**82.9**

Table 2. Recurrence, post-operative complications and mortality among the studied patients (n=308)

Item	No.	%
Recurrence (n = 304)	56	18.5
Systemic recurrence	43	14.1
Loco regional recurrence	13	4.4
30 –days postoperative complications (n = 308)		
No	180	58.4
Yes	128	41.6
30- days postoperative mortality(n=308)	4	1.3

Table 3. Grading of complications by severity (Clavien-Dindo classification)

Grade	Wound complications		Anemia	Cardiac	Respiratory	Neurological	Renal	Total
	Seroma	SSI						
I	35	21	-	-	-	-	3	59
II	22	8	8	2	6	4	5	55
IIIa	3	1	-	-	-	-	-	4
IIIb	-	2	-	-	-	-	-	2
Iva	-	-	-	2	1	1	-	4
IVb	-	-	-	1	2	1	-	4

Table 4. Distribution of the studied tumor characteristics regarding post-operative complications

Item	Complications (n = 308)				p value	Item	Complications (n = 308)				p value
	No (n=180)		Yes (n=128)				No (n=180)		Yes (n=128)		
	no	%	no	%			no	%	no	%	
Age (years)					-	**Site**					0.956
65-75 (n =201)	134	74.4	67	52.3	<0.001	UOQ (n=152)	86	47.8	66	51.6	
>75 (n=107)	46	25.6	61	47.7	*:OR=2.65(1.64-4.30)	UIQ (n=92)	55	30.6	37	28.9	
Co-morbidity						LOQ (n=24)	15	8.4	9	7.0	
Yes (n=215)	117	65.0	98	76.6	0.029*: OR=1.76(1.06-2.93)	LIQ (n=4)	3	1.7	1	0.8	
No (n=93)	63	35.0	30	23.4	-	UOQ + LIQ (n=8)	5	2.8	3	2.3	
Co-morbidity (n=215)	(n=117)		(n=98)			UOQ +UIQ (n=4)	2	1.1	2	1.6	
						Retro areolar (n=24)	14	7.8	10	7.8	
One (n=121)	65	55.6	56	57.1	-						
Two (n=66)	23	19.7	43	43.9	0.013*: OR=2.17 (1.17-4.03)	**Histological Type**					0.934
More than two (n=28)	9	7.7	19	19.4	0.039: OR=2.45 (1.03-5.85)	IDC(n=260)	153	85.0	107	83.6	
Surgery						IDC + ILC(n=20)	11	6.1	9	.0	
MRM (n=252)	140	77.8	112	87.5	0.029*OR=2.0 (1.06-3.76)	Others (n=28)	16	8.9	12	9.4	
CBS**(n=56)**	40	22.2	16	12.5	-	**HER2 (n=300)**	(n=177)		(n=113)		0.405
Mass size (cm)						Negative(n=248)	149	84.2	99	87.6	
1 – 2 (n=68)	38	21.1	30	23.4	0.442	Positive (n=52)	28	15.8	24	21.2	
2.1 – 5 (n=208)	120	66.7	88	68.8		**ER(n=300)**	(n=177)		(n=113)		0.549
>5 (n=32)	22	12.2	10	7.8		Positive(n=236)	140	79.1	86	76.1	
						Negative(n=64)	37	20.9	27	22.9	

*: significant OR: Odds ratio (CI95%)

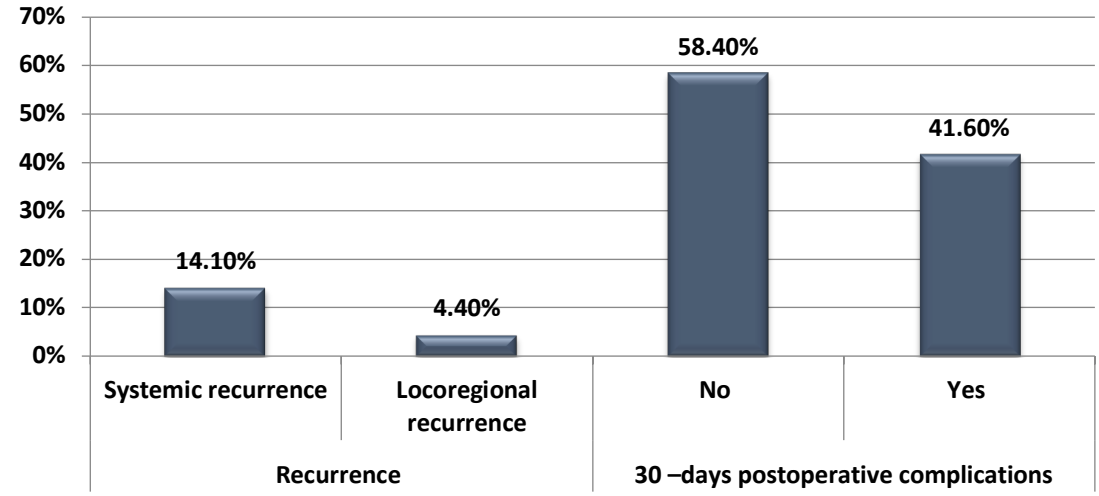

Figure 1. Recurrence, post-operative complications and mortality among the studied patients

Modified radical mastectomy was done in the majority of cases (81.8%), while conservative surgery was done in the remaining cases (18.2%) and no reconstruction attempts were recorded to any patient in this study. Some investigators have proved that the risk of node involvement, mainly in small tumors, increased by increasing age due to decreased immune mechanisms in old patients (Wildiers et al., 2009).

Axillary lymph node dissection (ALND) was done in all studied cases and the mean lymph nodes harvested was 15.6+ 8.2 in this study. This was aggressive approach in some of our cases in contrary with two large randomized studies compared ALND versus no ALND in older women with clinically node-negative disease, which revealed that omission of ALND did not affect overall survival with very low axillary recurrence of 1.8% and 3%, compared with recurrence rates of 0% and 1% with ALND (Martelli et al.,2205, Rudenstam et al., 2006).

There are common biological features in elderly female breast cancer patients which are: lower aneuploidy, low expression of HER-2, low proliferative index Ki67 levels, p53 and EGF receptor and higher estrogen (ER) and progesterone (PR) receptor expression (over 80%) (Syed et al., 2013). This is coinciding with results obtained from this study where, 78.7% of patients were ER+ve, 65.3% were PR +ve, only 17.3% were HER2/neu +v and the mean percentage of KI67 expression was 23.8 ± 19.4%.

The comprehensive geriatric assessment (that includes measures of function, comorbidity, nutrition, medication, socioeconomic issues, and geriatric syndromes) and estimation of life expectancy must be considered before any adjuvant treatment in these patients, and this is best accomplished by cooperation between oncology and geriatric medicine departments, (Stotter et al., 2010).

Neoadjuvant therapy could be offered to elderly patients with breast cancer to downstage the tumor and test the efficacy of the drugs and because most of these tumors are HER2/neu-ve and ER+ve they have good response to neoadjuvant aromatase inhibitors (Hind et al., 2007).

In this study, only 5.2% of patients had neoadjuvant treatment, 43.4% had adjuvant chemotherapy, 56.5% had adjuvant radiotherapy, while the majority of them (82.9%) had hormonal treatment.

By analysis of the above mentioned trends of management offered to the patients in this study, we noticed that there are more aggressive surgical approaches (more mastectomies, ALNDs, no reconstructions and less neoadjuvant treatment), and this could be attributed to the false concept between some surgical oncologists that elderly breast cancer patients should be treated mainly by surgery to avoid the hazards of adjuvant therapy.

Surgery for breast cancer is generally considered as low-morbidity surgery, and variety of complications can occur with serious consequences. For example, surgical site infections and postoperative seroma can lead to increased morbidity, additional costs and delay of postoperative adjuvant therapies (Vitug and Newman 2007). The 30-days post-operative mortality in this study was 1.3% (4 patients); two of them had pulmonary embolism, one had massive myocardial infarction and the fourth had cerebral stroke, while the postoperative morbidity in the same period reached 41.6% (128pts.), but most of them (89%) was minor (grade 1 or 2) according to Clavien-Dindo classification that necessitate only minimal treatment and follow up.

This is coinciding with the results of K. Lavalle and his colleagues in their large multicenter cohort study on 662 elderly breast cancer patients ,which revealed that (41.0 %) of the older women in their study experienced one or more complications, which were predominantly seroma or minor infections and relatively low percentage (6·5%) experienced serious complications that necessitated delayed discharge, readmission or further procedures, (Lavelle et al., 2015) and little more than revealed by Chatzidaki and colleagues who reported overall and major complication rates of 37.1 and 5.7 % respectively (Chatzidaki et al., 2011). The second endpoint of this study is to benchmark the factors affecting the incidence of post-operative complications in this category of patients.

For statistical purposes, the studied patients were divided into two groups (<75 and >75), and age of the patient more than 75y served as a risk factor for occurrence of complications (p<0.001*: OR=2.65, CI 95%:1.64-4.30), and this contradict with the results of many studies (El-Tamer et al., 2007, de Glas et al., 2013, de Blacam et al., 2012), that revealed that older age predicted neither number nor seriousness of complications.

The extent of surgery affected the rate of post-operative complications, where MRM served as a risk factor for occurrence of complications (P=0.029: OR=2.0 (1.06-3.76)) in comparison to conservative surgery and this is consistent with the results obtained by many investigators (Chatzidaki P et al., 2011, El-Tamer MB et al., 2007, de Glas NA et al., 2013), and this is could be explained by the fact that the majority of the encountered complications were wound complications. Comorbidity has been suggested to be associated with poor survival and had a detrimental influence on postoperative complications of breast cancer elderly patients (Dehal et al., 2013), and this is clearly demonstrated in this study, where the presence of comorbidity (P=0.029: OR=1.76, CI95%:1.06-2.93)) and the presence of more than one co-morbidities served as a risk factor in comparison to one morbidity (P=0.013: OR=2.17, CI 95%: 1.17-4.03), (P=0.039: OR=2.45, CI95%:1.03-5.85).

This is almost the same as the results of De Glas et al. and Chatzidaki et.al. that found that older patients with comorbidity have a higher risk of postoperative complications compared with elderly without comorbidity (Chatzidaki et al., 2011, de Glas et al., 2013). There are some limitations in this study; the retrospective design, which might induce an underestimation of the number of reported complications and the relatively small number of patients having serious complications (14 patients), who were insufficient for multi-regression analysis.

CONCLUSION

The incidence of serious postoperative complications is not high for breast cancer elderly patients and should have the same consideration for surgery as younger women, by tailoring the treatment decision on fitness for surgery rather than chronological age alone. More conservative surgical approaches must be offered to these patients because of its low morbidity, and more studies with large number of patients are needed to further identify the risk factors for developing postoperative complications in these patients.

AUTHORS' CONTRIBUTION

Data collection and idea of the topic: E. Elshiekh, Design of results: A. Elgammal, Statistics: Z. Kasemy, Data collection: E. Elgammal

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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