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Matched case-control survival analysis of older chinese breast cancer patients treated with surgery or primary endocrine therapy☆

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ABSTRACT

Background: Primary endocrine therapy (PET) has been used as an alternative to primary surgery for elderly with estrogen receptor (ER) positive breast tumors. Such practices are less commonly performed in Asian countries and the response to PET in Chinese cohort is still lacking. This study aims to compare the clinical outcome of PET to primary surgery.

Patients and Methods: Medical records of Chinese patients aged 70 and above with stage I to III, ER positive breast cancer treated at a University affiliated tertiary hospital from 2008 to 2017 were reviewed. Excluding those with extreme comorbidity, a one-to-one case-control survival analysis of patients treated with PET or primary operation was performed, using propensity score case-match analysis to adjust for confounding factors.

Results: 292 patients fulfilled the inclusion criteria during the study period. 209 patients received primary operation, whereas 83 patients received PET. Excluding those with extreme comorbidity, a one-to-one matching was performed, and the dataset was stratified into survival time within 0–5 years and beyond 5 years. Both groups had similar survival within 0–5 years ($p = 0.63$). The survival curves diverged beyond 5 years, with a significantly better outcome in patients operated than those treated with PET ($p = 0.0029$).

Conclusions: For frail older patients with limited life expectancy, PET may be appropriate since equivalent survival can be achieved for PET with or without surgery. Those patients with longer life expectancy may gain survival benefits from local treatment. A comprehensive geriatric assessment is useful to predict the survival probability and guide the optimal treatment.

Introduction

Deciding on the optimal treatment for an older breast cancer patient is a challenge [1,2]. Surgery still remains the mainstay of treatment for operable breast cancer, yet it is associated with comparatively high postoperative morbidities and mortalities in older patients [3,4]. Since 1980s, primary endocrine therapy (PET) has been adopted as an alternative treatment to surgery for estrogen receptor (ER) positive disease [5]. The European Society of Breast Cancer Specialists (EUSOMA) and International Society of Geriatric Oncology (SIOG) guidelines have recommended that PET may be considered in patients with a shorter life expectancy of two years who were unfit for surgery or refused surgery [6].

However, recent studies showed survival benefits for some older patients received surgical treatment. A systemic review of randomized controlled trials and cohort studies comparing surgery versus PET for elderly women with operable breast cancer showed surgery was superior to PET in respect of local disease control and a possibly survival gain in patients with an estimated life expectancy of five years or more [7].

Although PET has been widely studied in Western countries, research on the response and clinical outcomes of PET in a Chinese cohort is still lacking. Hence, we conducted a study to evaluate the outcomes of PET in older Chinese patients with breast cancer compared to those who received primary surgery.

Patients and methods

Between January 2008 to December 2017, consecutive patients

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Table 1
The characteristics of the matched cohort between primary endocrine therapy (PET) and primary operation (OT) excluding elderly patients with extreme condition.

Variables	Before matching			One-to-one matching		
	PET $N = 47$	OT $N = 205$	p-value	PET $N = 47$	OT $N = 47$	p-value
Age[#]	82.19 ± 4.07	76.60 ± 4.55	<0.001	82.19 ± 4.07	80.43 ± 4.80	0.058
Charlson comorbidity index						
0	14 (29.79%)	104 (50.73%)	0.02	14 (29.79%)	16 (34.04%)	0.925
1	24 (51.06%)	80 (39.02%)		24 (51.06%)	23 (48.94%)	
2	9 (19.15%)	21 (10.24%)		9 (19.15%)	8 (17.02%)	
American Society of Anaesthesiologists grade						
1	9 (19.15%)	18 (8.78%)	<0.001	9 (19.15%)	11 (23.4%)	0.772
2	16 (34.04%)	147 (71.71%)		16 (34.04%)	18 (38.3%)	
3	22 (46.81%)	40 (19.51%)		22 (46.81%)	18 (38.3%)	
Functional status						
1	19 (40.43%)	189 (92.2%)	<0.001	19 (40.43%)	31 (65.96%)	0.022
2	28 (59.57%)	16 (7.8%)		28 (59.57%)	16 (34.04%)	
Overall Stage						
1	12 (25.53%)	98 (47.8%)	0.013	12 (25.53%)	13 (27.66%)	0.854
2	27 (57.45%)	76 (37.07%)		27 (57.45%)	24 (51.06%)	
3	8 (17.02%)	31 (15.12%)		8 (17.02%)	10 (21.28%)	

[#] mean ± standard deviation.

treated at a university affiliated tertiary breast center who satisfied the inclusion criteria, i.e. Chinese, aged 70 and older, clinical stage I to III and ER positive breast cancer, were included into this retrospective study. ER positivity was considered as Allred scores of 3–8 [8].

Information was collected regarding premorbid status, tumor characteristics, modalities of treatment received, and survival outcomes. The plan of treatment was made conjointly by the multidisciplinary team including surgeons and oncologists with the patient, and often together with her caretaker(s). The treatment decision was not influenced by the present study. Charlson comorbidity index (CCI), American Society of Anaesthesiologists (ASA) grade, and functional status were used to assess the premorbid condition. For CCI, a list of comorbid conditions is classified into different weights scoring 1, 2, 3, or 6. Scores are summed to provide a total score to ascertain comorbidities [9]. ASA grade is a tool used commonly by the anesthetists to assess a patient's fitness before surgery [10]. The survival outcome was measured by overall survival, which was defined as the period of time from the date of diagnosis of breast cancer that patients were still alive.

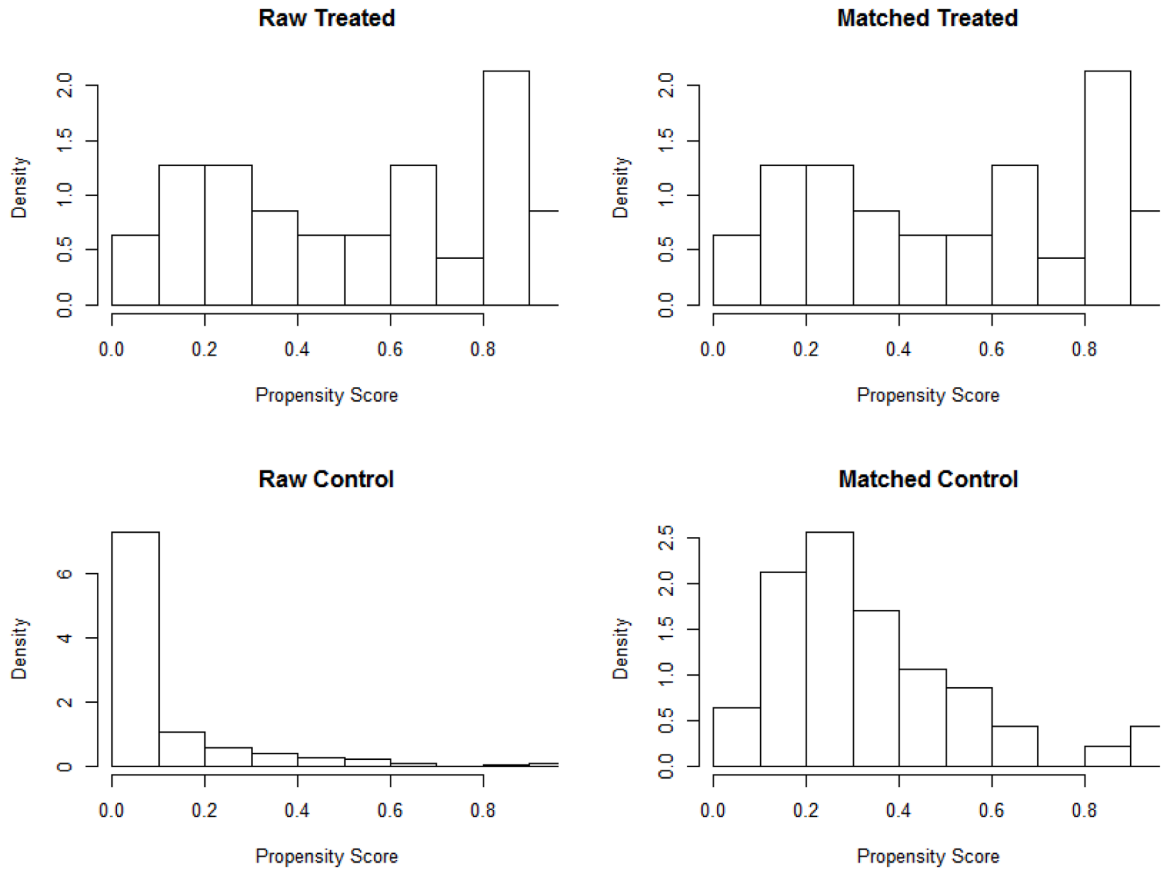


Fig. 1. Histograms showing the density of propensity score distribution in the primary operation (treated) and primary endocrine therapy (control) groups before and after matching.

Table 2
Types of treatment given in the primary operation group.

Types of treatment		Number of patients (%) $n = 209$
Surgery	Lumpectomy only	7 (3.35%)
	Lumpectomy + SLNB*	9 (4.31%)
	Lumpectomy + axillary dissection	8 (3.83%)
	Mastectomy only	2 (0.96%)
	Mastectomy + SLNB*	88 (42.11%)
	Modified radical mastectomy	95 (45.45%)
Adjuvant therapy#	Neoadjuvant chemotherapy	2 (0.96%)
	Neoadjuvant chemotherapy + RT**	5 (2.39%)
	Adjuvant chemotherapy	8 (3.83%)
	Adjuvant chemotherapy + RT**	10 (4.78%)
	Adjuvant RT without chemotherapy	61 (29.19%)

All patients received adjuvant hormonal therapy after surgery.
* SLNB = sentinel lymph node biopsy.
** RT = radiotherapy.

The initial response to PET was assessed at the sixth month of treatment by bi-dimensional caliper or ultrasound measurement of tumor size. If there were discrepancies between the two, response status was determined by the ultrasound measurement. The response was categorized into complete response (CR – no palpable or ultrasound detectable tumor); partial response (PR – reduction of more than or equal to 50%); static disease (SD – reduction of less than 50% to 25% increase) or progressive disease (PD – increase of more than 25% or appearance of new lesions according to the International Union Against Cancer (UICC) criteria [11]. The time to response and time to progression of PET was also recorded.

Continuous data were presented as the mean and standard deviation. Comparison between the groups was made with a Student's t-test, chi-squared test or Fisher's exact test when appropriate. Logistic regression was used to identify independent factors. Propensity score matching with optimal matching was executed to match cases from the primary operation group to the PET group by selecting the closest age, CCI, ASA grade, functional status, and overall stage [12,13]. The propensity scores were first computed by logistic regression using these variables. The matched subject was then chosen by minimizing the average absolute logistic distance. By excluding those extreme conditions as being not fit for general anesthesia and curative surgery: aged over 90, CCI > 5 (severe comorbidity), ASA grade IV (severe systemic disease that is life threatening), and functional status totally dependent, a one-to-one case match comparison of the overall survival of patients treated with PET to those who were treated surgically was performed. The quality of the matching was presented in Table 1 and Fig. 1. Table 1 showed the characteristics of the matched cohort. After performing one-to-one matching, all variables except functional status were comparable between the primary operation and PET groups with no statistically significant difference. The histograms in Fig. 1 demonstrated the density of propensity score distribution between the primary operation and PET groups. The density distributions of the two groups differed significantly before matching and became similar after matching. Statistical analyses were undertaken using the SPSS statistical package v24. R program with "MatchIt" package was used for the matching process [14].

Ethical approval for the present study was obtained from the Institutional Review Board (IRB) of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (IRB Reference Number: UW 09–045).

Table 3
Comparison between primary endocrine therapy (PET) and primary operation (OT) in terms of age and premorbid status.

		PET	OT	p-value
Age (years), mean ± standard deviation		84.17 ± 6.152	76.73 ± 4.650	0.000
Age (years), median, range		84, 70–103	76, 70–90	
CCI*	normal, 0	18/83	104/209	0.000
	mild, 1–2	(21.7%)	(49.8%)	
	moderate, 3–4	42/83	82/209	
	severe ≥5	(50.6%)	(39.2%)	
		18/83	22/209	
		(21.7%)	(10.5%)	
		5/83 (6.0%)	1/209 (0.5%)	
ASA** grade	I	9/83	18/209 (8.6%)	0.000
	II	(10.8%)	149/209	
	III	26/83	(71.3%)	
	IV	(31.3%)	42/209	
		45/83	(20.1%)	
		(54.2%)	0 (0.0%)	
		3/83 (3.6%)		
Functional status	Independent	23/83	191/209	0.000
	Partial	(27.7%)	(91.4%)	
	dependent	43/83	16/209 (7.7%)	
	Totally	(51.8%)	2/209 (1.0%)	
	dependent	17/83		
		(20.5%)		

* CCI = Charlson comorbidity index.
** ASA = American Society of Anaesthesiologists.

Table 4
Comparison between primary endocrine therapy (PET) and primary operation (OT) in terms of stages of disease.

		PET ($n = 83$)	OT ($n = 209$)	p-value
T stage	T1	18 (21.7%)	122 (58.4%)	0.000
	T2	46 (55.4%)	75 (35.9%)	
	T3	12 (14.5%)	9 (4.3%)	
	T4	7 (8.4%)	3 (1.4%)	
N stage	N0	57 (68.7%)	134 (64.1%)	0.340
	N1	20 (24.1%)	45 (21.5%)	
	N2	2 (2.4%)	16 (7.7%)	
	N3	4 (4.8%)	14 (6.7%)	
Overall stage	I	16 (19.3%)	99 (47.4%)	0.000
	II	54 (65.1%)	78 (37.3%)	
	III	13 (15.7%)	32 (15.3%)	

Results

Of a consecutive series of 357 older patients (aged ≥ 70) with clinical stage I to III breast cancer managed in our breast center from 2008 to 2017, 292 (81.8%) had ER-positive tumors. 209 patients received a primary operation (OT) followed by adjuvant therapy if indicated (table 2), whereas 83 patients were treated by PET. The mean follow-up time was 67.2 months.

Table 3 showed a comparison of premorbid status between PET and OT groups. Those patients treated with PET were older, and of higher CCI (more severe comorbidity), higher ASA grade (higher anesthetic risk), and more functionally dependent ($p = 0.000$).

Larger tumor size and more advanced overall stage was observed in the PET group ($p = 0.000$). (Table 4) There was no statistically significant difference between the groups in term of histology, grading and HER2 status. (Table 5)

Those extreme conditions as being not fit for general anesthesia and curative surgery was excluded and a one-to-one case match analysis was

Table 5
Comparison between primary endocrine therapy (PET) and primary operation (OT) in terms of histology, grading and HER2 status.

		PET	OT	p-value
Histology	IDC	67/83	166/209	0.120
	ILC	(80.7%)	(79.4%)	
	Mixed IDC and	0 (0.0%)	14/209 (6.7%)	
	ILC	0 (0.0%)	3/209 (1.4%)	
	Papillary	4/83 (4.8%)	6/209 (2.9%)	
	Tubular	0 (0.0%)	2/209 (1.0%)	
	Mucinous	7/83 (8.4%)	11/209 (5.3%)	
	Apocrine	0 (0.0%)	1/209 (0.5%)	
	Neuroendocrine	4/83 (4.8%)	6/209 (2.9%)	
	Unknown	1/83 (1.2%)	0 (0.0%)	
Histology grading	Grade I	8/28	66/194	0.751
	Grade II	(28.6%)	(34.0%)	
	Grade III	17/28	103/194	
		(60.7%)	(53.1%)	
		3/28	25/194	
		(10.7%)	(12.9%)	
HER2	Positive	12/83	34/209	0.757
	Negative	(14.5%)	(16.3%)	
		71/83	174/209	
		(85.5%)	(83.3%)	

performed to minimize the confounding effect to the survival data.

Fig. 2 showed the overall survival curves comparing the two groups. In the first five years after treatment, the two groups had similar survival rates. The survival curves diverged after five years. Those patients who underwent surgery had a significantly better outcome than those treated with PET beyond five years ($p = 0.0029$).

Among the patients treated with PET, 55% had tamoxifen and 45% had aromatase inhibitors. Overall 49% had clinical complete or partial response, and 48% had stable disease after six months of treatment (Table 6). The median time to response (TTR) was 4 months (range 1–15 months). 47% of the patients, with or without prior response, eventually had progression of the disease. The median time to progression (TTP) was 24 months (range 3–131 months). There was no significant difference in TTR and TTP for prescribing on tamoxifen or aromatase inhibitors.

Discussion

Breast cancer is the most common female cancer in Hong Kong. According to Hong Kong Cancer Registry, among the 4737 new breast cancer cases in 2017, 793 patients (16.7%) were aged 70 or above [15]. There is also a steadily rising trend of breast cancer patients diagnosed with increasing age. In addition, from the latest published Hong Kong Population Projections, the proportion of the population aged 70 or over was projected to rise from 10.5% to 16.5% in the coming ten years [16]. As a result, the number of older breast cancer patients in Hong Kong is expected to be increasing.

Management in the older age group is less clearly stated as compared to their younger counterparts partly because evidence from randomized trials in elderly is lacking [6]. Surgery is the gold standard for treating breast cancer. However, surgical treatment is sometimes omitted in elderly due to comorbidity and comparatively higher surgical risks [17]. Nonetheless, modern medical advances have helped older patients remain healthier and perform better for all breast cancer treatments. Some studies have demonstrated survival improvement with addition of surgical treatment [18-19]. Up to date, international guidelines recommended PET is an alternative for patients with a life expectancy of two to three years [6].

Our study showed PET and surgery could achieve similar survival within the first five years, whereas improved survival outcome was seen in the operated group beyond five years. It could be argued that PET is justified in patients with life expectancy up to five years instead of the recommended two to three years. This finding is in line with the results of a recent study, which showed similar survivals for PET with or without surgery during the first five years [20]. The author postulated that the emergence of aromatase inhibitors has improved the efficacy of PET, giving rise to a comparable survival to those with surgical treatment.

Being a retrospective study, bias due to confounding by indication was likely present, and we had tried to minimize confounding as much as possible by performing a case match analysis taking age and comorbidity into account. We are also the first to publish the outcomes of PET giving consideration to comorbidity in Chinese cohort.

The efficacy of PET demonstrated in our study was comparable to the findings in other Western studies [6]. However, the superiority of aromatase inhibitors over tamoxifen as showed in a number of clinical trials [21-22] had not been seen in our study. In addition, the time to progression for PET was approximately two years, which was far shorter than that reported in the Western literature [23]. These findings could be chance effect due to small sample size of the present study, or due to genuine difference in the biology, notably ER positivity, of Chinese women. Further studies are warranted to draw the plausible explanation.

The present study demonstrated the need of personalized approach to cancer treatment in older patients, as the decision of the optimal treatment depends very much on comorbidity and estimation of the life expectancy. Geriatric assessment can help differentiate those frail patients with limited life span who may be benefit from PET alone, from those long-lived patients who may have survival gain from surgery.

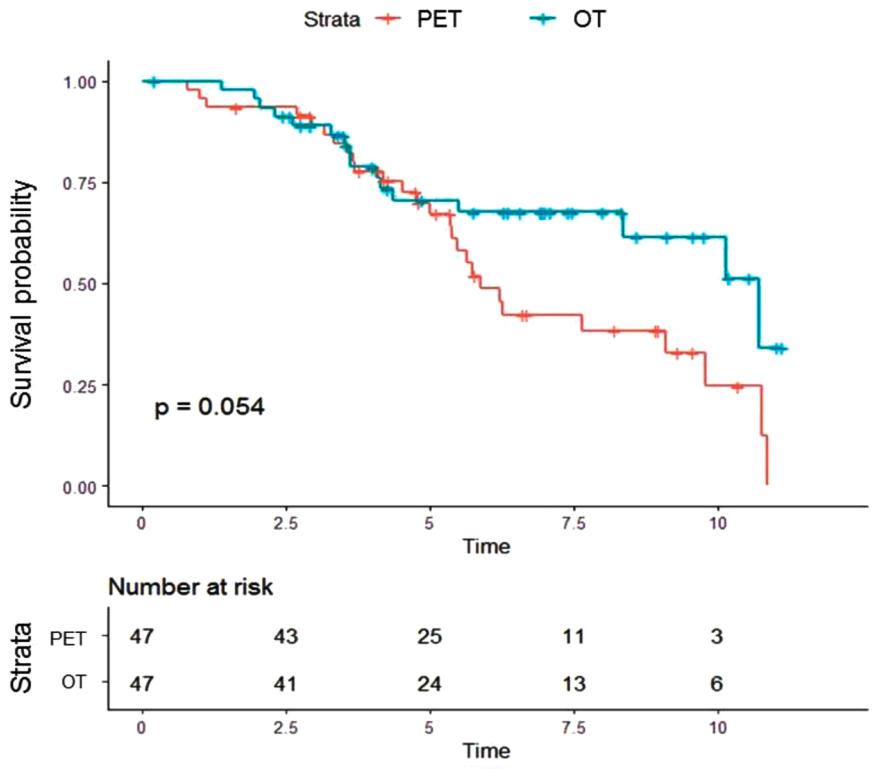
Comprehensive geriatric assessment (CGA) has been developed as a quantitative measure of an elderly's physical and psychosocial functioning. It is considered an objective way to determine the life expectancy among older adults. The SIOG and the National Comprehensive Cancer Network (NCCN) have recommended the incorporation of geriatric assessment in treatment planning [24-26]. A number of studies have investigated various domains within CGA to identify the variables with a significant impact on outcome or survival [27]. By incorporating the predictive factors, a scoring system or a risk score was developed to predict the survival probability in older patients. Due to biological and cultural differences [28], further studies are required to identify relevant components of CGA and draw a scoring system for Chinese elderly.

Conclusion

The incidence of breast cancer in the elderly is increasing worldwide and among the Chinese population. Fewer studies were conducted in the older age group, and the optimal management recommendation is not as clear as in the younger age group. We are the first study in a Chinese population that demonstrated an advantage for surgery in terms of survival for those patients with a longer life expectancy. For frail elderly patients with a limited life expectancy of less than five years, PET alone may be appropriate, since equivalent survival can be achieved for PET with or without surgery. To better predict the survival probability and guide optimal treatment, further research will be needed to tailor-make a comprehensive geriatric assessment for the Chinese population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



	Overall survival probability (95% confidence interval)		
	PET	**OT**	**p-value**
5-year	0.700 (0.575, 0.852)	0.706 (0.577, 0.863)	0.63
10-year	0.247 (0.114, 0.534)	0.615 (0.461, 0.819)	0.0029

Fig. 2. The overall survival curves comparing between primary endocrine therapy (PET) and primary operation (OT), one to one case matching excluding extreme comorbidity.

Table 6
Primary endocrine therapy treatment response of tamoxifen and aromatase inhibitors (AI).

		Tamoxifen ($n = 45$)	AI ($n = 37$)	p-value
Age (years), mean ± standard deviation		85.19 ± 5.39	83 ± 6.92	0.123
Age (years), median, range		85, 76–94	84, 70–103	
Initial response at the 6th month	Complete response	3 (6.7%)	5 (13.5%)	0.542
	Partial response	16 (35.6%)	16 (43.2%)	
	Stable disease	24 (53.3%)	15 (40.5%)	
	Disease progression	2 (4.4%)	1 (2.7%)	
Disease progression	Yes	22 (48.9%)	17 (45.9%)	0.756
	No	19 (42.2%)	18 (48.6%)	
Time to response, mean (months)		4.75 ± 3.04	4.56 ± 2.77	0.820
Time to progression, mean (months)		28.09 ± 26.43	31.59 ± 24.41	0.674

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