Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Research Article
Volume 25 Issue 4 - November 2023
DOI: 10.19080/CTOIJ.2023.25.556166

Cancer Ther Oncol Int J

Actual Status of Perioperative Treatment for Patients with Early-Stage Breast Cancer in Asia

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Submission: November 08, 2023; **Published:** November 17, 2023

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Abstract

Introduction: To develop an optimal therapeutic regimen for Asian breast cancer (BC) patients, it is important to determine how treatments for patients with BC are performed in Asian countries and regions.

Methods: We conducted a questionnaire-based survey of physicians performing perioperative treatment for BC at cancer centers or university hospitals in Asian countries and regions between October 2021 and April 2022. The survey included questions regarding neoadjuvant chemotherapy (NAC), adjuvant chemotherapy, adjuvant hormonal therapy, and adjuvant radiation therapy.

Results: A total of 37 physicians from 15 Asian countries and regions participated in the survey. Most respondents recommended NAC for stage III cases, with varying results for stage I and II cases. In NAC for HER2-positive BC (HER2+ BC), 91.9% of the respondents (34/37) used HER2-targeted therapy, whereas 70.3% (26/37) used pertuzumab. In NAC for triple-negative BC (TNBC), 62.2% of the respondents (23/37) selected dose-dense therapy. Dose-dense therapy use for luminal BC tended to be lower than that for TNBC (48.6% (18/37 respondents). Only 62.2% of the respondents (23/37) selected trastuzumab emtansine (T-DM1) as adjuvant chemotherapy for patients with HER2+ BC in non-pathological complete response (non-pCR). Meanwhile, 89.2% of the respondents (33/37) selected capecitabine as adjuvant therapy for patients with non-pCR TNBC. In addition, 91.9% of the respondents (34/37) used pathological diagnosis to determine adjuvant chemotherapy indications for luminal BC, whereas 62.2% of the respondents (23/37) used Oncotype DX.

Conclusion: The survey revealed that perioperative treatment for BC varies among Asian countries and regions, particularly pertuzumab, TDM-1, dose-dense therapy, and gene expression assays.

Keywords: Breast Cancer; Perioperative Treatment; Asia; Prognosis

Abbreviations: BC: Breast cancer, NAC: Neoadjuvant chemotherapy, HER2+ BC: HER2-positive breast cancer, TNBC: Triple-negative breast cancer, T-DM1: Trastuzumab emtansine, pCR: Pathological complete response, ASCO: American society of clinical oncology, ESMO: The european society for medical oncology, NCCN: The U.S. national comprehensive cancer network, AC: Doxorubicin hydrochloride and cyclophosphamide, CMF: Cyclophosphamide, methotrexate, and fluorouracil, OFS: Ovarian function suppression, LH-RH: Luteinizing hormone releasing hormone, AIs: Aromatase inhibitors, PMRT: Postmastectomy radiation therapy, IM: Internal mammary, IDFS: Invasive disease free survival, DFS: Disease free survival, OS: Overall survival, G-CSF: Granulocyte colony-stimulating factor, HER2- BC: HER2 negative BC.

Introduction

The morbidity and mortality of breast cancer (BC) is the highest of all cancer types among women worldwide. BC related deaths in Asia are estimated to be the highest worldwide, with over 300,000 deaths in a population of 4.7 million in 2020 [1]. Although the number of BC survivors is increasing owing to the development of treatments, survival rates vary between countries

[2]. The 5 years survival rates of BC in Asia are as follows: > 80% in China, Korea, and Japan; 80% in Singapore; 69% in Thailand; 66% in India; and 65% in Malaysia [3]. Perioperative treatment is important for reducing BC mortality [2]. There are guidelines for BC treatment established by American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the U.S. National Comprehensive Cancer Network (NCCN), and the St. Gallen International Breast Cancer Consensus Conference [4-6]. Treatments with proven efficacy and acceptable side effects in clinical trials are recommended as standard BC treatments [5]. In addition, non-compliance with recommended treatments has been shown to be associated with poor survival [7]. However, actual data on cancer treatment in Asia is limited.

Factors that influence treatment decisions have been reported to include personal values [8], financial ability [9], fear of treatment-related side effects [10], and inadequate health education [9]. In particular, the Asian health insurance model (offering only public or private insurance, or a mix of the two) and reimbersment status of drugs are different from country to country. Therefore, some patients find it difficult to take expensive drugs. Previous reports suggest that basic cytotoxic agents are reimbursed, and their costs are decreasing owing to the release of generic drugs [11,12]. However, some approved cancer drugs, such as anti-HER2 drugs, are not reimbursed in some countries [13]. To reveal the actual treatment status and relationship between treatment and prognosis are important to build a local evidence base and develop cost-effective treatment strategies that are appropriate to the local culture [14,15]. This study aimed to reveal how perioperative treatment is performed in Asia, using a questionnaire survey.

Methods

Questionnaire

A questionnaire-based survey was conducted between October 2021 and April 2022. This questionnaire was designed to elucidate the actual situation of perioperative BC treatment in Asian countries and regions. The questionnaire included seven questions on neoadjuvant chemotherapy (NAC), seven questions on adjuvant therapy, two questions on hormonal therapy, and four questions on radiation therapy, for each BC subtype, that is, HER2-positive BC (HER2+ BC), triple-negative BC (TNBC), and luminal BC from stage I to III (Supplemental Table 1). Each question had a checklist on which the participants could choose their answers. This study followed the ethical guidelines for epidemiological research by the Ministry of Health, Labour and Welfare (MHLW), and the regulations of the National Cancer Center Hospital (NCCH) institutional review board (IRB). These guidelines and NCCH IRB do not require the ethical approval of institutes for the questionnaires to medical staff without individual chart reviews. This study was allowed to be done without informed consents of patients according to ethic guidelines for epidemiological research by the MHLW and the regulations of NCCH IRB.

Supplemental Table 1: Questionnaire list.

Q1. How many cases does your department give NAC for invasive BC annually?	
Q2. Question about NAC	
Q2.1. HER2+ BC	Q2.1.1. For which of the stages does your department recommend NAC?
	Q2.1.2. Which of the regimens are used in your department?
Q2.2. TNBC	Q2.2.1. For which of the stages does your department recommend NAC?
	Q2.2.2. Which of the regimens are used in your department?
Q2.3. Luminal BC	Q2.3.1. For which of the stages does your department recommend NAC?
	Q2.3.2. Which of the regimens are used in your department?
Q3.1. HER2+ BC	Q3. Question about adjuvant chemotherapy
	Q3.1.1. Does your department use HER2-targeted therapy?
	Q3.1.2. Which of the regimens are used in your department?
	Q3.1.3. Does your institution add TDM-1 for non-PCR cases?
Q3.2. TNBC	Q3.2.1. Which of the regimens are used in your department?
	Q3.2.2. Does your institution add capecitabine for non-PCR cases?
Q3.3. Which factors does your department consider when deciding whether to add chemotherapy in cases of luminal-type invasive BC?	
Q3.4. Which regimens does your institution use in cases of luminal BC?	
Q4. Question about adjuvant hormonal therapy	
Q4.1. Which of treatments does your institution use as adjuvant hormonal therapy in premenopausal patients?	
Q4.2. Which of factors does your institution refer to when you perform hormonal therapy for 10 years?	

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Q5. Question about adjuvant radiation therapy
Q5.1. Does your institution perform PMRT?
Q5.2. Does your institution perform whole breast irradiation after lumpectomy?
Q5.3. Which RT protocol does your department routinely use for whole breast irradiation after lumpectomy or PMRT?
Q5.4. Does your department include IM nodes in cases of suspicious IM metastasis?

NAC: neoadjuvant chemotherapy; BC: breast cancer; HER2+: HER2-positive; TNBC: triple negative breast cancer; TDM-1: trastuzumab emtansine; non-PCR: non pathological complete response; PMRT: postmastectomy radiation therapy; RT: radiation therapy; IM: internal mammary.

Table 1: NAC for each subtype of stage I-III BC.

Question	Answer	N (/37)	%
Stages recommended NAC (multiple choice)			
HER2+ BC	Stage I	10	27
	Stage IIA	27	73
	Stage IIB	32	86.5
	Stage III	37	100
TNBC	Stage I	13	35.1
	Stage IIA	27	73
	Stage IIB	32	86.5
	Stage III	37	100
Luminal BC	Stage I	2	5.4
	Stage IIA	11	29.7
	Stage IIB	27	73
	Stage III	34	91.9
HER2-tageted therapy			
Trastuzumab including regimens	Use	34	91.9
	Not use	3	8.1
Pertuzumab including regimens	Use	26	70.3
	Not use	11	29.7
Dose-dense therapy			
TNBC	Use (total)	23	62.2
	Both use dose-dense and non-dose-dense therapy	13	35.1
	Not use	14	37.8
Luminal BC	Use (total)	18	48.6
	Both use dose-dense and non-dose-dense therapy	11	29.3
	Not use	19	51.4
Regimen of dose-dense therapy (multiple choice)			
TNBC	Does-dense AC followed by weekly paclitaxel	17	45.9
	Dose-dense AC followed by paclitaxel every 2 weeks	17	45.9
Luminal BC	Does-dense AC followed by weekly paclitaxel	11	29.7
	Dose-dense AC followed by paclitaxel every 2 weeks	13	35.1
Regimen of non-dose-dense therapy (multiple choices)			

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TNBC	Anthracycline-based regimen followed by docetaxel every 3 weeks	10	27
	Anthracycline-based regimen followed by weekly paclitaxel	9	24.3
	CMF	5	13.5
	Only anthracycline-based regimen	1	2.7
	Only taxane-based regimen	0	0
	Other	5	13.5
Luminal BC	Anthracycline-based regimen followed by docetaxel every 3 weeks	19	51.4
	Anthracycline-based regimen followed by weekly paclitaxel	22	59.5
	CMF	3	8.1
	Only anthracycline-based regimen	9	24.3
	Only taxane-based regimen	4	10.8
	Other	3	8.1

NAC: neoadjuvant chemotherapy; BC: breast cancer; HER2+: HER2-positive; TNBC: triple negative breast cancer; AC: doxorubicin and cyclophosphamide; CMF: cyclophosphamide, methotrexate, and fluorouracil.

Participants

An online questionnaire was distributed to 251 physicians in 22 countries in collaboration with the National Cancer Center, Japan. The selected participants were physicians performing perioperative chemotherapy for early-stage BC at cancer centers or university hospitals in Asian countries and regions. One physician was selected from each institution. However, in some large institutions that treat BC in multiple departments, physicians working in different hospitals or departments were also selected. To confirm the affiliations of respondents, we collected data on institutional addresses and respondents' job titles and eliminated duplicate responses.

Results

Backgrounds of Respondents

Overall, 37 physicians from 15 countries completed a survey questionnaire. The number of respondents from each country is presented in Supplemental Table 2. Most of the respondents (22/37) were medical oncologists, 11 were surgeons, two were radiologists, and two were of unknown subspecialties. Most of the participants (29.7%) reported that < 50 cases of NAC therapy were performed in their respective institutions annually.

Supplemental Table 2: Characteristics of participants.

Characteristics	Category	N (/37)	%
Country	India	6	16.2
	Japan	6	16.2
	Malaysia	5	13.5
	Vietnam	4	10.8
	Taiwan	3	8.1
	Thailand	2	5.4
	Myanmar	2	5.4
	Philippines	2	5.4
	Republic of Korea	1	2.7
	Singapore	1	2.7
	Pakistan	1	2.7
	Hong Kong Administrative Region	1	2.7
	Bhutan	1	2.7
	Bangladesh	1	2.7
	Indonesia	1	2.7

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Specialty	Medical oncologist	22	59.5
	Surgeon	11	29.7
	Radiologist	2	5.4
	Unknown	2	5.4
Number of NAC patients/year	<50	11	29.7
	50-100	9	24.3
	100-200	8	21.6
	>200	9	24.3

NAC: neoadjuvant chemotherapy.

NAC for each Subtype of Stage I-III BC

The rate of NAC recommendation varied according to stage and subtypes (Table 1). NAC is recommended less commonly for stage I and II luminal BC than for HER2+ BC and TNBC. In addition, all respondents answered that they administer NAC for stage III HER2+ BC and TNBC. However, not all respondents administered NAC for stage III luminal BC (91.9%). Most respondents (91.9%) used HER2-targeted NAC for HER2+ BC, of which 100% utilized trastuzumab and only 76.5% (26/34) used pertuzumab. Institutions that use and do not use pertuzumab coexist within the same country (Figure 1). For TNBC, 62.2% of respondents preferred dose-dense therapy as a NAC regimen, whereas 35.1% of respondents selected both dose-dense therapy and non-dose-dense therapy (Table 1). In each country, the dose-dense therapy usage ratio of NAC for TNBC varies by institution. The use of dose-dense therapy is particularly high in India; however, in Japan, there are variations among institutions (Figure 2). For patients with luminal BC, only 48.6% of the respondents preferred dose-dense NAC therapy but 29.3% selected both (Table 1). Respondents equally chose dose-dense doxorubicin hydrochloride and cyclophosphamide (AC) followed by weekly paclitaxel and dose-dense AC followed by paclitaxel every two weeks as a dose-dense NAC regimen. For non-dose-dense therapy, anthracycline-based followed by taxane regimens are predominantly used. A few respondents use cyclophosphamide, methotrexate, and fluorouracil (CMF) in both TNBC and luminal BC. However, only anthracycline-based regimen or only taxan-based regimen were more selected for luminal BC than TNBC.

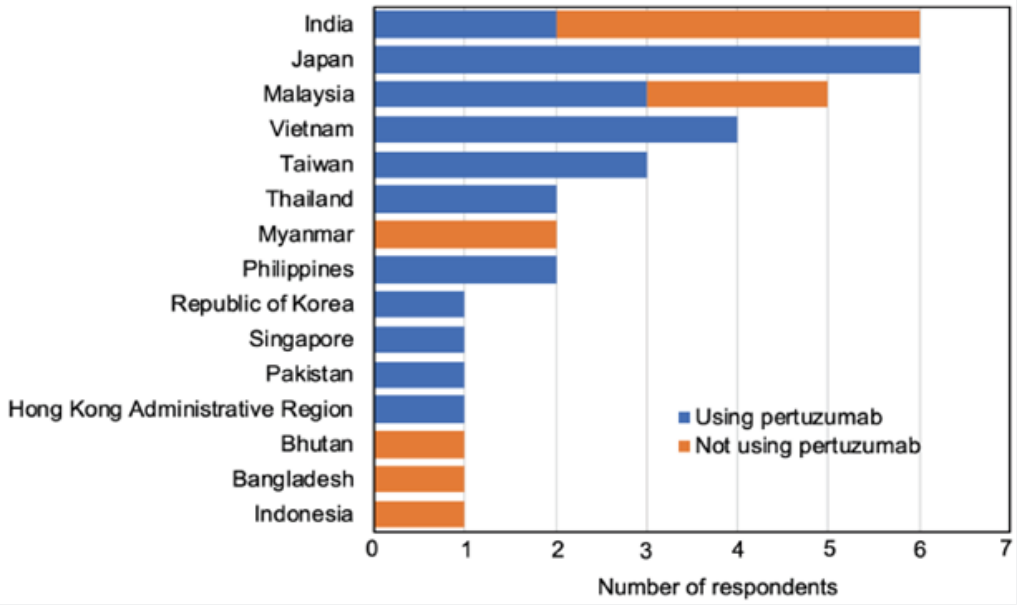

Figure 1: The number of participants using and not using pertuzumab in each country.

Adjuvant Chemotherapy for each Subtype of Stage I-III BC

For adjuvant chemotherapy for non-pathological complete response (non-PCR) in patients with HER2+ BC, 62.2% of the respondents used trastuzumab emtansine (T-DM1) (Table 2). Focusing on each country, T-DM1-using and non-using institutions coexisted within the same country (Figure 3). In TNBC, 89.2% of the respondents used capecitabine as adjuvant therapy for non-

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PCR patients (Table 2). Adjuvant capecitabine was more commonly used than adjuvant T-DM1. In addition, all respondents answered that they used HER2-targeted therapy as an HER2+ BC adjuvant chemotherapy. In T1N0 HER2+ BC, 83.8% of the respondents used trastuzumab-including regimens, and 62.2% selected a lower-intensity regimen, such as trastuzumab plus taxane (Supplemental Table 3). Moreover, 16.2% of the respondents answered that they did not administer adjuvant chemotherapy. In contrast, 13.5% of the respondents selected pertuzumab-including regimens, even at the early stage. For T2N1 HER2+ BC, 100% of respondents used trastuzumab-including regimens, and 67.6% used pertuzumab-including regimens. Adjuvant chemotherapy for T1N0 and T2N1 TNBC was administered by 89.2% and 97.3% of respondents, respectively. Anthracycline-based regimens followed by taxane were used by most respondents (T1N0, 51.4%; T2N1, 75.7%). A few respondents selected only anthracycline-based regimens (T1N0; 29.7%, T2N1; 5.4%), only taxane-based regimens (T1N0, 35.1%; T2N1, 13.5%), and CMF (T1N0; 10.8%, T2N1; 5.4%). Dose-dense adjuvant chemotherapy tended to be used more frequently utilized in T2N1 TNBC than in T1N0 TNBC (64.9% vs. 37.8%).

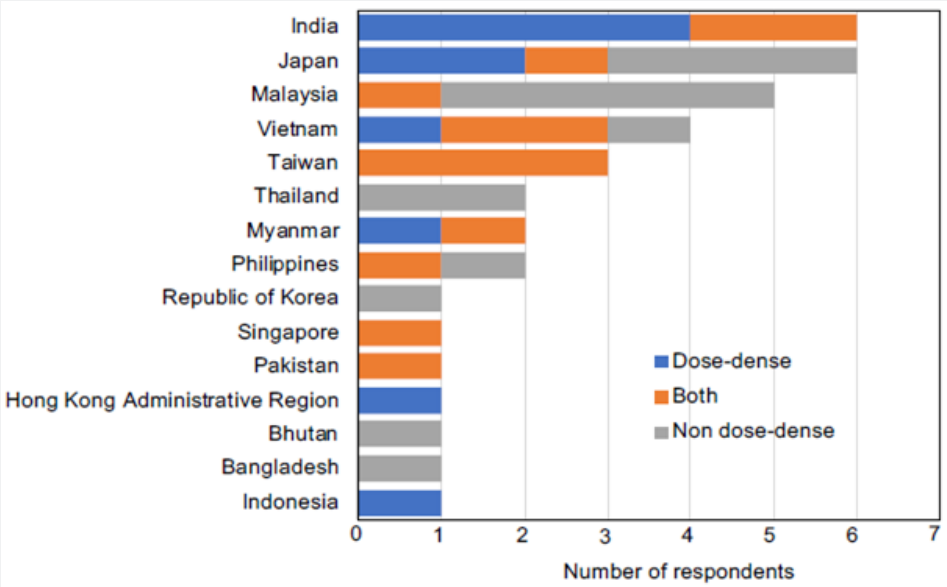

Figure 2: The number of participants using dose-dense therapy and non-dose-dense therapy in each country. "Both" means the participants using both dose-dense and non-dose-dense therapy.

Table 2: Adjuvant chemotherapy for each subtype of stage I-III BC.

Question	Answer	N (/37)	%
Adjuvant chemotherapy for non-PCR patients			
Adding T-DM1 for non-pCR HER2+ BC	Yes	23	62.2
	No	14	37.8
Adding capecitabine for non-pCR TNBC	Yes	33	89.2
	No	4	10.8
Regimens for HER2+ BC (multiple choice)			
T1N0 HER2+ BC	Trastuzumab-including regimens	31	83.8
	Pertuzumab-including regimens	5	13.5
	No chemotherapy	6	16.2
T2N1 HER2+ BC	Trastuzumab-including regimens	37	100
	Pertuzumab-including regimens	25	67.6
	No chemotherapy	0	0
Regimens for TNBC (multiple choice)			

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T1N0 TNBC	Anthracycline based regimens followed by taxane	19	51.4
	Dose-dense therapy	14	37.8
	CMF	4	10.8
	Only anthracycline based regimens	11	29.7
	Only taxane based regimens	13	35.1
	No chemotherapy	4	10.8
T2N1 TNBC	Anthracycline based regimens followed by taxane	28	75.7
	Dose-dense therapy	24	64.9
	CMF	2	5.4
	Only anthracycline based regimens	2	5.4
	Only taxane based regimens	5	13.5
	No chemotherapy	1	2.7
Factors to consider adjuvant chemotherapy for luminal BC (multiple choice)	Pathological diagnosis	34	91.9
	Oncotype DX	23	62.2
	PAM50	7	18.9
	MammaPrint test	2	5.4
	Other	4	10.8
Regimens for luminal BC (multiple choice)	Anthracycline based regimens followed by taxane	30	81.1
	Dose-dense therapy	20	54.1
	CMF	5	13.5
	Only anthracycline based regimens	16	43.2
	Only taxane based regimens	14	37.8
	No chemotherapy	5	13.5
	Other	1	2.7

BC: breast cancer non-pCR: non pathological complete response; HER2+: HER2-positive; TNBC: triple negative breast cancer; CMF: cyclophosphamide, methotrexate, and fluorouracil

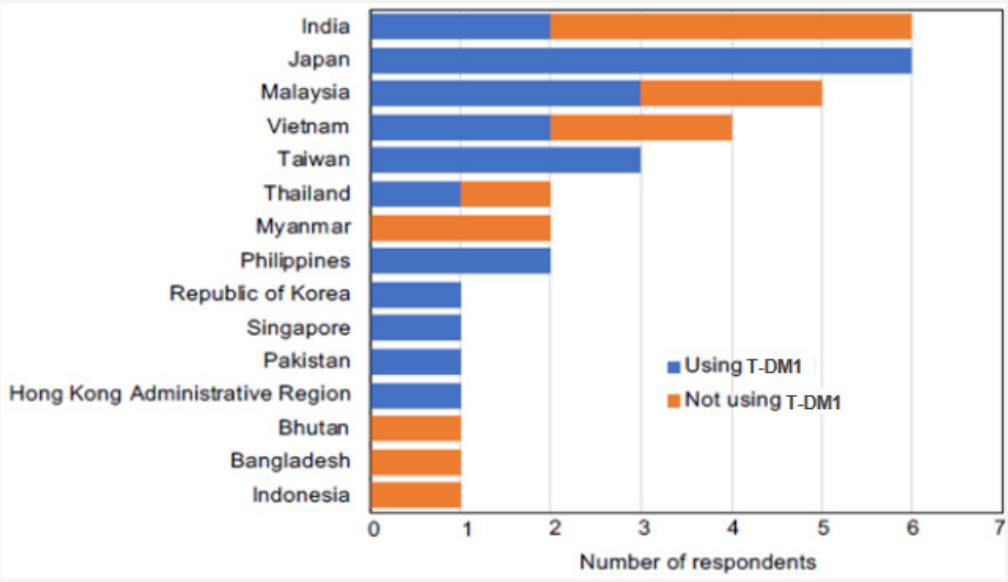

Figure 3: The number of participants using and not using adjuvant T-DM1 for non-pCR HER2+ BC in each country.

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Table 3: Adjuvant hormonal therapy for luminal BC.

Question	Answer	N (/37)	%
Treatment for premenopausal patients (multiple choices)	Tamoxifen	37	100
	Ovarian suppression (LH-RHa)	28	75.7
	Ovarian suppression (Oophorectomy)	15	40.5
	No use of ovarian suppression	8	21.6
	AIs	17	45.9
	Toremifene	2	5.4
	Other	1	2.7
Factors to consider when proposing 10-year hormonal therapy (multiple choice)	Lymph node metastasis	33	89.2
	Tumor size	29	78.4
	Age	27	73
	Histological grade	22	59.5
	Presence of lymphovascular invasion	17	45.9
	Other	3	8.1

BC: breast cancer; LH-Rha: luteinizing hormone releasing hormone agonist; AIs: Aromatase inhibitors.

Supplemental Table 3: Regimens of adjuvant chemotherapy.

Question	Answer	N (/37)	%
Regimens for HER2+ BC (multiple choice)			
T1N0 HER2+ BC	Anthracycline-based regimens followed by taxane plus trastuzumab	19	51.4
	Anthracycline-based regimens followed by taxane plus trastuzumab plus pertuzumab	4	10.8
	TCHP	4	10.8
	TCH*1	12	32.4
	TCH*2	10	27
	TH	23	62.2
T2N1 HER2+ BC	Anthracycline-based regimens followed by taxane plus trastuzumab	25	67.6
	Anthracycline-based regimens followed by taxane plus trastuzumab plus pertuzumab	24	64.9
	TCHP	18	48.6
	TCH*1	21	56.8
	TCH*2	11	29.7
	TH	11	29.7
Regimens for TNBC (multiple choices)			
T1N0 TNBC	Anthracycline based regimens followed by weekly paclitaxel	15	40.5
	Anthracycline based regimens followed by docetaxel every 3 weeks	16	43.2
	Dose-dense anthracycline based regimens followed by paclitaxel every 2 weeks	11	29.7
	Does-dense anthracycline based regimens followed by weekly paclitaxel	10	27

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T2N1 TNBC	Anthracycline based regimens followed by weekly paclitaxel	18	48.6
	Anthracycline based regimens followed by docetaxel every 3 weeks	19	51.4
	Dose-dense anthracycline based regimens followed by paclitaxel every 2 weeks	23	62.2
	Does-dense anthracycline based regimens followed by weekly paclitaxel	21	56.8
Regimens for luminal BC (multiple choice)	Anthracycline based regimens followed by weekly paclitaxel	22	59.5
	Anthracycline based regimens followed by docetaxel every 3 weeks	21	56.8
	Dose-dense anthracycline based regimens followed by paclitaxel every 2 weeks	13	35.1
	Does-dense anthracycline based regimens followed by weekly paclitaxel	15	40.5

HER2+: HER2-positive; BC: breast cancer; TCHP: docetaxel, carboplatin, trastuzumab, and pertuzumab; *1 TCH: docetaxel, carboplatin, and trastuzumab; *2 TCH: docetaxel, cyclophosphamide, and trastuzumab; TH: paclitaxel and trastuzumab; TNBC: triple negative breast cancer.

To decide whether to administer adjuvant chemotherapy to patients with luminal BC, a pathological diagnosis was commonly considered (91.9% of respondents). This was followed by Oncotype DX (62.2%), PAM50 (18.9%), and MammaPrint (5.4%). Others considered age, EndoPredict score, Ki67 score, and OncoFREE. As adjuvant chemotherapy for luminal BC, 81.1% of the respondents selected anthracycline-based regimes followed by taxanes. Subsequently, dose-dense therapy (54.1%), only anthracycline-based regimens (43.2%), only taxane-based regimens (37.8%), and CMF (13.5%) were selected. Among the respondents, 13.5% did not administer chemotherapy. Details of each regimen are presented in Supplemental Table 3.

Hormonal Therapy

All respondents selected tamoxifen as adjuvant hormonal therapy for premenopausal patients (Table 3). For ovarian function suppression (OFS), 75.7% and 40.5% of the respondents selected luteinizing hormone releasing hormone (LH-RH) agonist and oophorectomy, respectively. Among the respondents, 45.9% selected aromatase inhibitors (AIs). This question was multiple-choice, and almost all respondents who selected AIs selected OFS (16/17 respondents). However, 21.6% of the respondents did not use OFS. Only 5.4% selected toremifene. Factors considering 10-year hormonal therapy included, 89.2% selected lymph node metastasis, 78.4% selected tumor size, 73% selected age, 59.5% selected histological grade, and 45.9% selected lymphovascular invasion. Of the respondents, one answered that all hormone receptor-positive patients had received hormonal therapy for 10-years, and the other answered that they administered hormonal therapy according to the status of thrombosis or osteoporosis.

6.5. Radiation therapy

94.6% respondents answered that they conducted postmastectomy radiation therapy (PMRT), defined as radiation therapy including the chest wall and regional lymph nodes, administered to patients after mastectomy (Table 4). Whole-breast irradiation after lumpectomy was also performed in 94.6% of respondents. The radiation therapy protocol varied by institution: 48.6% selected 50 Gy/25 Fr, 29.7% selected 42.5 Gy/16 Fr, and 21.6% selected others. Among others, 62.5% (13.5% of all respondents) answered that they had administered RT at 40 Gy/15 Fr. In patients with suspected internal mammary (IM) lymph node metastasis, 75.7% of the respondents indicated that radiation therapy would be administered in this area.

Discussion

This study conducted an online questionnaire survey to determine the actual status of perioperative therapy in patients with early-stage BC in Asia. There is heterogeneity in BC treatment strategies in Asia, especially the use of HER2-targeted therapy, dose-dense therapy, and gene expression assays, which vary by institution. This heterogeneity may be caused by differences in approval and reimbursement status, insurance systems, patient characteristics, and problems with adverse effect management. The difference in the usage of pertuzumab and TDM-1 may be due to cost [16-19]. HER2 targeted therapy for NAC and adjuvant chemotherapy dramatically reduced recurrence risk [20-24]. In fact, four-years invasive disease-free survival (IDFS) rates are reported to be 90% in patients with HER2+ BC who achieved pCR after neoadjuvant pertuzumab plus trastuzumab followed by adjuvant trastuzumab [25]. In addition, the use of TDM-1 in

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patients with residual disease improved disease-free survival (3-years IDFS 88.3% with T-DM1 vs 77.0% with trastuzumab) [24]. However, our study suggested that not all institutions recommended pertuzumab and T-DM1 for preoperative treatment of HER2+ BC in Asia. Although the use of pertuzumab in NAC and TDM-1 in adjuvant therapy has been approved in India, Japan, South Korea, Malaysia, China, Singapore, and Taiwan [5]. Some respondents commented that these drugs were not covered by insurance and are too expensive to use. In contrast, the usage ratio of trastuzumab and capecitabine was higher than that of pertuzumab and T-DM1. Currently, trastuzumab and capecitabine are included in the WHO model list of essential medicines [26]. Trastuzumab biosimilars and generic forms of capecitabine, which are available on the market, are considered cost-effective and offer significant cost savings for BC patients. However, some institutions that use anti-HER2 drugs commented that they would not prescribe trastuzumab to patients who could not afford it. Unfortunately, cancer patients who are unable to afford these prescription drugs, especially when they lack insurance coverage, are more likely to report non-compliance with medication and forgo further treatment, leading to poorer clinical outcomes and increased cancer burden [27]. The low usage of gene expression assays for predicting prognosis might also be caused by their approval status and high cost.

Table 4: Adjuvant radiation therapy for BC.

Question	Answer	N (/37)	%
PMRT	Performed	35	94.6
	Not performed	2	5.4
Whole breast irradiation after lumpectomy	Performed	35	94.6
	Not performed	2	5.4
Protocol	50Gy/25Fr	18	48.6
	42.5Gy/16Fr	11	29.7
	Other	8	21.6
Irradiation of IM lymph nodes for cases of suspicious IM metastasis	Performed	28	75.7
	Not performed	8	21.6

BC: breast cancer; PMRT: postmastectomy radiation therapy; IM: internal mammary.

The heterogeneity of the dose-dense therapy usage rate might have been caused by the balance between positive and adverse effects. Meta-analyses have indicated that dose-dense therapy improves disease-free survival (DFS), especially in patients with hormone receptor-negative, lymph node involvement, and highly proliferative BC however, the results of overall survival (OS) are controversial [28-31]. In addition, the ratio of adverse effects was higher than that of standard therapy. Granulocyte colony-stimulating factor (G-CSF) is required for preventing neutropenia. The incidence of anemia and transaminase elevation were higher than those in non-dose-dense therapy [31]. Thus, evaluation of the risk of recurrence and basic health conditions is important for dose-dense therapy. Although NCCN guideline recommends dose-dense therapy for HER2 negative (HER2-) BC patients [6], some institutions use only non-dose-dense therapy.

Similarly, indications of OFS and 10-year hormonal therapy for premenopausal patients and the protocol of adjuvant radiation therapy also varied by institution In high-risk premenopausal patients e.g., young age, high-grade tumor, lymph node involvement who need chemotherapy should be considered OFS [32], but its effects are not clear in low-risk cases not requiring chemotherapy. The 10-years hormonal therapy has been reported to reduce recurrence and mortality rates. However, the risk of pulmonary embolism, ischemic heart disease, and endometrial cancer tend to increase with longer exposure to tamoxifen [33,34]. The decision to use OFS may depend on the overall risk assessment based on patient and tumor characteristics and may follow consideration of all the adverse effects that may develop with the addition of OFS in combination with hormonal therapy. In radiation therapy, clinical studies have shown that the effectiveness and safety of moderate hypofractionation schedules (15-16 fractions of ≦3 Gy/fraction) are like those of conventional treatments [35-38]. The difference in hypofractionated irradiation therapy usage may depend on the approval status, reimbursement status, and availability of equipment [5]. In addition, clinical trials of hypofractionated irradiation therapy are being conducted. This study had some limitations. First, the number of respondents was insufficient. Therefore, when interpreting these results, it should be noted that this study represents the actual situation in some Asian facilities. The small number of responses from each country suggests that the results do not fully reflect their actual status. Second, this study was conducted between October 2021 and April 2022, and the timing of insurance approval of T-DM1 for non-PCR patients may differ between countries. Third, the answers were self-reported, making it difficult to assess the accuracy of the estimated data. Fourth, there was heterogeneity in the respondents' specializations, which could also explain

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the variation in their practices in terms of experience and level of expertise. In conclusion, the current study revealed that perioperative treatment for early-stage BC varies among Asia-Pacific countries and regions, particularly pertuzumab, TDM-1, dose-dense therapy, and gene expression assays. For improvement of treatment outcomes in BC patients throughout Asia, we should focus on promoting the use of therapeutic drugs and tests, setting guidelines, and conducting multicenter clinical trials in Asia [39].

Conclusion

The results of this online questionnaire survey revealed that perioperative BC treatment in Asia is heterogeneous in real-world practice. Particularly the use of pertuzumab, TDM-1, dose-dense therapy, and gene expression assays varies by institution.

Acknowledgement

We thank all the participants for their participation in this study. We thank Aya Watanabe for secretarial assistance. Editage-Cactus Communications provided editorial support in the form of medical writing, assembling tables, creating high-resolution images based on the authors' detailed directions, collating author comments, copying, editing, fact-checking, and referencing. This study was funded by the Japan Agency for Medical Research and Development as part of the "Project Promoting Clinical Trials for Development of New Drugs" (20lk0201002j0001, 21lk0201005j0001, 22lk0201007j0001). The funder had no role in the design, data collection, data analysis, and reporting of this study.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

MT, YK, and SS designed the study and interpreted the data. MT, YK, SY, and SS analyzed the data. KS, TS, KY, AS, and KN supervised the project. MT, MA, YK, and SS wrote the manuscript and MT prepared all figures and tables. All authors have approved the final edition of the manuscript.

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DOI: 10.19080/CTOIJ.2023.25.556166

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