Management of Breast Cancer in Adjuvant Chemotherapy Settings in the Kanagawa Breast Oncology Group

Mayako TERAO[*1], Naoki NIIKURA[*1], Yasuhiro SUZUKI[*1], Norihiko SENGOKU[*2], Hitoshi ARIOKA[*3], Takashi ISHIKAWA[*4], Koichiro TSUGAWA[*5] and Yutaka TOKUDA[*1]

[*1]*Department of Endocrine and Breast Surgery, Tokai University School of Medicine*
[*2]*Department of General Surgery, Kitasato University School of Medicine*
[*3]*Department of Medical Oncology, Yokohama Rosai Hospital*
[*4]*Department of Breast and Thyroid Surgery, Yokohama City University Medical Center*
[*5]*Department of Breast and Endocrine Surgery, St. Marianna University School of Medicine*

(Received May 26, 2017; Accepted August 9, 2017)

Objective: Many different options for adjuvant chemotherapy are recommended in guidelines for the treatment of breast cancer. Therapeutic strategies vary among physicians. The major goals for this project were to gain a better understanding of how biomarkers are integrated into practice and how physicians select adjuvant chemotherapy.
Methods: We assembled a questionnaire with 23 example scenarios of breast cancer cases, including 6 items relevant to postoperative adjuvant therapy. During October–November 2012, the questionnaire was submitted to 131 physicians engaged in breast cancer treatment in Kanagawa Prefecture, Japan.
Results: Forty-eight physicians responded to the questionnaire, 46 of whom provided valid responses. Their responses revealed a notable lack of consensus regarding therapeutic choices. We analyzed 6 scenarios relevant to postoperative adjuvant therapy. In general, the selection of postoperative adjuvant therapy appeared to be based on hormone sensitivity, human epidermal growth factor receptor 2 (HER2) expression, lymph node metastasis, tumor size, histological/nuclear grade, vascular/lymphatic system invasion, Ki67 level, Oncotype DX score, and the patient's age.
Conclusion: Given the varied therapeutic choices that we observed, clinical research is needed to provide appropriate, unified therapeutic strategies.

Key words: breast cancer, postoperative adjuvant therapy, questionnaire survey

INTRODUCTION

Many different options for adjuvant chemotherapy are recommended in guidelines for the treatment of breast cancer. Currently, physicians determine the adjuvant chemotherapy regimen for individual patients. When selecting therapeutic strategies, physicians refer to hormone sensitivity, human epidermal growth factor receptor 2 (HER2) expression, lymph node metastasis, tumor size, histological/nuclear grade, vascular/lymphatic system invasion, Ki67 level, Oncotype DX score, patient age, and other similar factors.

Oncotype DX (Genomic Health, Redwood City, CA) is a commercially available 21-gene breast cancer recurrence score (RS) assay, which has both prognostic and predictive value for early stage invasive breast cancer in estrogen receptor-positive, HER2-negative cases. Oncotype DX RS predicts the benefits of adding adjuvant chemotherapy to hormonal therapy. Oncotype DX is currently endorsed by the American Society of Clinical Oncology (ASCO) [1], the National Comprehensive Cancer Network (NCCN) [2], and others for routine guideline-driven application. However, because Oncotype DX is expensive, the test is performed for a limited proportion of patients.

Ki67, a nuclear protein associated with cellular proliferation, is a marker for predicting the outcomes of patients with breast cancer. Ki67 expression is typically detected via immunohistochemistry (IHC) and reported as the Ki67 index, which represents the percentage of labeled cells within the investigated cell population. A tumor with high Ki67 expression carries a poor prognosis [3, 4]. Ki67 evaluation has not been standardized. At the 2015 St. Gallen International Breast Cancer Conference, the panel recommended that Ki67 should be interpreted based on local laboratory values [5]. Therefore, although detection of Ki67 has been used for many years to assess cancer proliferation, this biomarker is still not recommended for routine use in clinical management [4].

Regardless, there are cases for which the appropriate therapeutic strategy is unclear, and for which therapeutic strategies vary among physicians. Therefore, it is important to understand individual physicians' therapeutic preferences.

In addition, clinical trial studies of new drugs for breast cancer treatment are being increasingly reported worldwide; learning about how these results are used in real-world clinical practice and about the therapeutic strategies employed at different centers provides an

Mayako TERAO, Department of Endocrine and Breast Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-95-8601 E-mail: mayako.t@is.icc.u-tokai.ac.jp

opportunity for physicians to evaluate the problems and shortcomings of their own therapeutic strategies.

Previous surveys of therapeutic preferences have been conducted outside of Japan. In 2011, Winer *et al*. conducted a breast cancer treatment survey of 100 medical oncologists. They published analyses of survey responses related to treatment prior to breast cancer surgery, postoperative treatment, and treatment for relapse [6]. We expected that conducting a multi-center survey on breast cancer treatment, publishing the results, and sharing the information would provide insight into the current state of breast cancer treatment. Therefore, we planned and performed the survey reported in the present article. Our major goals for this project were to gain a better understanding of how biomarkers are integrated into practice, and to clarify how physicians use this information to refine or validate practical treatment decision-making.

MATERIALS AND METHODS

We drafted questions regarding chemotherapy before and after surgery for breast cancer, chemotherapy in cases of breast cancer recurrence, and tests related to breast cancer treatment. We created the questionnaires to examine physician responses in regard to variables such as age, hormone sensitivity, HER2 expression, tumor size, and lymph node metastasis, on the basis of Winer's medical oncology research [6]. After the initial drafting, the KBOG staff discussed and revised these questionnaires. From October to November 2012, we distributed the questionnaires, and collected the complete, anonymized questionnaires from physicians who treated patients with breast cancer in the Kanagawa Prefecture. The questionnaire comprised content from 23 cases of breast cancer. The aggregated results were used to examine trends in breast cancer treatment in the Kanagawa Prefecture. Six hypothetical case studies that deal with postoperative adjuvant therapy were presented to assess physician therapeutic preferences.

Additionally, we analyzed physician responses based on experience and qualification. Physicians who are "Fellows of the Japanese Breast Cancer Society" or "Diplomats of the Subspecialty Board of Medical Oncology of the Japanese Society of Medical Oncology" possess considerable clinical experience and knowledge. Physicians with these certifications were considered experienced doctors that are skilled in breast cancer chemotherapy. We analyzed the differences in anticancer drug regimen selection between experienced doctors and doctors who did not carry advanced certification by using the chi-square test, with IBM SPSS Statistics version 24.

RESULTS

We distributed questionnaires to 131 physicians who treated patients with breast cancer in the Kanagawa Prefecture. We received anonymous responses from 48 physicians (response rate: 36.6%), 46 of whom provided responses to all questions (Table), which were then aggregated. The youngest physician respondents were in their twenties, while the oldest were in their sixties; physicians in their thirties comprised the largest group of respondents, based on age (n=20). Reported treatment experience ranged from 1 to 40 years, with a median of 11.0 years and a mean of 13.8 years. Physicians who performed preoperative chemotherapy reported treating a median of 10 cases of breast cancer per year, with a mean of 19.87 cases. Physician respondents who performed postoperative adjuvant therapy reported a median of 40 cases of breast cancer per year, with a mean of 41.51 cases.

Respondents included physicians who were Fellows of the Japanese Breast Cancer Society (n=23), as well as Diplomats of the Subspecialty Board of Medical Oncology of the Japanese Society of Medical Oncology (n=3). Two doctors held both qualifications. These physicians comprised the "experienced doctor" group, and accounted for 52% of 46 valid responses that were analyzed.

Experience with Oncotype DX

Respondents were asked about their experience using the Oncotype DX genomic test for predicting cancer. Fifteen of the 46 respondents (32.6%) answered that they had used Oncotype DX; of these 15 respondents, 73.3% had used Oncotype DX fewer than 5 times. Thirty-eight physicians responded to a question that asked about reasons for not using Oncotype DX. Multiple responses were permitted. Twenty-seven physicians responded that Oncotype DX is too expensive, 9 responded that it is unnecessary, 7 responded that the submission method is complicated, 2 responded that it takes too long to obtain results, and 5 responded that patients do not want to receive the test.

Measurement of Ki-67

A total of 97.7% of physicians in the present study responded that they measure Ki-67 in daily practice, including those who responded that they do so depending on the case. The physicians stated that threshold values for what is considered a high level of Ki-67 ranged from 10% to 40%; the median response was 20%, while the most common response was 30%. Responses for what is considered a low level of Ki-67 ranged from 5% to 30%; the median response was 14%, while the most common responses were 10% and 14%. Depending on the clinical scenario, 80.4% to 100% of physicians responded that they use Ki-67 levels as an indicator to determine therapeutic strategies, depending on the case.

In each of the 6 clinical scenarios, we asked about the use of Oncotype DX and Ki67. Further, we asked how the Oncotype DX and Ki67 findings influenced the choice of adjuvant therapy.

Clinical Scenarios

Clinical Scenario 1: Age, 50 years; Sex, female; hormone therapy was scheduled; the tumor diameter was 12 mm; ER+/HER2-; LN-; IDC, postoperative adjuvant therapy was considered.

Nearly all physicians responded that they would not administer anticancer drug therapy for a patient with low-risk Oncotype DX RS and low Ki-67 levels. In contrast, many physicians responded that they would administer anticancer drug therapy for a patient with high or intermediate Oncotype DX RS and/or high Ki-67 levels (Fig. 1).

Table Backgrounds of the responding physicians

The background of responders	n
The length of treatment experience	
1～5	14
6～10	9
11～20	13
21～30	5
31～40	5
The qualifications of the respondents included	
Board Certified Members of the Japanese Breast Cancer society	18
Fellows of the Japanese Breast Cancer Society	23
Board Certified Surgeons of the Japan Surgical Society	35
Board Certified Members of the Japanese Society of Internal Medicine	2
Diplomats of the Subspecialty Board of Medical Oncology of the Japanese Society of Medical Oncology	3
General Clinical Oncologist of Japanese board of Cancer Therapy	5
The others	7
Number of annual cases of chemotherapy	
preoperative chemotherapy	
≦10	23
11～50	19
≧51	3
postoperative chemotherapy	
≦10	9
11～50	27
≧51	9
metastatic and recurrent breast cancer	
≦10	23
11～50	20
≧51	2

Clinical Scenario 2: Age, 70 years; Sex, female; hormone therapy was scheduled; the tumor diameter was 12 mm; ER+/HER2-; LN-; IDC, postoperative adjuvant therapy was considered.

In Clinical Scenario 2, the patient's age was changed from 50 years old to 70 years old. Respondents were asked about postoperative adjuvant therapy for an elderly patient. The number of physicians who responded that they would not perform adjuvant anticancer drug therapy for an elderly patient, even a patient with a high or intermediate Oncotype DX RS and high Ki-67 levels, was higher than in Clinical Scenario 1. Advanced age appeared to be a factor in the decision not to perform adjuvant anticancer drug therapy (Fig. 2).

Clinical Scenario 3: Age, 50 years; Sex, female; hormone therapy was scheduled; the tumor diameter was 40 mm; ER+/HER2-; LN-; IDC, postoperative adjuvant therapy was considered.

In Clinical Scenario 3, the breast tumor was larger than in Clinical Scenario 1. Consequently, more physicians responded that they would perform postoperative adjuvant chemotherapy, compared to that in Clinical Scenario 1. Increased tumor size appeared to increase the likelihood of the physician selecting adjuvant therapy. Additionally, all physicians responded that they would measure the Ki-67 index in Clinical Scenario 3, presumably owing to the large tumor size. Regarding the chemotherapy regimen, compared to that in Clinical Scenario 1, more physicians responded that, due to the Oncotype DX RS and Ki-67 level in Clinical Scenario 3, they would administer a combination anticancer drug therapy consisting of anthracyclines and taxanes (Fig. 3).

Clinical Scenario 4: Age, 70 years; Sex, female; hormone therapy was scheduled; the tumor diameter was 40 mm; ER+/HER2-; LN-; IDC, postoperative adjuvant therapy was considered.

In Clinical Scenario 4, the patient was elderly. In a comparison of therapeutic strategies for a 50-year-old patient versus a 70-year-old patient, the number of physicians who responded that they would use Oncotype DX and Ki67 as indicators to determine postoperative adjuvant therapy was slightly higher when considering a 50-year-old patient. The number of physicians who responded that they would administer an adjuvant chemotherapy regimen of anthracycline anticancer drugs to a patient with high levels of Ki67 was higher when considering a 50-year-old patient. For patients aged 50 years and 70 years, more than

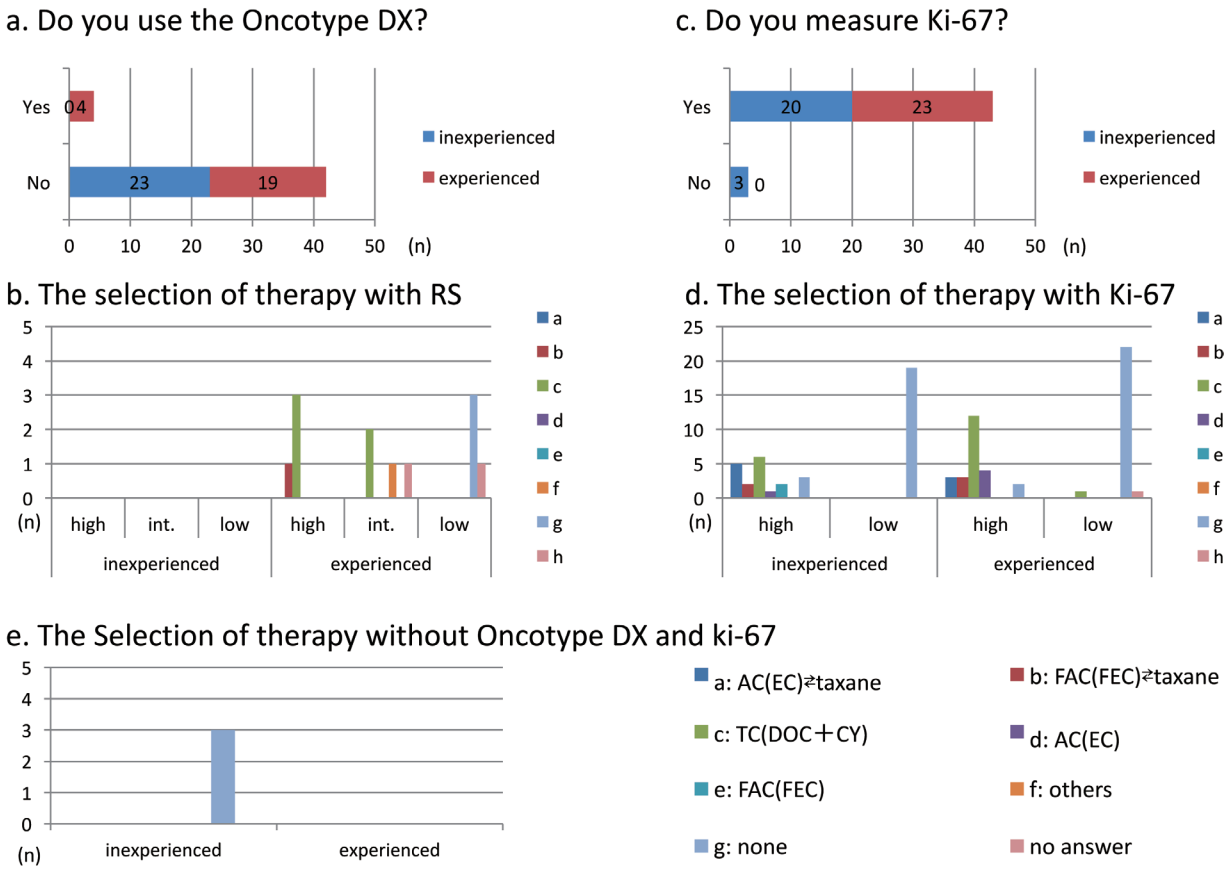

Fig. 1 Clinical Scenario 1. Postoperative adjuvant therapy for a 50-year-old woman with hormone-positive and HER2-negative T1cN0 breast cancer

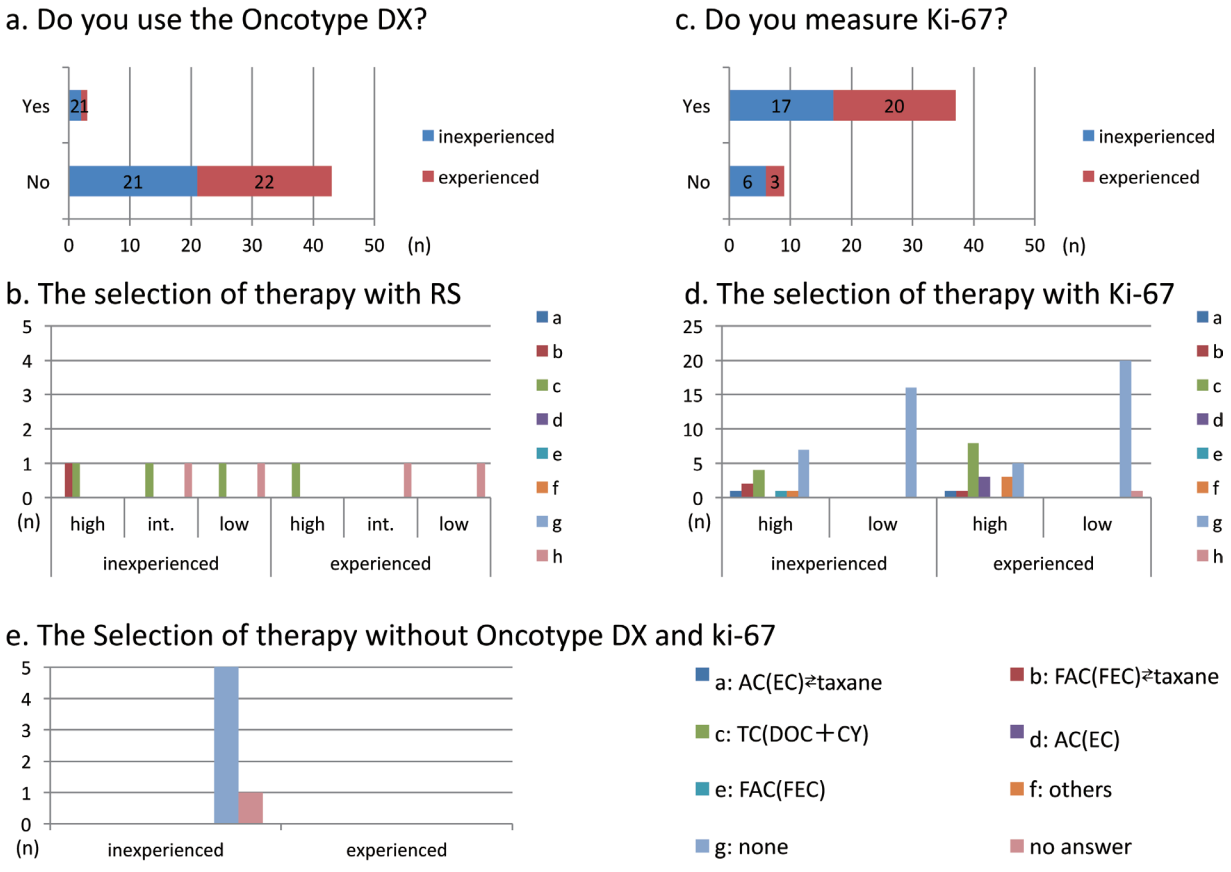

Fig. 2 Clinical Scenario 2. Postoperative adjuvant therapy for a 70-year-old woman with hormone-positive and HER2-negative T1cN0 breast cancer

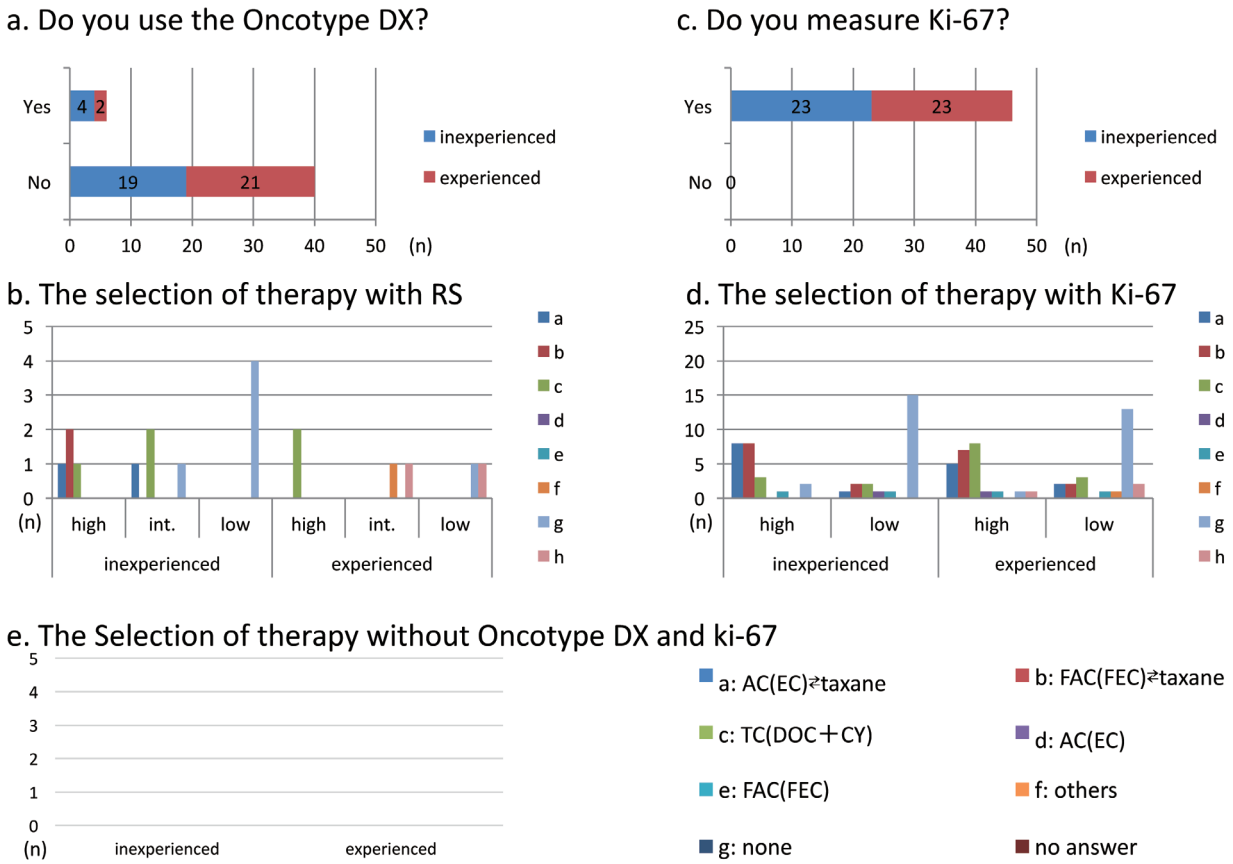

Fig. 3 Clinical Scenario 3. Postoperative adjuvant therapy for a 50-year-old woman with hormone-positive and HER2-negative T2N0 breast cancer

half of the physicians responded that they would use anticancer drugs for hormone-sensitive breast cancer in patients with high levels of Ki-67 (Fig. 4).

Clinical Scenario 5: Age, 50 years; Sex, female; hormone therapy was scheduled; the tumor diameter was 12 mm; ER+/HER2-; LN+ (2); IDC, postoperative adjuvant therapy was considered.

In selecting postoperative adjuvant therapy for a patient with hormone-sensitive and HER2-negative breast cancer, the number of physicians who responded that they would use the Oncotype DX increased when considering a patient who has lymph node metastasis. However, no change was observed in the numbers of responses regarding the measurement of Ki-67. Regarding the selection of drugs for anticancer drug therapy, the presence of lymph node metastasis resulted in more physicians responding that they would administer a combination of anthracyclines and taxanes (Fig. 5).

Clinical Scenario 6: Age, 70 years; Sex, female; hormone therapy was scheduled; the tumor diameter was 12 mm; ER+/HER2-; LN+ (2); IDC, postoperative adjuvant therapy was considered.

The number of physicians who responded that they would measure Ki67 in Clinical Scenario 6 was higher than that in Clinical Scenario 2; consequently, a larger number of physicians responded that they would administer a combination of anthracyclines and taxanes when the Ki67 level is high. However, the number of physicians who responded that they would not perform anticancer drug therapy when the Ki67 level is low changed in consideration of Clinical Scenario 1 compared to Clinical Scenario 5, but not Clinical Scenario 2 compared to Clinical Scenario 6, which differed in the presence versus absence of lymph node metastasis in a 70-year-old patient (Fig. 6).

DISCUSSION

In this study, the selection of a postoperative adjuvant drug regimen for breast cancer, including the decision of whether to include anticancer drugs, appeared to be based on Ki67 levels, tumor size, lymph node metastasis, hormone sensitivity, HER2 expression, and patient age.

The number of physicians who responded that they would not use anticancer drugs was the highest in Clinical Scenario 1, followed by Clinical Scenarios 3 and 5. In these cases, for patients with low Ki67 levels, a large number of physicians responded that they would not use anticancer drugs; thus, Ki67 appeared to be an important indicator for determining the use of anticancer drug therapy in postoperative adjuvant therapy for patients with hormone-sensitive HER2-negative breast cancer. Furthermore, regarding the anticancer drug regimen, the number of physicians who responded that they would administer a combination of anthracyclines and taxanes for patients with high Ki67 levels was the highest in Clinical Scenario 1,

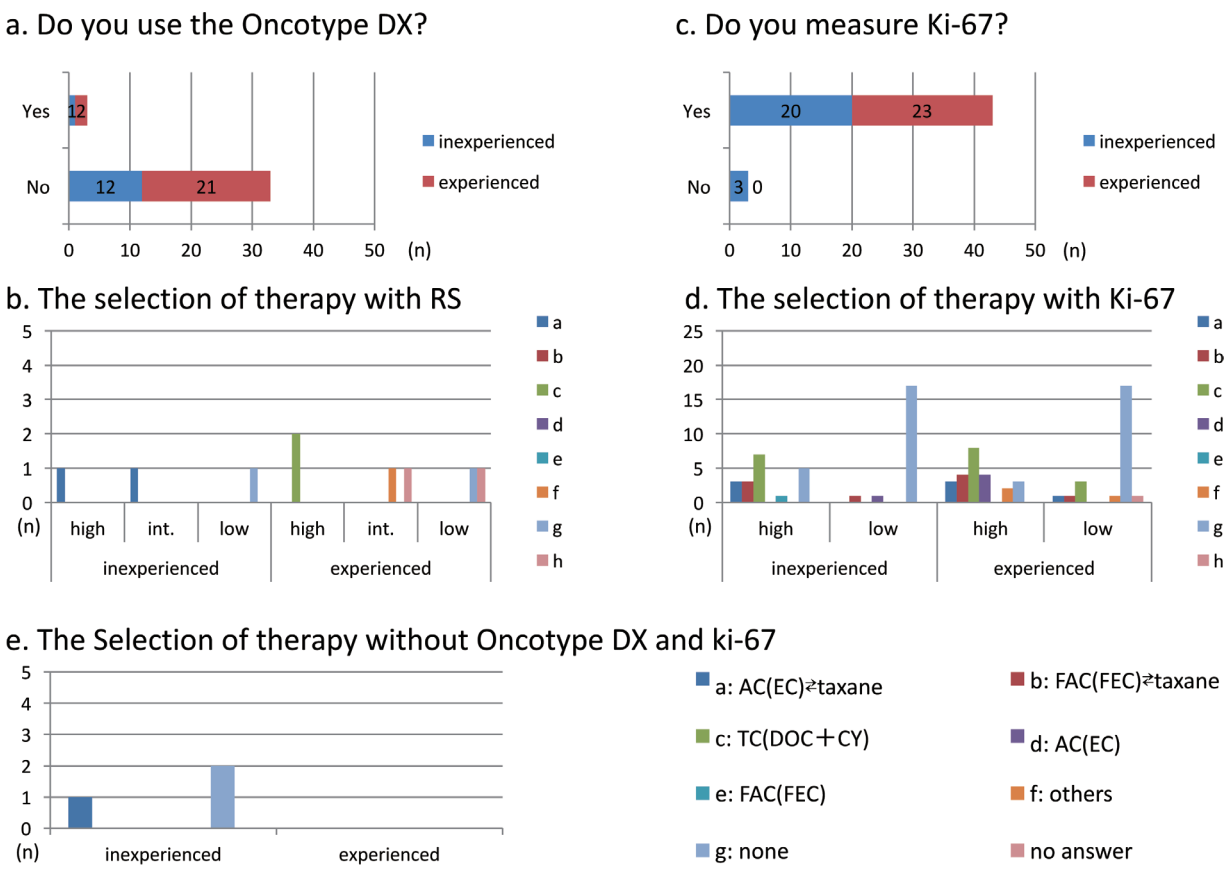

Fig. 4 Clinical Scenario 4. Postoperative adjuvant therapy for a 70-year-old woman with hormone-positive and HER2-negative T2N0 breast cancer

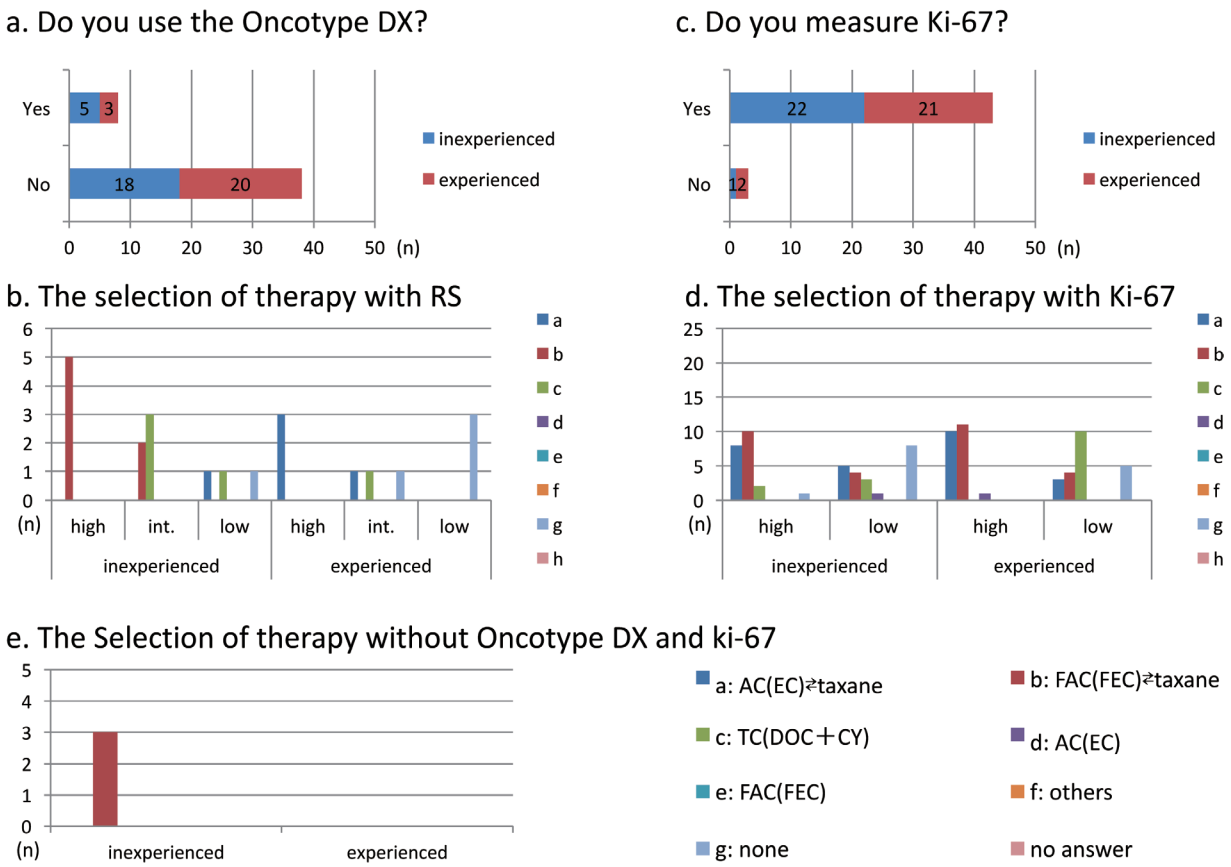

Fig. 5 Clinical Scenario 5. Postoperative adjuvant therapy for a 50-year-old woman with hormone-positive and HER2-negative T1cN1 breast cancer

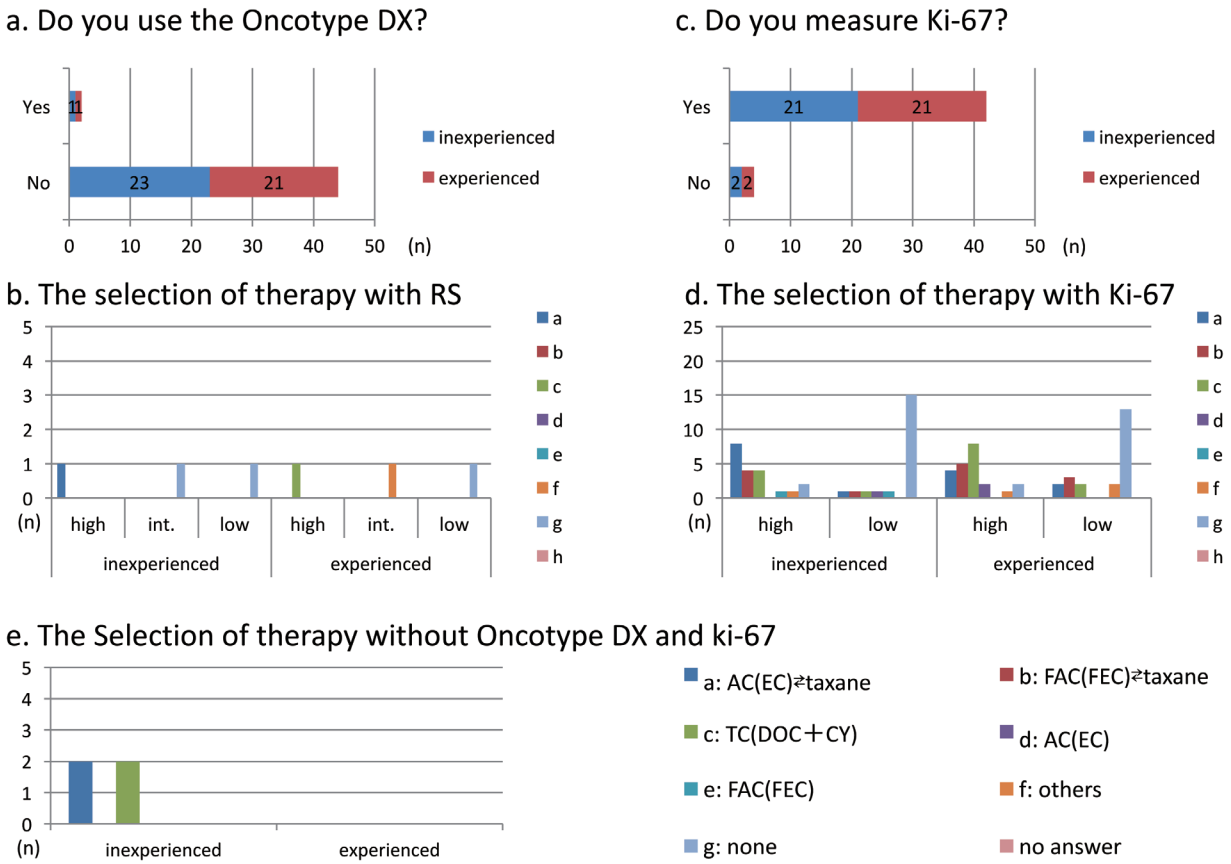

Fig. 6 Clinical Scenario 6. Postoperative adjuvant therapy for a 70-year-old woman with hormone-positive and HER2-negative T1cN1 breast cancer

followed by Clinical Scenarios 3 and 5. These results indicate that while both tumor diameter and lymph node metastasis serve as indicators for determining postoperative adjuvant therapy, lymph node metastasis has a greater effect on the content of anticancer drug therapy.

In the 2015 Japanese Breast Cancer Society Clinical practice guidelines for the pathological diagnosis of breast cancer [7], it is noted that Ki67 assessment may be considered for the purpose of prognostic prediction for invasive breast cancer (Grade C1: limited-suggestive), and is not generally recommended to predict therapeutic response to chemotherapy and endocrine therapy (Grade C2: probable). Because methods for measuring Ki67 are not strictly consistent across centers, it is difficult to compare scores across centers [8, 9]; nonetheless, Ki-67 is considered to be associated with breast cancer prognosis [3, 9]. Ki67 can be measured easily in-center, a factor that has led to the use of Ki67 assessments of proliferation as indicators for administering postoperative adjuvant therapy.

In the 2015 Japanese Breast Cancer Society's Breast Cancer Treatment Guidelines [10], Oncotype DX is acknowledged as a prognostic factor; however, in regard to the prediction of therapeutic effects, Oncotype DX was given a recommendation grade of C1 (limited-suggestive) because of the lack of sufficient data. (Grade C1 means that it may be worth considering, but sufficient evidence is unavailable.) Few physicians in the present study use Oncotype DX, viewing it as unnecessary and expensive; the physicians who do use it responded that they would not use anticancer drugs if the Oncotype DX RS were low, while most of them responded that they would use anticancer drugs if the Oncotype DX RS were high. An intermediate RS would thus be expected to cause physicians to vacillate, and be uncertain about whether they should provide anticancer drug therapy. However, in the results of the present study, most physicians responded that they would provide anticancer drug therapy if the Oncotype DX RS results were intermediate.

In Clinical Scenario 1, only experienced physicians responded that they would use the Oncotype DX (Fig. 1). This suggests that experienced physicians were more cautious about selecting chemotherapy for premenopausal patients with hormone-sensitive breast cancer and without lymph node metastasis. It is possible that patients were still administered chemotherapy owing to a lack of lymph node metastasis and a premenopausal status. In this patient scenario, physicians may consider using the Oncotype DX to select the adjuvant therapy.

In almost all cases, experienced doctors tended to select TC (docetaxel/cyclophosphamide) chemotherapy more often than inexperienced doctors, although this difference did not achieve statistical significance (Fig. 7). TC chemotherapy has become an option for postoperative adjuvant therapy because it significantly extends disease-free survival and overall survival compared to AC (doxorubicin/cyclophosphamide) chemotherapy [11].

In the overall responses to questions regarding anticancer drug regimens in postoperative adjuvant therapy, the number of physicians who responded that they would administer TC chemotherapy was comparable

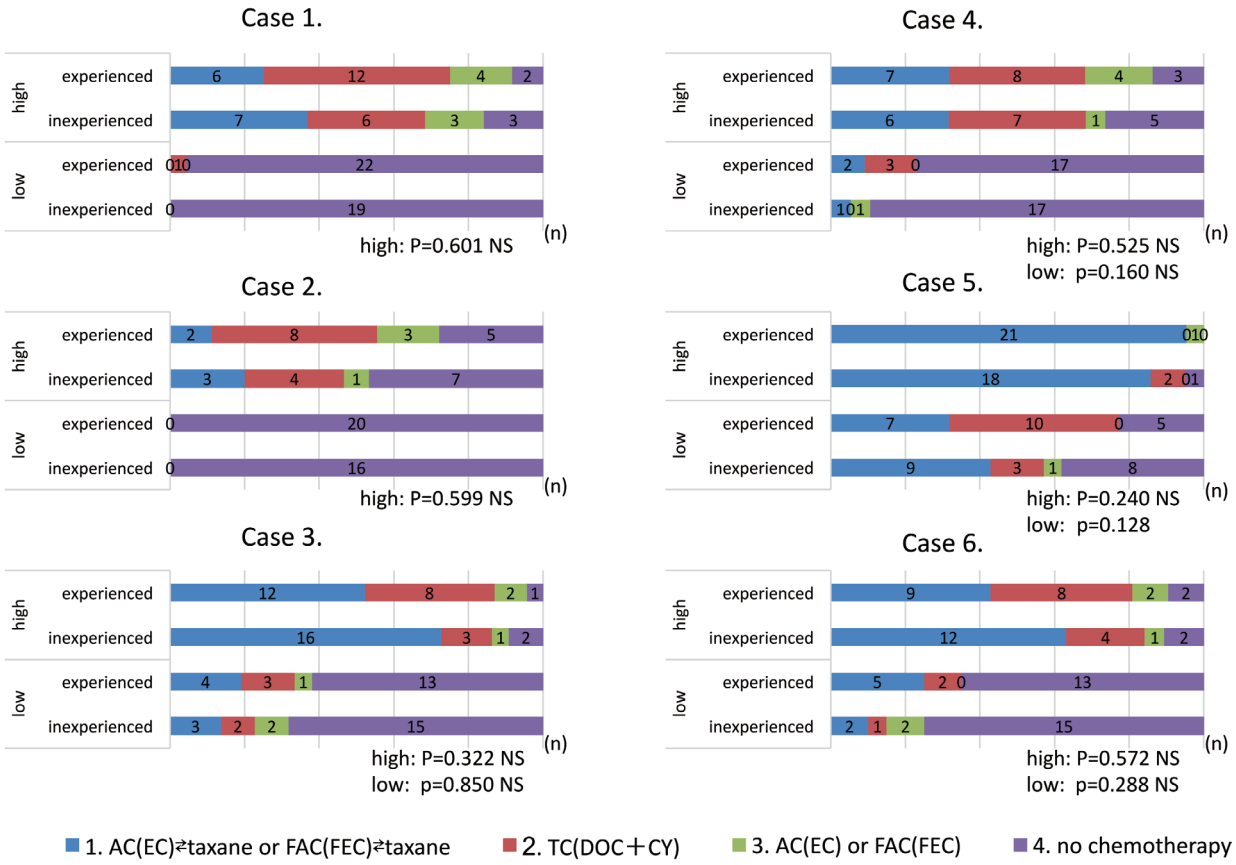

Fig. 7 Therapy selection, based on the Ki-67 index, between experienced and inexperienced physicians

with the number of physicians who would administer a regimen combining anthracyclines and taxanes; these response patterns reveal that TC chemotherapy has become widespread as a regimen for postoperative adjuvant therapy. The same trend was observed in the United States, where Giordano *et al.* showed that the use of anthracycline-based chemotherapy has declined, and that the majority of patients with breast cancer are instead receiving taxane-based chemotherapy [12].

Compared to the number of physicians in Clinical Scenario 5, which concerned a 50-year-old patient, a high number of physicians responded that they would not administer anticancer drugs based on Ki67 for the elderly patient featured in Clinical Scenario 6. For elderly patients with high levels of Ki67, many physicians responded that they would administer TC chemotherapy. Many physicians also responded that they would avoid anthracycline anticancer drugs for elderly patients (Fig. 6).

Typically, the more experienced physicians, as compared to the inexperienced physicians, selected TC chemotherapy, except in Clinical Scenario 5 where the patient had high Ki67 levels. Although there was no statistically significant difference, the results indicate that experienced physicians may use clinical trial results to guide their clinical practice, more so than inexperienced physicians.

In the future, continuing to survey breast cancer management practices may shed light on changes in the approach to breast cancer treatment. In addition, the results of clinical trials on the Oncotype DX score and Ki67 as predictors of prognosis and therapeutic effects may lead to changes in therapeutic strategies. The results of these clinical trials will elucidate how physicians at other centers assess these results and how physicians apply these results in clinical practice; if there are differences in therapeutic strategies, new clinical questions may arise, potentially leading to the implementation of clinical trials to pursue more refined therapeutic strategies.

The present surveys were distributed and collected in 2012; some of these surveys were limited to questions about postoperative adjuvant therapy. In future studies, we intend to review the results of preoperative chemotherapy and the therapeutic strategies for recurrent and metastatic breast cancer.

ACKNOWLEDGEMENTS

We would like to extend our profound gratitude to all the physicians for taking time out of their busy schedules to complete our questionnaire survey. Additionally, we extend our profound gratitude to the members of the Kanagawa Breast Oncology Group for their instruction and cooperation in the planning stage of the present study.

REFERENCES

1) Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, *et al.* Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34: 1134–50.
2) Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, *et al.* NCCN Guidelines Insights; Breast Cancer, Version 1. Journal of the National Comprehensive Cancer Network: JNCCN 2017; 15, 433–451.

3) Viale G, Regan MM, Mastropasqua MG, Maffini F, Maiorano E, Colleoni M, *et al*. Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J Natl Cancer Inst 2008; 100: 207–12.
4) Niikura N, Masuda S, Kumaki N, Xiaoyan T, Terada M, Terao M, *et al*. Prognostic significance of the Ki67 scoring categories in breast cancer subgroups. Clin Breast Cancer 2014; 14: 323–29 e3.
5) Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, *et al*. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015; 26: 1533–46.
6) Neil L. Management of Breast Cancer in the Neoadjuvant, Adjuvant and Metastatic Settings: Patterns of Care in Medical Oncology, Miami, Research to Practice, 2011: Vol 7, Issue 1.
7) Horii R, Honma N, Ogiya A, Kozuka Y, Yoshida K, Yoshida M, *et al*. The Japanese Breast Cancer Society clinical practice guidelines for pathological diagnosis of breast cancer, 2015 edition. Breast Cancer 2016; 23: 391–9.
8) Crawford NW, Heath JA, Buttery JP. Immunisation practices of paediatric oncologists: an Australasian survey. J Paediatr Child Health 2007; 43: 593–6.
9) Niikura N, Sakatani T, Arima N, Ohi Y, Honma N, Kanomata N, *et al*. Assessment of the Ki67 labeling index: a Japanese validation ring study. Breast Cancer 2016; 23: 92–100.
10) Aihara T, Toyama T, Takahashi M, Yamamoto Y, Hara F, Akabane H, *et al*. The Japanese Breast Cancer Society Clinical Practice Guideline for systemic treatment of breast cancer, 2015 edition. Breast Cancer 2016; 23: 329–42.
11) Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, *et al*. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 2009; 27: 1177–83.
12) Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. J Clin Oncol 2012; 30: 2232–9.