

SPECIAL REPORT

Survey of the Application of the Korean Clinical Practice Recommendations on Breast Cancer Treatment: The Utility of the Korean Breast Cancer Society Guidelines

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This survey was performed to analyze the usability of the third edition of the Korean breast cancer clinical practice guidelines (KBCCPG) in clinical practice. We made a questionnaire composed of 18 general and 82 specific questions regarding benign breast disease (B; 1 question); non-invasive disease (N; 12 questions); early-stage disease (E; 26 questions); advanced disease (A; 24 questions); and metastatic (M) breast cancer-related problems (19 questions). A total of 100 questionnaires, with a link to an online survey, were delivered via e-mail to over 700 members of the Korean Breast Cancer Society (KBCS), and associated academy members, over 20 days between 26th February and 16th May 2010. Out of 270 respondents who read the e-mail, 96 answered the questionnaire. Participants included 87 surgical oncologists, 5 radiation oncologists, 2 oncoplastic surgeons, 1 pathologist, and 1 medical oncologist. The third KBCCPG were perceived as differing from the second guidelines in terms of the

level of clinical evidence required before choosing a recommendation. For the progress of the KBCCPG, the guideline committee should try to reinforce all courses of guideline development with several elements including data from clinical trials of Korean breast cancer patients, securing a multidisciplinary approach, developing consistent and reasonable processes for each step of the revision of the guidelines, induction of liberal scientific and ethical discussion about all issues with all KBCS members. The cost-effectiveness of healthcare and the logical development of the KBCCPG would also be ensured. Timely updates of the clinical guidelines for breast cancer treatment are essential to facilitate optimal decision-making in daily practice, and to ensure adequate patient feedback.

Key Words: Breast neoplasms, Guideline, Korea, Surveys

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INTRODUCTION

The aim of clinical practice guidelines is to reduce inappropriate variations in physician-ordered treatment and to optimize the care given to every patient [1]. The first Korean breast cancer clinical practice guidelines (KBCCPG) were issued in 2002 by the Guidelines Committee of the Korean Breast Cancer Society (KBCS). The second iteration employed systematic literature review to ensure evidence-based guideline development. The first edition of the KBCCPG was formatted in an

abridged version. In 2006 and 2008, the second and third edition of the KBCCPG included more detailed content, reinforced via systematic literature reviews and consensus built in a multidisciplinary manner. The third KBCCPG was developed with financial assistance from the department of medical resource of the welfare administration body, in cooperation with the Korean Academy of Medicine (KAM). The KBCS has sought to improve the CPG developmental process by widening the multidisciplinary approach, via the use of external review. The evolutionary process leading to the development of the fourth KBCCPG, in which the KAM participates, included an online survey of 96 members of the KBCS, which corresponded to approximately 13% of all KBCS members. These 96 members were asked to complete a questionnaire revealing the practical utility of the third KBCCPG in real-life daily practice in breast cancer clinics. The purpose of our survey was to apply this valuable feedback to the construction of the fourth KBCCPG.

Seven academic societies related to breast cancer management collaborated to produce the third edition of the KBCCPG. The collaborating groups were the Korean Society for Therapeutic Radiology & Oncology, the Korean Society of Pathologists, the Korean Society of Plastic and Reconstructive Surgeons, the Korean Society of Radiology, the Korean Society of Nuclear Medicine, KBCS, and KAM. Development of the third edition of the KBCCPG was officially supported by the Korean Ministry of Health & Welfare.

During the developmental process, the Guidelines Committee organized a task force team (TFT), all members of which had the workshop training for systematic literature searches and evidence grading before initiating the guideline development. The Guidelines Committee requested that members of the TFT to systematically review the literature cited on websites; which included the National Comprehensive Cancer Network (NCCN) guidelines [2,3], the Cochrane database [4], EMBASE, and PubMed.

The strength of any recommendation is important to permit informed clinical decision-making; any suggestion is effectively a judgment of the benefits, risks, harm, and cost of adherence. The quality of evidence reflects the extent to which a guideline panel has confidence that the study of a particular aspect of a disease is adequate to support a particular recommendation [5,6].

We performed the present survey to ascertain the utility and practical use of the third edition of the KBCCPG, and the application of these guidelines in the daily practice of KBCS members working in breast cancer clinics. The data will be used to guide drafts of the fourth edition of the KBCCPG. In Addition, we reevaluated key grade of recommendations and level of evidences of the third KBCCPG; we will seek to update these

guidelines in the fourth KBCCPG.

The fourth Korean Breast Cancer Society Guideline Committee (KBSCGC) was composed of five subgroups (one benign breast disease committee; four breast cancer committees) that prepared guidelines. A questionnaire was developed by TFT formed from subgroups of the KBSCGC and contained 19 general questions exploring the utility of the third KBCCPG and 81 specific questions (1 on benign disease, 12 on non-invasive breast cancer, 26 on early-stage breast cancer [EBC], 24 on locally advanced breast cancer, and 19 on metastatic breast cancer). We amended the draft of the questionnaire between the 1st December 2009 and 25th February 2010, and delivered the final version to all members of the KBCS and partners within the multi-disciplinary teams containing KBCS members. We e-mailed the questionnaire three times between 26th February 2010 and 16th March 2010. Among 270 members of the KBCS who downloaded the e-mailed questionnaire file sent by an online survey company (Oz-survey, Seoul, Korea) under contract with the KBCS, a total of 96 members sent us responses. We analyzed all completed questionnaires and presented the results of our online survey at a symposium conducted by the fourth KBSCGC group, held on 30th March 2010.

The demographic characteristics of surveyed respondents were representative of those from surgeons in university hospitals in Korea. Although the third KBCCPG was rated as the first preferred reference material in daily practice, most respondents simultaneously referred to the NCCN guidelines, the St. Gallen Oncology Conference guidelines, and the American Society of Clinical Oncology (ASCO) guidelines. About 80% of members are satisfied with the third edition of the KBCCPG, but fewer than 5% are deeply satisfied. The use of a multidisciplinary approach, the publication of a well-organized booklet, and the utility of the booklet in terms of the education of trainees have been advanced and considered strengths of the third KBCCPG; whereas a lack of data on various preclinical conditions, on metastatic and recurrent breast cancer, and on life-long care after cancer treatment, are recognized weaknesses.

One of the most important issues is the novel content requested for the fourth KBCCPG. Most respondents chose atypical duct hyperplasia, papillary neoplasm, and non-cancerous lesions, as deserving of special attention. Thus, the committee has added these topics as appendices to the fourth KBCCPG.

NON-INVASIVE BREAST CANCER

In real practice, when ductal carcinoma *in situ* (DCIS) patients exhibit negative margins in frozen intraoperative sec-

tions but the margins were positive when permanent sections were examined, about 50% of physicians perform secondary operations to guarantee negative margins. In addition, approximately 30% of physicians at least consider scheduling a secondary operation, depending on the number and extent of positive marginal lesions. However, about 20% eschew further axillary procedures.

Sentinel lymph node biopsy (SLNB) is generally not recommended for patients with simple DCIS but is recommended for select patients treated with mastectomy or excision in an anatomic setting which may compromise the performance of any future sentinel lymph node procedure [7,8]. About 60% of respondents selectively perform SLNB in DCIS patients, and about 40% do not require that any clinical precondition should be met.

DIAGNOSIS

Eighty percent of physicians performed breast magnetic resonance imaging (MRI) in EBC patients, whereas the proportion was 94% for metastatic breast cancer (MBC) patients. In EBC patients, 26% of physicians always perform a breast MRI, without any clinical precondition, but 20% never order an MRI under any clinical circumstance. However, for MBC patients, 37% of physicians always perform breast MRI, without any clinical precondition, whereas 6% never order the test under any clinical circumstance. The NCCN guidelines recommend that breast MRI should serve as an optional additional modality for evaluation of the extent of ipsilateral disease, and to screen the contralateral breast, particularly in women at increased risk for mammographically occult disease (both EBC and MBC) [9,10].

Most respondents (85%) conduct tumor estrogen receptor (ER)/progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) determination on preoperative biopsy samples, and the principal methods of HER2 testing are immunohistochemistry (IHC) stain and fluorescence *in situ* hybridization (FISH). These practices almost meet the NCCN recommendations. Chromogenic *in situ* hybridization (CISH) is a relatively new method for the detection of gene amplification via a peroxidase reaction, with the results obtained using a standard light microscope [11]. CISH, as a HER2 test, is performed by about 9% of survey respondents. Current studies have revealed that the concordance rate between CISH and FISH data is high, and that the CISH test is very accurate. We expect that CISH may be a valuable option in terms of HER2 testing, but no DNA probe kit is yet available in the United States.

CHEMOTHERAPY

Our questions exploring the chosen chemotherapy regimens for EBC patients focused on nodal and ER/PR status. In node-negative patients, some differences between the choice of chemotherapy regimen for ER-positive and -negative patients were evident. Four cycles of adriamycin+cyclophosphamide (AC) are preferred for ER-positive patients, but six cycles of 5-fluorouracil+adriamycin+cyclophosphamide (FAC) for ER-negative patients, among those who are node-negative. In the node-positive group, no difference in terms of ER positivity were evident, and the preferred regimen is four cycles of AC followed by four cycles of paclitaxel. However, six cycles of adriamycin+docetaxel (AT) or epirubicin+docetaxel (ET) are preferred when neoadjuvant chemotherapy is used to treat patients with locally advanced breast cancer.

TRASTUZUMAB THERAPY

The evaluation methods appropriate to and the proper intervals for assessment of trastuzumab-induced cardiac toxicity during and after trastuzumab therapy remain unclear. Our survey data reveal inconsistencies in the clinical modes by which respondents screen for trastuzumab-induced cardiac toxicity. However, in general, tests are conducted at 3 to 6 months intervals, and employ echocardiography; the screening is accepted as appropriate [12].

ENDOCRINE THERAPY

We asked our respondents to report on the use of hormonal therapy in patients with locally advanced breast cancer. Most physicians preferred 2 years of treatment with a GnRH agonist concurrent with 5 years of tamoxifen in premenopausal women or 5 years of aromatase inhibitor therapy in postmenopausal women. A minority of physicians preferred 5 years of tamoxifen for premenopausal women. These data seem to reflect the generally accepted consensus of the utility of hormonal therapy to treat those with local breast cancer. A related study has been performed in Korea; this is the ASTRRA trial (encoded KBCSG005) which evaluated the utility of the addition of ovarian function suppression therapy to tamoxifen use in young women (≤ 45 years of age) with hormone-sensitive breast cancer who remained in a premenopausal state or who resumed menstruation after chemotherapy. The results of this trial may facilitate optimal decision-making in terms of hormonal therapy for premenopausal women with breast cancer.

RECONSTRUCTION

In the present survey, after mastectomy, we found that about two-thirds of physicians perform reconstruction in patients with EBC but only one-third do so in those with local breast cancer. Use of a pedicled transverse rectus abdominis myocutaneous flap was preferred after mastectomy. Reconstruction in patients with locally advanced breast cancer is less often performed than is the case in those with EBC. Most respondents use one of several plastic techniques to achieve better cosmetic results in EBC patients. These techniques include local tissue rearrangement, mesh application, and placement of a latissimus dorsi flap after breast-conserving surgery. Mesh application is popular, and is preferentially used in some Korean institutions. Precise indications for the application of mesh to a surgical site are needed and both the short- and long-term results require evaluation.

SENTINEL LYMPH NODE BIOPSY

In the present survey, over 80% of physicians perform additional standard level I/II axillary lymph node dissection (ALND) if micrometastasis is evident, or when three or more sentinel lymph nodes are initially removed, whereas about 15% of physicians do not perform standard level I/II axillary dissection. When the St. Gallen consensus conference met in 2011, most panels agreed to consider the omission of ALND completion for patients with isolated tumor cells who were scheduled for mastectomy or breast conserving surgery. However, the Panel also remarked very clearly, that the omission of completion of the ALND should not be extended more generally, to (for example) patients undergoing mastectomy, or to those not scheduled for whole-breast tangential field radiation therapy, or to those exhibiting involvement of more than two sentinel nodes, or to those receiving neoadjuvant therapy [13].

This survey clearly showed the disassociation between the guidelines actual clinical practice. As there is an increased level of evidence, respondents answered by treating the patient as recommended by the guidelines. For example, adjuvant chemotherapy in early breast cancer has been well established higher level of evidences from large scale multicenter randomized clinical trials. In related questions, most respondents chose one or two standard therapies. However, the definition of the negative margin in DCIS, secondary operation for the positive margin of DCIS, SLNB after neoadjuvant chemotherapy, and systemic therapy in recurrent or metastatic breast cancer are lacking a higher level of evidence. In related questions, answers from respondent demonstrate a wide spectrum of practices. Especially, the proportion of young women with breast cancer

in Korea is higher than Western. This different epidemiology might affect the physicians' decision to treat recurrent or metastatic breast cancer in patients. Regardless of the recommendation of the guidelines, physicians have a tendency to choose more aggressive systemic cytotoxic therapy with several expectations such as relief of pain, improving the quality of life, delaying the disease progression, and possibly curing of the disease.

In Korea, the medical insurance system is relatively well organized and most cancer patients receive benefits which covers about 95% of the total cost for cancer therapy. This unique medical environment might affect the details of the KBCCPG. Although the effect of new innovative therapy was recently confirmed by an increased level of evidence, it takes times in Korea for medical insurance to cover the cost of new therapy. Consequently, the KBCCPG and the physicians' practices are affected by medical insurance and the health insurance review agency as another factor with the scientific evidences and cultural characteristics.

LIMITATIONS AND PROSPECTIVE

This survey demonstrated real clinical practices for breast cancer patients in Korea, but also exhibited several limitations. First, respondents who are mostly in their fourth or fifth decade as surgeons working in large hospitals were potentially represented bias in this survey. When we analyzed the answers after closing the online survey, most respondent were representative of younger surgeons. Consequently, the results were a representative opinion of specific groups within the KBCS regardless of the initial intention. This is far from the multidisciplinary politics of the KBCS and it could not demonstrate real circumstances of practice in Korea. Second, the questionnaire in this survey is often arbitrary and the replied answers include very subjective factors that may have disturbed the objective analysis of the survey and demand more cautious interpretation. Third, respondents often skipped some essential questions which were requested in the online survey and, in consequence, different denominators between each question may have caused confusion with the analysis of the results of the survey.

Therefore, we keenly realized the necessity of a well organized questionnaire for the focus on key issues through the process of this survey. However, we can predict the progress of the KBCS CPG by reason of persistent trials including official or unofficial discussions about clinical issues between the KBCS CPG panels, KBCS members, and third parties in various academic circumstances. Furthermore, any feedback or query systems from guideline users might be seriously considered

for realistic and useful guidelines.

CONCLUSION

For the progress of the KBCCPG, the guideline committee should attempt to reinforce all courses of guideline development with several elements including, data from clinical trials of Korean breast cancer patients, securing a multidisciplinary approach, development of consistent and reasonable processes in each step of the revision of the guideline, and induction of liberal scientific and ethical discussion about all issues with all KBCS members.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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