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Letter to the Editor

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Should All Low-Grade Ductal Carcinoma *In Situ* Be Excised? Implications and Challenges of the COMET Trial

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To the Editor

Ductal carcinoma *in situ* (DCIS) has long been recognized as a pre-cancerous lesion with the potential to progress to invasive breast cancer. Thus, surgical excision with more than 2 mm margin with adjuvant radiation and with or without adjuvant endocrine therapy when estrogen receptor (ER)-positive has been recommended by the guidelines and is the standard of care. DCIS is a condition in which cancer cells remain confined within the mammary duct without forming an invasive focus. Theoretically, pure DCIS should not metastasize, and surgical intervention is considered curative. In fact, the 10-year disease-specific survival rate for DCIS is extremely high at 98% [1]. The widespread adoption of breast cancer screening has led to an increase in the detection of DCIS, but it has not reduced the detection of invasive breast cancer nor breast cancer mortality [2]. This suggests that DCIS is less likely to progress to invasive cancer over time. An analysis of the SEER database found no difference in prognosis of low-grade DCIS patients between who did or did not undergo surgery [3].

Given this background, concerns have been raised regarding overdiagnosis and overtreatment of DCIS, and active monitoring has gained attention in recent years. The results of one of the highly anticipated trials, the Comparison of Operative to Monitoring and Endocrine Therapy for DCIS (COMET) trial, were recently presented at San Antonio Breast Cancer Symposium 2024 and published in Journal of American Medical Association (JAMA) [4]. The trial tested the hypothesis that active monitoring without surgery is not inferior to standard DCIS management. Multiple clinical trials are ongoing to seek this possibility, which are The LOw RISk DCIS (LORIS) study [5], LOw Risk Dcis (LORD) study [6], and LOw-Risk DCIS with Endocrine Therapy alone-TAm (LORETTA) study (Japan Clinical Oncology Group (JCOG) 1505), and now COMET trial was the first to report its result.

COMET trial is a phase 3 randomized study with eligibility criteria including patients aged 40 years or older, histological grade 1 or 2 DCIS, ER-positive, human epidermal growth factor receptor 2 (HER2)-negative, and without clear evidence of invasive cancer on imaging. Participants were randomly assigned to either active monitoring group or guideline-concordant care group, which underwent surgical excision and optional adjuvant radiation. The primary endpoint was the 2-year cumulative incidence of ipsilateral invasive breast cancer, and the study evaluated whether the active monitoring group was non-inferior to the guideline-concordant care group. Endocrine therapy was administered at the physician's choice, and approximately 70% of patients in both groups received it. This trial demonstrated that a non-surgical approach for low-grade DCIS was non-inferior to guideline-concordant care in terms of the 2-year cumulative risk of ipsilateral invasive breast cancer. However, while the reported results are noteworthy, there are critical issues that must be considered when interpreting the findings, as outlined below.

First of all, the high incidence of invasive breast cancer in the guideline-concordant care group particularly within a month after randomization may be simply because surgical excision enabled detection of undiagnosed invasive cancer within DCIS that existed at the time of randomization, which remained undiagnosed in the active monitoring group, which lacked thorough histopathological examination of the excised specimen. It has been reported that 26-28% of DCIS has an invasive lesion that was undiagnosed preoperatively and incidentally found by histopathological examination of the removed specimen [7, 8]. COMET trial excluded the patients with a high risk of upstaging (invasive cancer found in DCIS), which were the patients with mass-forming lesions, histological grade 3, ER-negative, and HER2-positive. As a result, the risk of upstaging was estimated to be approximately 10%. In the intention-to-treat (ITT) analysis, surgery was performed in

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264 patients in the guideline-concordant care group. Applying the same proportion, it is estimated that invasive breast cancer would be detected in approximately 26 cases. In fact, 27 cases of invasive breast cancer were detected in the guideline-concordant care group, which is consistent with the expected outcome.

On the flip side of the coin, the lower number of invasive breast cancer cases in the active monitoring group is most likely due to the absence of surgery. The primary endpoint of the trial is the incidence of invasive breast cancer, and it is expected that approximately 10% of active monitoring group should have undiagnosed invasive breast cancer assuming adequate randomization. The fundamental objective of the COMET trial is to examine whether monitoring undiagnosed invasive cancer in the breasts, estimated to be present in approximately 10% of the active follow-up group, until it becomes detectable by imaging is non-inferior to immediate excision at the time of DCIS diagnosis when compared to standard treatment. In other words, it is necessary to prove that the occurrence of invasive cancer in the active follow-up group is non-inferior to that after guideline-concordant standard of care in the long run. In the RTOG 9804 trial, the 10-year cumulative incidence of invasive breast cancer after surgery was extremely low at 1.5% when combined with radiation therapy [9]. To demonstrate the non-inferiority of the active monitoring group, a long-term observation period and an adequate sample size are required. When radiation therapy was not performed, the 10-year cumulative incidence of invasive breast cancer was relatively higher at 9.2% [9]. Moreover, whether to administer endocrine therapy was determined by the treating physician, which may complicate the interpretation of trial results. According to the previous clinical studies that evaluated the addition of adjuvant endocrine therapy for DCIS, ipsilateral breast recurrence rates were reduced by 5-44% [10-12]. When endocrine therapy is used for primary prevention, tamoxifen has been shown to reduce the risk of breast cancer by 38% [13]. These findings indicate that endocrine therapy has a significant effect on outcomes of DCIS. There is even a clinical trial suggesting that endocrine therapy may cure DCIS [14]. Given that adjuvant radiation and endocrine therapy was not mandated in the guideline-concordant care group in the COMET trial, interpretation of this endpoint may be challenging.

Another limitation is the challenge in distinguishing DCIS from invasive cancer by currently available imaging modalities. In COMET trial, magnetic resonance imaging (MRI) was not a mandatory of the eligibility criteria. However, discrepancies are frequently observed, where cases considered as localized on mammography or ultrasound exhibit more extensive disease on MRI. Some reports indicate that when MRI shows tumor extension of 2 - 3 cm or more, the risk of concurrent invasive cancer increases significantly [15, 16]. The lack of mandatory risk assessment for invasive cancer using multiple imaging modalities is also a limitation of this trial.

Early results of the COMET trial demonstrated the possibility of active monitoring to be an option for low-grade DCIS; however, careful consideration regarding the study design and its interpretation to translate the findings into practice are necessary. In particular, given the challenges on the detection of invasive cancer by the images, the short observation period, protocol adherence rates, and the lack of protocol-mandated endocrine therapy or radiation therapy, it is premature to conclude that active monitoring becomes the standard of care for low-grade DCIS at this time. On the other hand, patient-reported outcome results in COMET trial demonstrated no significant differences between the groups in quality of life such as, anxiety, depression, worries about DCIS, and symptom trajectories during the first 2 years [17], which implicates that the patients are satisfied in the outcomes regardless of the groups. Moving forward, a long-term follow-up and consistency with the results of other studies will be essential to clearly determine the safety and efficacy of active monitoring for low-grade DCIS.

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Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Hiroki Kusama: conceptualization and writing - original draft preparation. Yoshiya Horimoto: conceptualization, writing - review and editing. Takashi Ishikawa: project administration. Kazuaki Takabe: project administration and writing - review and editing.

Data Availability

No new data were generated or analyzed in this manuscript.

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