2019 Health Technology Reassessment Report

# Cancer Antigen CA-50

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Summary (English)

## □Background

Cancer Antigen (CA) 50 is a xenoantigen detected by C-50 (IgM), a monoclonal antibody obtained from human colorectal cancer cell lines. The technology is utilized as a serological tumor marker test by measuring the CA 50 level in the blood, and it is used to diagnose various cancers (including malignant tumors in the gastrointestinal tract) and for follow-up on treatment response.

The Health Insurance Review & Assessment Service (HIRA) sought the opinions of relevant academic societies (and associations) on currently not-covered technologies that had been listed before the introduction of the Innovative Health Technology Assessment system to determine whether or not to change the coverage status of any of the items to preliminary coverage. An opinion was presented that CA-50 should be assessed on safety and effectiveness, and the Korea National Evidence-based Healthcare Collaborating Agency (NECA) was requested to assess the technology. Accordingly, NECA assembled a subcommittee and performed a safety and effectiveness assessment of Cancer Antigen CA-50.

## □ Committee operation

To assess the safety and effectiveness of the said technology, the subcommittee of 9 members (2 clinical pathologists, 2 gastroenterologists, 2 hematologists, 1 pulmonologist, 1 obstetrician-gynecologist, and 1 evidence-based medicine specialist) held 4 meetings within approximately 4 months from May 30 to September 26, 2019.

## □ Methods

The safety and effectiveness assessment of Cancer Antigen CA-50 was performed by conducting a systematic review. In this assessment, target patient groups were defined with a focus on the target diseases (malignant tumors) listed in the health insurance benefit payment list (No-282) and diseases reported in the literature for which the technology's clinical effectiveness needs to be demonstrated. Reference and comparison tests were evaluated for each target disease. The safety of the said

technology was evaluated by examining the adverse effects of the test and harm due to inaccurate test results. The effectiveness was evaluated by examining diagnostic accuracy, relationship with prognosis, and healthcare impact.

For the systematic review, 5 domestic databases and 3 foreign databases were searched using the core questions. Two reviewers independently searched and selected articles based on the predetermined selection and exclusion criteria. Only studies published in 2001 and thereafter were selected, reflecting the period after the addition of the said technology to the no-coverage list.

The two reviewers independently assessed bias risk during the article selection using QUADAS-2 and RoBANS and reached a consensus. The reviewers independently extracted data using a predetermined data extraction form. Regarding the items they disagreed on, a consensus was reached by discussing with a third reviewer. A qualitative review was performed to examine the extracted data.

## □ Results

The systematic review conducted to assess the safety and effectiveness of the Cancer Agent CA-50 test involved 20 articles (all foreign studies). Grouped by study type, 12 of the 20 articles were cross-sectional studies reporting diagnostic accuracy, and 8 were cohort studies. Grouped by target disease, 9 articles were on pancreatic cancer, 7 were on stomach cancer, and 4 were on colorectal cancer. No findings were found regarding other target disease groups (gallbladder, liver, ovarian, and lung cancers).

Regarding the safety of the said technology, no articles reported the adverse effects and harm due to inaccurate test results. However, the subcommittee thought that there was little concern about safety, because the test is conducted on biopsied tissues and it does not directly cause harm during a biopsy.

The effectiveness of the said technology was assessed based on diagnostic accuracy (diagnosis/prognosis prediction) and prognostic indices.

Diagnostic accuracy was reported in 13 articles. Based on the cancer type, the sensitivity, specificity, and AUC of the index diagnostic test (a total of 6 articles) were 0.13-0.78, 0.68-1.00, and 0.73-0.74 (2 articles), respectively, for the studies in which pancreatic cancer was diagnosed in patients with pancreatic or non-pancreatic cancers (including benign tumors of the pancreas). The sensitivity, specificity, and

AUC were 0.19–0.84, 0.60–1.00, and 0.81–0.82 (2 articles) for the tests that used CA 19-9 as the reference standard (a total of 6 articles) and 0.2–0.64, 0.60–0.94, and 0.64–0.71 (2 articles), respectively, for those that used CEA as the reference standard (4 articles). A study in which CA 125 was used (1 article) reported a sensitivity of 0.51 and a specificity of 0.89. Compared to CA 19-9, the reference standard most commonly used in practice, the index test, showed relatively low sensitivity. Though it is difficult to generalize based on a single study, a study involving Lewis-negative patients reported sensitivities of 0.13 and 0.19 for the index test and the test using CA 19-9, respectively. In practice, the existing test using CA 19-9 has a limitation because the antigen is not expressed in Lewis-negative patients. Thus, it was difficult to determine the clinical significance of the index test. In studies involving stomach cancer patients and healthy controls (2 articles), the sensitivity, specificity, and AUC of the index test was 0.37-0.5, 0.97-0.99, and 0.81-0.83, respectively. The sensitivity, specificity, and AUC were as follows: 0.26–0.67, 0.67, and 0.63–0.64, respectively, for CA 19-9; 0.13–0.17, 0.98, and 0.66–0.68, respectively, for CEA; 0.10–0.28, 0.98–0.99, 0.67, respectively, for CA 72-4. For stomach cancer patients, the sensitivity was 0.14–0.43 for the index test (4 articles), 0.17–0.35 for CA 19-9 (4 articles), 0.095-0.20 for CEA (4 articles), and 0.22 for CA 72-4 (1 article). In colorectal cancer patients, the sensitivities were 0.81 and 0.39 for the index test and CEA, respectively. The index test showed higher sensitivity, but it was difficult to generalize given that only a few studies had been conducted.

Diagnostic accuracy related to prognostic prediction was reported in 3 articles. In a study that examined the accuracy of prognostic prediction regarding post-surgical metastasis (stage IV) in pancreatic patients, the AUC of the index test was 0.554, whereas the AUCs of diagnostic testing based on a reference standard were 0.722, 0.716, and 0.892 for CA 19-9, CEA, and CA 125, respectively. The other 2 articles involved colorectal cancer patients. One of the articles, which examined prediction accuracy, reported that the AUC of the index test was 0.75, while both CEA and CA 19-9 showed an ACU of 0.77. In the other article, which reported the accuracy of the prognostic prediction of recurrence within 5 years after surgery, the sensitivity and specificity were 0.46–0.57 and 0.77–0.82 for the index test and 0.63–0.79 and 0.64–0.82 for CEA, respectively. Because only a few articles were included in the review, it was difficult to conclude on the clinical effectiveness of the test.

The association with prognosis was reported in 10 articles (3 articles for pancreatic cancer, 4 for stomach cancer, and 2 for colorectal cancer). For pancreatic and stomach cancers, the elevation of the pre-surgery index test results above a threshold and the lack of a reduction in the post-surgery index test results were significant risk factors against overall survival and disease-free survival in the studies in which univariate analysis was conducted. However, they were not significant for most studies in which multivariate analysis was conducted with the other risk factors controlled. For colorectal cancer, they were significant in one of 2 articles and insignificant in the other; hence, the study findings were conflicting.

## □ Conclusion

Based on the systematic review, the subcommittee determined that the Cancer Antigen CA 50 test does not have a safety issue when used for the differential diagnosis of a malignant tumor (such as pancreatic cancer) or prognostic prediction in cancer patients. The subcommittee indicated that the test is rarely used in South Korea, and it is not recommended as a tumor marker in clinical practice guidelines in or outside South Korea. The committee added that evidence in the literature is insufficient for concluding on the effectiveness of the said test for diagnosing a malignant tumor and following-up on cancer patients.

Based on the subcommittee's review, the Health Technology Reassessment Committee made the following assessment on "Cancer Agent CA-50" (November 8, 2019).

The Health Technology Reassessment Committee does not recommend the use of the Cancer Agent CA50 for diagnosing patients with suspected malignant tumors (such as pancreatic, stomach, and colorectal cancers), predicting prognosis, or following-up on treatment response (Grade of recommendation grade - II).