IQWiG Reports – Commission No. D19-01

Biomarker-based tests to support the decision for or against adjuvant systemic chemotherapy in primary breast cancer – update to Commission D14-01[1]

Extract

[1] Translation of the executive summary of the rapid report *Biomarkerbasierte Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mammakarzinom – Aktualisierung zum Auftrag D14-01* (Version 1.1; Status: 26 February 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Biomarker-based tests to support the decision for or against adjuvant systemic chemotherapy in primary breast cancer – update to Commission D14-01

Commissioning agency:

Federal Joint Committee

Commission awarded on:

12 July 2019

Internal Commission No.:

D19-01

Address of publisher:

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This report was prepared without the involvement of external experts.

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Keywords: Tumour Markers – Biological, Breast Neoplasms, Systematic Review

Executive summary

On 12 July 2019, the Federal Joint Committee (G BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess biomarker-based tests to decide for or against adjuvant systemic chemotherapy in primary breast cancer as an update to Commission D14-01.

Research question

The aim of the present investigation is to search for, present and assess the current state of knowledge on a biomarker-based strategy to decide for or against adjuvant systemic chemotherapy compared with a biomarker-independent decision strategy

- in patients with primary hormone receptor-positive, HER2-negative breast cancer and 0 to 3 affected lymph nodes

taking into account the following aspects:

- the biomarker-based tests uPa/PAI-1 (Femtelle), Oncotype DX, EndoPredict / EPclin, MammaPrint, Breast Cancer Index, Prosigna, and the IHC4 test,
- the outcomes of overall survival, disease-free survival and recurrence-free survival, each over a period of at least 5 years.

Methods

The target population for the assessment was patients with primary hormone receptor-positive, HER2-negative breast cancer and 0 to 3 affected lymph nodes. The test intervention was a biomarker-based strategy to decide for or against adjuvant chemotherapy. The comparator intervention was a biomarker-independent decision strategy.

Taking IQWiG's current General Methods [1] into account, the methods of the final report D14-01 [2], as well as the results of the final report D14-01 and the Addendum D18-01 [3], formed the basis for this updating assessment. The present assessment was limited to the biomarker-based tests uPa/PAI 1 (Femtelle), Oncotype DX, EndoPredict / EPclin, MammaPrint, Breast Cancer Index, Prosigna, and the IHC4 test.

In addition to randomized controlled trials (RCTs), prognosis studies (prospectively planned cohort studies) with an observation period of at least 5 years were included. Here, the outcomes of overall survival, disease-free survival and recurrence-free survival were considered. Since in Addendum D18-01, a hint of a benefit of the biomarker-based test Oncotype DX had been inferred, the present rapid report also examined via concordance studies (concordance of Oncotype DX with the other biomarker tests to be considered) to what extent the risk classifications of the other biomarker tests correspond to those of Oncotype DX.

A systematic literature search for studies was conducted in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In addition, the following information sources and search techniques were considered: study registries and the screening of reference lists. The

selection of relevant studies was performed by 2 persons independently of each other. Discrepancies were resolved by mutual discussion.

The update of the information retrieval was conducted for the period not covered by the search for the benefit assessment on Commission D14-01 (i.e. from November 2015), for publications in German or English. In addition, a focused information retrieval for concordance studies was conducted.

The results were presented in a descriptive form and in tables. In contrast to the final report D14-01, they were also considered when they were based on studies with a proportion of less than 70% of patients included in the analysis. The qualitative certainty of results of the prognosis studies was determined using the criterion “proportion of patients included in the analysis”.

Results

On the basis of the information retrieval, 12 prognosis studies and 7 concordance studies were considered relevant to the present research question, in addition to the 3 RCTs already known from previous projects. Furthermore, 5 ongoing RCTs and 3 ongoing prognosis studies as well as 1 discontinued RCT (without reported results) were identified. The last search was conducted on 23 September 2019.

One additional publication (on the already known TAILORx study) was identified by the update search for RCTs. From this publication, no reason arose challenging the conclusion of the benefit assessment for Oncotype DX test in Report D18-01. The further analyses published now do not contradict the assumptions made at that time in the project.

Results from prognosis studies are available for patients with and without lymph node involvement. The following applies to patients without lymph node involvement: The risk of dying without chemotherapy (all-cause mortality) was examined in 4 prognosis studies, 2 of which showed a low certainty of results. Patients assigned to the low risk group using Oncotype DX had a mortality rate in the range of at most 7% to 14% (upper limits of the confidence interval [CI] of the 4 studies). The corresponding values for the tests examined were of a similar magnitude (EndoPredict: 11%, MammaPrint: 12%, and Prosigna: 13%).

The risk of suffering distant recurrence without chemotherapy was examined in 10 prognosis studies, 6 of which showed a low certainty of results. Patients assigned to the low risk group in 4 studies using Oncotype DX showed a distant recurrence in the range of at most 5% to 10% (upper limits of the CI of the 4 studies). The corresponding values for the tests examined were of a similar magnitude (Breast Cancer Index: 7%, EndoPredict: 6% and 7%, EPclin: 6% and 10%, IHC4: 9%, and Prosigna: 6%, 8% as well as 41% from a single small study).

The following applies to patients with lymph node involvement: The risk of dying without chemotherapy (all-cause mortality) was examined in 1 prognosis study with a high certainty of

results. The patients assigned to the low risk group using Oncotype DX had a mortality rate of at most 15% (upper limit of the CI). The corresponding value for EndoPredict was 11%, for MammaPrint 12%, and for Prosigna 8%.

The risk of suffering a distant recurrence without chemotherapy was examined in 5 prognosis studies, 4 of which showed a low certainty of results. The patients assigned to the low risk group in 1 study using Oncotype DX had a distant recurrence rate of at most 30% (upper limit of the CI). The corresponding values for the tests examined were 25% for the Breast Cancer Index, 25% and 32% for EndoPredict, 8% and 21% for EPclin, and 23% and 6% for Prosigna. Across all studies and biomarker tests, this corresponds to a range from 6% to a maximum of 32%.

For the outcomes of disease-free survival and breast cancer-specific survival, only data on Oncotype DX and Prosigna were available. No prognosis study was identified for the uPa/PAI-1 (Femtelle) test.

It is noticeable that the proportion of patients in the prognosis studies who the tests assign to the low-risk group (test-negative) varies greatly depending on the study and the biomarker test (corresponding range: 19% to 86%). The biomarker-based tests examined in this report thus all identify more than 15% of patients who can consider omitting chemotherapy. However, the wide range reflects an uncertainty as to which patients actually belong in this group.

This uncertainty as to which patients can be assigned to the low risk group is also evident in the overall 7 studies in which the concordance of Oncotype DX with other tests was investigated. When evaluating the concordance studies, the following must be taken into account:

The concordance between Oncotype DX and the other tests examined was between 43% (Prosigna) and 74% (MammaPrint), which is problematic if the conclusion on the benefit of Oncotype DX is to be transferred to further tests. Furthermore, Oncotype DX as a reference test was not used with the threshold values from the TAILORx study in any of the available concordance studies. Neither was a distinction made between patients over 50 and patients under 50 years of age, for whom different cut-offs apply for the decision to omit chemotherapy on the basis of the TAILORx study.

Conclusion

The update search for RCTs did not yield any new findings. New results are available from prognosis studies and concordance studies. The current G-BA decision [4] covers breast cancer patients without lymph node involvement; the following results from prognosis and concordance studies were shown for these patients:

Data from prognosis studies on disease-free survival were only available for Oncotype DX, so that no comparison with another test is possible.

The all-cause mortality in hormone-only treated patients treated from the respective low risk groups was in the same magnitude for all tests examined (EndoPredict, MammaPrint and Prosigna) as for Oncotype DX.

The same applies to the risk of a distant recurrence for the tests Breast Cancer Index, EndoPredict, EPclin, IHC4, and Prosigna, which was below 10% in most cases, as is the case for Oncotype DX.

However, the results are largely based on studies with a low certainty of results and the proportion of patients who the tests assign to the low risk group varies greatly depending on the study and the biomarker test.

The studies on the concordance of Oncotype DX with other tests show accordingly that the different tests assign different patients to different risk categories. The concordance between the assignment of patients by Oncotype DX and the assignment by other tests is between 43% (Prosigna) and 74% (MammaPrint). In addition, with regard to the threshold values used, the reference test (Oncotype DX) was not used in any of the available concordance studies in the same way as in TAILORx study.

Key problems are thus shown in the low concordance between the assignment of patients by Oncotype DX and by the other biomarker tests, as well as the resulting different proportions of patients assigned to the low risk group depending on the test. A mere comparison of recurrence rates in the low risk group identified should therefore be viewed very critically, especially against the background of low concordance.

References for English extract

Please see full rapid report for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/d-projekte/d19-01-biomarker-based-tests-to-support-the-decision-for-or-against-adjuvant-systemic-chemotherapy-in-primary-breast-cancer-state-of-knowledge.12356.html.