



Recommendation of adjuvant trastuzumab treatment in HER-2-positive breast cancer patients: insights from quality indicator data collected in certified breast cancer centers in Germany, Italy, Austria, and Switzerland

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Abstract

Purpose In 2003, a certification system was introduced to ensure high standards of oncological care in breast cancer patients in Germany. Certified breast cancer centers (BCCs) must fulfill specific requirements including quality indicators (QI) derived from the clinical guidelines that are evaluated in annual audits. When target values for QIs are not fulfilled, centers need to give explanations. We analyzed data from BCCs for a selected indicator: the recommendation of trastuzumab for patients with early HER-2-positive invasive breast cancer. We investigated explanations given in cases when trastuzumab was not recommended to see whether this was justified.

Methods Patient data from 274 BCCs treating 53,777 primary cases in 2015 were analyzed using descriptive statistics.

Results In the 274 BCC sites, 5700 primary patients with early HER-2-positive breast cancer were treated in 2015. 128 sites (46.7%) did not reach the target value of 95% trastuzumab recommendation and thus had to give explanations. In these 128 sites, 2663 primary HER-2-positive breast cancer patients were treated, 343 (12.9%) of whom did not receive a recommendation for adjuvant trastuzumab treatment. All 128 sites delivered explanations. Overall, 450 explanations were given, allowing multiple explanations for single patients. No explanation was given for 8 of the 343 patients (2.3%). The most common given explanation was multi-/comorbidity (45.5%).

Conclusions The analysis suggests thorough decision-making when quality indicator target values for a trastuzumab recommendation were not fulfilled. Our data do not provide information on whether such decisions have an impact on treatment outcome for these patients.

Keywords Breast cancer · Certification · Quality indicator · HER-2 · Trastuzumab

Background

In 2003, the German Cancer Society (Deutsche Krebsgesellschaft—DKG) and the German Society for Breast Diseases (Deutsche Gesellschaft für Senologie—DGS) introduced a certification program for cancer centers to ensure high standards of care for breast cancer patients. In the following years, cancer centers were established for the most prevalent solid tumors, among them colorectal, lung, prostate, and gynecological cancer [1]. A certified cancer center according to the German National Cancer Plan is defined as “a network of qualified and jointly certified interdisciplinary [...] institutions that [...] if possible represent the entire chain of health care for those affected [...]” [1]. By means of the certification system, the multidisciplinary, trans-sectoral,

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and multi-professional cooperation should be improved and evidence-based guidelines should be implemented in daily clinical practice. Certified cancer centers have to fulfill guideline-based criteria for the treatment of the respective cancer site. Many of these criteria are specified as quality indicators (QI), which are measurable elements of practice performance [2], derived from the guidelines [3, 4]. Evaluation of adherence to these recommendations takes place in annual data-based and on-site audits in the centers. QIs are thus meant to give an indication of whether health-care providers deliver good quality of care or not [1]. However, often situations are very complex in routine care and conclusions from raw QI data on quality of care are not easily possible. For example, QIs results not reaching a pre-defined threshold (target value) do not necessarily indicate insufficient performance of the providers, but may be due to factors, such as comorbidities or patients' preferences. Under such circumstances, additional information is needed to decide whether quality of care is adequate or not.

In the present study, we present an example from the breast cancer center (BCC) certification system to illustrate this issue using the example of trastuzumab recommendation in HER-2-positive breast cancer patients [5]. In BCCs certified by the DKG, about 54,000 primary breast cancer cases were treated in 2015, accounting for approximately 75% of all primary cases in Germany after subtracting numbers from sites in Austria, Switzerland, and Italy.

Overexpression and/or amplification of HER-2 occurs in about 15–25% of breast cancer patients [6]. In these patients, treatment with trastuzumab—a recombinant humanized monoclonal antibody directed against the extracellular domain of the transmembrane HER-2 receptor—in combination with or sequentially after chemotherapy is indicated for 1 year according to current guidelines [7]. In 2006, trastuzumab was approved for adjuvant therapy of HER-2-positive breast cancer in Europe. This treatment improves both disease-free (DFS) and overall survival (OS) [8–12].

Trastuzumab is thus “strongly” recommended (cf. “Principles of indicator collection”) by the German guideline and a QI was defined accordingly:

“Patients with HER-2 overexpressing tumors with diameter ≥ 1 cm (immunohistochemical score 3+ and/or ISH positive) should receive (neo-)adjuvant treatment with trastuzumab for one year [LOE 1b, Grade of recommendation A]” [7].

However, a recent analysis of registry data showed that many HER-2-positive patients do not receive guideline concordant therapy with trastuzumab, which is especially true for the elderly [13]. This study included patients diagnosed between 2000 and 2012. Since trastuzumab approval for adjuvant therapy, the number of HER-2-positive patients receiving the antibody continuously increased in premenopausal women contrary to postmenopausal women. In

postmenopausal patients, trastuzumab was rather used at a constant rate. However, over time the use of trastuzumab in total increased substantially, suggesting a learning curve and showing the implementation in routine clinical care [13]. To better implement trastuzumab therapy, the QI target value for certified centers was implemented. For use in the certification program, the denominator of the guideline QI was modified, including tumors smaller than 1 cm and excluding patients with metastasized breast cancer at first diagnosis. It thus contains all patients with HER-2-positive, non-metastasized, early invasive breast cancer. This was done because the evidence-based guideline notes that even for patients with smaller tumors, trastuzumab could be given after individual risk–benefit evaluation if the risk of recurrence is greater than 10% in the first 10 years after diagnosis [7]. With the modification of the denominator, a better documentation of the data is allowed combined with a sensitive measure that encourages reflection of trastuzumab use. The target value was set at 95%, i.e., requiring centers that 95% of HER-2-positive primary breast cancer patients are recommended trastuzumab for adjuvant treatment by the post-surgical multi-disciplinary tumor board (MTB). The MTB recommendation typically considers tumor biology and tumor-specific characteristics such as tumor size, nodal status, risk factors like negative hormone receptor status, high grading and lymphatic/vascular invasion as well as comorbidities, but not necessarily patients' preferences, as this is typically discussed with the patients afterward. If less than 95% of these patients are recommended trastuzumab, centers have to give an explanation for each patient. Analyzing data from audit protocols in this article, we investigated whether the explanations for not recommending trastuzumab to HER-2-positive breast cancer patients were in line with guideline recommendations.

Methods

Principles of quality indicator collection

To be awarded the certificate, cancer centers need to treat patients according to the clinical guidelines of the highest standard, i.e., “S3” according to the German classification system (“S3” stands for “step classification 3”) [14]. Contrary to S1 guidelines that are based on expert consensus only, S3 guidelines need to be evidence based, i.e., based on a systematic literature review with defined criteria, having a representative expert panel including patients, and using a formal consensus finding process [15]. Based on the core (i.e., “strong”) recommendations of the guidelines, QIs are derived. Several QIs include target values that need to be reached in certified centers [3]. Documentation of these QIs is part of the certification requirements and is therefore used

to investigate whether the centers adhere to the guidelines or not. The documentation of the QIs is validated via both mathematical plausibility checks and insights into patient file samples during on-site audits. QI data are published in annual benchmark reports [16]. If centers deviate from target values, they are obliged to give plausible explanations. In the absence of individual data that would allow for case mix adjusted analyses, these explanations are discussed in on-site audits and documented in audit reports. This procedure leaves a margin to the physicians' careful evaluation to a certain extent and the patients' personal preferences while at the same time bearing the risk of rash decisions due to pre-conceived ideas of, e.g., potential side effects of treatment.

Data

QI data are reported annually to OnkoZert, the Certification Institute of the German Cancer Society, checked for plausibility and used for the annual on-site audits. Thereafter, data are stored in a database including data from all centers, for all indicators for each year. For audits in 2016 which are investigated here, patient data from the previous calendar year, i.e., 2015 were analyzed. When submitting the data, the centers must give written explanations whenever target values or plausibility thresholds for indicators are not reached for a patient, i.e., in case of deviation from the guideline recommendation. When target values or plausibility thresholds are reached, centers do not have to give explanations for patients not treated accordingly. Thus, data investigated here are limited to those from centers that did not fulfill the target value of recommending to 95% of HER-2-positive breast cancer patients the use of trastuzumab. The flowchart (Fig. 1) gives an overview of the sample selection. Of the

280 breast cancer center sites certified as of 31 December 2016, 274 contributed data. Three of those not contributing were certified for the first time in 2016 which does not require the center to deliver data for the whole calendar year, two were excluded due to discontinuation of the certification process and one did not report data on this specific indicator.

Analysis

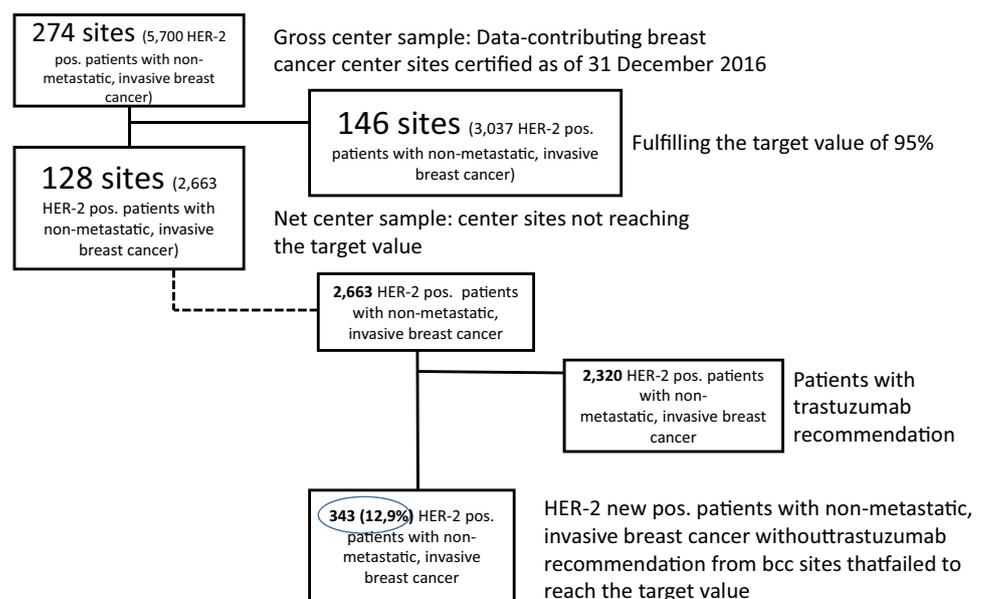
We analyzed data from 274 BCC sites that treated 53,777 primary cases in 2015 for the adherence to the current guideline recommendation of trastuzumab for patients with early HER-2-positive breast cancer. We grouped explanations accordingly and calculated frequencies to identify the most common explanations.

Results

In the 274 BCCs, 5700 of the 53,777 patients were HER-2 positive (10.6%) and treated in 2015. Of the 274 BCCs, 128 (46.7%) did not reach the target value of 95%. In these 128 sites, 2663 HER-2-positive breast cancer patients were treated, 343 (12.9%) of whom did not receive a recommendation of trastuzumab in the MTB. 146 BCCs reached the target value of 95%. In these BCCs, of 3037 HER-2-positive breast cancer patients, 59 (1.9%) did not get a trastuzumab recommendation. Since BCCs fulfilling the target value do not have to give explanations for their decisions and deviations, there is no information available for these patients.

All 128 sites delivered explanations. Overall, 450 explanations were given, allowing multiple explanations for single patients. No explanation was given for 8 of the 343 patients

Fig. 1 Flowchart sample selection



(2.3%). We classified the explanations into 19 categories (Table 1). The most commonly given explanation was multi- or comorbidity (156 of 343 patients; 45.5%), age (107 of 343 patients; 31.2%), and small carcinomas < 10 mm (43 of 343 patients; 12.5%).

Discussion

In patients with HER-2-positive breast cancer, treatment with trastuzumab is indicated for 1 year according to current guidelines [7]. However, population-based studies showed a considerable proportion of patients not receiving appropriate treatment [13]. Problematically, non-certified centers do not have to give explanations in case of guideline deviation. Moreover, non-certified centers are not audited. However, there are relevant publications showing highly significant improvement in guideline adherence and survival in breast cancer patients when treated at certified breast cancer centers [17, 18]. Guideline adherence and validation of guideline adherence come along with higher expenditure, but result in improved survival rates [17, 18].

In the present study, we analyzed data from certified BCC sites and evaluated the implementation of trastuzumab recommendation in 5700 patients with HER-2-positive early

breast cancer. In cases of missing the target value of 95%, explanations given by the centers were analyzed carefully. It must be kept in mind that the indicator for certification is a more sensitive measure than the guideline QI.

Our analysis showed that centers gave explanations in almost all cases when target values were not fulfilled. Investigating the center documentation alone, it would be impossible to judge whether the explanations are adequate or not. For example, 156 (45.5%) of the 450 explanations given refer to multi-/comorbidity which is clearly too unspecific to allow for evaluating its adequacy. Therefore, the explanations are discussed with the auditor during the on-site audit. If explanations of the centers seem to be not adequate, the auditors pronounce “deviations” that need to be remedied by the centers [1]. The central contraindication for trastuzumab is a preexisting cardiac disease and we can assume that “multi-/comorbidity” often includes heart conditions. However, based on the documentation alone this cannot be verified. Age—itself no reason for non-use of trastuzumab—was mentioned in one-third of patients’ explanations. Since age may serve as a proxy for cardiovascular comorbidity, it may be concluded that this fact is the underlying factor. Furthermore, trastuzumab is given in combination with chemotherapy and this component of adjuvant treatment may have limited the recommendation for trastuzumab. Besides medical reasons for clinical decision-making, the data give valuable insight into both quality of care and quality of data collection. For only a few patients no recommendation was given because of either death or external or discontinuation of treatment. This also needs to be taken into account when we attempt to collect data as completely as possible.

During the certification process, BCCs are additionally asked to provide follow-up data, i.e., to indicate the share of HER-2-positive breast cancer patients that were recommended trastuzumab and actually received trastuzumab over one year. However, reporting these data is optional. These data are also reported in the annual report [16]. For the patient cohort in our sample (i.e., primary patients diagnosed in 2015), for example, follow-up data were reported by 171 sites with a median of 94.1% of patients that were recommended trastuzumab actually receiving it for 1 year.

This research presents a so far new approach to the analysis of QI data. We used routine data including many sites and patients covering around 75% of the primary breast cancer patients in Germany. Moreover, some sites from neighboring countries were included. Data analysis was based on the audits’ relevant documentation for issuing the certificate. Data were validated before (data based) and during (through insight into patient files and discussions with colleagues) audits and thus reflect well daily clinical practice. Nevertheless, there are some limitations: The explanations regarding the deviations are typically brief and often superficial, i.e., without the assessment by the auditors on-site these

Table 1 Explanations given when trastuzumab was not recommended

Explanation	<i>n</i>	%
No indication		
Small carcinoma < 10 mm	43	12.5
Only micro-invasive cancer	15	4.4
Micro-invasive cancer with DCIS	8	2.3
No indication (without further explanation)	7	2.0
Secondary carcinoma	4	1.2
Morbus Paget	2	0.6
Genetic expression—low risk	1	0.3
Contraindications and morbidity		
Multi-/comorbidity	156	45.5
Age	107	31.2
Cardiac comorbidity	26	7.6
Contraindication	23	6.7
General condition	20	5.8
Patients’ wishes and conditions		
Patient wish	10	2.9
External treatment	8	2.3
Discontinuation of treatment	4	1.2
Patient deceased	3	0.9
Retrospective recommendation	1	0.3
Others		
Not specified	8	2.3
Neoadjuvant chemotherapy	4	1.2

explanations would not suffice to decide whether quality of care was adequate or not. During the audit, auditors and physicians of the BCC discuss if the missing indication of trastuzumab treatment is justifiable. Another difficulty that might require additional research is the categorization of the given explanation. An attempt to further group categories suggests three dimensions: tumor size/missing indication, contraindications/comorbidities, and treatment process factors, especially patients' wishes. However, some of the categories were not disjunctive or mutually exclusive, some explanations were too superficial and others were in conflict with the indicator reporting system of temporal order, i.e., the indication of "patient wish" should typically only matter after the recommendation was given by the MTB and discussed with the patient but not before. Nevertheless, there may be cases in which patients' preferences were available for the discussion in the MTB. Due to the small number of HER-2-positive breast cancer patients in single centers (the denominator), it is often a matter of a single patient whether a center reaches the target value or whether it had to give an explanation. Also, the data investigated here cannot be linked to survival data from registries. On a positive note, data reveal explanations for nearly every patient for whom giving an explanation was required. Furthermore, data cover over 75% of the patient population treated in Germany in 2015 allowing for a sufficiently large sample even when the target population is small. Practically, there are good reasons to assess deviations from QI target values via written reports as done here. For most cases, it is impossible to validly and plausibly document all possible reasons for deviations (or: confounders) in a standardized manner, i.e., to assure quality in a fully quantitative data-based procedure. This does not mean to solely rely on qualitative statements, of course, but to allow for a mix of measures that is as standardized as possible but gives room for information that may not be put into the documentation matrix. When interpreting the results, we have to bear in mind the primary purpose of the data collection, i.e., creating a basis for the decision of whether or not the certificate should be issued.

Conclusions

The analysis suggests no quality deficit, but instead thorough decision-making when quality indicator target values for a trastuzumab recommendation were not fulfilled.

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Author contributions OO conceptualized the research design. JF and SW collected data and checked these for plausibility. CK and ECI developed the plan of analysis, analyzed the data and drafted the manuscript. All of the authors contributed in writing the manuscript during

several rounds of discussion. All of the authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest SW and CK are employees of the German Cancer Society and JF is an employee of the OnkoZert certification institute. OO is the President of the German Cancer Society. OO has received research funding and advisory board honoraria from pharmaceutical companies that are not related to the research presented here. A full list will be provided by the corresponding author upon request. ECI declares that she has no conflict of interest.

Ethical approval The study used data from the oncological certification program of the German Cancer Society. Data are collected during the certification process using anonymized data regarding clinical parameters as well as quality indicators. Informed consent is automatically obtained from the patients by signing the hospital treatment contract. Therefore, the Local Ethical Committee of the University of Regensburg stated that an ethical vote was not necessary.

References

1. Kowalski C, Graeven U, von Kalle C, Lang H, Beckmann MW, Blohmer JU et al (2017) Shifting cancer care towards multidisciplinary: the Cancer Center Certification Program of the German Cancer Society. *BMC Cancer* 17(1):850. <https://doi.org/10.1186/s12885-017-3824-1>
2. Campbell SM, Braspenning J, Hutchinson A, Marshall MN (2003) Research methods used in developing and applying quality indicators in primary care. *BMJ* 326(7393):816–819
3. German Guideline Program in Oncology (2017) (German Cancer Society, German Cancer Aid, Association of the Scientific Medical Societies). Development of guideline-based quality indicators: methodology for the German Guideline Program in Oncology, version 2.0. 2017. <https://www.leitlinienprogramm-onkologie.de/methodik/informationen-zur-methodik/>. Accessed 10 Dec 2018
4. Becker M, Breuing J, Nothacker M, Deckert S, Steudtner M, Schmitt J, Neugebauer E, Pieper D (2018) Guideline-based quality indicators—a systematic comparison of German and international clinical practice guidelines: protocol for a systematic review. *Syst Rev* 7(1):5. <https://doi.org/10.1186/s13643-017-0669-2>
5. Kowalski C, Ferencz J, Brucker SY, Kreienberg R, Wesselmann S (2014) Quality of care in breast cancer centers: results of benchmarking by the German Cancer Society and German Society for breast diseases. *Breast* 24(2):118–123. <https://doi.org/10.1016/j.breast.2014.11.014>. [Epub 13 Dec 2015]
6. Slamon DJ, Clark GM, Wong GS et al (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235(4785):177–182
7. Wöckel A, Festl J, Stüber T, Brust K et al (2018) Interdisciplinary screening, diagnosis, therapy and follow-up of breast cancer: guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017)—Part 1 with recommendations for the screening, diagnosis and therapy of breast cancer. *Geburtshilfe Frauenheilkd.* 78(10):927–948. <https://doi.org/10.1055/a-0646-4522> (Published online 19 Oct 2018)
8. Petrelli F, Barni S (2012) Meta-analysis of concomitant compared to sequential adjuvant trastuzumab in breast cancer: the sooner the better. *Med Oncol* 29(2):503–510

9. Dahabreh IJ et al (2008) Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Oncologist* 13(6):620–630
10. Gianni L et al (2011) Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol* 12(3):236–244
11. Madarnas Y et al (2008) Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: a systematic review. *Cancer Treat Rev* 34(6):539–557
12. Yin W et al (2011) Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. *PLoS One* 6(6):e21030
13. Inwald EC, Ortmann O, Zeman F, Koller M, Hofstadter F et al (2014) Guideline concordant therapy prolongs survival in HER2-positive breast cancer patients: results from a large population-based cohort of a cancer registry. *BioMed Res Int*. 2014:137304
14. Nothacker MJ, Muche-Borowski C, Kopp IB (2014) Guidelines in the Register of the Association of Scientific Medical Societies in Germany—a quality improvement campaign. *Geburtshilfe Frauenheilkund* 74(3):260–266
15. Langer T, Follmann M (2015) The German Guideline Program in Oncology (GGPO): a central core of an evidence-based, patient-centered interdisciplinary oncology? *Z Evid Fortbild Qual Gesundhwes*. 109(6):437–444. <https://doi.org/10.1016/j.zefq.2015.09.007>. [Epub 26 Sep 2015]
16. Society GC, Senology GSf, Centres CCBC, Blohmer JU, Scharl A, Wesselmann S, et al. (2017) Annual Report 2017 of the Certified Breast Cancer Centers. Berlin; 2017. <https://doi.org/10.13140/RG.2.1.1805.7204>
17. Kreienberg R, Wöckel A, Wischnewsky M (2018) Highly significant improvement in guideline adherence, relapse-free and overall survival in breast cancer patients when treated at certified breast cancer centres: an evaluation of 8323 patients. *Breast* 40:54–59. <https://doi.org/10.1016/j.breast.2018.04.002>
18. Beckmann MW, Brucker C, Hanf V, Rauh C, Bani MR et al (2011) Quality assured health care in certified breast centers and improvement of the prognosis of breast cancer patients. *Onkologie* 34(7):362–367. <https://doi.org/10.1159/000329601>

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