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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

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ABSTRACT

Objectives: Certified multi-disciplinary breast cancer centres (CBCs) have been established worldwide. Development of CBCs, guideline-adherent systemic therapy and surgical management should now show an impact on outcomes. This analysis aimed to investigate whether guideline adherence (GA) rates, relapse-free survival (RFS) and overall survival (OS) have significantly improved at CBCs compared to the pre-certification period.

Materials and methods: 8323 patients with primary breast cancer were treated in 17 German CBCs, which had been certified between 2003 and 2007 [2003 (n = 1), 2004 (n = 6), 2005 (n = 3), 2006 (n = 6) and 2007 (n = 1)]. 3544 patients (42.6%) were treated before certification and 4779 patients (57.4%) after certification.

Results and conclusion: A highly significant ($p < 0.001$) difference in 100%-GA was found between the various hospitals before certification (min 25.0%; max 54.6%). In 2008, when all participating hospitals were certified, the GA rate was 61.8% (min 39.5%, max 74.4%) and 69.2% (min 45.9%, max 86.4%) for patients <75 y (n = 6675). The difference between pre-certification 100%-GA (46.9%) and post-certification (57.2%) was highly significant ($p < 0.001$). RFS and OS were both significantly better after certification compared to the pre-certification period (RFS: HR = 0.79; 95% CI: 0.68–0.92; $p = 0.003$; OS: HR = 0.75; 95% CI: 0.65–0.85; $p < 0.001$). 5-year RFS (OS) of patients <75 y was 89.6% (85.4%) pre-certification and 91.4% (89.5%) post-certification.

Since improvement in GA and outcomes correlated as well, GA remains a highly significant prognostic factor for RFS and OS regardless of NPI, intrinsic subtype and adjuvant systemic therapy. This suggests that the certification process is strongly associated with improvements in outcome.

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1. Introduction

Certified multi-disciplinary breast cancer centres (CBCs) have been established worldwide. For the record, the goal of establishing a nationwide network of certified multi-disciplinary breast cancer centres (CBCs) has largely been achieved in Germany, where 228 breast centres at 279 sites were certified by the end of 2015 [1]. These 228 CBCs treated 54,400 patients in 2015 (mean of 239 per centre), accounting for approximately 75% of all breast cancer cases [1]. The Breast Centre Certification scheme complies with standard Eusoma guidelines on "The requirements of a specialist Breast Centre" and with OnkoZert, commissioned by the German Cancer Society. It is a voluntary certification process to establish minimum standards and ensure specialist multidisciplinary care in compliance with the international regulation on certification ISO/IEC 17065, accredited by ACCREDIA in the frame of Multilateral

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Agreement (MLA). As the development of CBCs has been ongoing for more than 13 years, high-quality, guideline-adherent systemic therapy and surgical management should now show an impact on outcomes.

In the past the outcome of the certification process was primarily checked by quality indicators (QIs). QIs are measures of health care quality that make use of hospital inpatient administrative data. They can be used to highlight potential quality concerns, identify areas that need further study and investigation, and track changes over time. It was shown in several papers, that the use of QIs for breast cancer care, combined with regular internal and external audits of performance, are effective to improve adherence to guidelines in a breast cancer unit (McCarthy et al., 2008 [17]; Brucker et al., 2011 [15]; Verbeek L et al., 2011 [26]; Wallwiener M et al., 2012 [3]; Caldarella et al., 2012 [18]; Kowalski et al., 2015 [16], Ferrua et al., 2012 [19]; Stordeur et al., 2012 [20]; Vrijens et al., 2012 [21]; van Dam et al., 2013 [12]; van Dam et al., 2015 [11]; van Dam et al., 2017 [13] and Biganzoli L. et al., 2017 [14]). In their review of the most important publications van Dam et al. [12] came to the conclusion: "Quality control by means of internal and external audit and benchmarking leads to better breast cancer care. Adherence to guidelines improves markedly and there are data emerging which show that this results in a better outcome". Beckmann et al., 2011 [24] had shown that independent from common prognostic factors, diagnosis and treatment of breast cancer at a CBC improves OS compared to patients outside of CBCs. Heil et al., 2012 [25] analysed local control rate (LCR), disease-free survival (DFS), distant disease-free survival (DDFS), observed overall survival (OS) and age-adjusted relative overall survival (ROS) treated at a certified academic breast unit. They found nominally higher survival rates compared with population-based reports from Germany. These results are in contrast to Schrodi et al., 2015 [2]. They found a survival difference neither between patients with treatment before and after certification of specialized units nor between CBC patients and non-CBC patients aged up to 75 years. Some critical remarks to this result can be found in Kowalski et al. (2015) [22].

The primary aim of this analysis was to investigate whether guideline adherence (GA) rates, relapse-free survival (RFS) and overall survival (OS) significantly improved at CBCs compared to the pre-certification period (pre-CBCs). In addition, we examined the impact of known prognostic factors on these outcome variables in multivariate analyses. As a secondary aim, we wanted to confirm the rationale for the establishment of breast centres and obtain proof of principle for a voluntary, external benchmarking programme as well as proof of concept for third-party dual certification of breast centres and their mandatory quality management systems according to the recommendations of the German Cancer Society (DKG) and German Society of Senology (DGS).

2. Methods

Within the scope of the BRENDA project ('Breast Cancer Care Under Evidence-based Guidelines'), the records of a total of 8323 primary breast cancer patients from the Department of Gynaecology and Obstetrics at the University of Ulm and from 16 partner clinics in Germany were analysed for the period 2001–2008. The mean number per participating BC was 490 (median 450; min 180, max 1668). The 17 participating clinics were certified between 2003 and 2007 (2003 (n = 1), 2004 (n = 6), 2005 (n = 3), 2006 (n = 6) and 2007 (n = 1)). 3544 patients (42.6%) were treated before certification and 4779 patients (57.4%) after certification.

For all patients, date of birth, date of diagnosis, detailed information on diagnostic and treatment variables were abstracted from hospital records. Follow-up for recurrent disease was based on local medical records and completed by telephone contacts to patients and their physicians. Follow-up for vital status was done by chart review and queries to death registries and physicians.

2.1. Definition of guideline-adherence (GA)

Guideline adherence was defined based on a systematic analysis of the guideline recommendations and statements of the interdisciplinary consensus S3 guideline issued by the German Cancer Society in 2008 [30]. A comparison of the treatment recommendations of the S3-guideline and other national breast cancer guidelines from the USA (NCCN, ASCO), Canada (CCO), Australia (NBOCC) and the UK (NICE, SIGN) can be found in Ref. [9]. The corresponding recommendations differ only marginally.

To evaluate GA, each therapeutic modality, A–surgical therapy, B–radiotherapy, C–endocrine therapy and D–chemotherapy was reviewed separately and subjected to testing within the model. Non guideline adherent (non-GA) treatments were additionally divided into over- and undertreatment. 100%-GA was confirmed if evaluation of each separate form of therapy did not reveal any deviations from the guidelines. Further details can be found in Refs. [6–10].

2.2. Surrogate definition

Because information on Ki-67 was not available, we used a surrogate classification of intrinsic subtypes according to tumor Grade to include the cell proliferation and ER/PR/HER2 as described before by von Minckwitz et al., 2012 [27] or Parise CA et al., 2014 [28]: Luminal A (HR+/HER2−/grade1 or 2), luminal B-HER2-negative like (HR+/HER2−/grade 3), luminal B-HER2-positive like (HR+/HER2+, all grades); HER2 overexpressing (non-luminal, HR−/HER2+) and triple-negative (basal-like, HR−/HER2−).

2.3. Statistical analysis

Continuous variables are presented as means ± standard deviations (SD), or medians and interquartile ranges, whilst categorical variables are stated as frequencies and percentages. The Shapiro-Wilk test was used to test for normality of distribution. Continuous variables were tested for differences with the Mann-Whitney *U* test or the related-samples Wilcoxon signed rank test, respectively; categorical variables were tested with the Pearson's $\chi 2$ or the Fisher's exact test. The effect size was defined as the difference between the means of GA of CBCs and pre-CBCs, divided by the pooled estimate of standard deviation. It calibrates the difference between CBCs and pre-CBCs (i.e. the effect of certification) in relation to standard deviation. In general, the effect size estimate was slightly biased and was therefore corrected using a factor provided by Hedges and Olkin [23].

If a patient was lost to follow-up, data were censored at the date of the last known contact. If no information was available, the status was coded as missing data. Survival distributions and median survival times were estimated using the Kaplan–Meier product-limit method. The log-rank test was used to provide a formal statistical assessment of the differences between groups. The Cox proportional hazards model was used to estimate the hazard ratio and confidence intervals (CI). In addition, the impact of known prognostic factors on outcome variables was examined in univariate and multivariate Cox analyses. A two-sided p value of <0.05 was considered statistically significant. All statistical analyses

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