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CLINICAL TRIAL

Explaining variation in quality of breast cancer care and its impact: a nationwide population-based study from Slovenia

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Abstract

Purpose To assess and explain variation in quality of care in breast cancer patients and estimate its impact on disease outcome.

Methods The Slovenian National Cancer Registry database and clinical records of 1053 women with unilateral primarily non-metastatic invasive breast cancer diagnosed in 2013 were reviewed in this retrospective analysis. Quality care was defined as care fully compliant with quality indicators (QI) defined by European Society of Breast Cancer Specialists (EUSOMA). Multivariate logistic regression was used to determine the predictors of receiving quality care. Differences in overall survival (OS) and event-free survival (EFS, relapse, or progression of disease or death considered an event) based on adherence to QI were analyzed using Kaplan–Meier method and Cox models.

Results Younger age, no comorbidities, and HER2-negative tumor were associated with increased odds ratios for receiving quality care, whereas tumor stage and type of hospital had no significant association. Median follow-up was 54.5 months. Not receiving quality care resulted in an increased risk of dying [hazard ratio (HR) 1.68; 95% confidence interval (CI) 1.06–2.66; $p=0.026$]. Difference in EFS between two groups was significant after adjusting for case mix and type of hospital (HR 1.80; 95% CI 1.29–2.52; $p=0.001$) but disappeared when type of treatment was added into the model (HR 1.30; 95% CI 0.89–1.90; $p=0.178$).

Conclusion Observed comorbidity and age bias in delivering quality breast cancer care could be medically justifiable, whereas observed deviations dependent on HER2 status are puzzling. Complete adherence of treatment to quality indicators resulted in better OS.

Keywords Breast neoplasm · Quality indicators · EUSOMA · Health services · Survival

Introduction

Assuring regional accessibility to cancer care comes with inherent risk of variation in quality of care. Elements of high-quality care have been defined by Vardy et al. as the use of evidence-based treatment in high-volume setting with proficiency in treatment processes, and orientation of care toward the patient as a whole [1]. Of these three, evidence-based treatment and high-volume setting are easily measurable, and their prognostic impact was studied by several authors across different cancer diagnoses [2–5]. Effect of caseload on outcome is not completely unambiguous, though, and confounders such as hospital type and access to specialized equipment are to be aware of [6]. Extensive research has confirmed various patient-related and organizational factors having a significant impact on receiving quality breast cancer care [5, 7, 8]. However, improper adjustment for differences in case mix and other pertinent covariates in an important volume of related research on quality of care calls for further assessment [6]. A strong correlation between evidence-based care and breast cancer outcomes is recognized, but again this correlation is not always straightforward, as optimally individualized therapy often violates evidence-based guideline recommendations [9–11].

Herein, we sought to further elucidate the factors influencing the provision of quality breast cancer care and its

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impact on breast cancer outcomes in a nationwide population-based setting.

Methods

Setting and data collection

The study was set in Slovenia with its population of 2.0 million in 2013. The Slovenian National Health Insurance Institute provides compulsory health insurance to all of its citizens guaranteeing free access to cancer care. No breast cancer patients are treated in a private setting. In total, a cohort of 1351 female patients diagnosed in 2013 with breast cancer (topography codes C50 based on the 3rd edition of International Classification of Diseases for Oncology) were identified from Slovenian Cancer Registry, a population-based cancer registry covering the entire Slovenian population since 1950 [12]. Individual clinical records were additionally reviewed and searched for data not included in Registry's database. Primarily the data were collected in the setting of the TRANSCAN-2 HighCare study. Slovenian research group collected additional variables in order to assess national quality of breast cancer care presented in this paper. Study population selection flowchart is presented in Fig. 1.

Covariates

General epidemiologic data and established factors influencing provision of quality breast cancer care and breast cancer prognostic factors were included as covariates. Age at diagnosis was included as a continuous variable. Stage was determined according to American Joint Committee on Cancer, 8th Edition Cancer Staging Manual. Data on clinical and pathological stage were collected with the latter being used in primarily operated patients. For the analyses, in detail determined stages were merged into stage I, II, and III. Comorbidity was measured using Charlson comorbidity index (CCI) and subgroups with CCI scores 0, 1, and 2 or more were formed [13]. Intrinsic subtypes of breast cancer were defined using clinicopathologic surrogate definitions as defined in St Gallen international expert consensus on the primary therapy of early breast cancer in 2013 [14]. In statistical analysis, Luminal A-like subtype was defined as the reference category. Data on whether the patient received surgical treatment, chemotherapy, hormonal therapy, targeted therapy, and radiotherapy were collected. Hospital of treatment was defined as a hospital where the patient was operated or received chemotherapy or was irradiated or received hormonal therapy or was diagnosed, in descending order of importance, since patients are often diagnosed and treated in more than one hospital. Subsequently, hospitals were classified according to their type. The only comprehensive cancer center (CCC, defined as the reference category in analyses) in Slovenia, which offers surgery, systemic treatment, and radiotherapy, was compared to

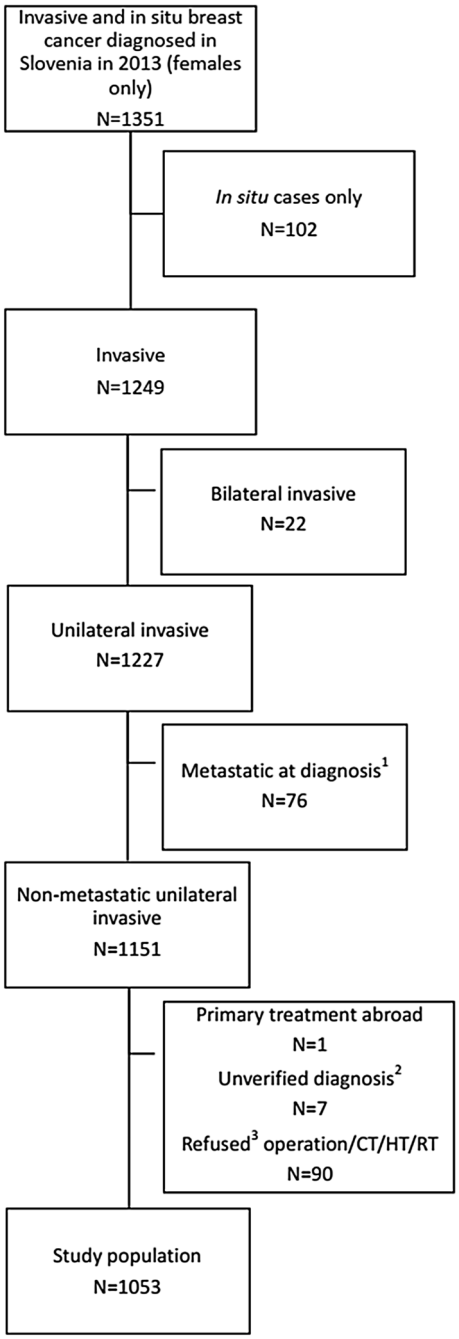

Fig. 1 Study population selection flowchart. *1* metastases diagnosed during primary diagnostics (first 4 months after the diagnosis); *2* diagnosis made on a basis of death certificate or clinical examination only; *3* refused a part of the treatment or the whole treatment; *N* number of patients, *CT* chemotherapy, *HT* hormonal therapy, *RT* radiotherapy

the only university medical center treating breast cancer patients with surgery and systemic therapy at that time (further defined as a university teaching hospital), and to all the other five general hospitals (offering surgery and systemic therapy) combined. All the hospitals offer sentinel lymph-node biopsy. A decision on whether the patient needs any neoadjuvant or adjuvant treatment beside surgery is always made on a multidisciplinary tumor board. Quality care was defined as diagnostic and treatment process in complete accordance with eligible selected quality indicators (QI) defined by European Society of Breast Cancer Specialists (EUSOMA) from 2010, which reflect Slovenian national guidelines from 2011 and recommended practice in Slovenia in 2013 [15, 16]. Out of all EUSOMA QI, we selected 13 indicators, consisting of EUSOMA mandatory QI on diagnosis and treatment processes, supported by level of evidence I or II, and pertinent for invasive cancer only. It should be noted that requirements of QI 4b were considered to have been met even without distance to the nearest radial margin being reported, as these data were not systematically collected during clinical records review. Selected EUSOMA QI and their descriptions are shown in Table 1.

Outcomes and statistics

The survival times were calculated from the date of the diagnosis and were censored at the close-out date January 31, 2018. The end points considered were overall survival (OS; death from any cause considered as an event) and event-free survival (EFS; any relapse or progression of breast cancer or death considered as an event).

Statistical analyses were performed using SPSS version 25. Pearson's Chi-square test was used for comparing categorical variables between two groups. Binary multivariate logistic regression was used to identify factors significantly associated with receiving quality breast cancer care. The Kaplan–Meier method was used for univariate analysis of survival estimates with 95% confidence intervals (95% CI) reported and the differences between EUSOMA QI 100% adherent group and EUSOMA QI < 100% adherent group were tested by a log-rank test. The hazard ratio (HR) calculations of death and progression in a multivariate analysis including pertinent prognostic factors were performed by the Cox proportional hazard regression model. To investigate the association of survival with adherence to EUSOMA QI, models adjusting for case mix, type of hospital, and type of treatment were formed and likelihood ratio (LR) tests were performed for adding EUSOMA QI adherence status. All statistical tests were 2-sided and a p value < 0.05 was considered significant.

Results

Population and compliance with EUSOMA QI

Summary of compliance with individual QI for 1053 patients included in the study is presented in Table 1.

Patients' demographic and clinical characteristics are presented in Table 2 where characteristics are compared between group of patients that were treated in complete adherence to eligible EUSOMA QI versus others.

In multivariate analysis, treatment non-related factors were included: age, CCI, simplified stage, intrinsic subtypes, and type of hospital. Younger age [odds ratio (OR) per year increase 0.98 (95% CI 0.97–0.99, $p = 0.003$)], absence of comorbidities ($p = 0.000$), and HER2-negative tumor were found to be associated with receiving care that is 100% compliant with EUSOMA QI. HER2-positive tumors were less likely associated with receiving quality care with OR for Luminal B-like HER2-positive 0.56 (95% CI 0.35–0.90, $p = 0.017$) and OR for HER2-positive tumor 0.42 (95% CI 0.19–0.91, $p = 0.029$). The biggest differences in adherence between HER2-positive and HER2-negative patients were observed in EUSOMA QI 10b (84.2% vs 95.5%, respectively), 11a (62.4% vs. 70.9%, respectively), 12a (87.0% vs. 97.0%, respectively), and 13a (81.0% vs. 87.5%, respectively).

Type of hospital and stage appeared to have no significant impact on receiving quality care.

Overall survival

Median follow-up was 54.5 months. Total number of deaths was 135. There were 83 relapses after a disease-free interval and 24 progressions of disease in patients with persistent disease. 5-year OS and EFS were both significantly better in the group of patients treated in complete accordance with eligible EUSOMA QI, 93.2% (95% CI 91.0–95.4) versus 75.9% (95% CI 71.6–80.2; $p = 0.000$) and 88.5% (95% CI 85.8–91.2) versus 71.2% (95% CI 66.5–75.9; $p = 0.000$), respectively.

Multivariate analysis of correlation of OS with quality of care that was performed to adjust for unequal distribution of patient's demographic and clinical characteristics is shown in Table 3. The addition of adherence to EUSOMA QI to any of the three models improved the models' fitting. Additionally, in Model 1, all the covariates constituting case mix appeared to be independent predictors of survival. In Model 2, adjustment for the type of hospital was added to the case mix and proved not to be a significant predictor of OS in this nor in the third model. In the third model, further adjusting for the type of treatment,

Table 1 Quality indicators

EUSOMA quality indicators[a]		Level of evidence	Minimum standard (%)[b]	Target (%)[b]	This study (%)	$N_{\text{satisfies criteria}}$	N_{eligible}
4a	Proportion of invasive cancer cases for which the following prognostic/predictive parameters have been recorded: histological type, grading, ER & PgR, HER 2	II	90	95	90.1	949	1053
4b	Proportion of invasive cancer cases with primary surgery, for which the following prognostic/predictive parameters have been recorded: histological type, grading, ER and PR, HER 2, pathological stage (T and N), size in mm for the invasive component, peritumoral vascular invasion, distance to nearest radial margin[c]	II	95	98	88.5	810	915
9c	Proportion of patients (invasive cancers) and a clinically negative axilla (+US ± FNA/CNB) who had sentinel lymph-node biopsy	II	90	95	89.1	704	790
10a	Proportion of patients (invasive cancer M0) who received postoperative radiotherapy after surgical resection of the primary tumor and appropriate axillary staging/surgery in the framework of BCT	I	90	95	92.0	562	611
10b	Proportion of patients with involvement of axillary lymph nodes (≥ pN2a) who received post-mastectomy radiotherapy	I	90	95	89.9	80	89
11a	Proportion of patients with invasive breast cancer not greater than 3 cm (total size, including DCIS component) who underwent BCT	I	70	80	67.5	495	733
11d	Proportion of invasive breast cancer patients with pN0 who do not undergo axillary clearance	II	80	90	94.0	500	532
12a	Proportion of patients with endocrine sensitive invasive carcinoma who received hormonotherapy, out of the total number of patients with this diagnosis	I	80	90	95.5	870	911
12b	Proportion of patients with ER– and PgR– carcinoma who did not receive adjuvant hormonotherapy out of the total number of patients with the same diagnosis	I	98	100	100.0	106	106

Table 1 (continued)

EUSOMA quality indicators[a]		Level of evidence	Minimum standard (%)[b]	Target (%)[b]	This study (%)	$N_{\text{satisfies criteria}}$	N_{eligible}
13a	Proportion of patients with ER– (T > 1 cm or Node+) invasive carcinoma who received adjuvant chemotherapy, out of the total number of patients with the same diagnosis	I	80	90	83.1	74	89
13b	Proportion of patients with N + or N– *T* > 1 cm HER2+ (IHC 3 + or in situ hybridisation positive FISH+) invasive carcinoma treated with chemotherapy and who had adjuvant trastuzumab, out of the total number of patients with the same diagnosis	I	80	90	87.3	89	102
13c	Proportion of patients with HER2 negative invasive carcinoma who did not have adjuvant trastuzumab, out of the total number of patients with the same diagnosis	II	98	100	100.0	802	802
13e	Proportion of patients with inflammatory breast cancer or locally advanced non-resectable ER- carcinoma who had neoadjuvant chemotherapy over the total of patients with the same diagnosis	II	90	95	83.3	15	18
Proportion of patients who satisfy all eligible quality indicators					59.8	630	1053

EUSOMA European Society of Breast Cancer Specialists, *N* number of patients, *ER* estrogen receptor, *PgR* progesterone receptor, *US* ultrasound, *FNA* fine needle aspiration, *CNB* core needle biopsy, *BCT* breast-conserving treatment, *DCIS* ductal carcinoma in situ, *IHC* immunohistochemistry, *FISH* fluorescent in situ hybridization

[a]European Society of Breast Cancer Specialists quality indicators from 2010

[b]As defined by European Society of Breast Cancer Specialists in 2010

[c]Distance to nearest radial margin was excluded from EUSOMA QI 4b as these data were not systematically collected

adherence to EUSOMA QI retained its prognostic value for OS and regarding correlation of treatment type with OS in this last model, surgery, hormonotherapy, and trastuzumab were found to have significant prognostic value.

Event-free survival

The same models were formed for the analysis of the independent correlation of quality of care with EFS (Table 4). Model 1 improved with the addition of adherence to EUSOMA QI and its impact on EFS was independent of the case mix with all the other covariates in this model also appearing to be significant predictors of EFS. In model 2, the correlation of EFS with quality of care was further adjusted for type of hospital and its significant prognostic impact was retained, but this statistical significance was lost in Model 3 where type of treatment was added. In this final model, all the covariates except for treating hospital and chemotherapy appeared to be significantly correlated with EFS.

Discussion

In the present study, younger patients, those without comorbidities, and those with HER 2-negative tumors were more likely to receive care which completely satisfied EUSOMA QI, whereas type of hospital appeared to have no influence. Whether the patient was treated in complete compliance with eligible EUSOMA QI was found to be significantly correlated with OS as well as EFS even after adjustment for unequal distribution of case mix and type of hospital. However, when the type of treatment was taken into consideration, compliance of care with EUSOMA QI appeared to have lost its significant impact on EFS, but not on OS.

Table 2 Demographic and clinical characteristics stratified by adherence to quality indicators

Patient characteristics			Adherence to selected EUSOMA quality indicators[a]				
	All ($N=1053$)		< 100% adherence ($N=423$)		100% adherence ($N=630$)		p value[b]
	N	%	*N*	%	*N*	%	
Age							
Median (years)	61		66		60		
Range (years)	25–97		25–97		30–92		
< 50	221	21.0	81	19.1	140	22.2	0.000
50–69	531	50.4	168	39.7	363	57.6	
> 69	301	28.6	174	41.1	127	20.2	
Stage							
I (IA + IB)	447	42.5	158	37.4	289	45.9	0.000
IIA	272	25.8	106	25.1	166	26.3	
IIB	134	12.7	63	14.9	71	11.3	
IIIA	90	8.5	35	8.3	55	8.7	
IIIB	38	3.6	25	5.9	13	2.1	
IIIC	56	5.3	22	5.2	34	5.4	
Unknown	16	1.5	14	3.3	2	0.3	
Simplified stage							
I (IA + IB)	447	42.5	158	37.4	289	45.9	0.000
II (IIA + IIB)	406	38.6	169	40.0	237	37.6	
III (IIIA + IIIB + IIIC)	184	17.5	82	19.4	102	16.2	
Unknown	16	1.5	14	3.3	2	0.3	
Intrinsic subtype							
Luminal A-like	340	32.3	106	25.1	234	37.1	0.000
Luminal B-like HER2-negative	390	37.0	130	30.7	260	41.3	
Luminal B-like HER2-positive	102	9.7	44	10.4	58	9.2	
HER2-positive	31	2.9	17	4.0	14	2.2	
Triple-negative	68	6.5	21	5.0	47	7.5	
Unknown	122	11.6	105	24.8	17	2.7	
CCI							
0	624	59.3	213	50.4	411	65.2	0.000
1	229	21.7	95	22.5	134	21.3	
≥ 2	148	14.1	71	16.8	77	12.2	
Unknown	52	4.9	44	10.4	8	1.3	
Therapy received							
Chemotherapy	473	44.9	155	36.6	318	50.5	0.000
Trastuzumab	119	11.3	46	10.9	73	11.6	0.720
Hormonotherapy	883	83.9	324	76.6	559	88.7	0.000
Radiotherapy	712	67.6	154	36.4	558	88.6	0.000
Surgery	985	93.5	359	84.9	626	99.4	0.000
Type of hospital[c]							
Comprehensive cancer center	686	65.1	257	60.8	429	68.1	0.003
Teaching hospital[d]	216	20.5	87	20.6	129	20.5	
Others combined	151	14.3	79	18.7	72	11.4	

N number, *HER2* human epidermal growth factor receptor 2, *CCI* Charlson comorbidity index

[a]Quality indicators of the European Society of breast cancer specialists (EUSOMA) presented in Table 1

[b]p value for difference in categorical variables between two groups based on Pearson's χ^2 test

[c]Type of the hospital where the patient was operated or received chemotherapy or was irradiated or received hormonal therapy or was diagnosed (in descending order of importance)

[d]A teaching hospital with more than 150 newly diagnosed primary breast cancer cases per year and without radiotherapy department at that time

Table 3 Cox proportional hazards analysis of overall survival according to adherence to quality indicators

	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
100% adherence to eligible EUSOMA QI	1.00	1.00	1.00
< 100% adherence to eligible EUSOMA QI	2.07 (1.37–3.13)	2.12 (1.40–3.20)	1.68 (1.06–2.66)
LR (*p* value)	12.19 (0.000)	12.91 (0.000)	5.03 (0.025)

LR likelihood ratio for addition of quality indicators-adherence status into model, *HR* hazard ratio of death, *EUSOMA QI* European Society of Breast Cancer Specialists quality indicators, *95% CI* 95% confidence interval

[a]Model adjusted for case mix (age, stage, Charlson comorbidity index, intrinsic subtype)

[b]Adjusted for covariates in Model 1 plus type of treating hospital

[c]Adjusted for covariates in Model 2 plus treatment type

Table 4 Cox proportional hazards analysis of progression-free survival according to adherence to quality indicators

	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
100% adherence to eligible EUSOMA QI	1.00	1.00	1.00
< 100% adherence to eligible EUSOMA QI	1.77 (1.26–2.47)	1.80 (1.29–2.52)	1.30 (0.89–1.90)
LR (*p* value)	10.86 (0.001)	11.82 (0.001)	1.82 (0.178)

LR likelihood ratio for addition of quality indicators-adherence status into model, *HR* hazard ratio of disease progression or death, *EUSOMA QI* European Society of Breast Cancer Specialists quality indicators, *95% CI* 95% confidence interval

[a]Model adjusted for case mix (age, stage, Charlson comorbidity index, intrinsic subtype)

[b]Adjusted for covariates in Model 1 plus type of treating hospital

[c]Adjusted for covariates in Model 2 plus treatment type

Factors influencing delivery of quality breast cancer care

There is a strong need to further assess factors influencing delivery of quality breast cancer care in different environments, even though abundance of comparable studies has thus far been published [6, 17–19]. Differences in healthcare organization and demographics across countries preclude direct application of findings from one country to another, which is especially true since these potential confounders are not always taken into account [6].

At first sight, the most apparent lever to improve quality of care in health system seems to be reallocation of resources and patients into hospitals with highest quality of provided care but identifying these is not an easy task. Even though the characteristics of treating hospital in relation to quality of care have been most exhaustively investigated of all organizational factors, the results are neither consistent nor easily implemented [6, 20]. However, there is a strong positive correlation between volume and quality. A large study from Belgium including more than 25,000 breast cancer patients reported better utilization of recommended processes of care in high-volume hospitals [5]. Similar results were reported by Yen et al. in a study including more than 500,000 breast cancer patients from United States [21]. Nevertheless, when clustering breast cancer patients in large volume hospitals, consequent geographical inequalities in access to specialized treatment should be kept in mind [22].

Additionally, considering outcome-related QI, not only volume but other characteristics of treatment center are important as well, such as involvement in research and teaching, and providing radiotherapy [23]. In present study, the only CCC in Slovenia was also the hospital with the highest volume. It was compared to the only university teaching hospital treating breast cancer patients, the second largest by patient volume with no radiotherapy department at that time, and to all the other five general hospitals combined. Therefore, the type of hospital can herein be interpreted as a volume surrogate as well. Despite this, no significant correlation was found between the type of hospital and quality of care. Possible reasons for this could be referral bias, centralized physician training leading to good conditions for knowledge dissemination among hospitals, and inter-hospital cooperation in means of multidisciplinary breast cancer meetings. For instance, decision to irradiate after breast-conserving surgery is always made in the setting of a multidisciplinary tumor board, which followed national guidelines. The fact that 277 (26.3%) patients were treated in more than one hospital is an important factor influencing the analysis and possibly obscuring the impact of treating hospital on quality of care. Nevertheless, within the group of "other hospitals," there was a great heterogeneity in number of treated patients per hospital (6–69 patients) as well as in the proportion of patients who satisfied all eligible EUSOMA QI (0.0–68.1%) which could mask the correlation of hospital of treatment and quality of care in our study.

Contrary to organizational factors, deviation from process quality due to patient-related factors could be medically justifiable in selected cases. For instance, according to PRIME II trial, omission of radiotherapy after breast-conserving surgery in older women with early hormone receptor-positive node-negative breast cancer receiving hormonal therapy is a viable option [24]. Even the authors of updated 2017 EUSOMA QI pointed out the complexity of breast cancer treatment in elderly. On the other side, they underscored worse outcomes of elderly who are undertreated and they encourage centers to consider all patients for standard treatment, regardless of age [25].

Our data add to the evidence of the negative impact of older age and comorbidities on delivering quality care, which again, could be medically justifiable in selected cases. What is more interesting, in the present study, patients with HER2-positive tumors were also more commonly treated divergently from EUSOMA QI. This correlation is puzzling, and no obvious explanation exists for the differences observed in EUSOMA QI 10b, 11a, 12a, and 13a between patients based on HER2 status. In search of explanation of these differences, we performed additional analysis comparing patient's characteristics based on HER2 status and some important differences were observed (Table 5). The real culprit for observed differences could, however, be a relatively small number of HER2-positive patients ($N = 133$) leading to misrepresentation of this patient group. Before further conclusions, findings should be confirmed on a larger time frame.

EUSOMA QI 13a, however, deserves closer inspection. Its definition is "Proportion of patients with ER– ($T > 1$ cm or Node+) invasive carcinoma who received adjuvant chemotherapy, out of the total number of patients with the same diagnosis." Since HER2-positive patients eligible for this QI are commonly treated with neoadjuvant but not adjuvant systemic therapy, they are all considered to be treated divergently from EUSOMA QI 13a. This results in skewed presentation of quality of care in our study and prompts further clarification of this QI in the next EUSOMA QI update.

To our best knowledge, no study showing negative influence of HER2-positive tumors on delivery of quality of care has thus far been published; however, the negative impact on survival of such non-adherent treatment in HER2-positive patients is well known [26].

Impact of quality of care on outcomes

The correlation of guideline-adherent breast cancer care with survival is well established [8–10, 27, 28]. With careful adjustment for covariates a survival benefit with 100% QI-adherent treatment was observed in our study as well.

Table 5 Demographic and clinical characteristics stratified by HER2 status

Patient characteristic	HER2 status				*p* value[a]
	HER2+ ($N = 133$)		HER2− ($N = 801$)		
	N	%	*N*	%	
Age (years)					
< 50	37	27.8	169	21.1	0.069
50–69	72	54.1	423	52.8	
> 69	24	18.0	209	26.1	
Stage					
I (IA + IB)	42	31.6	355	44.3	0.015
IIA	30	22.6	210	26.2	
IIB	23	17.3	101	12.6	
IIIA	18	13.5	68	8.5	
IIIB	7	5.3	20	2.5	
IIIC	12	9.0	42	5.2	
Unknown	1	0.8	5	0.6	
Simplified stage					
I (IA + IB)	42	31.6	355	44.3	0.005
II (IIA + IIB)	53	39.8	311	38.8	
III (IIIA + IIIB + IIIC)	37	27.8	130	16.2	
Unknown	1	0.8	5	0.6	
CCI					
0	87	65.4	487	60.8	0.025
1	35	26.3	173	21.6	
≥ 2	7	5.3	119	14.9	
Unknown	4	3.0	22	2.7	
Therapy received					
Chemotherapy	113	85.0	348	43.4	0.000
Hormonotherapy	87	65.4	702	87.6	0.000
Radiotherapy	96	72.2	579	72.3	0.980
Breast-conserving surgery	67	50.4	508	63.4	0.004
Mastectomy	62	46.6	280	35.0	0.010
Type of hospital[b]					
Comprehensive cancer center	71	53.4	551	68.8	0.000
Teaching hospital[c]	46	34.6	145	18.1	
Others combined	16	12.0	105	13.1	

CCI Charlson comorbidity index, *N* number, *HER2* human epidermal growth factor receptor 2

[a] *p* value for difference in categorical variables between two groups based on Pearson's χ^2 test

[b] Type of the hospital where the patient was operated or received chemotherapy or was irradiated or received hormonal therapy or was diagnosed (in descending order of importance)

[c] A teaching hospital with more than 150 newly diagnosed primary breast cancer cases per year and without radiotherapy department at that time

There are a few caveats, though, and correlation of guideline-adherent treatment with survival seems to be complex. For example, Andreano et al. found almost linear decrease in survival with increasing adherence to QI only up to 80% adherence, thus choosing 80% cut-off value for determining QI-adherent treatment [9]. Furthermore, Jacke et al. compared survival of a group of breast cancer patients treated before mandatory implementation of new German guidelines with those treated after implementation, further dividing these two cohorts in guideline-adherently and guideline-divergently treated patients. After guidelines implementation, survival significantly increased only within the group of guideline-divergently treated patients [11]. This could be explained to some extent by introduction of multidisciplinary expert panels and precise individual tailoring of the treatment [11].

Strengths and limitations of study

Quality of care can be measured based on structure, outcome, or process, of which latter seem to be most appropriate in this setting [29]. However, only process measures with sound evidence basis or formal expert consensus should be used [30]. Therefore, of all the EUSOMA QI on diagnosis and treatment, only those with level of evidence I or II were included in this study, providing reliable indicators with evidence-based effect on outcome.

As we wished to identify areas where healthcare providers could directly influence the quality of delivered care, 90 patients who refused proposed treatment were excluded from the study. Consequently, deviations from QI result solely from physicians' decisions.

To avoid widespread suboptimal adjustment for case mix in similar studies, careful attention was paid to including extensive patient data in multivariate analysis [6]. Another strength is a presentation of data from a recent cohort in which all patients were treated within a single year, thus eliminating time-related variability in treatment paradigm. The present study is a nationwide population-based study and as such avoids selection bias. Even though primarily metastatic patients were excluded from analysis, there was no other major exclusion criteria, resulting in a heterogeneous cohort. Identification of cases from cancer registry and subsequent review of individual clinical records offers high-quality data.

Regarding limitations, missing data were included in analyses as unknown values, and no imputation was performed. It is unknown if data are missing at random. Socioeconomic status was not assessed and therefore not included as a covariate, even though it is associated with receiving quality breast cancer care [30]. The same goes for attending physician volume, for which association with quality breast cancer care and outcomes is well established [6]. Since this paper did not focus purely on operated patients, the selection of attending physician was troublesome and these data were hence omitted from the analysis.

Conclusion

Herein presented results are akin to several previously published studies, but nevertheless offer some new insights. Known associations of age and comorbidities with quality of breast cancer care were confirmed on a set of carefully selected EUSOMA quality indicators. Additionally, negative association of HER2-positive tumor with quality care was observed which could only be partially explained. This finding in a group of patients with already unfavorable course of disease demands special attention in both daily clinical practice and further research on large patient groups. The complex relationship between the type of hospital, concerning either volume or other characteristics, with quality of provided care has been once again established, as the type of hospital appeared not to be associated neither with quality of care nor with outcomes. Finally, an improved overall survival was observed in those who were treated in complete accordance with EUSOMA quality indicators.

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Compliance with ethical standards

Conflict of interest The authors declare no further conflicts of interest.

Ethical approval The study protocol was approved by the Protocol Review Board and Ethics Committee of the Institute of Oncology Ljubljana.

Informed consent Informed consent for using their data for retrospective study purposes at the start of their treatment was obtained from all individual participants included in the study.

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