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Retrospective analysis of efficacy of trastuzumab in adjuvant treatment of HER 2 positive early breast cancer – single institution experience

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Addition of trastuzumab to chemotherapy is the cornerstone of adjuvant treatment of early HER2 positive breast cancer. Clinical trials and metaanalyses of adjuvant trastuzumab have shown significant reduction in risk of recurrence and death. Nevertheless, the real magnitude of the effect of any drug must be reevaluated in daily clinical conditions, due to the fact that daily clinical practice often differs from conditions in clinical trials. In order to measure the benefit of adding adjuvant trastuzumab in HER 2 positive early breast cancer treatment, we have performed retrospective analysis in a single institution on consecutive patients divided in 2 cohorts: one, treated in "pre – trastuzumab" and the other in "trastuzumab era". Between 2003 and 2012, 258 consecutive HER 2 positive patients with early breast cancer have been treated with adjuvant chemotherapy, 103 patients did not received trastuzumab (patients treated from 2003 till 2007), and 155 (patients treated from 2008 till 2012) received trastuzumab. Patients who received trastuzumab experienced significantly longer median disease-free survival (107 vs. 92 months, LR: 11.6, p <0.001); breast cancer-specific survival (130 vs. 117 months, LR: 10.7, p < 0.001) and median overall survival (123 vs. 108 months LR = 11.6, p < 0.001). The benefits of adding trastuzumab were independent of chemotherapy regimen and hormonal therapy. This retrospective analysis has shown a clear, statistically significant benefit of adjuvant trastuzumab in treatment of early, HER2 positive breast cancer in daily clinical practice, and confirmed the results of the registration clinical trials.

Key words: trastuzumab, adjuvant chemotherapy in HER2, early breast cancer, retrospective analysis

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012 [1]. Thus, breast cancer represents significant health care problem and rightfully considerable resources are spend in early diagnosis, treatment, surveillance and research of new treatments and drug development. Fortunately, due to recent introduction of new therapeutic modalities and earlier diagnosis of the disease, significant improvement in overall survival (OS) and disease-free survival (DFS) is observed. One of the milestones in oncology in general, and especially in breast cancer treatment, was the introduction of trastuzumab. Trastuzumab is a humanized monoclonal antibody targeting the extracellular domain of the transmembrane tyrosine kinase receptor HER2, used in HER 2 positive breast cancer patients [2]. The HER2 gene is amplified and/or over expressed in 15–25 % of breast cancers [3, 4]. HER2 positive cancers tend to be more aggressive, and consequently result in a significantly worse prognosis [4]. Marty and Slamon were the first who have shown significant survival improvement when trastuzumab has been given in combination with taxanes as first-line therapy in women with metastatic HER2 positive breast cancer (median OS, 31.2 vs. 22.7 months; $p = 0.0325$, and 25.1 vs. 20.3 months; $p = 0.01$ respectively) [5, 6]. Since then, prospective, randomized, international phase III trials of trastuzumab in adjuvant HER 2 positive breast cancer treatment have been initiated and more than 13 000 patients have been recruited. Four of the trials: HERA trial, NSABP B-31 trial, N9831 trial, and BCIRG 006 trial have shown consistent benefits in terms of relapse free survival (RFS) and OS [7-10]. FinHer trial has also shown positive results in terms of distant DFS, despite smaller size and shorter duration of adjuvant trastuzumab treatment [11]. However, one negative trial, PACS 004 was published and has

added some confusion in the field of HER2 adjuvant therapy [12]. All the above results were also confirmed in metaanalyses, showing a clinically and statistically significant effect of addition of trastuzumab on RFS and OS in therapy of early, HER2 positive breast cancer [13-16]. Adjuvant trastuzumab treatment lasts for one year [7]. However, the final verdict regarding the length of adjuvant trastuzumab therapy will be given after shorter regimens that are still under investigation in phase III trials will be published [17]. The aim of these trials is to find out whether shorter courses are as effective as the standard one year therapy by trastuzumab. In addition, there is a debate about the treatment of small HER2 positive tumors, i.e. would the size of tumor be without adjuvant trastuzumab being administered.

Based on these results adjuvant trastuzumab has been accepted as the gold standard in treatment of early HER2 positive breast cancer all over the world.

Randomized, controlled trials cannot always predict drug performance in real–world settings [18]. Consequently, observational studies and retrospective analyses are needed in order to evaluate the effects of anticancer therapies in broader, every–day cancer populations. Specifically, every–day cancer patients may not always mirror the characteristics of the patients treated in a study because of specific enrollment criteria, study-related procedures, ethical dilemmas, and differences inherent to those patients who chose to participate in clinical trials.

In this analysis, we describe, represent retrospectively, the impact of adjuvant trastuzumab on HER2 positive early breast cancer patients in a single institution.

Table 1. Main baseline patient characteristic and treatment characteristic

		Trastuzumab	
		No (N, %) (Cohort A)	Yes (N, %) (Cohort B)
Histological type	Ductal invasive	89 (86.4)	135 (87.1)
	Lobular invasive	8 (7.8)	7 (4.5)
	Ductal + lobular	4 (3.9)	5 (3.2)
	Other	2 (1.9)	8 (5.2)
Grade	1	1 (1)	6 (3.9)
	2	55 (53.4)	64 (41.6)
	3	47 (45.6)	78 (50.6)
	Unknown	0	7 (4.5)
Stage	IA	18 (17.5)	39 (25.2)
	IB	0	2 (1.3)
	IIA	26 (25.2)	42 (27.1)
	IIB	21 (20.4)	31 (20)
	IIIA	17 (16.5)	22 (14.2)
	IIIB	6 (5.8)	9 (5.8)
	IIIC	15 (14.6)	9 (5.8)
	Unknown	0	1 (0.6)
Estrogen receptors	Negative	35 (34)	57 (37)
	Positive	68 (66)	98 (63)
Progesteron receptors	Negative	40 (39)	72 (46.5)
	Positive	63 (61)	79 (51)
	Unknown	0	4 (2.6)
Age (year)	<50	34 (32.3)	41 (26.4)
	50-58	26 (25.2)	35 (22.6)
	59-66	17 (16.5)	34 (21.9)
	>65	26 (25.2)	45(29.1)
Surgical procedure	Mastectomy	80 (77.7)	100 (64.9)
	Quadrantectomy	20 (19.4)	51 (33.1)
	Biopsy	2 (1.9)	2 (1.3)
	Unknown	1 (1)	1 (0.6)
Neoadjuvant chemotherapy	No	101(98)	148 (95.4)
	Yes	2	7 (4.5)
Adjuvant chemotherapy	CMF	18 (17.5)	5 (3.2)
	FEC	70 (68)	86 (55.4)
	AC-T	12 (11.7)	53(34.8)
	AC-T D.D.	1 (1)	7 (4.5)
	Other	2 (1.9)	4 (2.5)
Adjuvant radiotherapy	No	33 (32)	39 (25)
	Yes	70 (68)	116 (75)
Adjuvant hormonal therapy	No	28 (27)	49 (32)
	Yes	75 (73)	106 (68)

Patients and methods

This retrospective analysis included consecutive 258 HER2 positive patients with early breast cancer, treated between January 2003 and December 2011. HER2 positive patients diagnosed in 2007 were not included in this analysis, due to fact that we have taken part in HERA and BCRG 006 trials and enrolled patients during that year in that adjuvant trastuzumab trials. The database was closed 1st August 2015. Patients between 2003 and 2007, (cohort A) (N = 103) did not receive trastuzumab. Patients between 2008 and 2012 received trastuzumab (cohort B) (N = 155). Patients who were considered eligible for adjuvant trastuzumab by the oncologist and received at least one application were included. All primary tumors were scored 3+ by immunohistochemistry or 2+/FISH positive, all prior to trastuzumab treatment. Patients between 2003 and 2007 were tested retrospectively, as, at that time, trastuzumab was not used in adjuvant treatment, and HER 2 testing was not routinely done. HER 2 over expression was tested with antibody A0485 (Dako) on all patients involved in this analysis, and it was considered positive if grade 3+ staining was detected, or with gene amplification by silver in situ hybridization, if HER2 2+ result by immunohistochemistry was detected. Trastuzumab was administered for one year according to the standard schedule and dose in cohort B. All other treatment options (surgery, chemotherapy, radiotherapy and hormonal therapy) and their sequencing were decided by the oncology team and have been administered according to tumor and patients characteristics as well as generally accepted guidelines at that time. Patient records related to demographic, clinical, pathological, molecular features and outcomes were analyzed

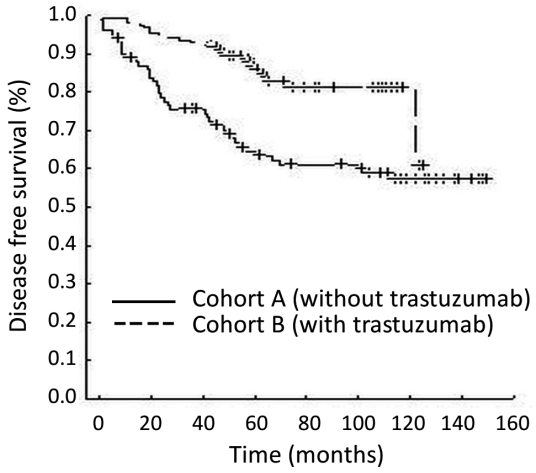

Figure 1. Kaplan-Meier curve for disease free survival according to adjuvant trastuzumab usage

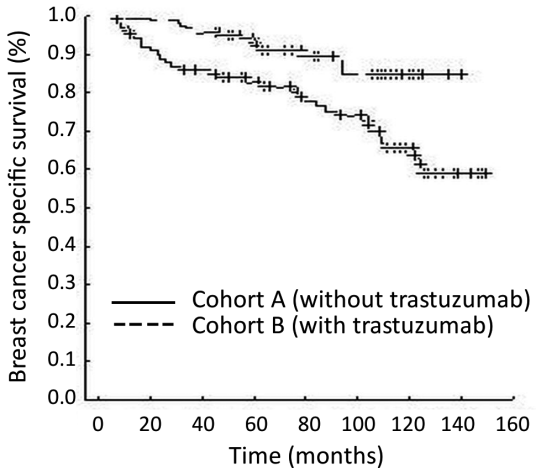

Figure 2. Kaplan-Meier curve of breast cancer specific survival according to adjuvant trastuzumab usage

and entered into a database. Institutional ethic committee approved this retrospective analysis.

The relative risk (RR) and confidence interval (CI) were estimated for each variable by using Cox univariate and multivariate analysis. Level of significance was defined at the $p < 0.05$ level. Survival was calculated by the Kaplan–Meier analysis from the date of surgery until the time of breast cancer death (Breast Cancer Specific Survival – BCSS), death by other cause (Overall Survival – OS), date of recurrence of disease or death due to any other cause (Disease Free Survival – DFS). The log–rank (LR) test was used to assess differences between sub groups. Significance was defined at $p < 0.05$ level. We used SPSS 20 statistical program.

Results

Between January 2003 and December 2011 we identified 258 consecutive HER2 positive patients with early breast cancer in our institution. Among 258 patients enrolled in the study, 103 (40 %) received adjuvant chemotherapy without trastuzumab, and 155 (60 %) received trastuzumab after adjuvant chemotherapy or concurrent with it. Median follow up for all patients included in analysis was 77.2 months (min – max 5.3 – 144.3 months). Median follow up for cohort of patients who did not received trastuzumab was 107.3 months (min – max 5.3 – 149.3 months), and 70.2 months (min – max 10.6 – 91.5 months) for cohort of patients who have received trastuzumab. Cumulative 5 year DFS, BCSS and OS were also calculated. Median of age was 56 years for the first group (min – max 37 – 78 years), and 59 years for the second one (min – max 27 – 85 years). Main characteristics of patients and the disease are listed in Table 1.

Disease free survival analysis. Among 258 patients 79 (30 %) of them experienced disease recurrence; 50 (19.6 %) in cohort A, 29 (11.3 %) in cohort B.

Median DFS for patients in cohort B (patients who received trastuzumab) was 107 months (95 % CI: 100.93 – 113.16) – dashed line, and cohort A (patients who did not receive trastuzumab) was 92 months – full line, (95 % CI: 83.43 – 104.24) (LR = 11.6, $p < 0.001$). (Figure 1)

Cumulative 5 year DFS for patients received trastuzumab (cohort B) was 87.7 % (95 % CI: 82.4 – 90.4 %), and 57.2 % (95 % CI: 47 – 67.4 %) for those who did not receive trastuzumab (cohort A).

Cox uninominal regression analysis showed that patients without trastuzumab had 2.6 times higher risk for disease recurrence ($p < 0.001$) (Table 2).

Multinominal Cox regression analysis included showed that the risk for disease recurrence was 1.8 times higher with each stage of disease ($p = 0.011$). Risk for disease recurrence, death or breast cancer death was 2.2–2.4 times higher in patients who did not received trastuzumab ($p = 0.012$), (Table 3).

Breast cancer specific survival analysis. Breast cancer specific survival was 130 months (95 % CI: 123–136) in cohort B – dashed line. Breast cancer specific survival was 117 months in cohort A (95 % CI: 106–126) – full line. Median BCSS was 13 months longer in patients who received trastuzumab (LR = 10.86, $p < 0.001$) (Figure 2).

Cumulative 5 year BCSS for patients who received trastuzumab (cohort B) was 93 % (95 % CI: 88.7–97.3 %), and 82.5 % (95 % CI: 74.9–90.1 %) for those who did not receive trastuzumab (cohort A).

Cox uninominal regression analysis for BCSS included treatment modalities (surgery, radiotherapy, chemotherapy according protocol, hormonal therapy and trastuzumab) showed that probability of death, due to breast cancer, was 3.1 times higher in patients who did not receive trastuzumab ($p < 0.001$), (Table 2).

Multinomial regression analysis of age, stage, histology, grade, hormone receptors, HER 2 positivity and all treatment

modalities – surgery, chemotherapy, radiotherapy, hormonal therapy and trastuzumab, showed that the relative risk of death from breast cancer was 2.4 times higher in patients who did not received trastuzumab ($p = 0.0037$) (Table 3).

Overall survival analysis. Of 258 patients 61 (23.6 %) died: 43 (16.7 %) in cohort A and 18 (7 %) in cohort B. Three patients were excluded because they were lost to follow up. Overall survival results are shown in Figure 3. Median OS was 123 months (95 % CI: 115–131) in cohort B – dashed line. Median OS in cohort A was 108 months (95 % CI: 97–118) – full line. Median OS was 15.3 months longer in patients who received trastuzumab (LR = 11.6, $p < 0.001$). (Figure 3)

Cumulative 5 year OS for patients who received trastuzumab (cohort B) was 92.2 % (95 % CI: 87.7–96.7 %), and 76.1 % (95 % CI: 67.7–84.5 %) for those who did not receive trastuzumab (cohort A).

Cox uninominal regression analysis for OS included all treatment modalities and showed that probability for death was 2.6 times higher in patients who did not received trastuzumab ($p < 0.001$), (Table 2). Patients who underwent mastectomy had 3.0 times higher risk of death ($p = 0.011$), (Table 2).

Multinomial regression analysis according to the treatment modalities given – surgery, chemotherapy, radiotherapy, hormonal therapy and trastuzumab, showed that the relative risk

Table 2. Cox uninominal regression analysis for DFS, OS and BCSS for cohort A and B regarding the treatment given

		RR	95 % CI	*p*
Disease Free Survival				
Surgical procedure	Mastectomy	15.5	1.1–35	0.030
	Quadrantectomy*			
Radiotherapy	No*	1.6	0.94–2.7	0.083
	Yes			
Chemotherapy	AC-T (AC-T D.D)*			0.221
	AC-T (AC-T D.D) vs CMF	1.7	0.82–3.7	0.149
	AC-T (AC-T D.D) vs FEC	1	0.57–1.8	0.983
Hormonal therapy	No*	0.98	0.60–1.60	0.935
	Yes			
Trastuzumab	No	2.6	1.6–4.2	< 0.001
	Yes*			
Overall Survival				
Surgical procedure	Mastectomy	3.0	1.3–7	0.011
	Quadrantectomy*			
Radiotherapy	No*	1.34	0.77–2.4	0.275
	Yes			
Chemotherapy	AC-T (AC-T D.D)*			0.606
	AC-T (AC-T D.D) vs CMF	1.2	0.49–2.9	0.696
	AC-T (AC-T D.D) vs FEC	0.85	0.43–1.7	0.634
Hormonal therapy	No*	0.86	0.5–1.5	0.594
	Yes			
Trastuzumab	No	2.6	1.6–4.2	< 0.001
	Yes*			
Breast Cancer Specific Survival				
Surgical procedure	Mastectomy	7	1.7 – 29	0.007
	Quadrantectomy*			
Radiotherapy	No*	1.64	0.81 – 3.3	0.173
	Yes			
Chemotherapy	AC-T (AC-T D.D)*	1.2	0.68 – 2.1	0.512
	AC-T (AC-T D.D) vs CMF			
	AC-T (AC-T D.D) vs FEC			
Hormonal therapy	No*	0.75	0.4-1.4	0.366
	Yes			
Trastuzumab	No	3.1	1.9–5.2	< 0.001
	Yes*			

*reference level, RR: relative risk, CI: confidence interval

Table 3. Cox multinomial regression analysis for DFS, BCSS and OS for cohort A and B regarding the treatment given

		RR	95 % CI	*p*
Disease Free Survival				
Surgical procedure	Mastectomy	2.23	1.15–4.1	0.009
	Quadrantectomy*			
Radiotherapy	No*	1.3	0.64–2.5	0.490
	Yes			
Chemotherapy	CMF*	0.92	0.55–1.55	0.766
	FEC			
	AC-T (AC-T D.D.)			
Hormonal therapy	No*	1.3	0.48–3.3	0.638
	Yes			
Trastuzumab	No	2.2	1.2–3.9	< 0.012
	Yes*			
Overall Survival				
Surgical procedure	Mastectomy	0.53	0.2–1.4	0.376
	Quadrantectomy*			
Radiotherapy	No*	1.1	0.52–2.3	0.814
	Yes			
Chemotherapy	CMF*	1.3	0.72-2.3	0.381
	FEC			
	AC-T (AC-T D.D.)			
Hormonal therapy	No*	1.7	0.65–4.8	0.270
	Yes			
Trastuzumab	No	2.3	1.1–4.6	0.019
	Yes*			
Breast Cancer Specific Survival				
Surgical procedure	Mastectomy	0.26	0.1–1.2	0.083
	Quadrantectomy*			
Radiotherapy	No*	0.94	0.4–2.4	0.890
	Yes			
Chemotherapy	CMF*	1.4	0.71–2.9	0.301
	FEC			
	AC-T (AC-T D.D.)			
Hormonal therapy	No*	1.2	0.36–4.1	0.746
	Yes			
Trastuzumab	No	2.4	1.0–5.7	0.0037
	Yes*			

*reference level, RR: relative risk, CI: confidence interval

of death was 2.3 times higher in patients who did not received trastuzumab (cohort A) ($p = 0.019$) (Table 3).

Discussion

The only way to really known the efficacy and toxicity of new drugs, is to investigate these in every-day clinical practice. Potential discrepancies, both in new drug efficacy and toxicity, between the results published in clinical trials and the results obtained from every-day clinical practice could be due to differences in patient selection, organizational issues or multidisciplinary use, as well as general level of oncological care [18]. Consequently, results from randomized phase III trials are often difficult to be repeated in general clinical practice [18]. For example, Tannock and colleagues compared outcomes of men with metastatic castrate–resistant prostate cancer (mCRPC) treated with docetaxel and prednisone, in routine practice and in clinical trials [18]. Survival of patients with mCRPC treated with docetaxel in routine practice was significantly shorter than for men included in trials, and is associated with more toxicity [18]. Base on that, strong recommendation should be made that all new drugs and treatment modalities should be reviewed regarding their clinical benefit, in terms of retrospective analysis in different setups, countries or healthcare systems. Large randomized phase III trials are done in selective centers, with certain level of excellence in oncology care, potentially significantly higher than is the case in an average oncology institute. Whilst majority of published articles are for phases I, II and III, our knowledge of the real impact of new drugs on outcomes in real life patients finds these questionable [19, 20]. Consequently, retrospective analyses, phase IV observational clinical trials, good cancer registries, institutional or even better country or region based, are essential to define the real impact of new therapies on our patients and health care systems.

Trastuzumab is a cornerstone of HER2 positive breast cancer treatment, early and metastatic, with strong evidence of efficacy from large clinical trials and metaanalyses [7-10, 13-16]. As such, trastuzumab is widely used throughout the world in treatment of HER2 positive breast cancer. Despite the large body of evidence from randomized trials, the amount of evidence from every–day practice is rather sparse. Only two retrospective analyses of trastuzumab efficacy and safety in everyday practice from Canada and Italy were conducted [21, 22].

RETROHER trial analyzed patients in "pre trastuzumab era" vs "trastuzumab era" [22]. Relapse rate at 3 – year (18.5 % without trastuzumab vs 7.8 % with trastuzumab, $p < 0.0001$), relapse free survival (88.6 % with trastuzumab vs 71 % without trastuzumab, $p < 0.0001$), and OS (88.4 % without trastuzumab vs 96 % with trastuzumab, $p < 0.0001$) were significantly more favorable in patients who received trastuzumab as well as 10 – year BCSS (73.3% without trastuzumab vs 93.5 % with trastuzumab, $p < 0.0001$) [22]. Similarly, Canadian trial retrospectively analyzed 703 patients with HER 2 positive

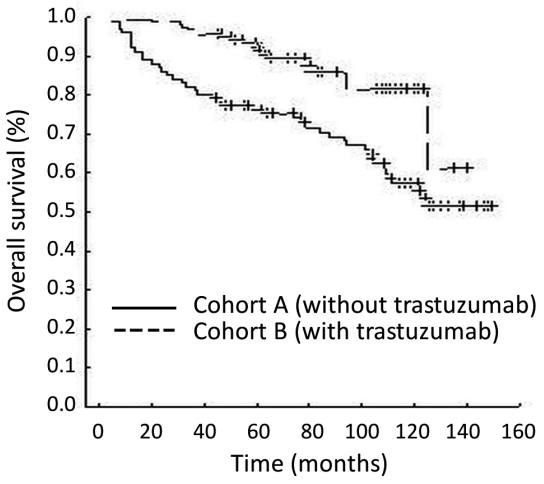

Figure 3. Kaplan-Meier curve of overall survival according to adjuvant trastuzumab usage

breast cancer. Of total population 68 % received trastuzumab. In cohort that did not receive trastuzumab only 28 % received chemotherapy and had overall more favorable baseline characteristics (stage, grade, lymphovascular invasion and estrogen receptor status). After median follow up period of 2 years, despite initially unfavorable prognostic features, the group of patients who received trastuzumab experienced better outcomes. The 2 year relapse free survival was 90.9 % vs 77.3 % ($p = 0.01$) [21]. One retrospective trial was also conducted in Slovenia where results were comparable to results obtained in international adjuvant trials [23].

In our retrospective analysis we have investigated the impact of adjuvant trastuzumab in terms of DFS, BCSS and OS on HER2 positive patients in a single oncology institute in a transitional country such as Croatia. Our results confirmed clear and meaningful trastuzumab benefit on clinical outcome in adjuvant treatment of HER 2 positive early breast cancer comparable to pivotal trials: DFS (107 vs. 92 months, LR = 11.6, $p < 0.001$), OS (123 vs. 108 months, LR = 11.6, $p < 0.001$) and BCSS (130 vs. 117 months, LR = 10.86, $p < 0.001$) [24-26].

In our study, the major difference between two cohorts was in chemotherapy regimens received. In patients who did not receive trastuzumab, 68 % of patients received antracycline based protocol, and only 12.7 % of patients received a combination of antracycline and taxane. On the other hand, in trastuzumab group, 38.9 % of patients received a combination of antracycline and taxane, and 55.8 % antracycline. The results are explained to be the result of introducing adjuvant taxanes usage in clinical practice in Croatia at almost the same time as trastuzumab. CMF was used in only 5 cases (3.2 %) in patients received trastuzmab, much less in comparison with those who did not – 17.5 %. We can speculate that benefits experienced in OS, DFS and BCSS may be partly attributed to difference in chemotherapy, but neither univariate nor multivariate Cox regression analysis have confirmed that. Another issue

represents stage distribution within the 2 observed cohorts. In patients received trastuzumab 26.5 % were in stage I, and 25.8 % in stage III of the disease. In patients who did not receive trastuzumab there were only 17.5 % with stage I and 36.9 % with stage III of the disease. This positive stage shift is probably the result of raising breast cancer awareness in Croatia, as well as the national prevention program. Patient cohorts were not different in hormonal receptor expression and age. Hormonal therapy and radiotherapy was used at similar frequency in both cohorts. There were marginally more patients treated with radiotherapy. We can speculate that this is partly due to more sparing surgery, which automatically requires adjuvant radiotherapy.

Potential limitations of our study was its retrospective nature, relatively small number of patients included in the study and imbalance in certain tumor and treatment characteristics, as well as different follow up length for two investigated cohorts of patients. In pre trastuzumab group, minority of patients received combination of antracyclines and taxanes which may have influenced the results, although multivariate analyses showed no impact of different chemotherapy regimen on OS, BCSS and DFS. In addition, the weakness of this retrospective study is lack of good toxicity data, which is always the case, due to rather weak follow-up quality of toxicity issues, as well as weak registration of toxicity. Despite those limitations, this study has certain strengths. It was conducted in only one institution which covers almost quarter of the whole country, and represents real population of patients, and real treatment, according to guidelines and legislative acts valid in Croatia during the observed time.

In conclusion, our results confirm the benefit of adjuvant trastuzumab administration on patients treated out of clinical trials with HER2 positive breast cancer.

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