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Not all small HER2 positive breast cancers have the same clinical outcome in the North-East of Scotland

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ABSTRACT

HER2-positive breast cancers, representing up to 20% of all breast cancers, are more aggressive and have poorer outcomes. Systemic therapy has been proven to prevent disease recurrence and improve survival. Existing literature provides only limited evidence to support this in smaller HER2-positive tumors. The study aimed to evaluate HER-2 positive breast cancer management and treatment of all T1N0 tumors in the North of Scotland, diagnosed 2012–2019. Clinical-pathological details, comorbidities, treatments and clinical events were retrieved from the Scottish North Cancer Alliance audit database and analyzed using univariate and multivariate analysis including cox-regression and log-rank testing (SPSSv23).Overall, 299 patients (41% screen detected/ 56.9% symptomatic /2.1% other), median age 63 years and median tumor size 13 mm, were included. Most cancers were grade 2/3 (43.1%/ 55.5%). Most patients (59.5%) received treatment with trastuzumab (tT); 40.8% concurrent with chemotherapy and endocrine therapy. 7.7% of patients received neo adjuvant chemotherapy. Median follow-up time was 2.6 years, with recurrence on average occurring 2.9 years after diagnosis. Patients receiving trastuzumab were younger, had a higher grade and larger size tumor. 78.5% of patients in the untreated group (non-tT) were ER positive compared to 65.2% in the treated group (tT). Trastuzumab significantly lowered breast cancer recurrence (Tt=3.4% versus non-Tt=8.3%, $p = 0.022$ HR= 0.096, 95% CI 0.025–0.361). In conclusion, receiving anti-HER2 treatment significantly improved clinical outcome in this T1N0 patient group. Consideration, at the very least informed discussions with patients, should be undertaken to treat these early stage HER2-positive breast cancers.

Introduction

In 1985, overexpression of Human epidermal growth factor receptor (HER)−2, a growth promoting cell membrane protein, was found to be a prognostic and predictive biomarker in breast cancer [1]. Breast cancers that have an amplification of the HER-2 gene are known to be more aggressive and have poorer outcomes [2].

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody directed against the HER2 receptor, which has become the mainstay of treatment of patients with early stage HER2 positive breast cancer, reducing recurrence rates and improving survival. Most adjuvant clinical trials have focused on patients with Stage II or III disease [3,4,5,6]. Patients with Stage I HER2-positive tumors may derive a clinical benefit from the use of Trastuzumab. A single arm trial of patients with predominantly Stage I HER2-positive breast cancer treated with adjuvant paclitaxel plus trastuzumab demonstrated low levels of recurrence at 5 and 7 years, with low levels of treatment related toxicity [7,8]. Within NHS Scotland, the online prognostic tool PREDICT, which

Abbreviations: ER, Estrogen Receptor; HR, Hazard Ratio; IQR, Inter-Quartile Range; LVI, Lymphovascular Space Invasion; tT, treated; non-tT, non treated; PR, Progesterone Receptor.

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estimates the survival benefit of systemic therapy, is used to guide decisions regarding the use of chemotherapy following surgery [9]. The rate of uptake of systemic therapy in women with small HER2 positive tumors within the North of Scotland is unknown. Therefore, a review of all patients of this region with small (up to 30 mm), node negative HER2 positive breast cancer was conducted. The patients' clinical and pathological data were collected and correlated to their treatment and clinical outcome to determine whether a change of current practice required.

Methods

All patients were selected from the Scottish North Cancer Alliance audit database. The Scottish North Cancer Alliance is a healthcare collaboration including NHS Grampian, NHS Highland and NHS Tayside. Caldicott approval from each health board was sought and granted. Only female patients with a HER2 positive tumor, smaller than 20 mm, lymph node negative, diagnosed between 2012 and 2019, were included in the analysis. Data was collected using each Health Board's computer-based Patient Information System [Trak Care], which records patients' comorbidities, types of presentation and treatment, tumor pathological details, screening or community referral, last clinical review, and clinical events, such as disease recurrence or death. Median follow-up was 2.6 years (IQR 1.3–4.6 years) using patients' last follow up or clinical event as data collection endpoint. Eligible patients were stratified by treatment group for analysis: Treated with trastuzumab (tT) and not treated with trastuzumab (non-tT).

Statistical analysis

SPSSv23 was used for univariate and multivariate analysis. Means, medians and total numbers were analyzed using descriptive statistics. Patient demographics were analyzed to investigate whether the untreated group had significantly different characteristics compared to the treated group. To undertake a comparable analysis the following potential confounders were adjusted for: age, tumor type, grade, breast surgery, ER (estrogen receptor) and PR (progesterone receptor) status and health board. One out of three health boards did not report PR status in their histological reports and multiple imputation was applied to predict the 65 missing values. To investigate clinical disease recurrence more closely, patients were stratified into two groups: treated (tT) and not treated (non-tT) with trastuzumab. Multinominal regression was used to predict which factors influenced whether patients received trastuzumab or not. Survival curves were generated by using log rank testing with Kaplan-Meier curves.

Cox proportional hazard ratios were calculated to compare recurrence rates between the treated and untreated groups, adjusted for age, tumor type, grade, ER and PR status and type of breast surgery. Additionally, independent samples t-tests and/or chi-squared tests were used to compare demographics of the treated and untreated populations. P-value <0.05 was classified as statistically significant.

Results

A total of 299 patients were identified. Median age was 63 years (IQR 56–72 years). The majority (90.6%) had invasive ductal carcinomas, while the remainder were classified as lobular (4.7%) or "other" (3.7%) including inflammatory, papillary and mixed type tumors. Most (55.5%) tumors were classified as grade 3, 43.1% were grade 2 and 1.3% were grade 1 (Bloom and Richardson grading). The median size was 13 mm (IQR 9–16) and lymphovascular space invasion (LVI) at presentation was found in the minority (12%) (Table 1).

Just over half of patients (n = 178) were treated with systemic therapy including chemotherapy with anti-HER2 therapy +/- endocrine therapy. The remaining 121 patients received either no additional systemic treatment or endocrine therapy only for estrogen positive disease (Table 2).

Table 1
Patient demographics.

Total Cohort$N$ = 299	Treated (tT)n = X (%)	Untreated (non-tT)n = X (%)	p-value Chi-Square
Number of patients	*178 (59.53)*	*121 (40.47)*	
Age			0.001
<50 years	36 (20.2)	5 (4.1)	
>50 years	142 (76.3)	116 (95.9)	
Referral			0.297
Screening	87 (48.9)	67 (55.4)	
Symptomatic	88 (49.4)	50 (41.3)	
Others	3 (1.7)	4 (3.3)	
Tumor type			0.045
Ductal	167 (94.4)	104 (87.4%)	
Lobular	4 (2.3)	10 (8.4)	
others	6 (3.4)	5 (4.2)	
missing	0	0	
Tumor grade			0.001
G1	2 (1.1)	2 (1.7)	
G2	51 (28.7)	78 (64.5)	
G3	125 (70.2)	41 (33.9)	
Tumor size			0.005
T1a	9 (5.1)	19 (15.7)	
T1b	36 (20.2)	27 (22.3)	
T1c	133 (74.7)	75 (62)	
Missing	0	0	
LVSI	26 (14.6)	10 (8.3)	0.098
ER			0.013
Positive	116 (65.2)	95 (78.5)	
Negative	62 (34.8)	26 (21.5)	

Referral Others= patient referred from other hospital specialities; missing= unreported; G= grade; ER= estrogen, LVSI= lymphovascular space invasion.

Table 2
Overview on clinical events and treatment in the untreated versus the treated cohort.

Total Cohort N = 299	Treated (tT) n = X (%)	Untreated (non-tT)n = X (%)	p-value Chi-Square
Number of patients	178 (59.53)	121 (40.47)	
Recurrences	6 (3.4)	10 (8.3)	0.065
Local recurrence	3 (50)	4 (40)	
Regional recurrence	0	0	
Distant recurrence	3 (50)	6 (60)	
Deaths			0.001
Death because of breast cancer	2 (1.1)	5 (4.2)	
Unrelated deaths	0	10 (8.3)	
	0	0	
Missing			
Neoadjuvant chemotherapy/ antiHER2	20 (11.2)	3 (2.5)	0.005
Adjuvant chemotherapy/ antiHER2	178	0	X
No treatment	0	29 (24)	<0.001
Oncological treatment strategies			
Chemotherapy with trastuzumab	56 (31.5)	0	
Endocrine treatment	0	92 (76)	
Combined endocrine and chemotherapy with trastuzumab treatment	122 (68.5)	0	
Radiotherapy	129 (72.5)	73 (60.3)	0.028
Type of surgery			0.133
Mastectomy	46 (25.8)	41 (33.9)	
Wide local excision	132 (74.2)	80 (66.1)	
Axillary surgery			0.578
Sentinel node biopsy	174 (97.8)	117 (96.7)	
Axillary clearance	4 (2.2)	4 (3.3)	

Within the total cohort, 16 patients suffered from disease recurrence during the follow-up period. 7 patients experienced a localized recurrence (3 tT vs 4 non-tT) and 9 patients developed distant metastases (6 tT vs 3 non-tT). 7 patients experienced a localised recurrence (3 tT vs 4 non-tT) and 9 patients developed distant metastases (6 tT vs 3 non-tT; $p = 0.001$, HR 0.096, 95% CI 0.025–0.361). 7 patients died from breast cancer related causes (1.1% tT patients vs 4.2% non-tT patients; $p = 0.064$). A difference in overall survival was noted (0 tT vs 10 non-tT/ tT 98.8% versus non-tT 87.6%; $p < 0.001$), (Table 2).

Median age at time of death was 77 years overall (IQR 46–58.25 years) and age at time of death due to breast cancer related causes was 51 years (IQR 43–78 years). Median time between initial diagnosis and recurrence was 3.4 years (IQR 1.5–5.1 years) and median time between diagnosis of recurrence and death was 1.6 years (IQR 8.3 months – 2.1 years).

Of the patients dying of breast cancer related causes, 1 had presented via screening, 4 had presented symptomatically and 2 were referred from other departments as incidental findings. 4 patients underwent breast conserving surgery and 3 patients had a mastectomy. None received neoadjuvant treatment, 2 patients received combined endocrine and chemotherapy with trastuzumab treatment, 2 received solely endocrine treatment and 3 had received no systemic treatment at all. 5 patients proceeded to adjuvant radiotherapy.

212 (70.9%) of the overall patient cohort underwent wide local excision/breast conserving surgery. A trend was noted towards breast conserving surgery in the later stages of the data collection. Almost all patients had a sentinel node biopsy (97.3%) as their axillary procedure. A small number proceeded to an axillary clearance (2.7%) despite preoperative lymph node negativity.

Within the entire cohort, 7.7% of patients proceeded to neoadjuvant chemotherapy, which had become more widely used in the later years of our analysis. 90.3% of all patients received adjuvant systemic therapy. Three general oncological treatment categories were created for analysis: chemotherapy with trastuzumab (18.7%), hormonal treatment alone (30.8%) and both hormonal therapy and chemotherapy with trastuzumab (40.8%). Out of 299 patients, 29 underwent surgical intervention only (9.6%). In total, 59.5% of patients received trastuzumab as anti-HER2 therapy. A high proportion within both patient groups underwent radiotherapy (72.5% tT vs 60.3% non-tT, table 2). Using multinominal regression analysis, predictors for trastuzumab treatment were younger age ($p < 0.001$) and higher grade ($p < 0.001$).

Reasons for not receiving trastuzumab varied. In the majority of patients there was no medical contraindication as to why they did not receive treatment, i.e. personal choice or no documentation of cause (56%). The other two most common reasons were previous treatment with anthracyclines (13%) and a high age (above 80) (9%).

Comparing patient populations using independent samples *t*-test for continuous variable and chi-square test for categorical variables, the average patient treated with trastuzumab was significantly younger (59 versus 69 years), had a higher grade (G3 versus G2, $p < 0.001$) and a larger sized (18 versus 15 mm) tumor. More patients in the untreated group were ER positive than in the treated group (78.5% non-tT vs 65.2% tT, $p = 0.013$).

Clinical disease recurrence was documented in 16 patients (5.4%). Kaplan Meier analysis showed a significant difference in recurrence rates between patients treated with or without trastuzumab ($p = 0.022$). Cox-proportional hazard ratio also showed a significant difference (Tt=3.4% versus non-Tt=8.3%, $p = 0.022$ HR= 0.096, 95% CI 0.025–0.361) (Fig. 1). Furthermore, age ($p = 0.006$, HR=0.916, 95% CI 0.86–0.975) was another statistically significant predictor, with a higher recurrence rate in younger patients.

Discussion

This study shows a variation in clinical outcome for HER2 positive patients with small tumors in the North of Scotland. Patient receiving systemic treatment have significantly lower clinical events, especially in view of dying from breast cancer related causes. The Scottish Cancer Audit Registry collects healthcare data prospectively. However, our study was limited by the retrospective analysis and the lack of randomization between the patients receiving or not receiving trastuzumab. Nevertheless, the comparison of these non-tT and tT patient groups demonstrates real world clinical practice in the North of Scotland.

In our study 178 patients with T1a/b/c tumors with no nodal disease received adjuvant treatment (59.9% of all T1a/b/c) compared to the Finnish study[10], where only 5% of all T1a/b/c HER2 positive breast cancer patients were treated.

In contrast to the MD Anderson Cancer center Study, where none of T1a/b N0 HER2 positive breast cancer patients ($n = 98$) received adjuvant systemic therapy[11], we have treated comparable 45 (49.5%) patients with HER2 positive, lymph node negative, less than 10 mm breast cancer patients within our overall cohort.

Informed decision making between the patient and the clinician is guided by existing evidence. However, the majority of evidence is based on retrospective studies comparing the clinical outcome of T1a/bN0 HER negative patients with HER2 positive patients[10,12,13], the indication of increased HER2 expression alone as an independent

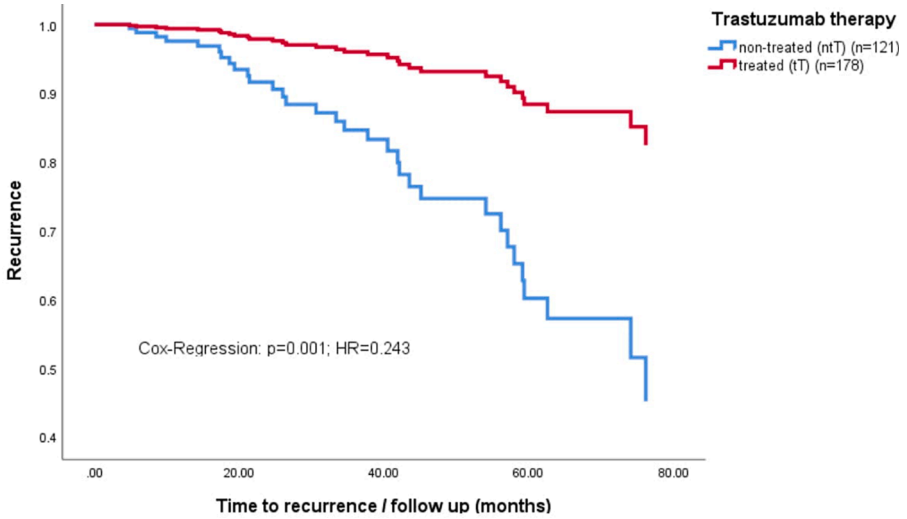

Fig. 1. Recurrence rate of treated vs untreated patients.

marker for poor prognosis[14] and retrospective subgroup analysis of larger randomized controlled anti-HER2 therapy trials[15,16]. All these studies indicate that small HER2 positive breast cancers have an increased risk of recurrence and may benefit from receiving systemic treatment.

Unique to our study is the comparison of systemic treatment versus non-treatment of consecutive small HER2 positive cases in three different health boards in the North of Scotland. Our sample size of all HER2 positive T1a/T1b cases is comparable with previous retrospective studies[10,11]. Reassuringly, one of our subgroup analyses demonstrated that there was no difference in treatment delivery between all three North Cancer Alliance health boards indicating a uniform approach across the North of Scotland.

In Tolaney's APT trial[8], 406 HER2 positive breast cancer patients were receiving adjuvant paclitaxel and trastuzumab. Only 9% of this cohort were T2 breast cancers with a maximum tumor size of up to 30 mm. This study demonstrated a 93% disease free survival rate after 7 years of follow-up. As expected our entire T1N0 only cohort achieved an excellent disease specific survival rate of 97.6% (tT 98.9% versus 95.5% non-tT). This disparity between the tT-group and non-tT group becomes greater with overall survival (tT 98.9% versus non-tT 87.5%). However, it needs to be acknowledged that the median follow-up in our cohort is currently only 2.6 years. Naturally this could leave concerns that not enough time has passed for clinic events to occur and to be comparable.

Nevertheless, it is of considerable concern and should be reported that, despite a relatively short follow-up time, a statistically significant higher rate of disease recurrence was observed in the not treated with trastuzumab (non-tT) cohort compared to the trastuzumab treated (tT) cohort. A 90.4% risk reduction for disease recurrence was demonstrated in our trastuzumab treated (tT) group.

Additionally it needs to be highlighted that the actual number of events in both groups is small. This is not surprising as these T1N0 breast cancers are classed as early stage.

Those not treated with trastuzumab (non-tT) were on average older with lower grade and smaller sized tumors and less lymph vascular invasion. Based on these clinical criteria this group could be classed as a lower risk group. Taking these more favorable tumor characteristics into account, our analysis still revealed a higher rate of disease recurrence in this non-tT group. Furthermore, we found that older age was a significant predictor of not receiving treatment. This, of course, could be as a consequence of the perceived toxicities from chemotherapy and those related to the cardio-toxic nature of trastuzumab as well as the underlying health issues of the older population. However, treatment with paclitaxel and trastuzumab has been shown to be well tolerated with a low risk of significant toxicity [17]. Nevertheless, caution needs to be raised to individualize treatment and to select older patients on their tumor biology and performance status rather numerical age. The International Longevity center UK published a report in 2019, citing that the evidence continues to suggest that ageist attitudes, both on the part of older patients themselves and on that of clinicians, may impact the rates of diagnosis and treatment received [18].

It has been noted that less radiotherapy was given in the non-tT patient group. This could be due to the higher percentage of older patients and proportionally more mastectomies than breast conserving procedures performed in this group. However, local radiotherapy should not influence distant disease recurrence events.

Small HER2 positive breast cancers are identified in the breast screening population; a cohort with asymptomatic disease deemed low risk. Under-treatment in this group could be detrimental. At present, data suggests that MammaPrint™ (70 gene assay) may identify a low (genomic) risk subgroup of HER2 positive (high clinical risk) breast cancers, who may not benefit from systemic treatment [19]. However, only small numbers of HER2 positive patients were incorporated into this study.

Within clinical practice, the online PREDICT prognostic tool is widely used in multidisciplinary meetings in the UK [20]. This incorporates influences on survival data. The majority of small HER2 positive breast cancers score a low percentage (<3%) with PREDICT Plus indicating a low survival advantage from systemic therapy but this does not quantify risk of cancer recurrence and need for subsequent therapies. Proportionally more G2 tumors were identified in the non-treated patients group. As tumor grading is an integral part of the NPI and the PREDICT model, less G2 tumors were considered for chemo-plus anti-HER2 therapy. Reflecting on the results of our analysis, further research is needed to determine if PREDICT provides accurate information to determine treatment outcome and whether a genomic assay should be incorporated into the model.

Conclusion

This study highlights the importance of individualized assessment and consideration of systemic therapy in women with small HER2 positive breast cancers to reduce their risk of disease recurrence. There is currently a lack of supporting evidence and a deficit of prognostic tools to accurately predict the benefit from systemic therapy for smaller HER2 positive breast cancer patients. Our evidence suggests that many still benefit from HER2 targeted systemic therapy.

Role of the funding source

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Ethics statement

All patients were selected from the Scottish North Cancer Alliance audit database. The Scottish North Cancer Alliance is a healthcare collaboration including NHS Grampian, NHS Highland and NHS Tayside. Caldicott approval from each health board was sought and granted.

CRediT authorship contribution statement

Karola Pawloy: Conceptualization, Software, Formal analysis, Investigation, Writing – original draft, Visualization. **Gordon Urquhart:** Conceptualization, Writing – review & editing, Funding acquisition. **Douglas Brown:** Resources. **Ian Daltrey:** Resources. **Feng-Yi Soh:** Resources. **Lesley Ann Anderson:** Validation. **Beatrix Elsberger:** Methodology, Data curation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

None to declare

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