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Human Epidermal Growth Factor-2 Receptor [HER2] Status in Patients Aged 70 years or more with Operable Early Breast Cancer — Multicentre Based Study with Review of 150 Cases

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ABSTRACT

Background: Breast cancer is the most common invasive cancer in females but often has more favourable tumour biology in the older age group. More than 30% of those diagnosed with breast cancer worldwide are aged ≥ 65 . Some report this percentage to be even higher, reaching up to more than 50% in developed countries that have a longer overall life expectancy.

Within this group, hormone receptor-positive and human epidermal growth factor-2 (HER-2) negative are the most favourable tumour biological patterns. In contrast, the triple-negative breast cancer group has the worst prognosis. Invasive breast cancers in younger age groups have a more poorly differentiated histological grade, more hormone receptor-negative status, a remarkable extent of lympho-vascular invasion and a greater expression/amplification of HER-2 than older age groups. HER-2 receptor is amplified and over-expressed in about 20–30% of invasive breast cancers within all age groups.

To analyse the status of HER-2 receptors early invasive breast cancer in relation to the histological subtype in the older age group.

Methods: The study group includes 150 patients with early breast cancer. The patho-morphological data and immune-histochemistry results of invasive cancer have been analysed, this included histology subtype, grade, oestrogen/progesterone receptor status as well as HER-2 expression.

Results: HER-2 expression was only seen in 17% of cases, it was seen mainly in Grade 3 cancers (9%), followed by Grade 2 (6%), with Grade 1 cancer accounting for only 1% of the study group.

Conclusions: Patients with breast cancer aged ≥ 70 are seen to have less aggressive biology and expression of HER-2 receptors.

Key words: breast cancer, HER-2 receptor, trastuzumab

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Introduction

Breast cancer is the most common cancer among females, accounting for one-third of female cancers, and is the second leading cancerous cause of death in women after lung cancer [1]. The risk of developing breast cancer in a woman aged ≥ 70 is much higher than in women aged below 70 years.

The estimated risk reaches 3.82% (1 in 26 women) at the age of 70, almost more than twice the risk of a 40-year old woman (1.47% or 1 in 62 women) [2].

HER-2 is a receptor for epidermal growth factor which stimulates different intracellular signal transduction pathways related to cell growth and differentiation control. HER-2 overexpression is detected in 20–30% of diagnosed invasive breast cancers and this is associat-

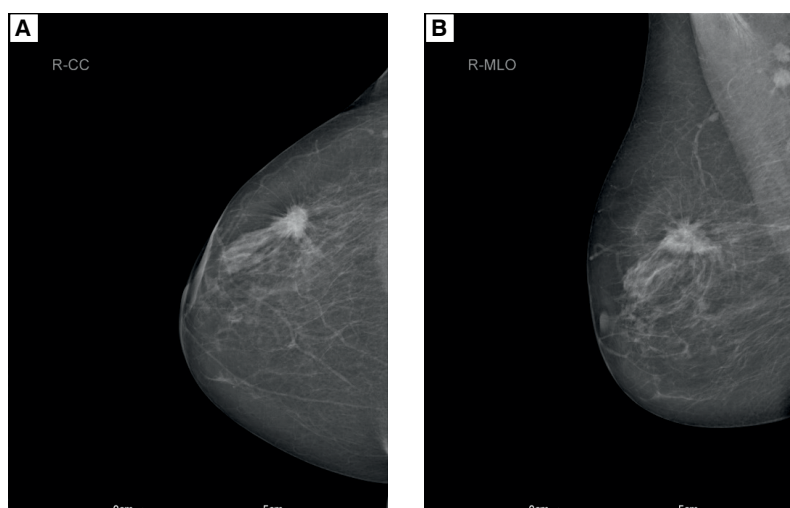


Figure 1. A — Mammogram — CC view; **B** — Mammogram — MLO view; Right mammogram — Spiculated mass lesion right UOQ measuring approximately 31 × 20 × 19 mm. Appearances are highly suspicious for malignancy. Prominent lymph nodes seen in the axilla, suspicious of metastatic disease

ed with aggressive tumour features, poor prognosis and an unfavourable outcome [3]. The aim of this paper is to analyse the status of HER-2 receptors early invasive breast cancer in relation to the histological subtype in the older age group.

Methods

Patients

A database of 150 patients aged ≥ 70 with early operable primary breast cancer has been analysed. The preoperative diagnosis was through triple assessment, including mammogram (Fig. 1) and histopathology. These patients had been managed at Basildon University Hospital (Essex-England) and Greater Poland Oncology Centre (Poznan, Poland). The treatment period was from 2011 to 2016. The patient information has been identified from the electronic records including demographic, clinical and histopathological details.

Immuno-histochemical analysis

The immuno-histochemical studies were performed by the local team in each hospital using local diagnostic techniques. Quick score (Q-Score) technique was used at Basildon University Hospital to examine oestrogen and progesterone receptor status. The final scores ranged between 0–8, where 0 was negative and 8 strongly positive. At the Poznan centre, oestrogen and progesterone receptor status was performed using immune-histochemistry on the core biopsy. If the histochemical score (H score) was 50% or more, the outcome was a positive result.

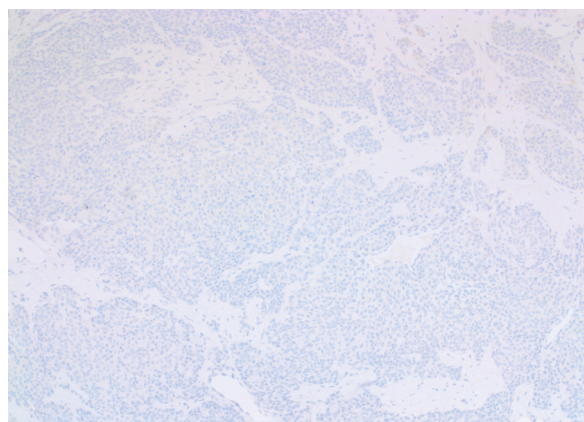


Figure 2. HER-2 negative invasive breast cancer

The technique to measure HER-2 protein uses an antibody which probes for HER-2 in tumour cells. Score (0) or (1+) were reported as negative (Fig. 2) and (3+) as positive [Figure 3]. The result was reported as borderline if the score was (2+). FISH test (Fluorescence In-Situ Hybridization) was used to measure HER-2 gene amplification in the tumour cells of borderline cases. When FISH score was ≥ 2 , the result was regarded as positive.

Results

The group was composed of 150 patients with an age range of 70–88 and a median age of 76. Grade 2 cancer was the most common among this group (53% of cases), followed by Grade 3 (23%) and Grade 1 (21%) (Tab. 1). HER-2 expression was only seen in

17% of cases (n = 25) (Fig. 4). HER-2 positive was seen mainly in Grade 3 cancers (9%), followed by Grade 2 (6%), with Grade 1 cancer accounting for only 1% of the study group (Fig. 5). Triple negative cancer was detected in just 10% (Tab. 1, Fig. 6).

Discussion

HER-2 is a cell membrane protein receptor mediated by the transmission of signals controlling normal cell growth and differentiation. In general, the number of existing HER-2 cell membrane receptors in normal cells is small (Fig. 7). When the number of HER-2 receptors is high, the cell signalling is stronger (Fig. 8), leading to amplified responsiveness to epidermal growth factors and carcinogenesis [4].

It has been reported that the incidence of breast carcinoma increases with age, with approximately 30% of new breast carcinoma cases being diagnosed in patients ≥ 70 [5]. Breast cancer in advanced age has different biological features and clinical behaviour. For example, elderly breast cancer often expresses remarkable positivity for oestrogen receptor (ER), lower histopathological grade, and HER-2 negative tumours [6–10]. The younger age groups tend to

have a more poorly differentiated histological grade, more hormone receptor negative status, a remarkable extent of lympho-vascular invasion and greater expression/amplification of HER-2. However, there is also data which reports that breast cancer is more aggressive in the elderly.

In 2008, Durbecq et al analysed the effect of ageing on the incidence of breast cancer molecular subtypes in 2723 breast cancer cases. The results showed almost 19% of older women had luminal B tumours. This group is more likely to present with a higher histopathological grade, larger tumour size, and increased predisposition to lymph node metastasis, despite being hormone receptor positive [11]. Recent studies indicate that the percentage of HER-2 positive cases amongst the older age group with breast cancer accounted for 10% to 20%, which is similar to the figures reported in the entire breast cancer population [12]. The data also suggests that tumour specific features should be used to assess the risk of relapse and to plan management. The age progression itself is associated with changes in biological breast structure and physiology, such as increased sensitivity to oestrogen hormone, epithelial

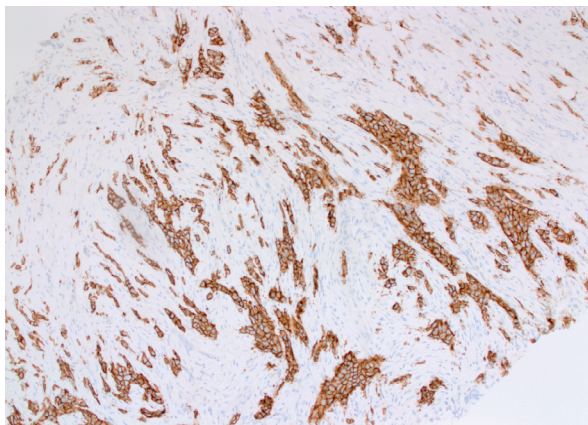


Figure 3. HER-2 positive invasive breast cancer

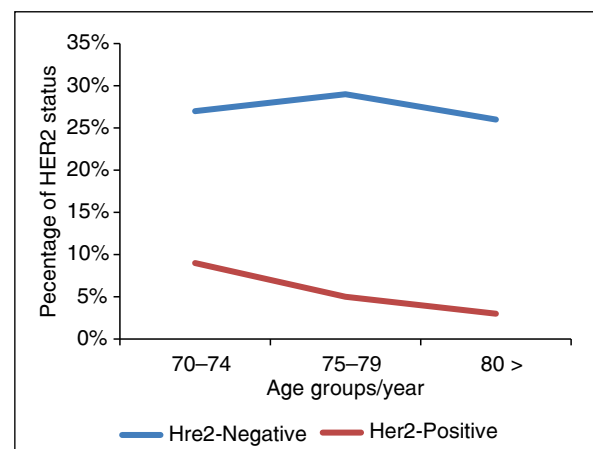


Figure 4. HER-2 status distribution pattern status in 150 breast cancer patients aged ≥ 70, operated on for early breast cancer

Table 1. HER-2 status in 150 breast cancer patients aged ≥ 70, operated on for early breast cancer

	Age	Grade I	Grade II	Grade III	Total
HER2 — Negative	70 –74	9 (6%)	25 (17%)	7 (5%)	41 (27%)
	75 –79	12 (8%)	24 (16%)	8 (5%)	44 (29%)
	80 >	9 (6%)	21 (14%)	10 (6%)	40 (26%)
HER2 — Positive	70 –74	2 (1%)	5 (3%)	6 (4%)	13 (9%)
	75 –79	0	3 (2%)	4 (3%)	7 (5%)
	80 >	0	2 (1%)	3 (2%)	5 (3%)
Total		32 (21%)	80 (53%)	38 (25%)	150 (100%)

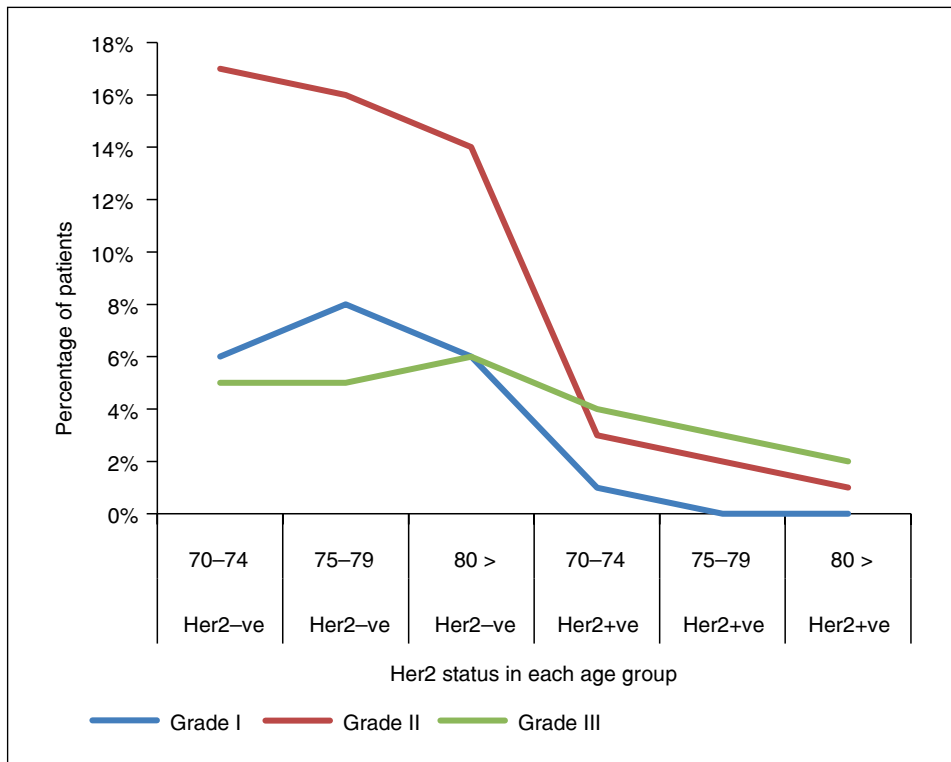


Figure 5. HER-2 receptor status in different tumour grades in 150 breast cancer patients aged ≥ 70 , operated on for early breast cancer

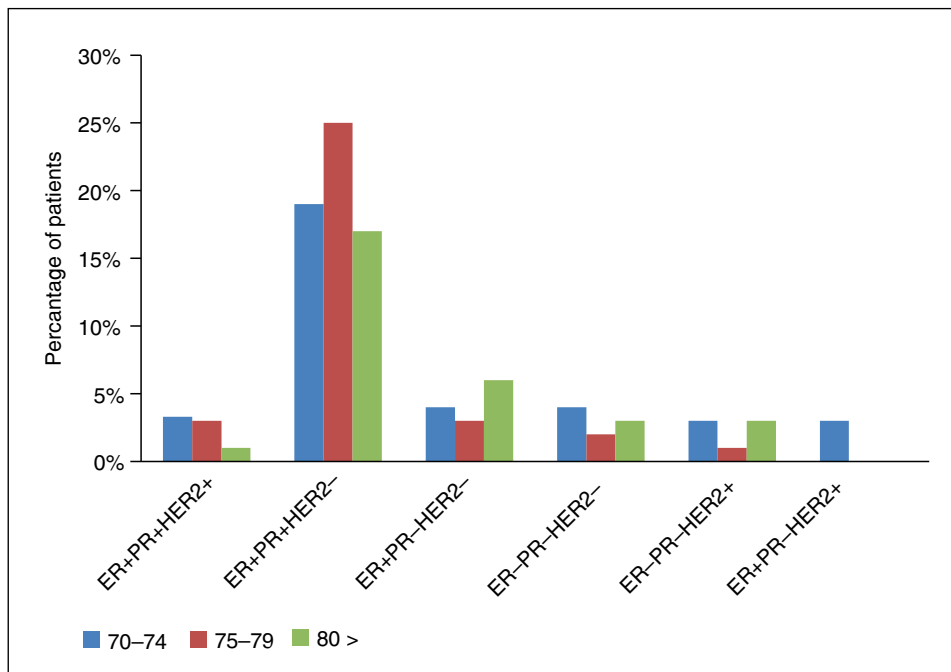


Figure 6. Receptor status in 150 breast cancer patients aged ≥ 70 , operated on for early breast cancer; ER — Oestrogen Receptor; PR — Progesterone Receptor; HER2 — Human Epidermal Growth Factor-2 Receptor

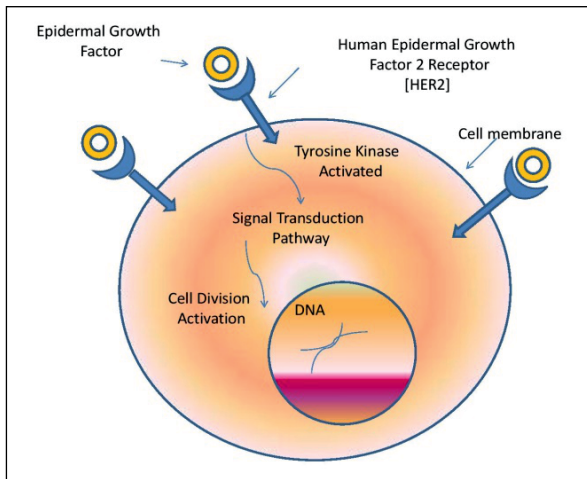


Figure 7. The normal number of Human Epidermal Growth Factor-2 Receptor (HER-2) in the cell

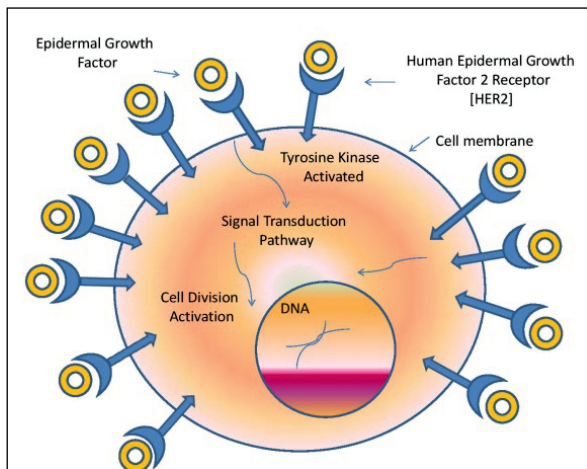


Figure 8. Over expression rate of Human Epidermal Growth Factor-2 Receptor (HER-2)

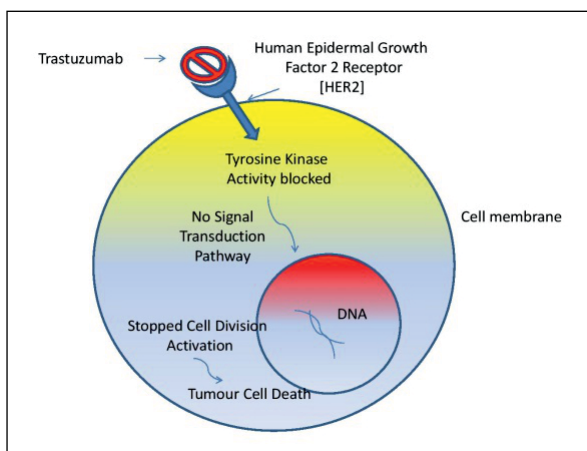


Figure 9. The monoclonal antibody Trastuzumab acting by blocking HER-2 receptors

cell alterations, immune senescence, and tumour microenvironment modifications. All of these factors could be related to an increased incidence of breast cancer and associated mortality [13].

A positive aspect of the disease is that many diagnosed breast cancer cases are at an early stage (non-metastatic), and can be classified as a potentially curable disease. Since the 1990s, the monoclonal antibody trastuzumab has greatly changed the treatment pattern and prognosis of human epidermal growth factor receptor-2 (HER-2) positive breast cancer. The trastuzumab attaches to the HER-2 receptor and prevents the human epidermal growth factor from attaching to the same site. This prevents cell proliferation and initiates tumour cell death (Fig. 9). Many HER-2 positive breast cancer patients have a good response to trastuzumab-based systemic therapy. This has been reported in long-term follow-up observations, where the overall survival in this patient group has improved by 37% [14–18].

When breast cancer systemic therapy was introduced, it did not have the same impact on the older age group as in younger age groups [12, 19–20]. The reason for this may have been that systemic therapy was less frequently given to the older age group, as the breast cancer was often less aggressive and showed positive expression for oestrogen hormone receptor and negative expression for human epidermal growth factor receptor-2 (HER-2). There were also concerns about toxicity related to adjuvant chemotherapy and trastuzumab use [21]. However, it is now agreed that age should not be the main driver in decision making for cancer therapy in the older age group; this is based on recent reports and observations [14, 22]. A holistic assessment for individual patient physiological reserve and quality of life following the intervention are needed to offer the most appropriate management option.

The mortality associated with older age group breast cancer can be explained by under-treatment, late diagnosis, and insufficient individual screening. Fit elderly breast cancer patients should be given a fair chance and offered treatment in the same way as their younger counterparts.

Conclusion

In conclusion, patients with breast cancer aged ≥ 70 are seen to have less aggressive biology and expression of HER-2 receptors. With the ageing population, there is an increase in the number of diagnosed women with breast cancer aged ≥ 70 years; treatment in this characteristic age group should be individualised to the tumour specific biological features and patient related factors. Elderly breast cancer patients should

be given the equal opportunity to be offered treatment in the same way as their younger counterparts.

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