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Original article

High estrogen receptor expression in early breast cancer: Chemotherapy needed to improve RFS?

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Abstract

Background:

One of the most controversial questions in early breast cancer treatment is the need of chemotherapy in patients with estrogen receptor positive disease. Therefore we analyzed a group of patients with high ER expression to scrutinize the role of chemotherapy in this situation. To gauge the effect of chemotherapy on RFS three treatment modalities were compared: endocrine treatment only, chemoendocrine treatment, and chemotherapy.

Patients and methods:

3971 breast cancer patients whose treatment modalities as well as ER level were known, were included in this retrospective analysis. Their level of ER expression was documented as IRS. A high ER group was defined as ER IRS ≥ 9 ; primary endpoint was RFS.

Results:

RFS was associated with ER, with the best outcome for strong and the worst result for negative expression. Adjusted to NPI, RFS did not differ between the treatment cohorts of endocrine treatment and chemoendocrine treatment ($p=0.828$) in the high ER group. Patients with chemotherapy alone fared significantly worse ($p=0.003$). Even in high risk patients (according to NPI) the chemoendocrine and the endocrine treatment only groups did not differ significantly (HR=1.15; 95% CI (0.56–2.34), $p=0.709$). Omission of endocrine treatment led to significantly worse outcome ($p=0.013$).

Conclusions:

RFS was significantly longer in patients with high ER expression than with weak or no ER expression. In the high expression group, there was no significant

difference in RFS between endocrine treatment only and chemoendocrine therapy – even in high risk patients, for whom chemoendocrine treatment is routinely indicated. It seems insufficient for high ER patients to only consider tumor size, nodal status, and grading in order to decide which patient will benefit from adding chemotherapy to endocrine treatment.

Key words:

Adjuvant chemotherapy, early breast cancer, endocrine treatment, estrogen receptor, immunoreactive score, quantitative hormone receptor expression

Introduction

The St Gallen consensus meeting in 2009 has proposed a treatment selection algorithm for the management of early breast cancer which is fundamentally different from that used in previous years [1]. The indications for the three treatment modalities – endocrine treatment (ET), anti-HER2 therapy and chemotherapy – are based on different criteria which need to be analysed separately for individual treatment decisions. One of the most urgent questions concerns the need of chemotherapy in estrogen receptor (ER) positive diseases [2-4].

The additional benefit of chemotherapy on top of ET is controversial and may be influenced by a variety of factors, the most important of which is the endocrine responsiveness of the tumor. The definition of the categories “highly endocrine responsive”, “incompletely endocrine responsive”, and “endocrine nonresponsive” relies mainly on the level of ER and PgR expression, but other factors such as grading, HER2/neu status, proliferation index, and levels of uPA/PAI1 also play an important role [1]. The cut point between the ER and PgR expression levels needed to define high endocrine responsiveness was according to St Gallen 2009 50% of positive tumor cells [1], a value chosen more or less arbitrarily.

We hypothesize that patients with highly endocrine responsive tumors may have only a minor or even no additional benefit by adding chemotherapy to ET. Retrospective analyses of prospective randomised trials [5-7], in which the benefit of chemotherapy decreased with increasing levels of ER/PgR expression have served to a high degree to support our hypothesis. In order to further address this issue we analyzed a group of patients with high ER expression as to the influence of the different treatment modalities of ET alone

versus chemoendocrine therapy versus chemotherapy alone. Our cohort – including 3971 patients – is part of the BRENDA project (breast cancer care under evidence-based guidelines), a large cohort study funded by the German Federal Ministry of Education and Research (BMBF).

Obviously retrospective observational studies have methodological caveats, the main problem being a selection or information bias and known as well as possibly unknown confounding factors [8]. While results are irreparably compromised by selection and information biases, confounding factors can be corrected by e.g. multivariate adjustment models. However, analysing “real life” cohorts has the advantage that effectiveness is tested in everyday practice with relatively unselected participants and under flexible conditions, whereas explanatory prospective randomized trials test efficacy in a research setting with highly selected participants and under highly controlled conditions [9,10]. We therefore believe that our results, since they have been derived from a large cohort study will help to answer the crucial question which ER positive patient will benefit from adding chemotherapy to ET.

Patients and Methods

Study Design

Within the BRENDA project (breast cancer care under evidence-based guidelines) funded by the BMBF a large clinical cancer register was established. Patients were diagnosed between 1992 and 2005 at the Department of Obstetrics and Gynecology, University of Ulm Medical Center, and affiliated breast cancer centers. This analysis included 3971 early breast cancer patients whose treatment modalities as well as ER immunoreactive score (IRS) levels were known. Baseline characteristics are shown in table 2.

The level of ER expression was documented as IRS. IRS is the product of a proportion score and an intensity score (table 1) with a range of 0-12. A high ER group was defined as ER IRS ≥ 9 .

Statistical analysis

The primary endpoint is recurrence free survival (RFS). Nominally scaled variables were tabulated in contingency tables and tested for differences in frequency distribution. Variables for location and variance were calculated whenever ordinally scaled and interally scaled continuous variables were involved. For each group we calculated numbers of cases, means, standard deviations, standard error of mean, minimum, maximum, 95% confidence interval [CI] for the mean, and medians. Levene's test for homogeneity of variance, analysis-of-variance tables and robust tests of the equality of means (medians) were similarly used. Normal distribution was tested using the Kolmogorov-Smirnov (K-S) goodness-of-fit test. In addition we also used the Anderson-Darling test and the Cramer-Smirnov-Von-Mises test, a modification of the K-S test giving more weight to the tails of the distribution. Standard survival analysis using a Kaplan-Meier approach was performed for assessing

RFS. Logrank test was used to provide a formal statistical assessment of the differences between treatment arms. Cox proportional hazards model was used to estimate the hazard ratio and confidence intervals. Comparisons of categorical variables between groups were made by using χ^2 tests.

In order to improve the internal validity we checked for selection bias, information bias and confounding factors. Results were adjusted by taking into account all measurable confounders and inhomogeneities in baseline status in the form of multivariate adjustment using the Cox proportional hazard regression method.

Results

We found the following distribution of levels of estrogen expression according to IRS: 27% negative, 7% weak, 26% intermediate, and 40% strong.

As described in table 2, the ER groups differ significantly in the clinical risk factors age, menopausal status, tumor size, nodal status, grading, and HER2/neu.

Recurrence free survival according to ER groups

As expected, RFS was associated with ER, with best outcome for strong and worst for negative expression (fig. 1). RFS for weak and negative expressions in relation to high expression was significantly worse (weak expression: HR=1.85; 95% CI (1.35–2.54), $p<0.001$; negative expression: HR=2.29; 95% CI (1.86–2.82), $p<0.001$; using logrank test). On the other hand, RFS for moderate in relation to high expression was not significantly worse (HR=1.23; 95% CI (0.97–1.56), $p=0.084$).

Outcome for patients with high ER expression according to adjuvant systemic treatment

We analysed the subgroup of patients with high ER expression (ER+, IRS ≥ 9 : $n=1595$ (40.2%)) with regard to the treatment modalities of chemoendocrine therapy (chemotherapy followed by ET) ($n=383$ (24.0%)), ET alone ($n=892$ (55.9%)) and chemotherapy alone ($n=51$ (3.2%)). 269 pts obtained either no or an unknown drug therapy.

Without adjustment to risk factors, RFS was significantly longer in patients with ET alone compared to chemoendocrine and chemotherapy alone (chemoendocrine vs. ET: HR=1.74; 95% CI (1.13–2.68), $p=0.012$; chemotherapy alone vs. ET: HR=3.52; 95% CI (1.95–6.35), $p<0.001$) (fig. 2A). After adjustment to standard prognostic factors (Nottingham prognostic index

(NPI), menopausal status, and HER2/neu), RFS did not differ between the groups with ET and chemoendocrine treatment (HR=1.05; 95% CI (0.67-1.65), p=0.828). However, patients treated with chemotherapy alone still fared significantly worse (HR=2.48; 95% CI (1.36-4.51), p=0.003) (fig. 2B).

The significant differences between the curves without and with adjustment reflect the fact that, due to the retrospective nature of the analysis, the treatment modality depends on the risk factors. Therefore these factors are not balanced between the treatment groups; i.e. patients with more risk factors are more likely to have received chemotherapy than patients with less risk factors.

The correlation that chemotherapy seems not to add any benefit to ET was shown for post- and premenopausal patients to a similar extent.

Nottingham prognostic index (NPI)

The high ER group was further analysed regarding NPI, which combines grading, nodal status, and tumor size. As expected, RFS curves differ significantly between the groups of low, intermediate, and high risk (intermediate vs. low: HR=2.33; 95% CI (1.41–3.84), p=0.001; high vs. low: HR=8.12; 95% CI (4.95–13.32), p<0.001) (fig. 3A).

We then analysed the NPI-groups separately according to treatment modalities. Even in the high risk group, ET alone showed the longest RFS. Chemoendocrine treatment did not differ significantly, and, as expected, the omission of ET led to significantly worse results (chemoendocrine vs. ET: HR=1.15; 95% CI (0.56–2.34), p=0.709; chemo vs. ET: HR=3.07; 95% CI (1.27–7.40), p=0.013) (fig. 3B).

The correlation described above - i.e. that chemotherapy seems to add no further benefit in high ER expression - was also found in the low and intermediate NPI groups.

Influence of the type of endocrine therapy

Tamoxifen or aromatase inhibitors were mainly used as ET. We included all patients who received aromatase inhibitors in this cohort, not distinguishing between upfront or sequential treatment and found no significant difference in the RFS of patients with high ER expression receiving either tamoxifen or aromatase inhibitors (data not shown).

Influence of the type of chemotherapy

Types of chemotherapy used in our cohort included mainly CMF, anthracycline or taxane containing regimens. Consequently we analysed the three main regimen types separately. CMF regimens were given to 25%, 49% received anthracycline containing regimens, and 26% taxane containing regimens. The survival curves showed the same pattern, regardless of the type of chemotherapy in the high ER group (see fig. 4) as was shown for chemotherapy as a whole cohort (fig. 2B). Thus fig. 4 - showing RFS for the high ER group stratified for ET, and taxane-endocrine treatment - can serve as an example for all chemotherapy groups. As described above in fig. 2B in which all chemotherapies are included, the RFS curves for ET only and taxane containing chemotherapy followed by ET are not separated.

Discussion

It has by now been widely accepted that the merely dichotomous reporting of ER and/or PgR status as positive resp. negative is oversimplified and thus the categories of “highly endocrine responsive”, “incompletely endocrine responsive”, and “endocrine nonresponsive” have been introduced [11, 1]. Although their definition relies mainly on the level of ER and PgR expression, other factors such as grading, HER2/neu status, proliferation index, and levels of uPA/PAI1, also play an important role. Thus the controversy about which HR positive patient will benefit from adding chemotherapy to ET, so important in clinical practice, comes more and more into research focus, too. In this analysis we have tried to define the role of chemotherapy in a group of patients with high ER expression measured by classical immunohistological ways.

As previously described, we found an association between the level of HR expression and outcome in early breast cancer. ER status has been used for decades as a predictive marker for the response to ET in all clinical indications and for all commonly used endocrine substances [12-15]. A moderate prognostic value has been described previously in patients not receiving any type of systemic therapy [16].

In this analysis, we have focused on the population of patients with a high expression of ER. The definition of high HR expression is not uniform. The St Gallen experts stated that a count of $\geq 50\%$ of positive tumor cells should be considered highly endocrine-responsive [1]. Other studies derived from the definition of the Allred-Score [17] have defined high expression as $\geq 33\%$ of positive cells, and still others even as $\geq 80\%$ [18].

The historically accepted scoring systems are using not only the percentage of positive cells but also staining intensity [19, 20]. The Allred score, widely used in

the USA, is calculated by summing staining intensity (0–3) and the percentage score (0–5) receiving values from 0–8 [21]. The Remmele score, widely used in Germany, is calculated by multiplying staining intensity (0-3) and percentage score (0–4) receiving values from 0–12 [22, 23]. The Remmele Score has two major limitations. Due to the calculation by multiplication valid values are not continuous. This is not in accordance with the fact that HR expression is a continuous biological variable ranging from no expression in any tumor cell to high expression in all tumor cells. The second limitation of the score is that the interpretation was not used uniformly. In the original work neither a cut-off value to define positive vs. negative expression nor a definition of high expression was given [22]. As the interpretations of the results thus differ remarkably, we have used the most common classification (see table 1). An IRS of 9 and higher defining the group of high ER expression in this analysis corresponds to at least 50% positive cells with a strong staining intensity.

The impact of quantitative measurement of ER expression as a prognostic and predictive test was analysed in various settings [5, 24-28]. For example in adjuvant patients DFS was significantly longer in patients with high ER levels (>10% positive cells) than in those with lower (1-10%) and negative (absent) expression [24]. This was also shown in a subgroup of the ATAC-trial population, who showed a significant relationship between ER level and time to recurrence [25]. Paik et al [26] described a significant test for the interaction of tamoxifen treatment and ER expression indicating that quantitative ER expression predicts benefit from tamoxifen treatment. The largest benefits of tamoxifen were observed with high quantitative ER.

Elledge et al [17] described a significant positive correlation of increasing ER levels and outcome in tamoxifen treated patients with metastatic breast cancer.

Conflicting results were described in a subgroup of patients from the PO25 trial comparing letrozole vs. tamoxifen in advanced breast cancer [29]. No correlation was found between the ER expression level and TTP, neither in letrozole nor in tamoxifen treated patients. However, there was a significant effect of PgR expression (negative vs low vs high) on TTP in both treatment arms.

Our finding that adding chemotherapy to tamoxifen in patients with high HR expression shows no additional benefit corresponds to findings by Viale et al [6]. Also retrospective analyses of adjuvant and neoadjuvant trials have shown a decreasing chemotherapy efficacy with increasing HR levels [5,7].

In our patient population the group of patients with high expression of ER has not proved an additional benefit from adding chemotherapy to ET. This holds true for all risk groups according to NPI, even for high risk patients. To our knowledge all treatment guidelines recommend chemotherapy to NPI high risk patients. The recent St Gallen recommendations differentiate indications for chemoendocrine therapy in patients with ER positive, HER2 negative disease [1]. Certain clinicopathological features such as ER/PgR, grading, proliferation index, nodal status, peritumoral vascular invasion, and tumor size, which together define the categories of “highly endocrine responsive”, “incompletely endocrine responsive”, and “endocrine nonresponsive”, need to be considered for treatment decisions. Our data supports this and might be used as additional information in the controversy over the need for chemotherapy in patients with high HR expression, even in high risk patients.

We also analysed the impact of the type of ET and of chemotherapy. We did not find a significant difference between tamoxifen and AI. For the chemotherapy groups we found the same RFS patterns regardless of the types of

chemotherapy. Even for taxane containing regimens, which are widely recognised as the most potent chemotherapy regimens up to now [30, 31], we did not find an additional benefit compared to ET alone. This is contradictory to the findings that the risk reduction effect due to taxanes was almost identical in HR negative and positive patients [2,18]. Other adjuvant or preoperative studies however, have found significant differences in the extent of the chemotherapy effect according to HR [32-35].

Recently gene expression profiles have been developed to analyse the individual recurrence risk in order to individualise adjuvant breast cancer treatment [36-39]. For example, the 21-gene panel [40] includes mainly genes involved in tumor cell proliferation and hormonal response. The score was developed in node negative, tamoxifen-treated patients [40] to predict the recurrence risk in these low risk patients. Paik et al then showed that the recurrence score (RS) also predicts the likelihood of benefit from chemotherapy [41]. Patients with high-RS tumors (i.e. high risk of recurrence) had a large benefit from chemotherapy; patients with low-RS tumors derived minimal if any benefit from chemotherapy. Similar results have recently been published [42-44].

There is a lively debate about the additional predictive value of these multi gene arrays to classical clinical, histopathological, and immunohistological parameters. It has been shown that the combination of classical parameters and RS has increased the prognostic power to define the risk of patients [43, 45]. We believe that the integration of quantitative HR expression into the treatment decision will help towards optimising this crucial decision.

Our data derives from a clinical cancer register and not from a trial population, with all the inherent advantages and disadvantages. The major problem is the

presence of known and possibly unknown confounding factors affecting both treatment and outcome (cp. fig. 2A and 2B). Therefore, in order to come as close as possible to the clinically most relevant subject-specific measure of treatment effect, we adjusted our results to the most important prognostic covariates. The three main reasons why we used covariate adjustment methods are the following: First, to correct for imbalances in baseline prognostic covariates; second, to increase power by modelling the variability in outcome explained by relationships with highly prognostic covariates, and third, to obtain treatment effect estimates that would be more closely relevant for individual patients than to an average population [46-48].

The interpretation of observational study data in regard to causality should be carried out with great caution [8]. The Hills criteria of causation (strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence with existing knowledge, evidence, and analogy) outline the minimal conditions needed to establish a causal relationship between two items. Since the Hills criteria of causation – even if met, as in our case – cannot bring indisputable evidence for or against a cause-and-effect hypothesis and none can be required as a *sine qua non*, we can only derive associations, and not causality, from our results.

We believe that reviewing the role of chemotherapy in ER high expressing patients is a very important issue, especially since this subgroup is the largest group of patients with HR positive diseases, representing approximately 40% of all breast cancer patients. Our findings of no significant difference between ET and chemoendocrine treatment in ER high expressing patients indicates that using the clinical routine parameters of tumor size, nodal status and grading is not sufficient for the crucial treatment decision of ET vs. chemoendocrine in

these patients. Whether the recurrence score derived from multiple gene arrays or parameters like Ki-67 are helpful for this decision is open to further discussion. We are confident that further individualisation of adjuvant treatment by means of modern multi-gene arrays as well as classical clinical and histopathological methods will help to maximise efficacy and minimise unnecessary toxicity.

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Figure legends

Fig. 1: Recurrence free survival stratified for ER IRS groups.

Fig. 2: Recurrence free survival of patients with high expression of ER stratified for endocrine treatment, chemoendocrine treatment, and chemotherapy without (A) and with adjustment (B) to prognostic factors (NPI, menopausal status, and HER2/neu).

Fig. 3: Recurrence free survival of patients with high expression of ER stratified for Nottingham prognostic index (NPI) (A). Recurrence free survival of high-risk (NPI) patients with high expression of ER stratified for endocrine treatment, chemoendocrine treatment, and chemotherapy and adjusted to HER2/neu (B).

Fig. 4: Recurrence free survival of patients with high expression of ER stratified for endocrine treatment, and taxane-endocrine therapy, adjusted to NPI, menopausal status, and HER2/neu.

Tables

Table 1: Calculation of IRS: Proportion and intensity score

proportion	staining intensity	proportion score (PS)/ intensity score (IS)
0%	negative	0
< 10 %	weak	1
10 % - 50 %	intermediate	2
51 % - 80 %	strong	3
> 80 %	-	4
Interpretation (PS * IS)		
0-1	negative	
2-3	positive: weak	
4-8	positive: moderate	
9-12	positive: strong	

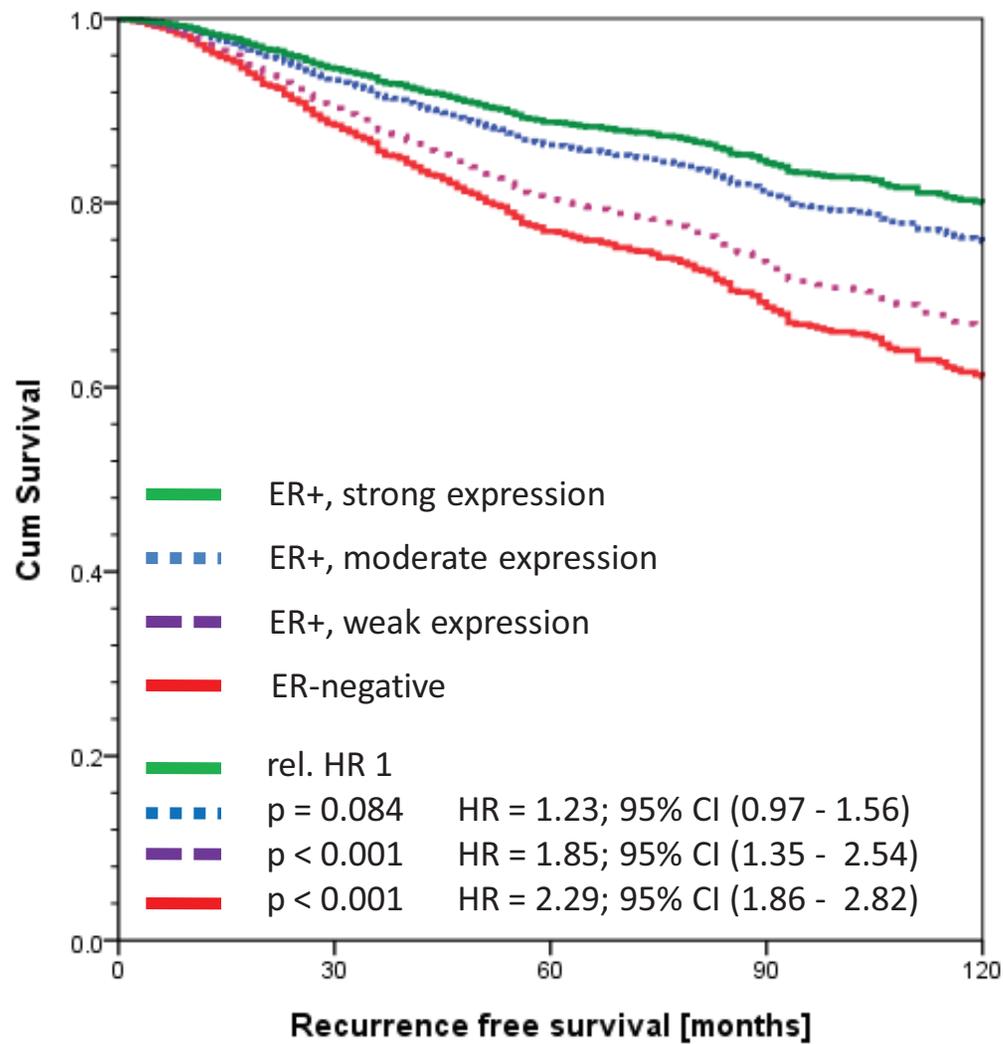
Table 2: Baseline characteristics

		Total	ER-Expression			Chi-Square
			negative	weak or moderate	high	
			(0-1)	(2-8)	(9-12)	
		N (%)	N (%)	N (%)	N (%)	(Sig)
Patients		3971 (100)	1079 (27.2)	1297 (32.6)	1595 (40.2)	
Age	Median (Mean; std)	61 (60.5; 13.1)	57 (57.1;13.4)	58 (58.3;12.7)	65 (64.6; 12.1)	
	Range	22-101	28-95	24-101	22-97	
Age categories	<35	59 (1.5)	24 (2.2)	22 (1.7)	13 (0.8)	< 0.001
	35-55	1365 (34.4)	483 (44.8)	543 (41.9)	339 (21.3)	
	56-75	1975 (49.7)	456 (42.3)	598 (46.1)	921 (57.7)	
	>75	572 (14.4)	116 (10.8)	134 (10.3)	322 (20.2)	
Menopausal status	unknown	185 (4.7)	55 (5.1)	79 (6.1)	51 (3.2)	< 0.001
	premenopausal	903 (22.7)	344 (31.9)	369 (28.5)	190 (11.9)	
	postmenopausal	2883 (72.6)	680 (63.0)	849 (65.5)	1354 (84.9)	
Tumor size	T1	2024 (52.8)	480 (46.6)	705 (56.0)	839 (54.4)	< 0.001
	T2	1377 (36.0)	433 (42.0)	411 (32.7)	533 (34.6)	
	T3	178 (4.6)	60 (5.8)	50 (4.0)	68 (4.4)	
	T4	251 (6.6)	57 (5.5)	92 (7.3)	102 (6.6)	
Nodal status	unknown	79 (2.0)	24 (2.2)	20 (1.5)	35 (2.2)	0.008
	nodal negative	2264 (57.3)	629 (58.5)	735 (56.8)	900 (56.8)	
	1-3	882 (22.3)	201 (18.7)	310 (24.0)	371 (23.4)	
	4-10	486 (12.3)	136 (12.7)	150 (11.6)	200 (12.6)	
	>10	242 (6.1)	85 (7.9)	78 (6.0)	79 (5.0)	
Grading	unknown	45 (1.1)	22 (2.0)	15 (1.2)	8 (0.5)	< 0.001
	1	268 (6.7)	40 (3.7)	111 (8.6)	117 (7.3)	
	2	2271 (57.2)	336 (31.1)	814 (62.8)	1121 (70.3)	
	3	1387 (34.9)	681 (63.1)	357 (27.5)	349 (21.9)	
HER2/neu	unknown	614 (15.5)	175(16.2)	220 (17.0)	219 (13.7)	

status	negative	2809 (70.7)	627(58.1)	934 (72.0)	1248 (78.2)	< 0.001
	positive	548 (13.8)	277(25.7)	143 (11.0)	128 (8.0)	
NPI	missing	141 (3.6)	49 (4.5)	39 (3.0)	53 (3.3)	< 0.001
	low	1193 (30.0)	180 (16.7)	447 (34.5)	566 (35.5)	
	intermediate	1819 (45.8)	565 (52.4)	567 (43.7)	687 (43.1)	
	high	818 (20.6)	285 (26.4)	244 (18.8)	289 (18.1)	
Systemic Therapy	Endocrine therapy	1550 (39.0)	80 (7.4)	578 (44.6)	892 (55.9)	< 0.001
	Chemotherapy	423 (10.7)	300 (27.8)	72 (5.6)	51 (3.2)	
	Endocrine and chemotherapy	913 (23.0)	107 (9.9)	423 (32.6)	383 (24.0)	
	others	1085 (27.3)	592 (54.9)	224 (17.3)	269 (16.9)	
Chemotherapy	All	1844 (100.0)	666 (36.1)	581 (31.5)	597 (32.4)	< 0.001
	CMF	467 (25.3)	196 (26.1)	151 (25.9)	120 (23.5)	
	Taxane-containing therapy	481 (26.1)	169 (22.5)	163 (28.0)	149 (29.1)	
	Anthracycline-containing therapy	896 (48.6)	386 (51.4)	268 (46.1)	242 (47.4)	

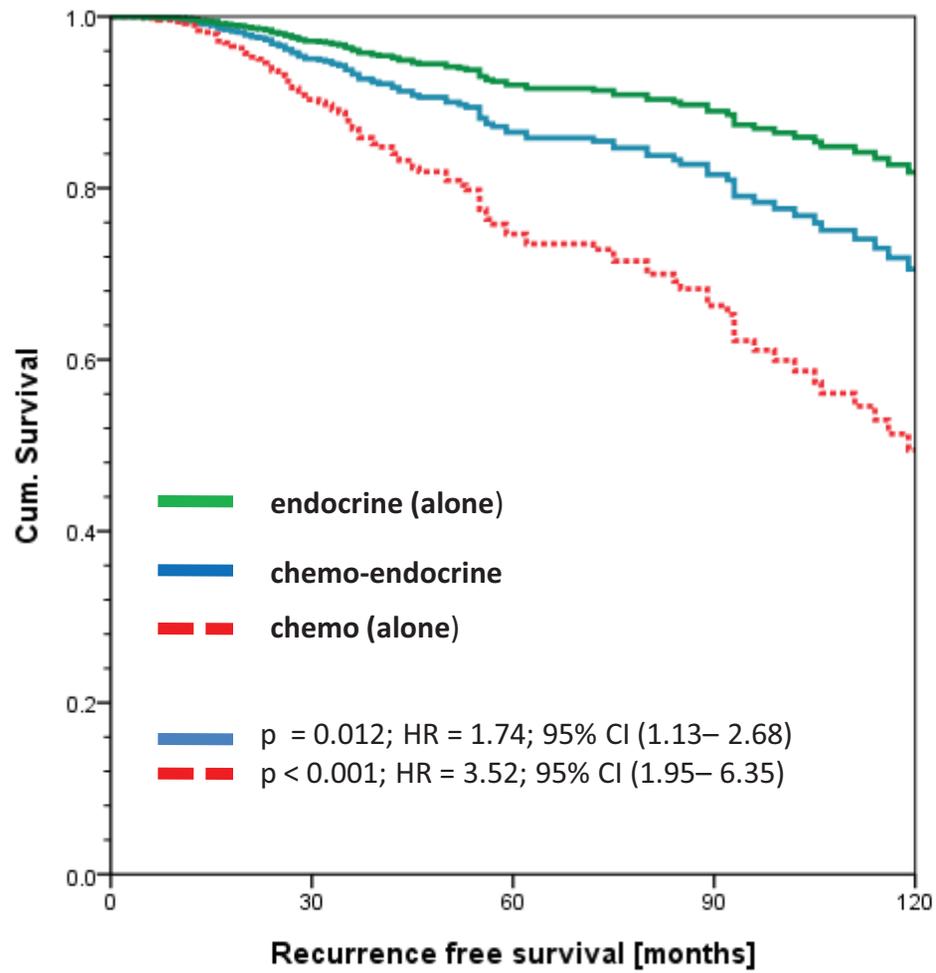
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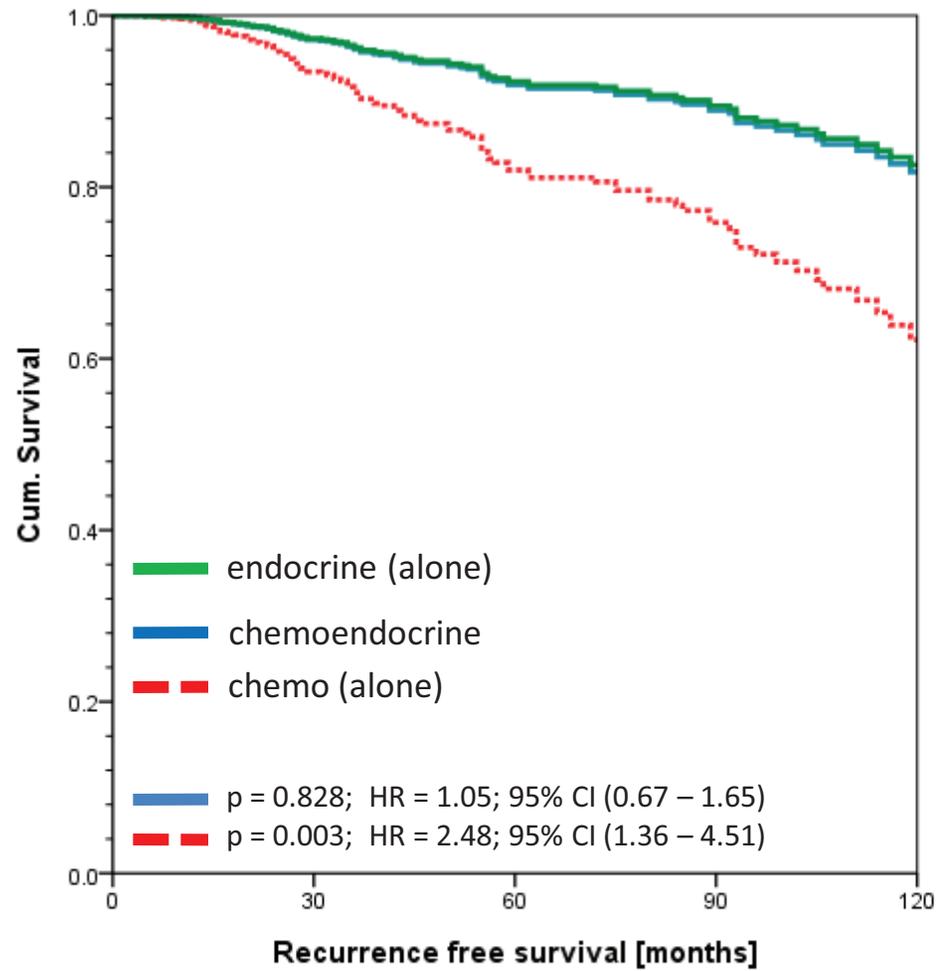
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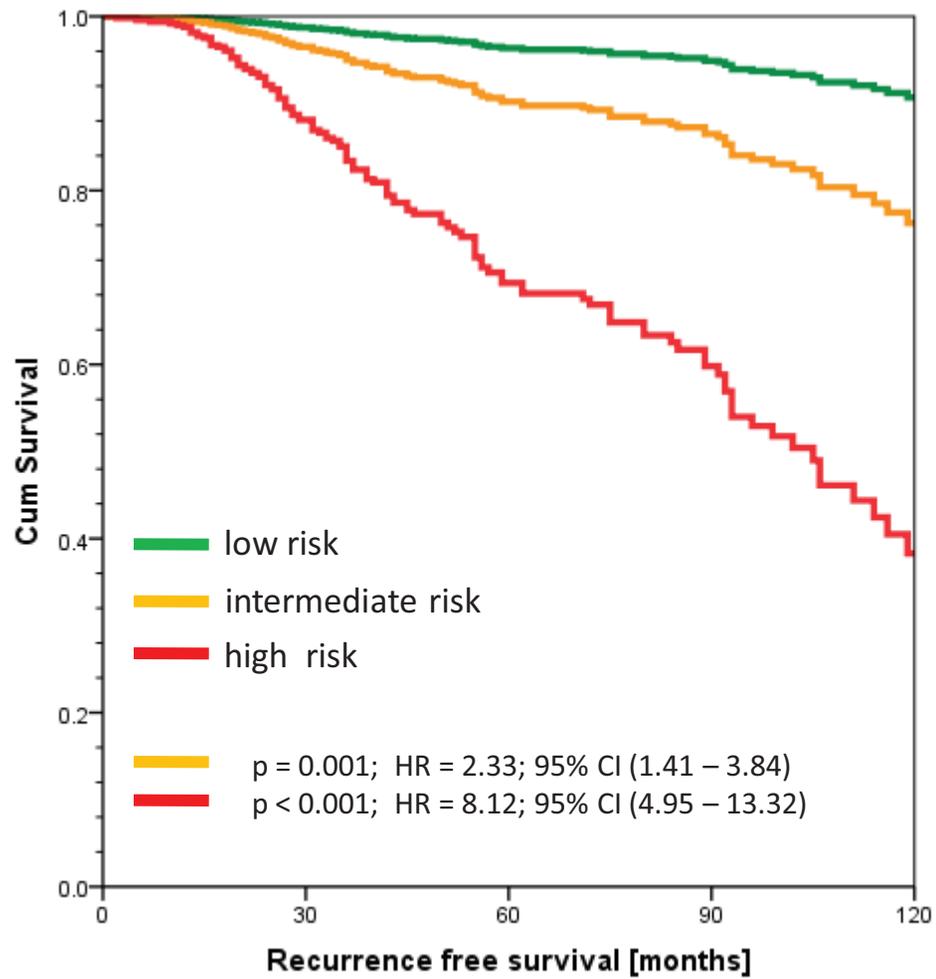
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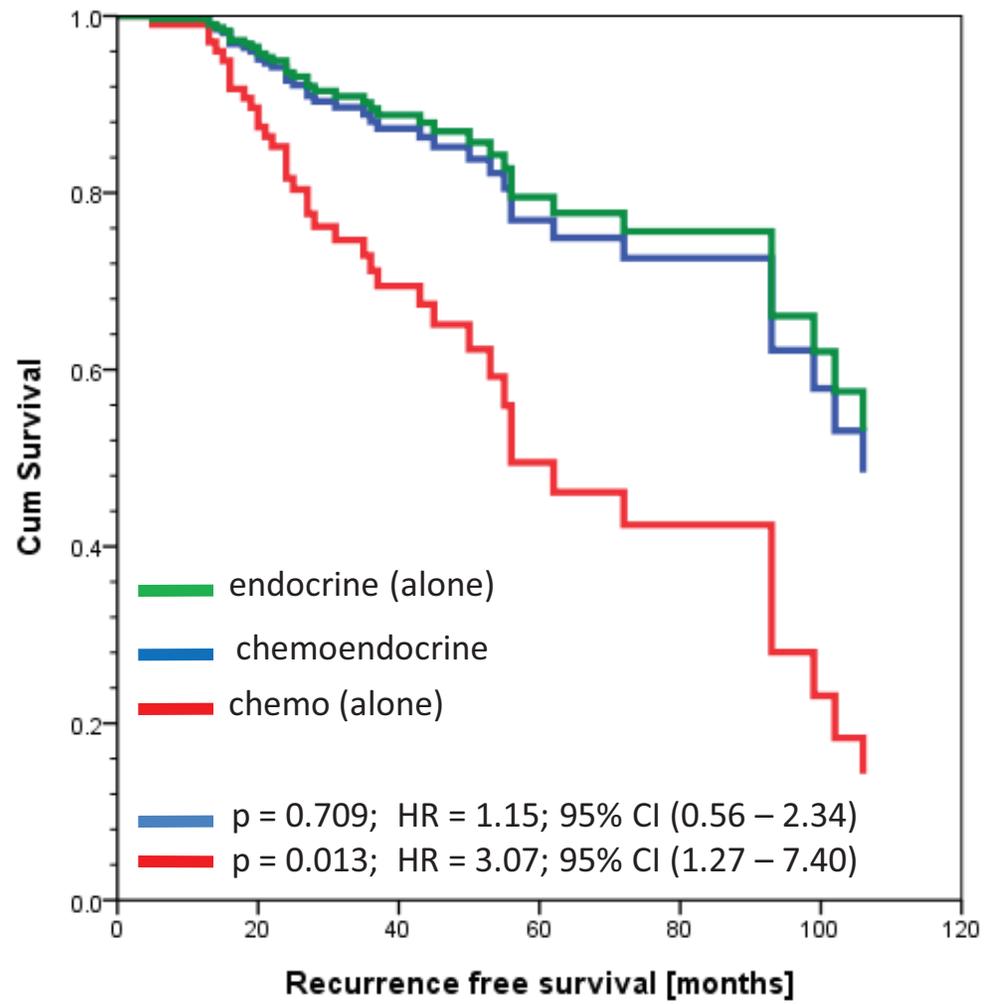
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