Recurrence of HEr2+ pAtients: evaluation of Long term outcome In patients receiving trastuzumab TherapY

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Abstract

Background Despite improved prognosis of HER2+ eBC since the introduction of trastuzumab in the adjuvant setting in 2006, disease recurrences still occur in some patients after a few years. We aimed to describe in real life the long-term follow-up to assess disease-free and metastasis-free survival of patients with HER2+ eBC treated with adjuvant trastuzumab. Methods This was a multicenter, retrospective, cohort study assessing HER2+ eBC patients diagnosed between 2009 and 2010 and treated with adjuvant trastuzumab. Data were collected from patient's medical charts. Disease-free survival (DFS), and metastatic-free survival (MFS) were evaluated in the overall population and within subgroups according to hormonal and nodal status. Results In the overall population (n=2,311) at 7 years, the DFS rate was 76.3% [95%CI 74.5%-78.2%], and the MFS rate was 84.2% [82.6%-85.8%]. According to hormonal status, the 7-year DFS rate was significantly higher in hormone-receptor positive (HR+) than hormone-negative (HR-) patients [80.5% vs . 69.2%; p <0.001], and the 7-year MFS rate [88.0% for HR+ vs . 77.7% HR-]. According to nodal status, the 7-year DFS rate was significantly higher for N- than for N+ patients [87.2% vs . 66.8%; p <0.001], and the 7-year MFS rate [94.7% for N- vs . 74.9% for N+; p <0.001]. Conclusions Despite introduction of adjuvant trastuzumab, prognosis of HER2+ eBC is still a matter above all in subgroups associated with a higher risk of disease recurrence. Our real-world study pointed out a particularly aggressive profile of N+ and HR- subgroups and the need for more efficient approaches for these particular group of patients.

Background

In breast cancer, Human Epidermal Growth Factor Receptor-2 (HER2) overexpression is independently associated with aggressive disease, poorer DFS and OS compared with tumors that do not overexpress HER2 [1,2]. The current standard treatment of patients with HER2-positive (HER2+) breast cancer involves chemotherapy combined with the HER2-targeted monoclonal antibody trastuzumab, followed by trastuzumab continued for a full year. Trastuzumab was approved approximately two decades ago for the treatment of patients with HER2+ positive metastatic breast cancer by the Federal food and Drug Administration and the European Medicines Agency (EMA) and in early breast cancer (eBC) in 2006 [3]. In eBC, the approval was based on the results of the early analyses of the large, international, open-label, multicenter, randomized phase III HERA (HERceptin Adjuvant) study, designed to compare one year of three-weekly trastuzumab (n=1694) to observation (n=1693) following surgery, established chemotherapy and radiotherapy in patients with HER2+ eBC. Trastuzumab significantly improved DFS recurrence-free survival and distant disease-free survival [4].

Other international, randomized, controlled phase III trials in the adjuvant setting (NSABP B-31, NCCTG N9831), confirmed the survival advantage conferred by the addition of trastuzumab to chemotherapy regimens in HER2+ eBC [5-7].

Long-term results of the HERA study after 11 years of median follow-up showed that adding a 1-year trastuzumab treatment to standard chemotherapy in HER2+ eBC led to an absolute gain of 6.8%

improvement in 10-year DFS compared to the observation group [HR= 0.76, 95% CI 0.68-0.87]. This benefit was observed even though 52% of the patients in the observation group crossed over and received trastuzumab after publication of the initial results [8]. These results also indicate that some patients are more prone to long-term recurrence than other patients.

Subgroups analyses of DFS showed differences. In the 1-year trastuzumab cohort, DFS at 10 years was greater in hormone-receptor positive (HR+) than hormone-negative (HR-) patients (72% *versus* 67%). In the same cohort, differences were even more marked when looking at nodal involvement. In the node negative subgroup (N-), DFS at 10 years was 80%, compared to 75% in the 1-3 positive nodes (N+) subgroup and 55% in the 4 or more N+ subgroup.

These results did not question the undisputable benefit of adding trastuzumab but brings to attention the need for improved DFS in specific subgroups associated with a higher risk of disease recurrence, notably HR- and N+. This consequently led to the conduct several phase III randomized clinical trials such as ALTTO assessing adjuvant lapatinib and trastuzumab for early HER 2 + eBC [9] and APHINITY assessing adjuvant pertuzumab and trastuzumab in HER2+ eBC [10] aiming to find new ways to improve DFS.

Even though trastuzumab was used in France as early as October 2005 in the adjuvant treatment of patients with HER2+ eBC, owing to a temporary use authorization granted by the French healthcare authorities prior to the EMA approval, there are no long-term RW data available for trastuzumab as adjuvant eBC in France. This retrospective observational cohort study was carried out to collect long-term outcomes data and particularly to assess DFS and MFS in the HR- and N+ subgroups.

Methods

This observational, multicenter, retrospective chart review study was conducted in a cohort of patients diagnosed with HER2+ eBC, between 1st January 2009 and 31th December 2010 and treated with adjuvant trastuzumab. Participating centers were selected among the 200 centers that prescribed 87% of adjuvant trastuzumab in HER2+ eBC in France in 2010 [11]. These centers were selected to be representative in terms of hospital setting and region. As control quality parameter, each center needed to treat at least 15 patients *per* year.

Eligible patients had to be ≥18 years old, presenting with a diagnosis of HER2+ eBC (non-metastatic) occurring between 1 January 2009 and 31 December 2010 and treated with at least one infusion of adjuvant trastuzumab regardless of the duration of the treatment. Hormonal status and regional lymph nodes involvement had to be documented at diagnosis. HER2 overexpression was defined as either 3+ by IHC and/or positive *in situ* hybridization testing according to local guidelines Patients who received a neo-adjuvant treatment (regardless of the composition of this treatment) and male patients with breast cancer were excluded from the study.

A standardized one-page case report form was used for collecting data from patient medical charts. Data included patient's characteristics (age, menopausal status), clinical profile (tumor size and nodal status)

at diagnosis and anti-tumor adjuvant treatments (chemotherapy and/or radiotherapy and/or endocrine therapy). Patients' status and events occurring before or on 31th December2017 were collected.

The primary endpoint was disease-free survival in the overall population and within subgroups according to hormonal and nodal status. Disease-free survival was defined as the time elapsed from the first trastuzumab administration to the first occurrence of any of the following events: recurrence of breast cancer at any site (local, regional or metastatic), contralateral breast cancer, development of a second non-breast cancer, death from any cause,

Secondary endpoints included patients and disease characteristics overall and according to hormonal (HR+/HR-) and nodal (N+/N-) status, the characterization of the type of recurrence, including the localization of the distant metastases if any, and the assessment of the metastasis-free survival of the patients.

The study protocol was submitted and approved by the INDS (Institut National des Données de Santé/National Institute for Health Data) based on a standardized methodology for a retrospective study (MR003/not requiring patient consent) and was submitted to the CNIL (Commission Nationale de l'Informatique et des Libertés/French data protection authority) which authorized the data processing of the study (agreement ID: DR-2018-072).

Statistical analysis

Statistical analyzes were mainly descriptive and exploratory using basic summary statistics. Continuous data were described as means (+/- standard deviation), median [range: minimum and maximum]. Nominal data, including some categories of continuous data, are presented in frequency tables.

Comparisons between subgroups were conducted using two types of bilateral tests (Chi-square test or Student's test). A significant difference was considered for a p-value $\leq$ 5%. No multivariate testing was performed.

Disease-free survival and metastasis-free survival (MFS) were assessed using the Kaplan-Meier method. The reference dates used to determine DFS and MFS were the date of the first trastuzumab administration to the date of the first event diagnosis (regardless of the site of recurrence for DFS and any distant recurrence for MFS). For each time point, the cumulative probabilities of disease recurrence were calculated as follows: 100 minus the DFS or MFS rate.

Data were analyzed by Kantar Health France using COSI software version 4.7.1. build 2 (MLI, Bourg-en-Bresse, France) for descriptive analyses and the R software version 3.0.2 (Foundation for Statistical Computing, Vienna, Austria) for Kaplan-Meier analyses.

Results

A total of 147 centers were contacted and about half of them participated in the study between May and July 2018. Among the 76 centers, offering a good representativeness, 27 (36%) were private clinics, 20 (26%) were public non-university hospitals, 17 (22%) were university hospitals and 12 (16%) were comprehensive cancer centers. The primary reason for refusal to participate in the study for the 71 centers was related to the impossibility or difficulty of ensuring the accrual of cases meeting the inclusion criteria.

A total of 2,524 patients were included in the study. Eleven patients were excluded from the analysis, 3 because they had received a neo-adjuvant treatment, 7 had undocumented lymph nodes status at diagnosis and 1 had missing follow-up information. Furthermore, a total of 202 were excluded from analysis, including those who did not received the standard treatment duration with trastuzumab (12 months) and who did not relapse during this 12 months period. This was done to have comparable exposure to trastuzumab between patients and to allow a direct comparison with clinical trials. Therefore, the final analysis was performed on 2,311 cases.

Overall, 62.8% (1,451) of patients had HR+ tumor (ER+ and/or PgR+) and 37.2% (860) had HR- disease.

A total of 1,091 (47.2%) patients had no lymph node involvement and 894 (38.7%) patients had 1 to 3 lymph nodes invaded, 326 patients (14.1%) had ≥4 or more positive lymph nodes, for a total of 1,220 patients (52.8%) with N + cancer (Table 1).

Regardless of hormonal and nodal status, almost all patients received chemotherapy and adjuvant radiation (Table 2). Almost all HR+ patients (98.5%) received adjuvant endocrine therapy, mostly aromatase inhibitor only (60.4%), anti-estrogen only (27.1%) or a sequence of anti-estrogen followed by aromatase inhibitor (12.0%).

More N+ patients received a combination of anthracyclines + taxanes than N- patients (83.0% *vs*. 69.1%; p <0.001) and had a radiation (97.2% *vs*. 92.2%; p <0.001). Conversely, more N- patients were treated with taxanes without anthracyclines than N- patients (24.7% *vs*. 13.8%).

DFS and MFS results for the overall population and for each subgroup (HR+/HR-, N+/N-), according to the number of positive nodes (1-3 *vs*. ≥ 4) and according to the combination of nodal and hormonal status (N-HR+, N-HR-, N+HR+, N+HR-) are shown in Table 4, Fig.2 and Fig. 3.

In the overall population, the DFS rate was 85.4% [95%CI 83.9%-86.8%] at 5 years and 76.3% [95%CI 74.5%-78.2%] at 7 years. At these two-time points, the MFS rate was respectively 89.5% [88.3%-90.8%] at 5 years and 84.2% [82.6%-85.8%] at 7 years (Table 4). The most frequently reported events were metastatic recurrence (64.7%), local/regional recurrences (17.3%), death without evidence of disease progression (6.0%), second malignancy (5.3%) and contralateral breast cancer (6.6%).

The DFS rate according to hormonal status was significantly higher for HR+ than for HR- patients: 89.0% *vs*. 79.1%; at 5 years, 80.5% *vs*. 69.2% at 7 years (HzR: 0.61 (95% CI:0.52-0.72); p <0.001). According to

nodal status, the DFS rate was significantly higher for N- than for N+ patients: 92.6% *vs.* 78.9% at 5 years, (87.2% *vs*. 66.8% at 7 years (HzR: 0.34 (95% CI:0.28-0.41); p <0.001).

The MFS was also significantly higher for HR+ compared to HR- patients: 93.1% vs. 83.4% at 5 years, 88.0% *vs*. 77.7% at 7 years (HzR: 0.51 (95% CI:0.41-0.62); p <0.001). The MFS of N- was significantly higher than those of N+ patients: 96.3% *vs*. 83.5% at 5 years, 94.7% *vs.* 74.9% at 7 years (HzR: 0.20 (95% CI:0.15-0.26); p <0.001).

The percentage of 7-year DFS was higher in patients with 1-3 positive nodes, compared to ≥4 positive nodes (73.0% *vs*. 50.0%; HzR: 0.41 (95%CI: 0.34-0.50); p <0.001). The 7-year-DFS in the HR-/N+ and the HR+/N- subgroups was 56.3% and 89.7%, respectively and it was 72.9% and 83.3%. in the HR+/N+ and HR-/N-subgroups, respectively (Fig. 2).

The percentage of 7-year MFS was higher when 1-3 positive nodes were present, compared to ≥4 positive nodes (80.8% *vs*. 58.7%; HzR: 0.35 (95%CI: 0.28-0.44) ; p<0.001). The 7-year MFS was the lowest in the HR-/N+ subgroup and the highest in the HR+/N- subgroup (63.5% and 95.7%, respectively). The results of the other subgroups, HR+/N+ and HR-/N-, were 81.4% and 92.9%, respectively (Fig. 3).

Overall, at 7 years, the main sites of metastases were visceral (with or without other site involvement), and bone (with or without other site involvement) (73.8% and 52.6%, respectively) (Table 3). In the HR+ subgroup,

72.5% of patients presented with visceral +/- other metastases and 62.1% with bone +/- other metastases. In the N- subgroup, 86.5% of patients presented with visceral +/- other metastases and 40.4% with bone +/- other metastases. Differences between sites of metastases in the HR- and HR+ subgroups were significant (p=0.007) as well as differences between the N- and N+ subgroups (p=0.056) (Table 3).

To assess the respective impact of the clinical profile variables on the survival time, Cox proportional hazard models have been run for both disease-free and metastases-free survival (figure 4). Both analyses show that 3 characteristics have independent and significative positive influence on the survival time: a tumor size less than 2 cm, no nodal involvement and HR+ status. Conversely, 4 or more positive nodes and a stage III at diagnosis impact negatively the survival but in a non-significative way at the threshold of 0.001.

Discussion

This retrospective cohort chart review study conducted in France assesses the long-term outcomes of patients with HER2+ eBC treated with adjuvant chemotherapy and trastuzumab, in a RW setting. The number of cases as well as the representativeness of participating centers, provides a unique dataset for evaluating the long-term efficacy of adjuvant trastuzumab.

Among the 11,185 patients who were treated with adjuvant trastuzumab in 2010 in France, it is difficult to precisely evaluate the percentage of eligible patients that were included in the final data base (n=2,311

cases) because the French medicalized information system program (PMSI) does not distinguish the categories of patients excluded or removed from the analysis (women treated with neo-adjuvant trastuzumab, men with HER2+ eBC, patients who did not received the standard duration treatment with trastuzumab). While the differences in eligibility criteria between patients in this study and in phase III interventional trials, assessing adjuvant trastuzumab such as HERA and APHINITY, excluded direct comparison [4,10], the general demographic and clinical characteristics of the patients in our cohort and these studies appeared very close, except for a higher rate of older patients (aged 60 years or older) in our cohort, i.e. 35% compared to 16% in the HERA trial, and 20% aged 65 years or older *versus* 13% in the APHINITY trial [4,10]. These differences reflect the exclusion of older patients from clinical trial as well as the propensity of physicians to propose participation in clinical trials to few elderly patients even if the protocol does not exclude them. The difference in the proportion of patients aged 60 years or over explains that the percentage of postmenopausal patients was higher in our cohort (56%) than in interventional trials where this criterion was described (i.e. 45% in the HERA trial). The ratio HR+/HR- observed (63/37) is close to 60/40 usually found in an incident breast cancer population, and notably in the APHINITY trial (64/36) [4,10].

In France, the usual recommendation in real-world practices is to regularly follow-up patients with disease-free eBC during a period of 5 years, and then to space out or even discontinue the follow-up. The impact of this recommendation can be observed in the rate of patients who no longer consult at 5 years after the initiation of trastuzumab. The overall cumulative proportion of these patients is 6.6% (7.7% based on disease-free patients) but increases to 14.4% and 17.4% respectively at 6 years.

Although the number of patients with disease-free eBC at least 6 years post-trastuzumab remains high, the significant drop at 5 years follow-up time may impact the population still documented over this period (less N+ patients lost to follow-up at 6 years, 11.8% *versus* N- 17.2%). This justifies reporting 5 years follow-up even if the results at 7 years remain relevant for each subgroup.

The 5- year and 7-year DFS in the overall population was 85.4% and 76.3% respectively but it varied significantly according to hormonal status and nodal involvement. The same observation can be made for both the 5-year MFS (89.5%) and the 7-year MFS (84.2%) which are respectively 83.4% and 77.7% in the HR- subgroup and conversely 83.5% and 74.9% in the N+ subgroup.

In the N+ subgroup, patients with 4 or more positive nodes have lower risk of recurrence: 64.4% at 5 years and 50% at 7 years for the DFS, 70.5% at 5 years and 58.7% at 7 years for the MFS.

The evaluation of DFS and MFS at 5 years in HER2+ eBC is of real interest, because most clinical trials limit the observation period to 3 or 4 years of follow-up.

Due to the differences in the characteristics of the population included, patient management, follow-up process and time elapsed until assessment, comparisons of the DFS and MFS rates of this study with those of other studies in a similar population must be interpreted with caution. The final analysis of the HERA study at 11 year-follow-up showed that the addition of 1 year of adjuvant trastuzumab resulted in a

constant 24% relative reduction in the risk of DFS event [8]. In the PHARE trial, a large phase III multicenter randomized French clinical trial assessing 6 months *versus* 12 months of adjuvant trastuzumab for patients with HER2+ eBC, the 3-year MFS (which equals to 3 years and 4 months in the present study) in the N+ subgroup (88.9%) was very close to those observed in this study at the same time point (90.7%). Beyond the fact that the 3-year MFS in the PHARE trial confirm our result, it shows that during the 4thand 5th year following post trastuzumab treatment, an additional 5% of N+ patients show a metastatic recurrence [12]. The trend pointed out by the Kaplan-Meier analysis seems to indicate a similar tendency in the 6th and 7th year.

The classification of the N+ subgroup (1-3 positive nodes and 4 or more positive nodes) is also particularly interesting. At 7-year follow-up, the DFS of patients with 1-3 positive nodes was 73.0% and the MFS 80.8%, while for patients with 4 or more positive nodes this was 50.0% and 58.7% respectively, showing 41.3% of metastatic recurrence.

Regarding the hormonal status, the differences between the 2 subgroups were less pronounced, but remained significant ($p < 0.001$) and confirmed by the Cox model: the 7-year DFS was 69.2% (30.8% of cumulative risk of event) and the 7-year MFS was 77.7% for HR- patients (*versus* 80.5% and 88.0% respectively in the HR+ subgroup).

Indirectly, these figures point out the difference in the nature of the recurrence for the different clinical profiles. For N+ patients most of recurrences were metastatic, especially in cases involving 4 or more positive nodes, whereas in the N- subgroup, the main recurrences were non-metastatic.

Overall, among patients who developed distant metastasis, the sites of involvement were visceral, mainly pulmonary and/or liver (73.8%), bone (52.6%) and brain (41.8%). There was a higher percentage of brain metastases in the HR- subgroup than in the HR+, and more in the N+ subgroup than in the N-. These differences have to be interpreted with caution, because in the N- subgroup the rate of distant recurrence was the lowest.

The limitations of this retrospective cohort study are inherent to the design of all RW studies, data interpretation should be taken cautiously. For instance, the rate of lost to follow-up patients after the end of the treatment may include both discontinuations based on patient decision and discontinuations decided by the sites for patients with no events. A comparison between the characteristics of the overall population and those of patients not lost to follow-up shows that the population not lost to follow-up at 8 years can be extrapolated to all patients and therefore that the cumulative rates of recurrence (whatever its nature) and metastatic recurrences observed at this time do not include any evaluation bias. Moreover, the comparison related to the N+ subgroup shows no difference between the distribution of the characteristics of all the patients included and that of the patients not lost to follow-up at 8 years. Although the slightly larger proportion of N+ patients not lost to follow-up at 8 years is likely to have a slight impact on the probability of recurrence for the entire population, there is no potential impact on the analysis on subgroups.

Since the publication of the results of the three phases III (NSABP B-31, NCCTG N9831, HERA) a decade ago, which provided solid evidence that adding trastuzumab to adjuvant treatment was indisputably increasing the PFS, time to first distant recurrence and OS in patients with HER2+ eBC, the prognostic paradigm has definitively changed for this population [4-7]. HER2+ eBC, remains associated with aggressive behavior in breast cancer, however, targeted therapy can significantly improve the outcomes of the disease and alleviate the burden associated with this characteristic.

The results of this study demonstrate less optimistic trends. In the HR+ and N- subgroups it is true that the 7-year probability of a recurrence (respectively 19.5% and 12.8%) and distant recurrence (12.0% and 5.3) is relatively low but in the two other subgroups (HR- and N+) the outcomes are not the same. The 7-year probability of a recurrence is 30.8% for HR- and 33.2% for N+ subgroups, with a probability of distant recurrence of 22.3% and 25.1% respectively. Both quantitatively, by the frequency of events, and qualitatively, by the nature of the recurrence observed, the HR- and the N+ are two subgroups for whom the 7-year outcomes are relatively poor.

Conclusions

This real-world study conducted in France, points out, and concurred with international clinical trials, that HER2+ eBC patients with nodal involvement and hormone-negative status need more efficient approaches than trastuzumab in the adjuvant setting. Taking into account the rates of DFS and MFS in these subgroups we can conclude that there is still an important unmet medical need in the HER2+ eBC patient population.

List Of Abbreviations

HER2	Human Epidermal growth factor Receptor-2
HER2+	HER2 positive
eBC	Early Breast Cancer
IHC	Immunohistochemistry
HR+	Hormone-receptor postive
HR-	Hormone-receptor negative
N+	Node positive
N-	Node negative
DFS	Disease-free survival
MFS	Metastatic-free survival
OS	Overall survival
HzR	Hazard ratio
CI	Confident interval
EMA	European Medicines Agency
INDS	Institut National des Données de Santé/National Institute for Health Data
CNIL	Commission Nationale de l'Informatique et des Libertés/French data protection authority
PMSI	Programme de Médicalisation des Systèmes d'Information/Medicalized information system program

Declarations

Ethical approval and consent to participate

The study protocol was submitted and approved by the INDS (Institut National des Données de Santé/National Institute for Health Data) based on a standardized methodology for a retrospective study (MR003/not requiring patient consent) and was submitted to the CNIL (Commission Nationale de l'Informatique et des Libertés/French data protection authority) which authorized the data processing of the study (DR-2018-072).

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing Interests

M. Saghatchian has received financial support for research from Roche France; and is consultant for Roche. M. Saghatchian has stated to have no conflicts of interest with Roche France.

E. Curtit has received financial support for research from Roche France; and is consultant for Roche, Novartis, Pfizer, Eisai, Genomic Health. E. Curtit has stated to have no conflicts of interest with the sponsor.

D. Coeffic has received financial support for research from Roche France; and is consultant for Roche, Novartis, Pfizer, Eisai, Genomic Health. D. Coeffic has stated to have no conflicts of interest with the sponsor.

C. Levy has received financial support for research from Roche France; and is consultant for Roche, Novartis, Pfizer, Eisai, Genomic Health, C. Levy has stated to have no conflicts of interest with the sponsor.

A. Flinois is employed by Kantar Health, and have received funding from Roche France to conduct this research. A. Flinois has stated to have no conflicts of interest with Roche France.

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Authors contributions

M. Saghatchian: study design, data interpretation and manuscript writing

E. Curtit: data interpretation and manuscript writing

D. Coeffic: study design and data interpretation

C. Levy: data interpretation and manuscript writing

A. Flinois: study design, data analyzing, data interpretation and manuscript writing

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Tables

Table 1: Patients and disease characteristics overall and according to hormonal and nodal status

	Overall	HR-	HR+	N-	N+
N (%)	*(n=2311)*	*(n=860)*	(n=1451)	*(n=1091)*	*(n=1220)*
Age at diagnosis (years)					
< 35	114 (4.9)	50 (5.8)	64 (4.4)	50 (4.6)	64 (5.2)
35-49	672 (29.1)	259 (30.1)	413 (28.5)	299 (27.4)	373 (30.6)
50-59	710 (30.7)	287 (33.4)	423 (29.2)	337 (30.9)	373 (30.6)
≥ 60	814 (35.2)	264 (30.7)	550 (37.9)	404 (37.0)	410 (33.6)
Missing data	*1 (0.0)*	-	*1 (0.1)*	*1 (0.1)*	-
p-value		*p=0.003*		*p=0.218*	
Median age (Min-Max)	55 (22-84)	54 (22-84)	56 (22-84)	56 (22-83)	55 (22-84)
Menopausal status at diagnosis					
Premenopausal	644 (27.9)	254 (29.5)	390 (26.9)	287 (26.3)	357 (29.3)
Uncertain (pre or per)	370 (16.0)	158 (18.4)	212 (14.6)	173 (15.9)	197 (16.1)
Postmenopausal	1294 (56.0)	446 (51.9)	848 (58.4)	631 (57.8)	663 (54.3)
Missing data	*3 (0.1)*	*2 (0.2)*	*1 (0.1)*	-	*3 (0.2)*
p-value		*p=0.006*		*p=0.214*	
Tumor size (cm)					
0 à 1 cm	348 (15.1)	131 (15.2)	217 (15.0)	20,3 (222)	10,3 (126)
1 à 2 cm	882 (38.2)	289 (33.6)	593 (40.9)	47,8 (522)	29,5 (360)
2 à 5 cm	960 (41.5)	384 (44.7)	576 (39.7)	29,9 (326)	52,0 (634)
> 5 cm	111 (4.8)	53 (6.2)	58 (4.0)	1,5 (16)	7,8 (95)
Missing data	*10 (0.4)*	*3 (0.3)*	*7 (0.5)*	*0,5 (5)*	*0,4 (5)*
p-value		*P=0.012*		*P<0.001*	
Median size (Min-Max)	2.3 (0-1.5)	2.4 (0-1.5)	2.2 (0-1.5)	1.9 (1-1.5)	2.6 (0-1.5)
Nodal status					
Negative	1091 (47.2)	406 (47.2)	685 (47.2)	1091 (100)	
1-3 positive nodes	894 (38.7)	311 (36.2)	583 (40.2)		894 (73.3)
≥ 4 positive nodes	326 (14.1)	143 (16.6)	183 (12.6)		326 (26.7)
p-value		*P<0.001*			

Table 2: Anti-tumor treatments combined with trastuzumab

	Overall	HR-	HR+	N-	N+
N (%)	*(n=2311)*	*(n=860)*	(n=1451)	(n=1091)	(n=1220)
Adjuvant chemotherapy					
Anthracycline + taxane	1767 (76.5)	685 (79.7)	1082 (74.6)	754 (69.1)	1013 (83.0)
Anthracycline w/o taxane	74 (3.2)	28 (3.3)	46 (3.2)	47 (4.3)	27 (2.2)
Taxane w/o anthracycline	438 (19.0)	140 (16.3)	298 (20.5)	270 (24.7)	168 (13.8)
Other regimens*	5 (0.2)	4 (0.5)	1 (0.1)	3 (0.3)	2 (0.2)
No adjuvant chemotherapy	27 (1.2)	3 (0.3)	24 (1.7)	17 (1.6)	10 (0.8)
p value		*p<0.001*		*p<0.001*	
Adjuvant radiotherapy					
Yes	2192 (94.9)	805 (93.6)	1387 (95.6)	1006 (92.2)	1186 (97.2)
No	114 (4.9)	55 (6.4)	59 (4.1)	82 (7.5)	32 (2.6)
Missing data	5 (0.2)	-	5 (0.3)	3 (0.3)	2 (0.2)
p value		*p=0.013*		*p<0.001*	

*other regimens = neither anthracycline nor taxane

Table 3: Metastasis localization classification at 7 years

	Overall	HR-	HR+	N-	N+
N (%)	(n=325)	(n=172)	(n=153)	(n=52)	(n=273)
Metastasis localization					
Brain +/- other sites	136 (41.8)	83 (48.3)	53 (34.6)	19 (36.5)	117 (42.9)
Visceral +/- other sites	240 (73.8)	129 (75.0)	111 (72.5)	45 (86.5)	195 (71.4)
Bones +/- other sites	171 (52.6)	76 (44.2)	95 (62.1)	21 (40.4)	150 (54.9)
Lymphatic +/- other sites	14 (4.3)	11 (6.4)	3 (2.0)	5 (9.6)	9 (3.3)
p value		*p=0.007*		*p=0.056*	

Table 4: Cumulative probability of occurrence (%) of events related to the disease or metastatic recurrences

	12 months	24 months	36 months	48 months	60 months	72 months	84 months	96 months
Events related to the disease								
Total	1.2	3.9	7.7	11.7	14.6	17.9	23.7	27.9
HR+	0.5	2.0	5.1	8.6	11.0	13.6	19.5	24.7
HR-	2.3	7.3	12.1	17.0	20.9	25.4	30.8	33.4
N-	0.5	2.0	3.6	6.0	7.4	9.3	12.8	15.4
N+	1.8	5.6	11.3	16.8	21.1	25.5	33.2	38.7
Metastatic recurrences								
Total	1.0	3.0	5.7	8.4	10.5	12.7	15.8	18.4
HR+	0.3	1.1	3.4	5.5	6.9	8.5	12.0	15.0
HR-	2.1	6.0	9.7	13.4	16.6	20.0	22.3	24.4
N-	0.1	0.9	1.7	3.0	3.7	4.5	5.3	6.5
N+	1.7	4.7	9.3	13.3	16.5	20.1	25.1	29.0

Figures

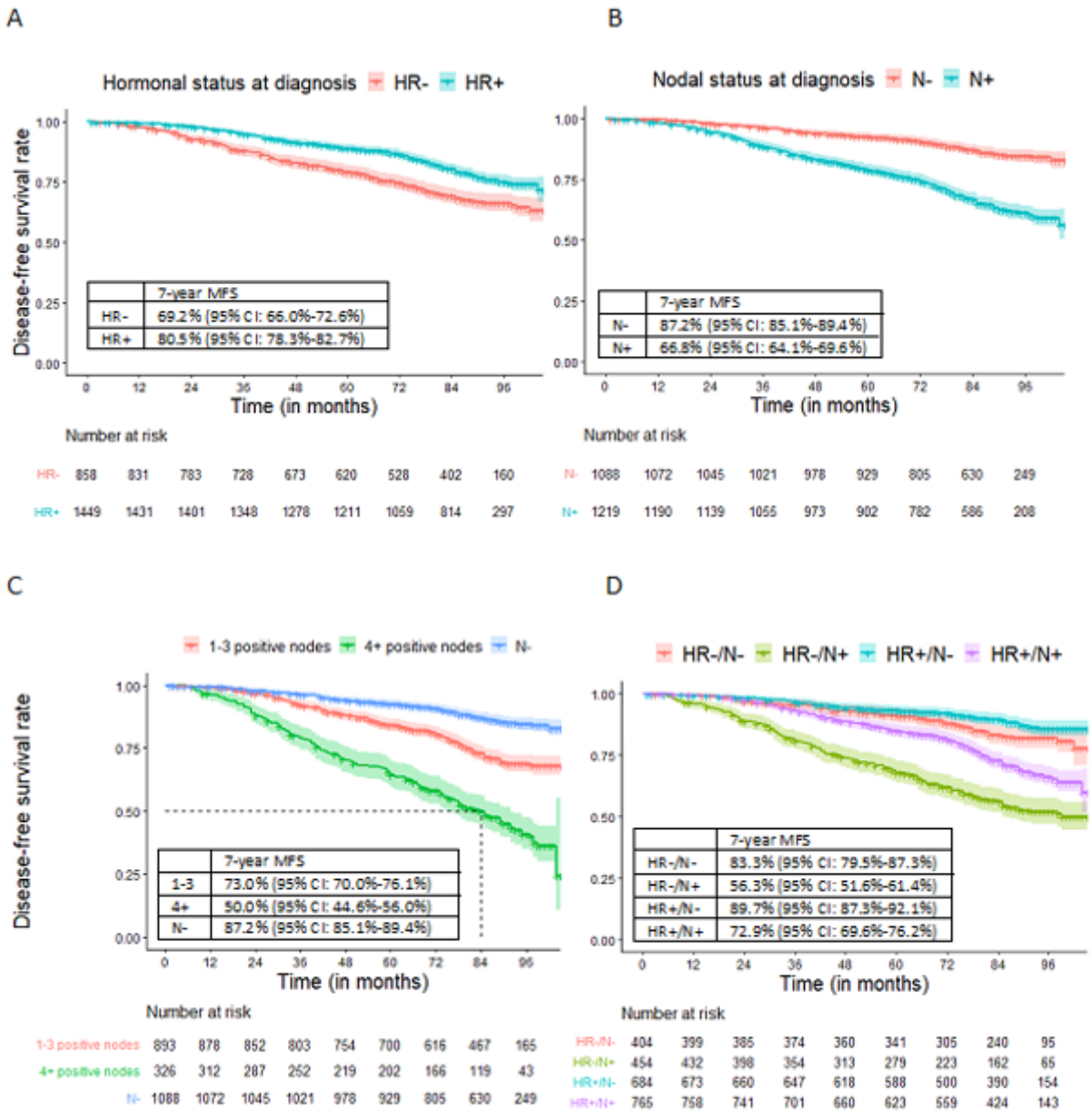

Figure 1

Kaplan-Meier disease-free survival curves for subgroups

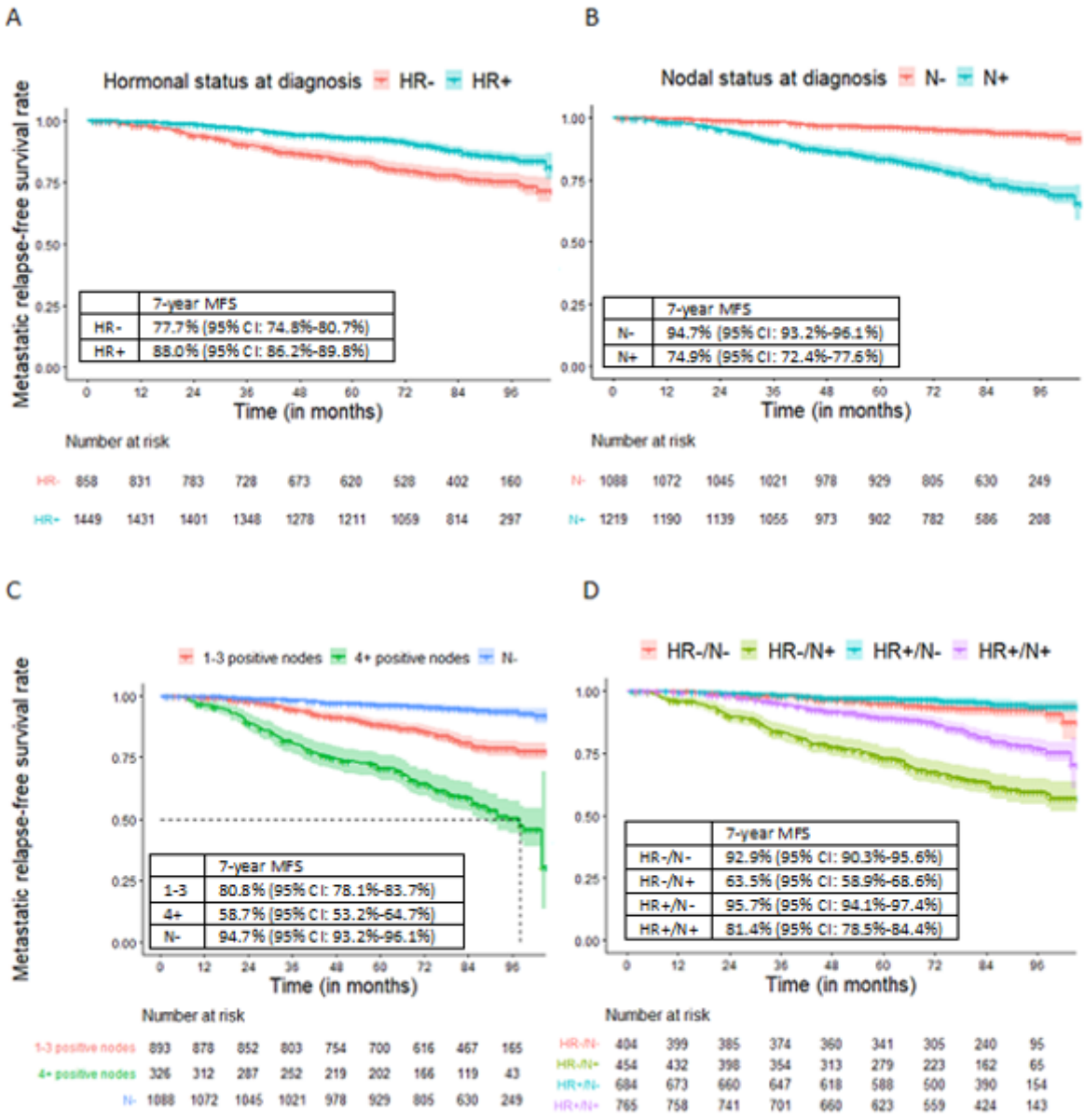

Figure 2

Kaplan-Meier metastatic-free survival curves for subgroups

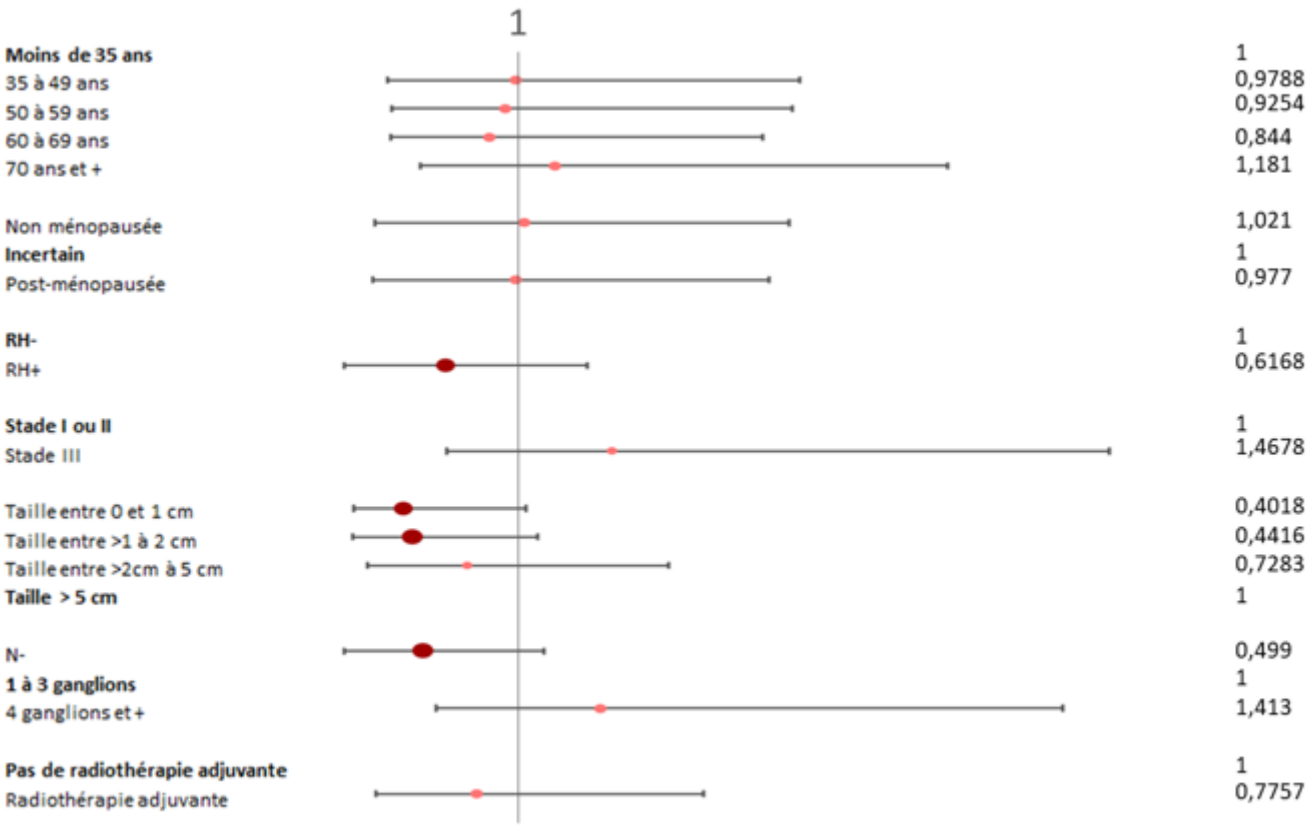

Figure 3

Cox model disease-free survival

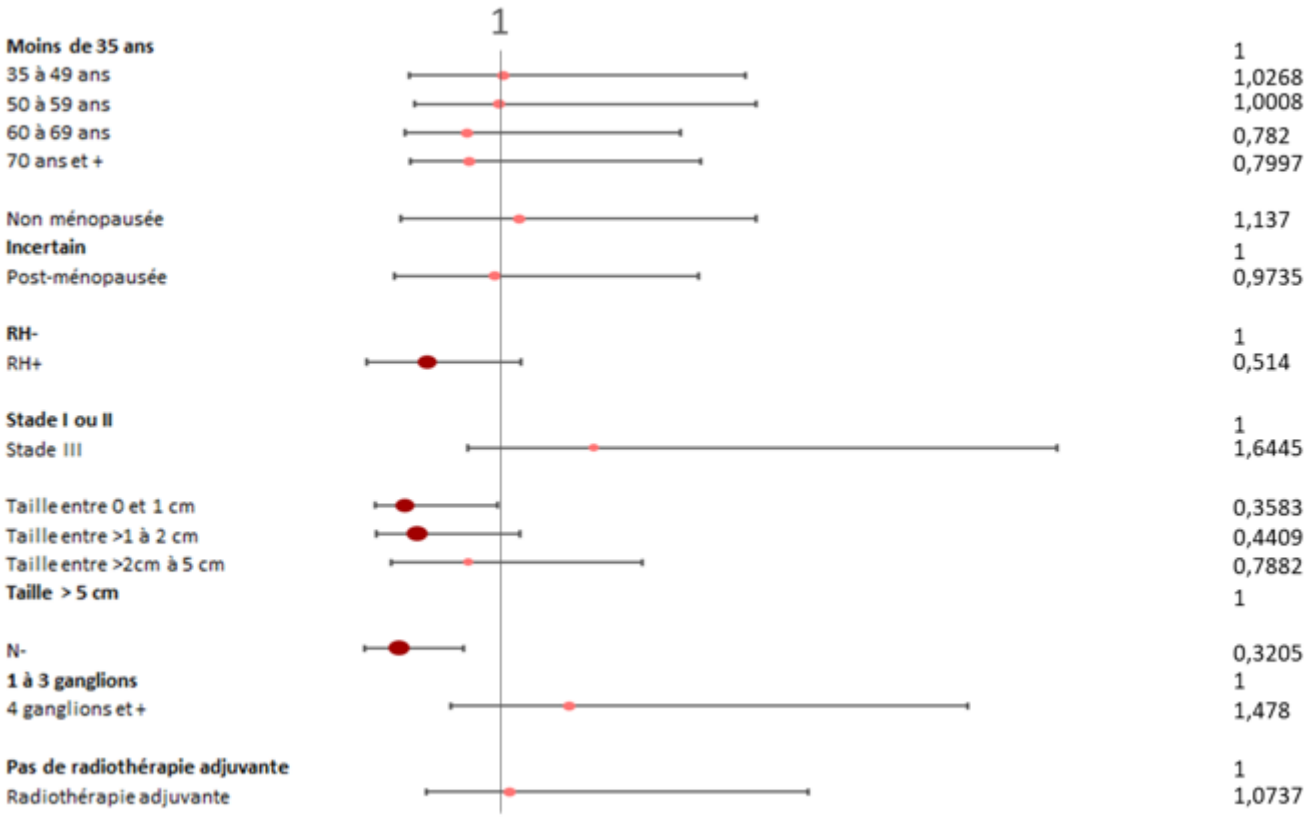

Figure 4

Cox model metastatic-free survival