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Trends in Adjuvant Chemotherapy Use in Endocrine-Sensitive, HER-2 Negative Breast Cancer, With 1 to 3 Positive Nodes: A Single-Centre Study

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ABSTRACT

Background: There is a tendency to decrease the intensity of breast cancer treatments, e.g. omitting adjuvant chemotherapy in endocrine-sensitive and HER-2 negative patients. The purpose of this study was to analyse changes in the frequency of the indication of adjuvant chemotherapy and the differences in survival over time for this subtype of breast cancer, with 1–3 positive nodes.

Methods: The study was based on descriptive, observational, retrospective, single-institution research between 2004–10 and 2011–18, on endocrine-sensitive, HER-2 negative breast cancer, stage pN1 (1–3 nodes). The analytical tests carried out for a comparison of the frequency of chemotherapy use the chi-square test with Fisher's exact test. Survival data in both periods are presented.

Results: A total of 236 patients were included, 66 for the period 2004–10, and 170 for 2011–18. More patients were treated with hormone therapy alone in 2011–18: hormone therapy alone 10/66 (15.20%) for 2004–10, and 83/169 (49.10%) for 2011–18; chemotherapy-hormone therapy 56/66 (84.80%) for 2004–10, and 86/169 (50.90%) for 2011–18 (P = 0.0001). For 2004–10, the 5-year overall survival probability was 100%. For 2011–18 it was 98.20% (95% CI 95.65–100). For 2004-10, 5-year disease free survival (DFS) was 96.9% (95% CI 92.7–101). For 2011–18 it was 87.7% (95% CI 81.8–93.5) (P=0,040). For 2004–10 the 5 year distant relapse free interval was 96.9% (95% CI 92.5–101.2). For 2011–18 it was 93% (95% CI 88.1–97.9) (P=0.312).

Conclusion: A decrease in the indication of adjuvant chemotherapy according to the clinical risk is confirmed in endocrine-sensitive, HER-2 negative breast cancer, with 1-3 positive nodes, over the period 2011–18 compared to 2004–10. Based on the results, 5-year DFS is slightly worse in the 2011–18 period.

Introduction

In recent years, there has been a tendency to de-escalate breast cancer treatment, by shortening or omitting adjuvant chemotherapy, reducing the extent of axillary lymph node surgery or reducing the cycles of radiotherapy.[1] Standard adjuvant systemic treatment for women with hormone-sensitive and HER-2 negative breast cancers is based on hormone therapy. Some women obtain additional benefit from chemotherapy, while others can avoid this. International consensus guidelines recommend adjuvant chemotherapy in this subtype of breast cancer in women with 4 or more positive lymph nodes, including those with lobular and grade 1 or

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luminal A carcinoma.[2] However, it is not recommended for women with negative lymph nodes and tumors smaller than 1 cm.[2] Between these extremes are those women with pN1 axillary lymph node involvement (1 to 3 metastatic nodes).

Data on the benefit of adjuvant chemotherapy in early breast cancer are derived from meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) with 100,000 patients randomised in 123 trials.[3] This benefit is independent of clinical and pathological factors such as lymph node involvement, oestrogen receptor status, age, and use of hormone therapy.[3] Clinical tools such as *Adjuvant! Online*[4] and *PREDICT Plus*[5] have been developed based on patients' primary tumors and their clinical-pathological markers such as age, tumor size and grade, and the number of lymph nodes with metastases, which help in deciding whether adjuvant chemotherapy is indicated. However, the degree of accuracy provided by clinical-pathological markers in indicating adjuvant chemotherapy is far from perfect, especially if patients have hormone-sensitive, HER-2 negative disease and 1–3 positive nodes.[6] For this reason, gene expression signatures have been studied in node-positive patients in order to discern which patients would benefit from adjuvant chemotherapy and which might avoid it.

In the Mindact trial, 6693 women, 21% of whom were node-positive, were randomised using discordant clinical or genomic risk (*MammaPrint*) to assign chemotherapy or not. In high clinical risk patients, 46.20% can be spared chemotherapy if their genomic risk is low, with no significant increase in the risk of distant recurrence.[7] The lack of statistical power and the short follow-up mean that the evidence from this trial is limited for node-positive patients; therefore, the benefit of chemotherapy cannot be excluded.

A retrospective analysis of the SWOG-8814 trial showed that using chemotherapy did not improve distant metastasis-free survival or overall survival in 146 patients with Recurrence Score (RS) (*Oncotype DX*, 21-gene signature) <18 (low genomic risk) or RS 18–30 (intermediate genomic risk). Once again, we encounter the limitations of low statistical power as a result of the small sample size, and its retrospective nature, for confirming that low genomic risk predicts no benefit from adjuvant chemotherapy in node-positive patients.[8] Other retrospective analyses show excellent survival rates among node-positive and RS <18 patients without adjuvant chemotherapy.[9] Lastly, the results of the retrospective analysis of the ATAC trial[10], and the prospective analysis of the PlanB trial[11] also support omitting chemotherapy, although with the same limitations of short follow-up and low sample size.

Other gene signature tests, such as Prosigna (PAM50) and EndoPredict, also provide retrospective evidence for identifying patients at low risk of metastasis in node-positive women treated with only adjuvant hormone therapy and no chemotherapy.[12-14]

For both node-negative and node-positive patients, the oncologists' recommendations on receiving adjuvant chemotherapy have decreased significantly over time, with no substantial change in clinical practice guidelines.[15] Incorporating genomic risk assessment bears much of the responsibility for this reduction in chemotherapy use[16], despite the lack of evidence, as we have seen, from prospective and randomised trials.[6,16]

The aim of our study is to analyse changes in the frequency of the indication of adjuvant chemotherapy over the past 15 years in patients with hormone-sensitive, HER-2 negative, 1–3 node positive breast cancer. The authors' hypothesis is that the relative frequency of use of adjuvant chemotherapy has decreased over time, with no impact on survival and without the incorporation of genomic risk being responsible for this, since its authorisation in our environment excludes patients with positive nodes.

Methods

This is a descriptive, observational, retrospective, single-centre study, carried out in the Medical Oncology department of a university hospital. It was registered on the website of the Spanish Agency for Medicines and Health Products (AEMPS) with code number JBC-EPI-2020-01. The study protocol was approved by the Cadiz Research Ethics Committee. It was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent updates. Since it is a retrospective study using data contained in clinical records, with no intervention or risk to the patients, their informed consent was not necessary. The Cadiz Research Ethics Committee authorised the absence of informed consent.

The cohort selected attended the hospital over the past 15 years (1 January 2004 to 31 December 2018). The patients were identified from the Medical Oncology department's database. The data on patients and treatment received from Medical Oncology health records were collected retrospectively. The Spanish National Register for Deaths was consulted to find out the patients' vital status and date of death. The data was collected between September 2019 and February 2020.

Missing data was kept to a minimum by good study planning and careful collection. A proactive database design was created to reduce or detect data entry errors. The methodology used for data collection and entry was disseminated in writing and a chat room was set up for communication between researchers. A single researcher (EBR) reviewed the database to improve its quality and correct any errors detected.

The participants were women and men with breast cancer undergoing surgical treatment for pathological

infiltrating carcinoma, oestrogen and/or progesterone receptor positive, HER-2 negative and 1–3 nodes with metastases (including micrometastases), with a tumour size of less than 5 cm. Those treated with adjuvant hormone therapy alone, no chemotherapy, or without any adjuvant systemic treatment were eligible for inclusion in the study, as were those treated in combination with chemotherapy and hormone therapy. Patients assessed as having genomic risk, those treated with neoadjuvant systemic therapy, those not treated surgically and those with distant metastases were excluded. The independent patient-related variables analysed were: age, sex, performance status (measured by the ECOG scale)[17], menopause status and comorbidity (measured by the Charlson scale).[18] The independent breast tumour-related variables analysed were tumour size, number of axillary nodes with metastasis, number of total axillary nodes analysed, tumour stage (American Joint Committee on Cancer - AJCC-, 8th edition), histological grade, histological type, oestrogen and progesterone receptor status (considered positive if immunohistochemical expression was equal or greater than 1%), and Ki67 proliferative index. The independent treatment-related variables were type of surgery, type of adjuvant hormonal treatment and type of adjuvant chemotherapy treatment, and year of treatment.

The dependent variables analysed were overall survival (OS), disease-free survival (DFS) and distant recurrence-free interval (DRFI).[19] The OS was calculated by measuring the time between surgery and one of the following events: death from breast cancer, death from any cause other than breast cancer, or death from an unknown cause. The DFS was calculated by measuring the time between surgery and one of the following events: local or regional infiltrating recurrence, distant metastasis, death from breast cancer, death from any cause other than breast cancer, death from an unknown cause, contralateral infiltrating breast carcinoma, or invasive non-breast cancer. The DRFI was calculated by measuring the time between surgery and one of the following events: distant metastasis or death from breast cancer.[19]

We compared the use of chemotherapy and all the other variables between two time periods (2004-10 and 2011-18). We have presented the survival data, shortening the observation time to 5 years. In this way, we increased the accuracy of the results, and we attempted to manage the different follow-up duration between the two time periods when we made formal comparisons.

As this was a retrospective study, all patients from the last 15 years were included. There were estimated to be around 250 patients with these characteristics in this period. A descriptive analysis of the variables was carried out. For the qualitative variables, the absolute and relative frequency, the mean, median, and standard deviation for the quantitative variables were used. The analytical tests carried out were: the chi-square test with Fisher's exact test for a comparison of the qualitative variables; the t-student test for quantitative variables, the Kaplan Meier method to calculate survival, and the Log-Rank test for comparison of curves. SPSS version 15 was used for statistical analysis of the data. In the statistical analysis, $p<0.05$ was considered to indicate statistical significance.

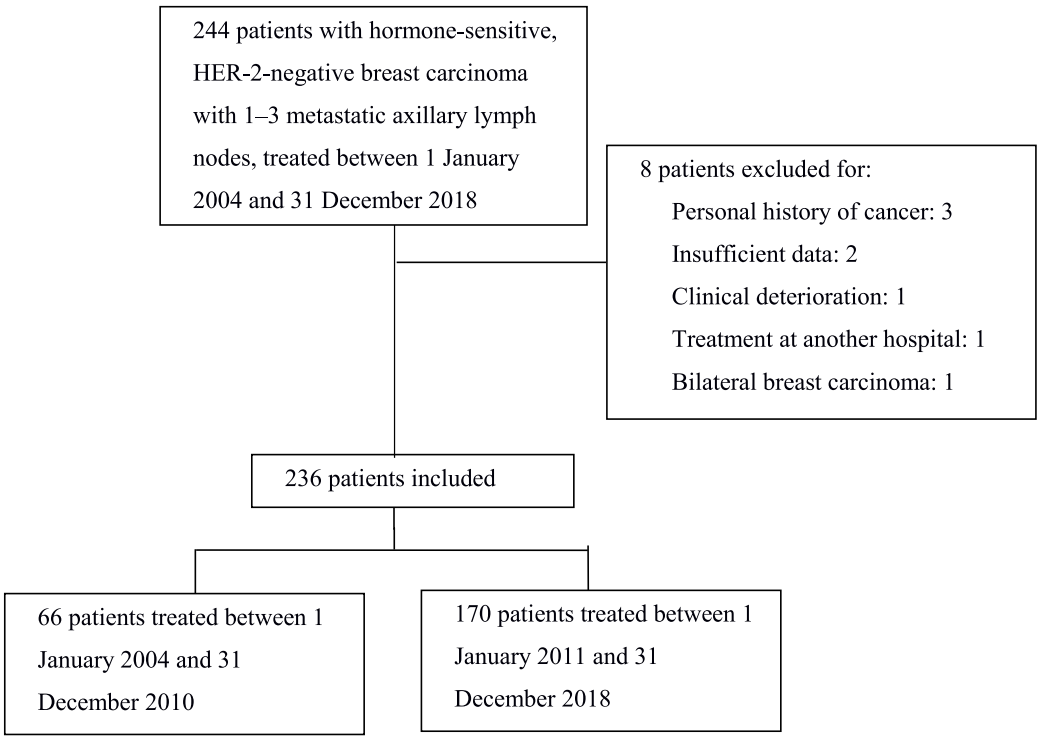

Figure 1. Study flow chart

Table 1. Characteristics of the 236 patients

Patient characteristics	N	%	2004-10 N (%)	2011-18 N (%)	P Value
Age (median and range)	55 (28–84)		54.63 (28-82)	55 (29-84)	0.831
Sex					0.518
Female	234	99.2	66(100)	168(98.8)	
Male	2	0.8	0 (0)	2 (1.2)	
Menopause status					0.559
Premenopausal	96	40.7	25(37,9)	71(42,3)	
Postmenopausal	138	58.5	41(62,1)	97(57.7)	
Male	2	0.8			
Performance status (Measured using the ECOG scale)					0.058
0	128	54.2	44(66.7)	84(49.4)	
1	103	43.6	21(31.8)	82(48.2)	
2	5	2.1	1(1.5)	4(2.4)	
Comorbidity (Measured using the Charlson scale)					0.307
0	151	64	40(60.6)	111(65.3)	
1	60	25.4	17(25.8)	43(25.3)	
2	17	7.2	8(12.1)	9(5.3)	
3	4	1.7	1(1.5)	3(1.8)	
>3	4	1.7	0(0)	4(2.4)	
Disease stage					0.040
IA	155	66.2	45(68.2)	110(65.5)	
IB	61	25.8	21(31.8)	40(23.8)	
IIA	16	6.8	0(0)	16(9.5)	
IIB	2	0.8	0(0)	2(1.2)	
Unknown	2	0.8	0(0)	2(1.2)	
Tumor					0.393
pTis	1	0.4	0(0)	1(0.6)	
pT1a-pT1b	29	12.3	7(10.8)	22(13)	
pT1c	110	46.6	37(56.9)	73(43.2)	
pT2	93	39.4	21(32.3)	72(42.6)	
pTx	3	1.3	0(0)	1(0.6)	
Palpability of the tumor					0.521
Palpable	162	68.6	45(68.2)	117(68.8)	
Non-palpable	74	31.4	21(31.8)	53(31.2)	
Tumor size in cm (median and range)	1.80 (0.30–5)		2.01(0.7-5)	2.05 (0,3-4.8)	0.753
Number of analyzed axillary nodes (mean and SD)	10.39 (6.69)		14.24 (8.91)	8.81 (4.73)	0.031
Number of positive axillary nodes (mean and SD)	1.50 (0.71)		1.63 (0.82)	1.46 (0.63)	0.445
Lymph node ratio (mean and SD)	0.14 (0.10)		0.11 (0.07)	0.16 (0.12)	0.750
Histopathological type					0.03
Ductal	202	86	49(74.2)	153(90.5)	
Lobular	27	11.5	15(22.7)	12(7.1)	
Other	6	2.6	2(3)	4(2.4)	
Unknown	1	0.4	0(0)	1(0.6)	
Histological grade					0.229
1	77	32.6	23(34.8)	54(31.8)	
2	131	55.5	39(59.1)	92(54.1)	
3	28	11.9	4(6.1)	24(14.1)	
Oestrogen receptors					
Positive	235	99.6	66 (100)	169 (99)	
Negative	1	0.4	0(0)	1(0.60)	
Progesterone receptors					
Positive	228	96.6	63(96)	165(97)	
Negative	8	3.4	3(4)	5(3)	
Ki67 proliferative index					
Median and range	10 (1–90)			18,83(1-90)	
≤20	123	52.1	0 (0)	123(72,4)	
>20	38	16.1	0(0)	38(22,4)	
Unknown	75	31.8	66(100)	9(5.3)	
Breast surgery					0.013
Conservative	129	54.7	45(68.2)	84(49.4)	
Mastectomy	107	45.3	21(31.8)	86(50.6)	
Axillary surgery					0.000
Sentinel lymph node biopsy	75	31.8	0(0)	75(44.1)	
Axillary lymph node dissection	161	68.2	66(100)	95(55.9)	
Year of treatment					
2004–2010	66	28			
2011–2018	170	72			
Adjuvant systemic treatment					0.000
Hormone therapy	93	39.4	10(15.2)	83(48.8)	
Chemotherapy-Hormone therapy	142	60.2	56(84.8)	86(50.6)	
None	1	0.4	0(0)	1(0.6)	
Hormone therapy					0.000
Tamoxifen	114	48.3	26(39.4)	88(52.1)	
Tamoxifen-goserelin	5	2.1	3(4.5)	2(1.2)	
Aromatase inhibitor	54	22.9	26(39.4)	28(16.6)	
Tamoxifen/Aromatase inhibitor	62	26.3	11(16.7)	51(30.2)	
None	1	0.4		1(0.6)	
Chemotherapy					0.301
Anthracyclines	8	3.4	5(8.9)	3(3.5)	
Anthracyclines and taxanes	95	40.3	38(67.9)	57(66.3)	
Other	39	16.5	13(23.2)	26(30.2)	
None	94	39.8			
Radiation therapy	180	76.2	50 (75.7)	130 (76.4)	0.840

Results

The medical records of 244 patients were reviewed. Of these, 8 were excluded for various reasons. In the end, 236 were valid for analysis: 66 of these attended between 1 January 2004 and 31 December 2010, and 170 between 1 January 2011 and 31 December 2018 (Figure 1). Information on patient characteristics, their tumours and treatment received is summarised in Table 1. Median patient follow-up was 59.50 months (range: 2–185 months). Between 2004-10, the median patient follow-up was 142 months (3-185), and between 2011-18, it was 40 months (2-104). A summary of the events can be found in Table 2.

Of these 236 patients, 93 (39.4%) were treated with hormone therapy, 142 (60.2%) with chemotherapy-hormone therapy and 1 (0.4%) did not receive any systemic adjuvant treatment. When we looked at the time period from 2004 to 2010 and compared it with the period from 2011 to 2018, we saw that more patients were treated with hormone therapy alone than chemotherapy-hormone therapy in the 2011-18 period. In the earlier period, 2004-10, 10/66 (15.2%) received hormone therapy and 56/66 (84.8%) chemotherapy-hormone therapy, and between 2011 and 2018, 83/169 (49.1%) received hormone therapy and 86/169 (50.9%) chemotherapy-hormone therapy (P=0.0001). The same differences were detected when the comparison was made year by year (P=0.0001). In Figure 2, the number of patients treated with chemotherapy in each year is presented.

Table 2. Events in the 236 patients

Events	N	%	2004-10 N (%)	2011-18 N (%)
Loco-regional recurrence	6	2.5	2 (3)	4 (2.4)
Local recurrence after conservative surgery	4	1.7	1 (1.5)	3 (1.7)
Local recurrence after mastectomy	1	0.4	1 (1.5)	
Lymph node recurrence	1	0.4		1 (0.6)
Metastasis[1]	15	6.4	5 (7.5)	10 (5.8)
Invasive second primaries	11	4.7	4 (6)	7 (4.1)
Contralateral breast	6	2.5	2 (3)	4 (2.4)
Non-breast	5	2.1	2 (3)	3 (1.7)
Contralateral ductal carcinoma in situ	1	0.4		1 (0.6)
Deaths	10	4.2	4 (6)	6 (3.4)
For breast carcinoma	5	2.1	2 (3)	3 (1.7)
For other reasons	4	1.7	2 (3)	2 (1.2)
Heart failure	2	0.8	1 (1.5)	1 (0.6)
Endocarditis	1	0.4		1 (0.6)
Sepsis	1	0.4	1 (1.5)	
Unknown	1	0.4		1 (0.6)

[1] Initial metastatic locations

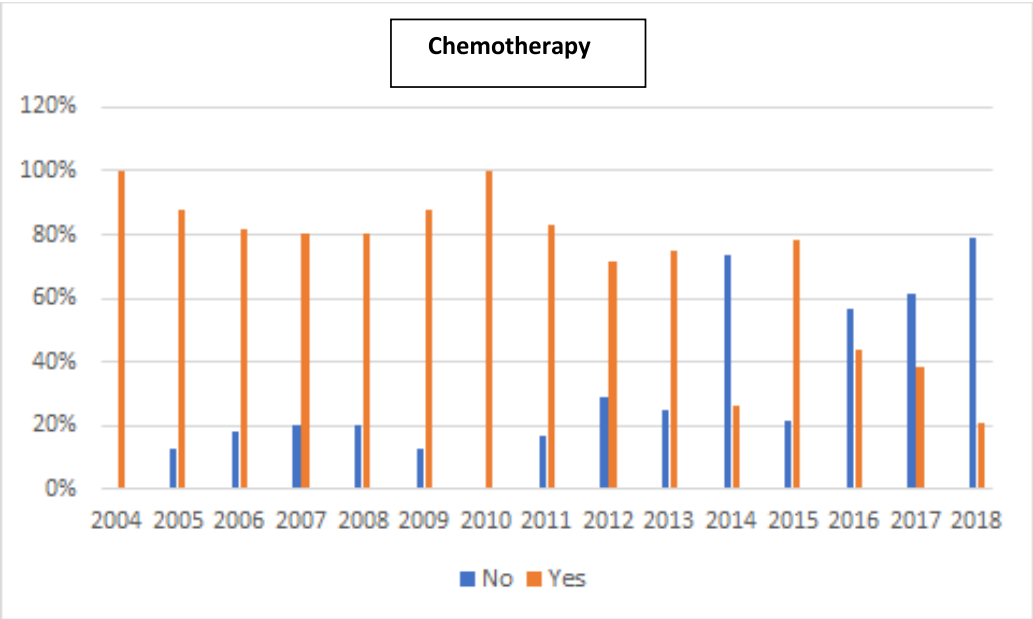

Figure 2. Use of adjuvant chemotherapy per year of treatment in patients with hormone-sensitive, HER-2 negative, and 1-3 node positive tumors

For all patients, the probability of OS, DFS and DRFI at 5 years was 98.9% (95% CI 97.3–100.4), 91% (95% CI 86.8–95.1) and 94.6% (95% CI 91.2–97.9) respectively. And at 10 years: 90.7% (95% CI 84.6–96.7), 70.6% (95% CI 60.9–80.2) and 87.9% (95% CI 81.2–94.5) respectively. And at 15 years, 88.8% (95% CI 81.7–95.8), 66.7% (95% CI 56.3-77.0) and 87.9% (95% CI 81.2–94.5), respectively.

In patients treated over the period 2004–10, the estimated probability of OS at 5 years was 100%. In patients treated over the period 2011-18, the estimated probability of OS at 5 years was 98.2% (95% CI 95.6–100). The median OS was never reached. In this case, no comparison was made because no event occurred in the 5 follow-up years in the group of cases diagnosed between 2004-10. Figure 3 shows the OS curves.

In patients treated over the period 2004-10, the estimated probability of DFS at 5 years was 96.9% (95% CI 92.7–101). In patients treated over the period 2011–18, the probability of DFS estimated at 5 years was 87.7% (95% CI 81.8–93.5). The median DFS was never reached. The differences were statistically significant (P=0.040). Figure 4 shows the DFS curves for the 5 years.

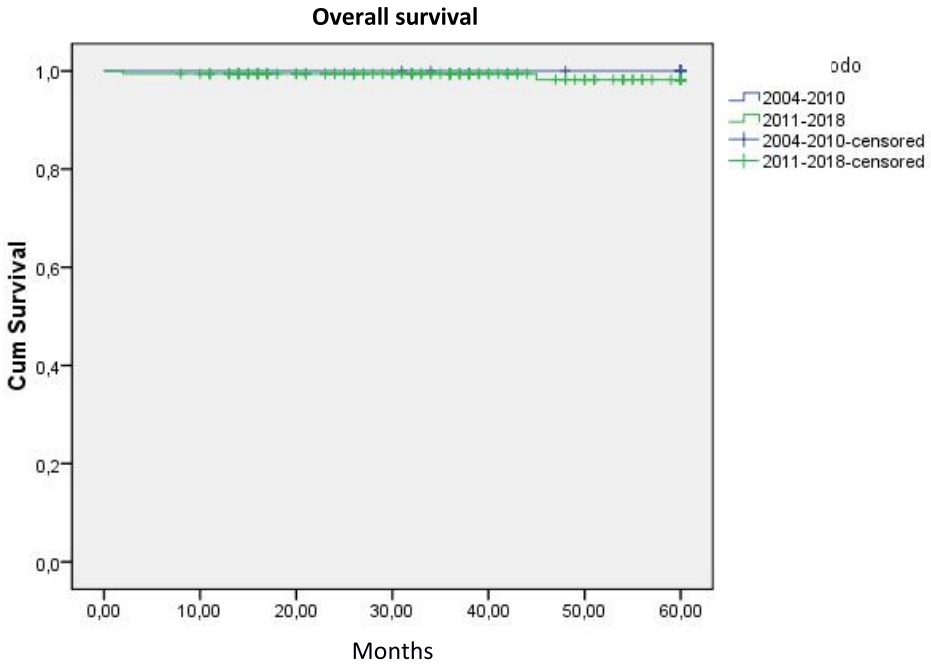

Figure 3. 5-year overall survival curve for 66 patients treated during 2004–10 and in 170 patients treated during 2011–18

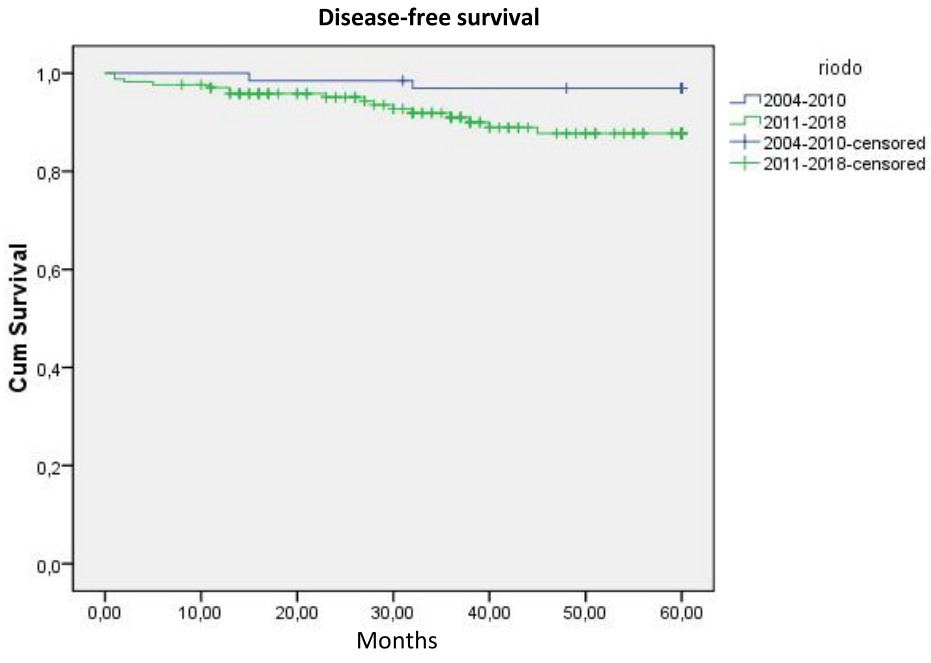

Figure 4. 5 year disease-free survival curve in 66 patients treated during 2004–10 and in 170 patients treated during 2011–18

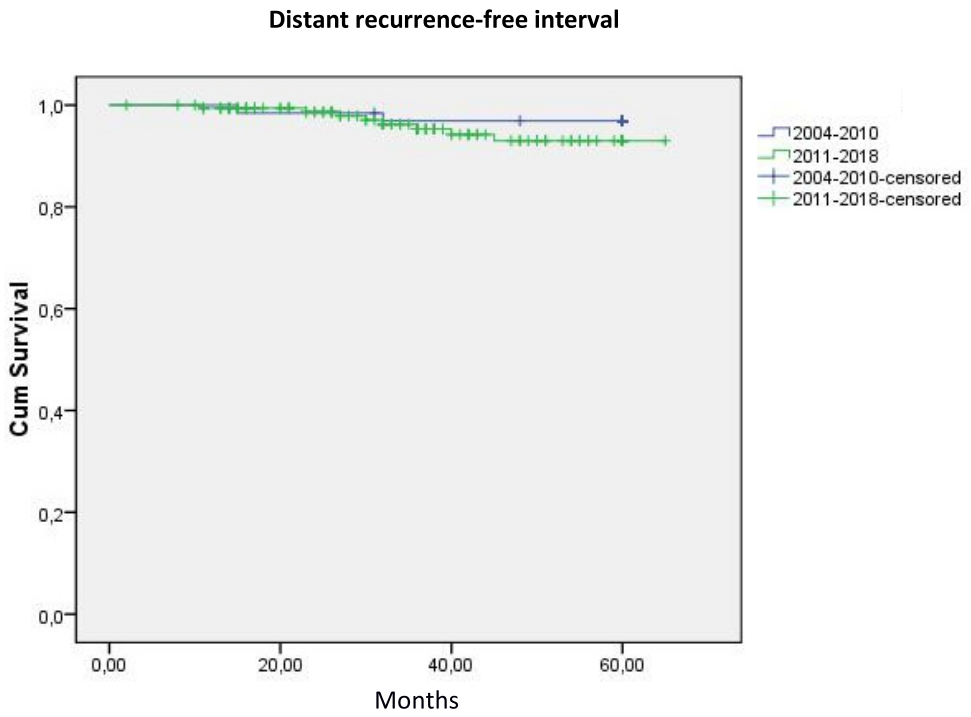

Figure 5. 5 year distant recurrence-free interval curve in 66 patients treated during 2004–10 and in 170 patients treated during 2011–18

In patients treated over the period 2004–10, the probability of DRFI estimated at 5 years was 96.9% (95% CI 92.5–101.2). In patients treated over the period 2011–18, the estimated probability of DRFI at 5 years was 93% (95% CI 88.1–97.9). The median DRFI was never reached. The differences were not statistically significant (P=0.312). The DRFI curves are shown in Figure 5.

Discussion

The results of this study provide evidence that this subgroup of patients have few events and enjoy long survival. These results have been obtained by indicating the type of systemic treatment based on classic prognostic factors, comorbidity, and the patient's decision. Overall, this is a population with a good prognosis (median tumour size 1.8 cm, median number of nodes with metastases 1 and a proliferative rate of 10%) for which chemotherapy treatment could constitute overtreatment.[6] Events related to breast cancer recurrence (locoregional recurrences, breast cancer metastases and deaths) were the most frequent, but the frequency of non-recurrence events (second primary tumours and deaths from other causes) was not negligible.

Oncologists are indicating increasingly less chemotherapy for this subgroup of patients.[20] Although incorporating genomic risk assessment is behind this reduction, in our study it is not justified by such assessment, since in Andalusia the determination of genome platforms in 2016 was only authorised for patients with negative nodes.[21]

There is growing concern regarding the overtreatment of breast cancer patients as results have improved over time and there is a sense that the use of chemotherapy has decreased in recent years, although little is known about how the use of chemotherapy and the recommendations of oncologists have changed. There are some studies that have found that for both node-negative/micrometastasis and node-positive patients, the use of chemotherapy and oncologists' recommendations for its use have decreased significantly over time, with no substantial change in clinical practice guidelines to justify it.[15] Kurian et al. show that the use of adjuvant chemotherapy in patients with stage I-II disease decreased from 26.6% to 14.1% and from 81.1% to 64.2% in node-negative and node-positive patients, respectively, between 2013 and 2015.[15] Previous studies have shown a decrease in the use of concomitant adjuvant chemotherapy with the increased use of genomic tumour profiles in patients diagnosed between 2006 and 2013.[22]

Once the results were known, the concern of our study was not focussed on overtreatment but on undertreatment, since we detected a slight advantage in the DFS of the women treated over the period 2004–10. However, it is risky to attribute this slight benefit to the use of more adjuvant chemotherapy where there is an imbalance in some patient characteristics between the two time periods (more cases of lobular carcinoma in the first period, more cases of stage IIA and IIB in the second period, plus a higher rate of mastectomy, more conservative axillary surgeries and higher use of tamoxifen than aromatase inhibitors in the second period). Survival improvement in a comparison of late versus early period could also be attributed to the Will Rogers

phenomenon of stage migration.[23] In the first period, 100% of the patients had axillary dissection, but in the second period this figure was only 55.9%. That implies patients considered as having 1-3 positive nodes in the second period are a heterogeneous group, more likely to contain patients with 4 or more positive nodes, as compared to patients of the first period. The large number of patients (living or non-event patients) censored at the end of the follow-up due to a reduced follow-up of many patients treated in the second period, without guaranteeing a minimum of 5 years, is a bias that underestimates the event and needs to be taken into account. Consequently, it would be reasonable to compare only 5-year survival, where, incidentally, the differences are not so great (96.9% DFS for the period 2004-10 and 87.7% in 2011-18, with no differences in OS and DRFS). However, analysing 5-year survival alone for a disease such as hormone-sensitive breast cancer, where late events are frequent, should be considered short. It is difficult for us to extend this to 10 years when only 30% have a follow-up of more than 5 years and approximately 1% have a follow-up for 100 months.

There was also concern where the decrease in chemotherapy use based on the incorporation of genomic risk assessment is confirmed.[6] The RxPONDER trial, now closed for recruitment of patients with hormone-sensitive, HER-2 negative breast cancer with 1–3 positive nodes and an RS of less than 25 who were randomly assigned to receive chemotherapy, will conclusively answer the question of whether adjuvant chemotherapy is necessary in this breast cancer subgroup.[24] The OPTIMA trial for patients with hormone receptor-positive, HER-2-negative, and 1–9 positive nodes or tumours larger than 3 cm, also randomly assessed chemotherapy assignment based on genomic risk.[25] Pending their results, no specific recommendations can be made. However, the inclusion criteria of the RxPONDER and OPTIMA trial are being used in clinical practice, prior to publication of their results, to suggest that patients abstain from chemotherapy.[16,26] Non-adherence to the recommendations of clinical practice guidelines and the incorporation of treatments or technology before the definitive results of clinical trials are available is common in Oncology. In a recent study, the highest percentage of treatment non-compliance in breast cancer patients was observed with chemotherapy (18%) and this treatment non-compliance was associated with worse survival.[27]

The main limitation of this study is the small sample size and its retrospective nature, with possible errors made during the selection of patients or during the collection and measurement of variables or errors in the comparison of groups, as well as in the generalisation of results in other populations. We have already commented on the bias of the large number of patients censored for the comparison of survival curves due to the short follow-up of the patients treated in the period 2011–18.

Over the years there has been a decrease in the indication for adjuvant chemotherapy according to the clinical risk in hormone-sensitive, HER-2 negative and 1-3 node positive breast cancers. This reduction cannot be attributed to the incorporation of genomic risk assessment. DFS was slightly worse over the period 2011–18, when less chemotherapy was indicated.

For hormone-sensitive, HER-2 negative, and 1-3 node positive breast cancer patients, the oncologists' recommendations on receiving adjuvant chemotherapy have decreased significantly over time. The decrease in chemotherapy use is based on the incorporation of genomic risk assessment, with no substantial change in clinical practice guidelines.

Over the years, a decrease in the indication for adjuvant chemotherapy is confirmed but this reduction cannot be attributed to the incorporation of genomic risk assessment in our study. The concern of our study was not focussed on overtreatment but on undertreatment, since DFS was slightly worse over the period when less chemotherapy was indicated. No specific recommendations can be made. However, the RxPONDER and OPTIMA trial inclusion criteria should not be used in clinical practice, prior to publication of their results, to suggest that patients abstain from chemotherapy.

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Conflict of Interest

There is no conflict of interests to declare.

Compliance with Ethical Standards

This study was approved by The Ethics Committee of Cádiz. It was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. As it is a retrospective study based on the data contained in the health histories of patients and there is no intervention or risks to them, there is justification for not requesting informed consent. The Research Ethics Committee authorised the absence of informed consent.

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