A RETROSPECTIVE ANALYSIS OF CLINICOPATHOLOGICAL DATA AND OUTCOMES OF HORMONAL POSITIVE HER2 NEGATIVE METASTATIC BREAST CANCER PATIENTS IN CLINICAL ONCOLOGY DEPARTMENT IN AIN SHAMS UNIVERSITY HOSPITALS IN EGYPT, AIN SHAMS CLINICAL ONCOLOGY REGISTRY (ASCOR).

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ABSTRACT:

Background: *Breast cancer is the most prevalent cancer in women in the world. Estrogen receptor modulators and estrogen deprivation have become standards of care for hormonal positive Her2 negative metastatic breast cancer patients. However, after traditional first-line endocrine monotherapy treatment, the disease typically progresses despite the initial high rate of clinical benefit. Multiple studies have aimed at optimizing treatment strategies to improve clinical benefit beyond the traditional single-agent endocrine treatment.*

Aim of the Work: *To analyse retrospectively clinic-pathological outcome of hormonal positive Her2 negative metastatic breast cancer patients treated in clinical oncology department in Ain Shams University hospitals in Egypt during the period from January 2017 till December 2019.*

Patients and Methods: *This is a retrospective study which included 104 hormonal positive Her-2 negative metastatic breast cancer female patients attending the breast clinic at the Clinical Oncology Department, Ain Shams University during the period between January 2017 till December 2019.*

Result: *Overall, of the 104 patients in the present study, eleven patients lost follow up, forty-two patients (40.4 %) died, and fifty-one patients (49 %) are alive till the end of our follow up. The median OS is 45.47 months, while the median PFS is 10.98 months. Age had a significant impact on PFS where patients aged more than 50 years had longer PFS (13.95 months) than those patients younger than 50 years (9.3 months) (P=0.034). Patients with metastatic breast cancer from the start were associated with longer progression free survival (PFS) (13.9 months), in comparison to patients metastatic after neoadjuvant chemotherapy (6.9 months) and after adjuvant chemotherapy (9.3 months),*

In the present study, regarding previous adjuvant hormonal treatment in recurrent breast cancer patients, those who received tamoxifen as prior adjuvant hormonal treatment had median OS 59.28 months and PFS 13.94 months, however, patients who did not receive tamoxifen as adjuvant hormonal treatment had median OS 37.68 months and PFS 7.86 months. Patients who received Aromatase inhibitors as prior adjuvant hormonal treatment had median PFS 13.94 months however, patients who did not receive AI as adjuvant hormonal treatment had median PFS 9.6 months.

Conclusion: *In general, endocrine therapy represents the mainstay for most patients with hormone receptor positive metastatic breast cancer patients. Many prognostic factors impact survival in patients with hormone receptor positive Her2 negative advanced breast cancer.*

Words: *metastatic, breast cancer, endocrine therapy, prognostic factor, progression free survival, overall survival.*

INTRODUCTION:

Breast cancer is the most common malignancy among women in the world and the leading cause of cancer death among females.(1) Despite the advances in the diagnosis and in the treatment of breast cancer, 6–10% of affected patients present metastatic breast cancer at diagnosis and 30–40% will develop metastasis during the evolution of their disease (2&3).

About two-thirds of breast cancers are hormone receptor positive(4). Hormone receptor-positive cancers tend to grow more slowly and are more likely to respond to hormonal therapy.

The treatment of metastatic breast cancer has evolved rapidly in the last 20 years(5) As 60–70% of metastatic breast cancer patients are hormonal receptor positive(6) the mainstay treatment is endocrine therapy (ET), this form of treatment targets the production of estrogen in the body or blocks the function of estrogen in the cancer cell directly(7).The hormonal therapy includes tamoxifen a selective estrogen receptor modulator (SERM) that binds competitively to estrogen receptors ,and can have both antagonistic and agonistic effect depending on the tissue action.

The use of aromatase inhibitors can be used in postmenopausal women, Aromatase inhibitors include nonsteroidal aromatase inhibitors (anastrozole and letrozole) and steroidal aromatase inhibitor (exemestane). Aromatase inhibitors block the action of peripheral aromatase, preventing conversion of androgen to estrogen.(8) The third class of endocrine therapy is fulvestrant, a selective estrogen receptor degrader. (9)

Traditional endocrine therapy at the frontline setting achieves an overall response rate in the range of 25–45% and median PFS around 8–10 months(10). Although ET is typically able to delay disease progression, almost invariably, patients will experience relapse of their disease. As disease progression is thought to represent the development of systemic resistance to ET, typically disease progression prompts a change in therapy often to a second-line ET(7).

Unfortunately, with time, disease progression will continue to occur, necessitating further changes in therapy often through multiple lines of endocrine therapy, targeted therapy, and cytotoxic therapy.

AIM OF THE WORK:

To analyse retrospectively clinic-pathological outcomes of hormonal positive Her2 negative metastatic breast cancer patients treated in clinical oncology department in Ain Shams University hospitals in Egypt during the period from January 2017 till December 2019.

PATIENTS AND METHODS:

This is a retrospective study which included 104 hormonal positive Her-2 negative metastatic breast cancer female patients attending the breast clinic at the Clinical Oncology Department, Ain Shams

University during the period between January 2017 till December 2019.

The study included females with hormonal positive Her2 negative metastatic breast cancer patients in clinical oncology department in Ain Shams University hospitals, while male patients, and females younger than 18 were excluded from the study.

The study was approved by Ain Shams University research ethics committee and all our extracted data which included name, age, sex, pathological diagnosis, time of surgery & time of the start of radiotherapy were kept confidential and the patients were kept unidentified.

The endpoints of interest were:

Primary End Point Progression free survival: Time from randomization to the first documentation of objective tumor progression or to death due to any cause or intolerable toxicity.

Secondary End Point: Overall survival (OS): Time from diagnosis to death from any cause.

Statistical analysis:

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (SPSS 15.0 for windows; SPSS Inc, Chicago, IL, 2001).

Data was presented, and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics: Mean, Standard deviation (± SD), Minimum and maximum values (range) for numerical data, Frequency, and percentage of non-numerical data.

Analytical statistics: The Independent-Samples T Test was used to assess the statistical significance of the difference between the study groups means. Chi-Square test was used to examine the relationship between two qualitative variables.

Kaplan–Meier survival analysis was carried out for progression free survival (PFS) and overall survival (OS).

The log-rank test was used to examine the statistical significance of the differences observed between the groups. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS:

Patients' clinicopathologic characteristics:

In this study, From January 2017 till December 2019, data of 104 patients were collected. The mean patient age was 53.63 years (range from 29 to 84 years old).

60.6 % of the patients were premenopausal at time of diagnosis while 39.4% of them were post-menopausal.

Table (1): Age distribution and menstrual status.

		No. = 104
Age (At Presentation)	Mean ± SD	53.63 ± 12.47
	Range	29 – 84
	≤ 50 years	42 (40.4%)
	> 50 years	62 (59.6%)

Histo-pathological confirmation of diagnosis was done for all patients through ultrasound guided- core needle biopsy from breast mass., the most common histological subtype of the pathologically examined tumors in the present study was invasive ductal carcinoma in 99 patients (95.2 %), while 5 patients had invasive lobular carcinoma (4.8%). The majority of patients with hormonal receptor (HR) positive and HER2 negative had grade II IDC, representing 81.7% of patients.

Of the 104 patients with confirmed metastatic disease, 53.8% had metastatic disease at initial diagnosis, while 30.8% %

were initially diagnosed at stage III breast cancer, and 11.5% had history of early disease (stage I and II).

Regarding the site of breast cancer metastasis, the most common site of metastasis was the bone in 78 patients (75%), followed by the liver in 38 patients (36.5%), the lung in 33 patients (31.7%), the brain in 9 patients (8.7%), and 4 of patients developed supra-clavicular lymph nodes metastases (3.8%). Twenty patients (19.2%) had metastasis in other places which included cervical lymph nodes, axillary lymph nodes, abdominal lymph nodes, mediastinal lymph nodes, peritoneum, pleura and leptomeninges. **(Table 2).**

Table (2): The site of breast cancer metastasis.

Metastasis		No. of patients	%
The site of metastasis	SCV	4	3.8%
	Bone	78	75.0%
	Liver	38	36.5%
	Lung	33	31.7%
	Brain	9	8.7%
	Others	20	19.2%

The majority of the studied patients were metastatic from the start (64 patients; 61.5%), while (34 patients; 23.1%) developed metastatic disease after adjuvant treatment, and (16 patients; 15.4%) developed metastatic disease after neoadjuvant treatment.

Concerning the first line management in metastatic breast cancer patients: out of the 104 patients in the present study, 64 patients (61.5%) received hormonal treatment. Aromatase inhibitors (anastrozole, letrozole and exemestane) were prescribed to 89.1% of patients who received hormonal treatment. Letrozole was the most common hormonal regimen used in 42 patients (65.6%). Other therapies (e.g., tamoxifen, fulvestrant) were also given was given to 11% of patients in first line.

Additionally, 59 patients received chemotherapy as first line regimen in metastatic breast cancer (56.7%). Among those who received chemotherapy, the most common used regimen was the combination of Capecitabine and aromatase inhibitors in 21 patients (35.6%) (the use of capecitabine plus AI combination therapy was part of a clinical trial for patients with hormonal receptor positive and Her2 negative metastatic breast cancer patients in our department). Other patients received chemotherapy as first line regimen due to presence of visceral crisis. Seventeen patients completed first line chemotherapy regimen then started maintenance hormonal treatment (26.15%).

Concerning the second line management in metastatic breast cancer patients, 73.8% of patient (48 patients) started second line regimen due to disease progression on first line regimen. Out of the 104 patients in the present study, 65 patients received second line treatment, 44 patients (42.3 %) received hormonal treatment as second line regimen, letrozole was the most common hormonal regimen used in 21 patients (47.7 %). Twenty patients received chemotherapy as second line regimen (19.2%), where the combination of Capecitabine and aromatase inhibitors was the most common used regimen in 11 patients (45%). Only one patient received targeted therapy (ribociclib) (1%).

Concerning Third line management in metastatic breast cancer patients, 18 patients received third line regimen, from which 12 patients received hormonal treatment (11.5%) and 6 patients received chemo-therapy regimen (5.8%).

Overall, of the 104 patients in the present study, eleven patients had lost follow up, forty two patients (40.4 %) died, and fifty one patients (49 %) are alive till the end of our follow up.The median OS is 45.47 months, while the median PFS is 10.98 months.

Table (3): First line management in metastatic breast cancer patients:

First line regimen		
Hormonal treatment	**No**	**40 (38.5%)**
	Yes	**64 (61.5%)**
Type of hormonal treatment	**letrozole**	**42 (65.6%)**
	anastrozole	**12 (18.8%)**
	Tamoxifen	**6 (9.4%)**
	Exemestane	**3 (4.7%)**
	Tamoxifen/ Fulvestrant	**1 (1.6%)**
Chemotherapy treatment	**No**	**45 (43.3%)**
	Yes	**59 (56.7%)**
Type of chemotherapy	**FEC**	**18 (30.5%)**
	Docetaxel	**2 (3.4%)**
	Capecitabine /AI	**21 (35.6%)**
	Paclitaxel	**4 (6.8%)**
	Paclitaxel /Carboplatin	**6 (10.2%)**
	Gemcitabine /Cisplatin	**1 (1.7%)**
	Adriamycin & Cyclophosphamide	**2 (3.4%)**
	Docetaxel/Cisplatin	**1 (1.7%)**
	Epirubicin & Cyclophosphamide	**1 (1.7%)**
	FEC+ Docetaxel	**1 (1.7%)**
	FEC+ Paclitaxel	**1 (1.7%)**
	Gemcitabine /Carboplatin	**1 (1.7%)**

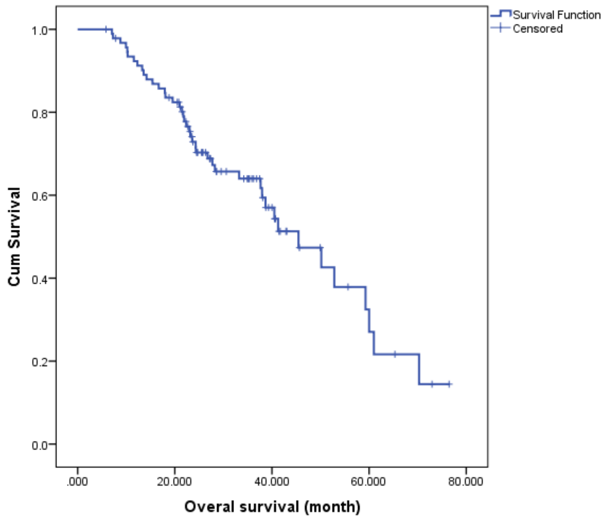

Diagram (1): OS of patients in our study

Table (4): Second line management in metastatic breast cancer patients:

2nd line regimen		
Hormonal treatment	No	60 (57.7%)
	Yes	44 (42.3%)
Type of homonal ttt	letrozole	21 (47.7%)
	Tamoxifen	5 (11.4%)
	Exemestane	9 (20.5%)
	anastrozole	4 (9.1%)
	Fulvestrant	4 (9.1%)
	Exemestane + Fulvestrant	1 (2.3%)
Chemotherapy treatment	No	84 (80.8%)
	Yes	20 (19.2%)
Chemotherapy	Paclitaxel	2 (10.0%)
	Capecitabine & AI	11 (45.0%)
	Capecitabine single agent	2 (10.0%)
	Vinorelbine	1 (5.0%)
	Epirubicin & Cyclophosphamide	1 (5.0%)
	Capecitabine & Vinorelbine	3 (15.0%)
	Paclitaxel & cisplatin	1 (5.0%)
	Gemcitabine & cisplatin	1 (5.0%)
Number of cycles	Median (IQR)	4.5 (3 – 17)
	Range	1 – 28
Targeted therapy	No	103 (99.0%)
	Yes(ribociclib)	1 (1.0%)

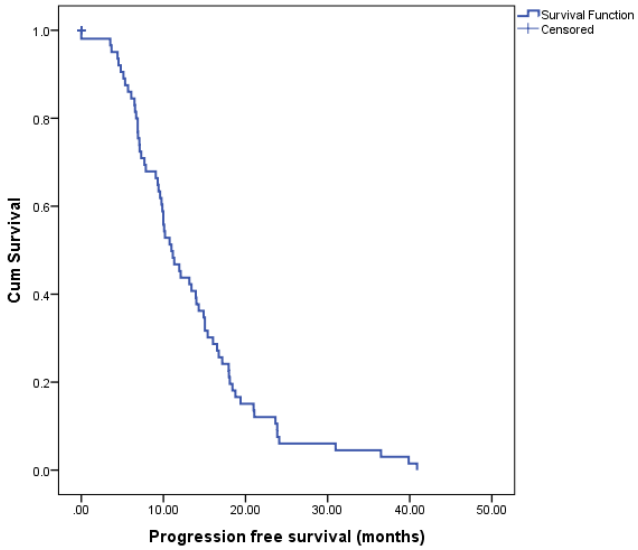

Diagram (2): PFS of patients in our study

Age had a significant impact on PFS where patients aged more than 50 years had longer PFS (13.95 months) than those patients younger than 50 years (9.3 months) (P=0.034). Patients with advanced initial clinical staging (stage III and stage IV) had worse outcome (PFS) than patients with early clinical stage (stage I and stage II).

Regarding site of metastasis, patients with lung metastasis were found to be associated with significantly worse prognosis and shorter progression free survival (PFS).

Patients with metastatic breast cancer from the start were associated with longer progression free survival (PFS) (13.9

months), in comparison to patients metastatic after neoadjuvant chemotherapy (6.9 months) and after adjuvant chemotherapy (9.3 months), however this was not consistent with OS.

In the present study, regarding adjuvant hormonal, recurrent breast cancer patients who received tamoxifen as prior adjuvant hormonal treatment had median OS 59.28 and PFS 13.94 months, however, de novo stage IV metastatic breast cancer patients who did not receive tamoxifen as adjuvant hormonal treatment had median OS 37.68 months and PFS 7.86 months. Recurrent breast cancer patients who received Aromatase inhibitors as prior adjuvant hormonal treatment had median PFS 13.94 months however, de novo stage IV metastatic breast cancer patients who did not receive AI as adjuvant hormonal treatment had median PFS 9.6 months.

The cases treated in our study with endocrinal therapy as first-line treatment had median OS 52.8 months and median PFS 13.9 months, while patients treated with chemotherapy as first-line treatment had median OS 41.2 months and median PFS 9.7 months. Accordingly, hormone receptor positive metastatic breast cancer patients treated initially with chemotherapy showed worse outcome in terms of PFS and OS compared with the patients treated initially with endocrine therapy.

DISCUSSION

Our study is a retrospective analysis of clinicopathological data and outcomes of hormonal positive Her2 negative metastatic breast cancer patients. All breast cancer patients' records in the period from January 2017 till December 2019 at Ain-Shams University Clinical Oncology department. In the present study, we investigated the factors potentially associated with the overall and progression free survival of patients, which may in turn provide a novel strategy in increasing survival.

The mean age at diagnosis our study was 53.6 years. The median overall survival in our study of metastatic hormonal positive Her2 negative patients was 45.47 months while the median PFS was 10.9 months.

Regarding age, we reported a significant correlation with progression free survival (PFS) where patients aged more than 50 years had longer PFS (13.95 months) than those patients younger than 50 years (9.3 months) (P=0.034). It is generally accepted that young age at diagnosis is associated with more aggressive disease and relatively poor survival from diagnosis.

In the present study, 90.4% of patients had initial diagnosis of infiltrating ductal carcinoma, and 4.8% had infiltrating lobular carcinoma. In a study done by **Cristofanilli et al. (2005)** [11], 76% had initial diagnosis of infiltrating ductal carcinoma, and 13 % had infiltrating lobular carcinoma**. Dawood et al. (2010)** [2] also observed that the median overall survival was affected by the histological grade where he found that high grade tumor (grade 3) had shorter median overall survival (1.78 years), in comparison to low grade tumor (grade 1 and 2) with median overall survival (2.48 years)**,** on the contrary this was not significant in our study.

Bone is the most frequently reported site of metastasis in the present study where 75% of patients had bone metastasis, this was also reported by a study done by **Largillier et al. (2008)**[16]. He also reported that patients with metastatic bone disease were associated with a relatively better survival, on the contrary, this was not significant in our study.

In the present study, patients with lung metastasis were found to be associated with significantly worse prognosis where progression free survival (PFS) was shorter in patients with lung metastasis (9.4 months) than those who didn't have lung metastasis

(12.1 months) which agrees with a study done by **Afef et al, (2013)** [17] which showed that lung metastasis tend to have shorter PFS and overall survival (OS). He also found that those with hepatic metastasis tend to have shorter overall survival (OS), which agrees with our study that showed shorter overall survival (OS) in patients with liver metastasis (41.26 months) than those who didn't have liver metastasis (45.47 months), (P=0.036).

The prognosis of metastatic breast cancer from the start was found to be better than those with recurrent tumors in several studies. In the present study, patients with metastatic breast cancer from the start were associated with longer progression free survival (PFS) (13.9 months), in comparison to patients metastatic after neoadjuvant chemotherapy (6.9 months) and after adjuvant chemotherapy (9.3 months). A study in USA estimated that Median overall survival (OS) among women with recurrent breast cancer (after adjuvant or neoadjuvant chemotherapy) was 27.2 months, which was shorter than median overall survival among women with metastatic breast cancer from the start, which was 39.3 months, making this difference being statistically significant[2].

Regarding recurrent breast cancer patients who previously received adjuvant hormonal therapy, several studies found that there is a significant relationship between prognosis of metastatic hormonal positive breast cancer patients and previous adjuvant hormonal treatment.

A study by **Gamucci et al., (2017)**[18] showed that patients who didn't receive adjuvant hormonal treatment were associated with worse overall survival, where among hormone-receptor positive recurrent metastatic breast cancer patients who previously received adjuvant hormonal treatment, had median PFS and median OS were 18.5 and 59 months, respectively. Conversely, among de novo stage IV breast cancer patients who did not receive adjuvant hormonal treatment, median PFS and median OS were 8.1 and 25 months, respectively.

Similarly, in the present study, recurrent breast cancer patients who received prior tamoxifen as adjuvant hormonal treatment had median PFS and OS 13.94 and 59.28 months, respectively. however, de novo stage IV breast cancer patients who did not receive tamoxifen as adjuvant hormonal treatment had median PFS and OS 7.86 and 37.68 months, respectively. Patients who received aromatase inhibitors as adjuvant hormonal treatment had median PFS 13.94 months, however, patients who did not receive aromatase inhibitors as adjuvant hormonal treatment had median PFS 9.6 months. There was no significance between adjuvant aromatase inhibitors and overall survival (OS).

In the present study, 64 patient received hormonal treatment as first line (61.5%), and 39 patients received chemotherapy as first line treatment (40.6%). The use of endocrinal therapy as first line treatment is supported by data showing a therapeutic benefit with less toxicity and better quality of life in comparison to chemotherapy. [19]

Regarding the addition of CDK4/6i in combination to endocrine therapy, A study by **Basile et al,. (2021)**[20] showed a prolonged PFS in patients who received a CDK4/6i-based second-line as compared to endocrinal therapy alone or chemotherapy alone (12 months for ET plus CDK4/6i, 7 months for ET alone and 6 months for CT alone**.** However, CDK4/6i-based second line regimen was only used in 1 patient in our study population.

Conclusion:

In recent years, a significant evolution has occurred in the management hormone receptor positive metastatic breast cancer patients. Given the emerging evidence, it is now essential to optimize therapy and to choose a treatment sequence strategy that considers both patients and tumor related factors. In general, endocrine therapy represents the mainstay for most patients with hormone receptor positive metastatic breast cancer patients, with palliative chemotherapy being reserved for life-threatening advanced disease or patients with visceral crisis.

Many prognostic factors impact survival in patients with hormone receptor positive Her2 negative advanced breast cancer. Treatment outcomes can vary considerably due to these factors. In the present study, many prognostic factors impacted survival such as age were younger patients had worse prognosis, site of metastasis were liver and lung metastasis were associated with worse prognosis, as well as whether the patient had recurrent breast cancer or de novo stage IV breast cancer, were recurrent breast cancer patients had worse prognosis in comparison to de novo stage IV breast cancer patients.

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دراسه بأثر راجعي للبيانات المرضيه السريرية و نتائج مرضى سرطان الثدي ذوي المستقبلات الهرمونيه الأيجابية وال Her2 السلبي في قسم الأورام بمستشفيات جامعة عين شمس.

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*قسم علاج الاورام والطب النووي - كلية الطب جامعة عين شمس**

المقدمه: سرطان الثدي هو أكثر أنواع السرطانات انتشارًا بين النساء في العالم. أصبحت مُعدِّلات مستقبلات الأستروجين والحرمان من الأستروجين معايير رعاية لمرضى سرطان الثدي ذوي المستقبلات الهرمونيه الأيجابية والHer2 السلبي ومع ذلك، بعد العلاج التقليدي للخط الأول من العلاج الهرموني، يتطور المرض عادةً على الرغم من المعدل الأولي المرتفع للفائدة السريرية. هدفت الدراسات المتعددة إلى تحسين استراتيجيات العلاج لتحسين الفوائد السريرية بما يتجاوز علاج الغدد الصماء التقليدي أحادي العامل.

الهدف من الدراسه :تحليل النتائج المرضية السريرية بأثر رجعي لمرضى سرطان الثدي النقيلي ذوي المستقبلات الهرمونيه الأيجابية و ال Her2 السلبي الذين تم علاجهم في قسم الأورام السريرية في مستشفيات جامعة عين شمس في مصر خلال الفترة من يناير ٢٠١٧ حتى ديسمبر ٢٠١٩.

النتائج: بشكل عام ، من بين ١٠٤ مريضًا في هذه الدراسة ، فقد ١١ مريضًا المتابعة ، وتوفي ٤٢ مريضًا (٤٠.٤٪) ، ولا يزال ٥١ مريضًا (٤٩٪) على قيد الحياة حتى نهاية المتابعة. متوسط البقاء الكلي هو ٤٥.٤٧ شهرًا، في حين أن متوسط البقاء على قيد الحياة بدون تقدم هو ١٠.٩٨ شهرًا. كان للعمر تأثير كبير على البقاء على قيد الحياة بدون تقدم حيث كان المرضى الذين تزيد أعمارهم عن ٥٠ عامًا يتمتعون ببقاء أطول بدون تقدم (١٣.٩٥ شهرًا) من هؤلاء المرضى الذين تقل أعمارهم عن ٥٠ عامًا (٩.٣ شهرًا) ($P = 0.034$). ارتبط المرضى الذين يعانون من سرطان الثدي النقيلي منذ البداية ببقاء على قيد الحياة أطول (١٣.٩ شهرًا)، مقارنةً بالمرضى المنتشر بعد العلاج الكيميائي المساعد (٦.٩ شهرًا) وبعد العلاج الكيميائي المساعد (٩.٣ شهرًا)، في الدراسة الحالية، فيما يتعلق بالعلاج الهرموني المساعد السابق لمرضى سرطان الثدي المتكرر، كان لدى أولئك الذين تلقوا عقار تاموكسيفين كعلاج هرموني مساعد سابق متوسط بقاء إجمالي ٥٩.٢٨ شهرًا وتطورًا مجانيًا على قيد الحياة ١٣.٩٤ شهرًا، ومع ذلك، فإن المرضى الذين لم يتلقوا عقار تاموكسيفين كعلاج هرموني مساعد كان متوسط البقاء الكلي ٣٧.٦٨ شهرًا والبقاء على قيد الحياة بدون تقدم ٧.٨٦ شهرًا. المرضى الذين تلقوا مثبطات الأروماتاز كعلاج هرموني مساعد سابق لديهم متوسط بقاء حر في التقدم ١٣.٩٤ شهرًا، ومع ذلك، فإن المرضى الذين لم يتلقوا الذكاء الاصطناعي كعلاج هرموني مساعد كان لديهم متوسط بقاء خالٍ من التقدم ٩.٦ شهرًا.