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Research article

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Evaluation of clinical features and risk factors related to late recurrence (>5 years) in patients with breast cancer

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Ethics Committee Approval
The study was carried out with the approval of the Ethics Committee of Istanbul University Istanbul Faculty of Medicine (File no: 2021/2173) on 24.12.2021.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Over the years, disease-free survival (DFS) has been considerably prolonged with effective treatments in resectable breast cancer patients. However, a limited number of studies evaluating the predictive and prognostic factors of the disease in breast cancer patients who develop late recurrence are available. In this respect, we investigated clinicopathological features and risk factors affecting the survival of patients who developed breast cancer recurrence (BCR) after 60 months (late BCR).

Methods: In this retrospective cohort study, clinicopathological features and survival outcomes of 45 late BCR patients were evaluated. The demographic and medical data of the patients were obtained from the retrospective registry system of our center. Statistical analyses were performed to determine the risk factors affecting DFS.

Results: The median age of the cohort was 49 (24–78) years. Twenty-three postmenopausal patients were included in the study, and the mean age of menopause was 50 (43–55) years. Fourteen (31.1%) patients were stage 3 at diagnosis. In the adjuvant period, 80% of the patients underwent radiotherapy, and 79.5% underwent chemotherapy. The mean duration of adjuvant hormone therapy was 64 (69–129) months. Adjuvant ovarian suppression therapy was applied to 14 patients. The three most common sites of recurrence were bones (57.8%), locoregional (26.7%), and distant lymph nodes (26.7%). The median DFS of the cohort was 116.9 (3.7) months (109.6–124.1 months). Disease-related deaths occurred in only five patients, and the median overall survival (OS) could not be achieved. Based on a log-rank analysis, the median DFS was longer in patients whose adjuvant hormone therapy duration was 5–10 years and in those with bone or lymph node recurrence (P = 0.025 and P = 0.001, respectively). DFS was significantly shorter in patients with liver metastases (P = 0.005). Based on a chi-squared analysis, bone and lymph node metastases were higher in luminal A-like group (P = 0.030), and liver metastasis was lower (P = 0.039). Luminal biology did not affect late BCR (P = 0.075).

Conclusions: Prolonged adjuvant hormone therapy (5–10 years) delays breast cancer recurrence. However, luminal features are insufficient to predict recurrence as the recurrence period increases. In addition, different sites of metastases are associated with long-term survival and luminal subgroups.

Keywords: Breast cancer, Recurrence, Survival, Hormonotherapy

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Introduction

Breast cancer is the most common cancer type worldwide with approximately one million cases annually. The 2018 data of the United States (US) reflect similar statistics, and it is the second most common cause of cancer-related death among women [1]. Although it is the leading cancer for both developed and developing countries, the 5-year survival rate in high-income countries, such as the US and Japan, is around 80%, it is 60% in middle-income countries, and 40% in low-income countries [2]. The sociocultural level, a significant risk factor, may result from country-associated differences, such as patient awareness of breast cancer, access to health services, screening programs, and estrogen exposure. Risk factors for the development of breast cancer can be listed as estrogen-related factors, such as early menarche, late menopause, low parity, having children at a late age, advanced age, excessive alcohol consumption, family history, exogenous and endogenous estrogen exposure, and BReast CAncer (BRCA) 1/2 mutation [3–6]. The average onset for breast cancer is 62 years [7]. Breast cancer-related mortality is higher under the age of 40 and again at over 80 years [8]. The majority of breast cancers originate from ductal or lobular epithelial components. The most common subtype is infiltrative ductal carcinoma (76%) followed by invasive lobular carcinoma (8%) and other rarer types [9, 10]. Lobular carcinoma tends to be multicentric, bilateral, and often hormone receptor-positive when compared with ductal carcinoma and is more common in older women as metastases are more likely to occur later in life and in atypical sites [11, 12].

The primary goal for operable tumors without distant metastases is to delay recurrence. In addition to pathological features, patient-related factors, such as age, menopausal status, hormone receptor positivity, human epidermal growth receptor factor 2 (Her2) expression status, and tumor genomic features are traditional indicators for prognostic and predictive evaluation. In the post-operative setting, the duration of disease-free survival (DFS) was significantly prolonged after undergoing chemotherapy, radiotherapy, and hormonal therapies. In hormone receptor positive patients, results of phase 3 randomized studies demonstrated that prolonging tamoxifen to 10 years in the adjuvant period significantly delays recurrence [13–15]. In addition, several clinical trials have demonstrated the efficacy of extended aromatase inhibitor therapy (>5 years) in post-menopausal women [16, 17]. Nonetheless, recurrence can be seen in patients even in the third decade after diagnosis [18]. In subsequent years, the rate of patients with late relapse will increase thanks to effective treatment methods. Therefore, we found it appropriate to contribute to the literature by identifying clinicopathological features and risk factors affecting survival in this patient group.

Materials and methods

Patients' selection criteria

Medical information from patients whose ICD 10 diagnoses between C50.0 and C50.9 at the Medical Oncology Department at Istanbul University Institute of Oncology was retrospectively scanned from the medical registry system between June 2005 and June 2016. Male patients, patients <18 years, patients who received chemotherapy before primary tumor surgery, de novo metastatic disease, bilateral breast cancer, recurrence <60 months after primary surgery, and unconfirmed pathological diagnosis were not excluded from the study. The demographic and clinical data of the remaining 45 patients with a histologically confirmed diagnosis of breast cancer based on surgical specimens were determined.

Demographic and histological variables

Demographic information of the patients, including age and menopause information, was recorded. Patients who did not have a menstrual cycle for at least one year before adjuvant therapy or who had bilateral oophorectomy were considered postmenopausal.

T and N stages were determined based on the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) 8 in surgical specimens. World Health Organization 2012 pathological calcification was used for histopathological types [19]. Primary tumor grade, estrogen receptor (ER), progesterone receptor [PR], and human epidermal growth factor receptor 2 (cERB2) status were recorded according to the modified Scarff–Bloom–Richardson system [20]. The tumors with <1% of hormone receptor (ER or PR) expression were considered as hormone receptor negative [21]. Immunohistochemically, 3+ staining of the cerbB2 receptor or Her2/centromeric region of chromosome 17 (CEP 17) Ratio ≥2.0 with *in situ* hybridization (in case of 2+ positive staining) were accepted as cerbB2 receptor positivity. The surrogate definition of intrinsic subtypes was based on Sn Gallen 2015 consensus [22].

Treatment Features and Survival

Patients were scheduled to receive adjuvant treatment 1–4 weeks after primary tumor surgery. Radiotherapy was administered to all patients with BCS and mastectomized patients with a high risk of local recurrence. Patients with positive hormone receptors were treated with tamoxifen, anastrozole, or letrozole for at least five years after radiotherapy. Ovarian suppression with luteinizing hormone–releasing hormone (LHRH) agonist was continued for 3 to 5 years in premenopausal patients who presented a high risk of relapse.

The patients with high risk for recurrence had received adjuvant chemotherapy protocol:

i. FAC/FEC: 600 mg/m^2 fluorouracil on day 1, 60 mg/m^2 doxorubicin (epirubicin 90 mg/m^2) on day 1, 600 mg/m^2 cyclophosphamide on day 1, every 21 days for six cycles.
ii. 4AC + 4T: 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide on day 1, respectively, every 21 days for four cycles, followed by 100 mg/m^2 docetaxel on day 1, every 21 days for 4 cycles.
iii. 4AC + 12P: 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide on day 1, respectively, every 21 days for four cycles, followed by 80 mg/m^2 paclitaxel on day 1, every 7 days for 12 cycles.
iv. 4TC: 600 mg/m^2 cyclophosphamide on day and 100 mg/m^2 docetaxel on day 1, every 21 days for four cycles.
v. Trastuzumab: after an 8 mg/kg loading dose, 6 mg/kg trastuzumab were given on day 1, every 21 days for one year.

The sites of metastasis at recurrence of all patients were recorded. OS and DFS were the primary targets in the survival analysis. Time-to-event endpoint for OS was considered disease-related death or the last follow-up date. Since all patients relapsed, DFS was calculated based on disease relapse date.

Statistical analysis

IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. was used for statistical analysis. For

descriptive statistics, numbers and percentages are given for categorical variables. Proportions in pathological response groups were analyzed using the chi-squared or Fisher's exact test. Survival rates were calculated using the Kaplan–Meier analysis. Risk factors were analyzed using univariate and multivariate Cox regression analysis. The statistical significance level was accepted as $P < 0.05$

Results

Clinicopathologic and treatment features

Detailed demographic and clinical findings at diagnosis are summarized in Table 1. The median age at diagnosis was 49 (24–78) years, and most of the patients were never smokers (77.8%). Fourteen of the patients reported a history of cancer in their first-degree relatives. The mean age of menarche was 14 (11–22) years. The mean of the first delivery was 22 (17–32), and the mean parity was 2 (1–6). Twenty-three postmenopausal patients were included in the study, and the mean age of menopause was 50 (43–55). Fifteen patients were stage I, 16 were stage II, and 14 were stage III at the time of diagnosis. The most common histological type was invasive ductal carcinoma (IDC; 91.1%). When luminal biology was evaluated, the most common subtype was luminal A-like (73.2%), which was followed by luminal B-like Her2 negative (12.2%), triple negative (9.8%), luminal B-like Her2 positive (2.4%) and Her2 positive only (2.4%), respectively. Grades 2 and 3 histology were 84.4% and 15.6%, respectively. Lymphovascular invasion was observed in 42.9% of the tumors. The incidence of necrosis was 19%.

Table 1: General demographic characteristics and disease findings at diagnosis

Baseline characteristics	n	%
Age at diagnosis*	49 (10)	24–78
Age at onset of menarche*	14 (2)	11–22
Age at onset of menopause*	50 (2)	43–55
Age of first pregnancy*	22 (3)	17–32
Number of parity*	2 (1)	1–6
Smoking status		
Active-smoker	3	6.7%
Ex-smoker	7	15.6%
Never-smoker	35	77.8%
Comorbidity	18	40.0%
Family history for cancer	14	31.1%
Menopause		
Premenopausal	22	48.9%
Postmenopausal	23	51.1%
Stage at diagnosis		
1	15	33.3%
2	16	35.6%
3	14	31.1%
Histology		
Invasive ductal carcinoma	41	91.1%
Invasive lobular carcinoma	3	6.7%
Other subtypes	1	2.2%
Luminal biology		
Luminal A like	33	73.3%
Luminal B like Her2 negative	6	13.4%
Luminal B like Her2 positive	1	2.2%
Her2 positive only	1	2.2%
Triple negative	4	8.9%
Histological grade		
1	0	0.0%
2	38	84.4%
3	7	15.6%
Nuclear grade†		
1	1	2.3%
2	37	84.1%
3	6	13.6%
Lymphovascular invasion	18	42.9%
Necrosis	8	19.0%

* "median and standard deviation" is used instead of "N", and "minimum–maximum" is used instead of "%".
†The tumor grade is missing in one patient.

All patients underwent surgery before systemic treatments. The mean pathological tumor diameter was 2.7 cm (0.9–3.5 cm), and the mean number of metastatic positive lymph nodes was 3 (0–20). In the adjuvant period, 80% of the patients underwent radiotherapy, and 79.5% underwent chemotherapy. When we examine the hormonotherapy profile, tamoxifen was the most common treatment (57.7%) followed by anastrozole (28.9%) and letrozole (2.2%). The mean duration of adjuvant hormone therapy was 64 (69–129) months. Adjuvant ovarian suppression therapy was administered to 14 patients. The three most common sites of recurrence were bone (57.8%), locoregional (26.7%), and distant lymph nodes (26.7%). Treatment features and metastasis sites at first relapse of patients are summarized in Table 2.

Table 2: Treatment features and metastasis sites at first relapse

Detailed clinical features	n	%
Primary tumor diameter	2,7 (1.8)	0.9–5.5
Number of dissected lymph nodes*	11 (8)	1–30
Number of metastatic lymph nodes*	3 (5)	0–20
Adjuvant radiotherapy	36	80.0%
Adjuvant chemotherapy	35	79.5%
Adjuvant trastuzumab therapy	2	4.5%
Adjuvant hormonotherapy		
None	5	11.2%
Tamoxifen	26	57.7%
Anastrozole	13	28.9%
Letrozole	1	2.2%
Adjuvant hormonotherapy duration	64 (27)	69–129
Recurrence under hormonotherapy treatment	10	22.2%
Adjuvant ovarian suppression	14	31.1%
Recurrence sites		
Bone	26	57.8%
Locoregional	12	26.7%
Lymph nodes	12	26.7%
Liver	7	15.6%
Lung	5	11.1%
Ovary	2	4.4%
Brain	1	2.2%
Peritoneum	1	2.2%

* "median and standard deviation" is used instead of "N", and "minimum–maximum" is used instead of "%".

Survival and risk factors

The median DFS of the cohort was 116.9 (3.7) months (109.6–124.1 months). Disease-related death occurred in only eight patients, and the median OS could not be reached. Fifteen and twenty-year survival rates were 81.7% and 72.6%, respectively (Figure 1).

In the log-rank analysis, risk factors affecting DFS were duration of adjuvant hormone therapy (<5 versus 5–10 years; $P = 0.025$), liver metastasis ($P = 0.005$), and presence of bone or lymph node metastasis ($P = 0.001$) as shown in Figure 2. The median DFS was significantly shorter in patients with liver metastases than without (87.2 versus 121.3 months). Bone or lymph node metastases were associated with a longer DFS than visceral metastases (132.8 versus 91.8 months). Since only two patients with luminal B like-Her2 positive and Her2 positive only were included in the study, these subgroups were excluded from the log-rank analysis. The median DFS was 130.5 (9.3) months (112.2–148.8 months) in those with luminal A-like, 89.1 (12.5) months (64.4–113.7 months) in those with luminal B-like Her2 negative, and 69.8 (28.6) months (13.7–126.0 months) in those with triple negative ($P = 0.075$). Those who received adjuvant hormone therapy <5 years had a shorter median DFS than those who received 5–10 years (104.6 versus 130.8 months). Comorbidity, menopausal status, disease stage, histological grade, nuclear grade, lymphovascular invasion, necrosis, ducal *in situ* carcinoma (DCIS) component, type of surgery, adjuvant radiotherapy, and adjuvant chemotherapy had no statistically significant effect on DFS ($P > 0.05$). The multivariate Cox regression analysis found no significant prognostic risk factor on DFS (Table 3).

Figure 1: Kaplan-Meier survival curves in patients with breast cancer relapse

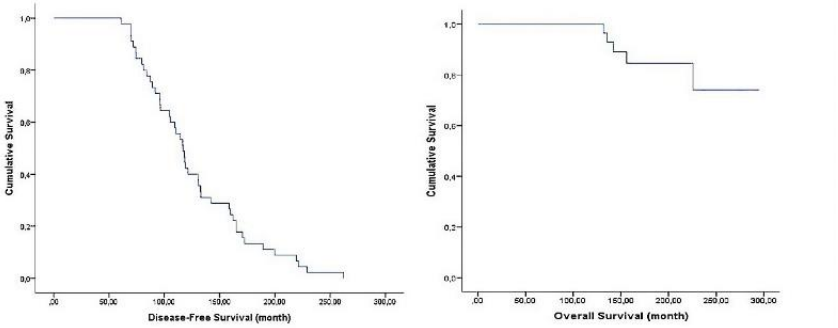

Figure 2: Survival analysis of risk groups affecting on disease-free survival

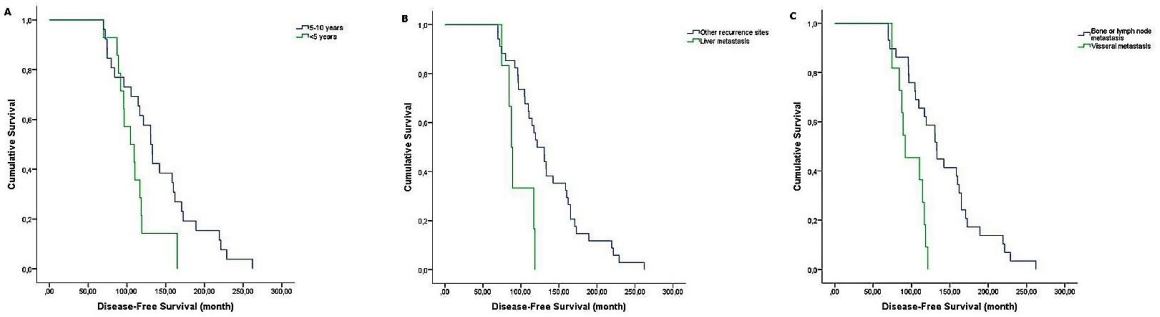

Table 3: Multivariate analysis for disease-related death

Risk Factors	n (%)	*P*-value	HR	95% CI
Adjuvant hormone therapy duration <5 years	28 (62.2)		1	
Adjuvant hormone therapy duration 5–10 years	17 (37.8)	0.115	0.54	0.25–1.16
Luminal A like	33 (73.4)		1	
Luminal B like Her2 negative	6 (13.5)	0.858	1.17	0.33–1.75
Triple negative	4 (9.1)	0.745	1.477	0.14–15.5
Other metastasis	38 (84.4)		1	
Liver metastasis	7 (15.6)	0.761	.812	0.21–3.11
Other metastasis	16 (35.6)		1	
Bone or lymph node metastasis	29 (64.4)	0.79	0.33	0.09–1.13

CI: Confidence interval; ECOG–PS: Eastern Cooperative Oncology Group–Performance status; HR: Hazard ratio

Discussion

In this study, we aimed to determine the clinical characteristics and risk factors of patients with late BCR five years after primary treatment. The mean age of our study patients was 45 years, and the rate of stage III disease was 31.1%. In a Danish study evaluating breast cancer patients with recurrence after ten years, the mean age at diagnosis was 55, and stage III breast cancer was 8.8% [23]. Likewise, in randomized prospective TEAM and IDEAL studies evaluating extended hormone therapies, the mean age was 55–63 years, and the rate of stage 3 patients was approximately 15% [17, 24]. It is noteworthy that our cohort was younger and had more stage 3 diseases compared to other population-based studies.

Pedersen et al. [23] found that tumor size larger than 20 mm, lymph node-positive disease, and ER positivity was associated with an increased risk of recurrence in 36,924 breast cancer patients who developed recurrence between 10 and 32 years. In a study evaluating late BCR in patients with ER positive breast cancer, nodal involvement and tumor diameter were found to be two crucial prognostic risk factors. In this study, none of the immuno-histochemical (IHC) markers (ER, PgR, cerbB2, and Ki67 score) were significant for late BCR [25]. In our study, no relationship was observed between the initial stage, which includes T and N, and late BCR. This difference may be related to the limited number of our cohorts compared to other studies. In our study, DFS was longest in patients with luminal A-like followed by luminal B-like Her2-negative and triple-negative patients, but statistical significance was not reached. Those who received prolonged hormone therapy (5–10 years) had a significantly longer DFS than those who did not. The essential factors in the emergence of late BCR seem to be the initial T and N stages. It has also been demonstrated in our study in line with phase 3 randomized studies, that hormone therapy is protective for the first ten years in hormone receptor positive tumors. Conflicting results about whether ER positivity is protective in late BCR have been published. In our cohort, liver metastases predicted an earlier recurrence, whereas lymph or bone metastasis was associated with longer DFS. In a study by Abha et al. [26] that investigated the relationship between luminal biology and distant metastasis in 531 breast cancer patients, they revealed that luminal tumors were present with bone metastasis. In another retrospective study evaluating site-specific metastasis in breast cancer, it was shown that liver, brain, and lung metastases were higher in non-luminal subtypes [27]. In addition, many studies have revealed that liver metastasis is associated with poor survival [28, 29]. In a chi-squared analysis, bone and lymph node metastases were higher in luminal A-like group, whereas liver metastasis was found to be lower. The results of our study are compatible with studies in the literature.

Limitations

Our major study limitations are the low number of patients and the single-center design of the study. In addition, we could not compare our findings with an earlier relapsed control arm. Therefore, our statistical results may have revealed different results compared to other clinical studies. Multicenter studies with larger samples are needed to confirm this finding.

Conclusions

Late BCR has unique clinical features compared to early BCR. Although prolonged hormone therapy appears effective, risk assessments based on luminal biology appear insufficient in late BCR. In addition, our results show that different sites of metastasis are associated with survival and luminal subgroups.

References

The National Library of Medicine (NLM) citation style guide has been used in this paper.

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians. 2018;68(1):7-30. doi: 10.3322/caac.21442. PubMed PMID: 29313949.
2. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). The Lancet Oncology. 2008;9(8):730-56. doi: 10.1016/S1470-2045(08)70179-7. PubMed PMID: 18639491.
3. Washbrook E. Risk factors and epidemiology of breast cancer. Women's Health Medicine. 2006;3(1):8-14. doi: 10.1383/wohm.2006.3.1.8.
4. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians. 2017;67(1):7-30. doi: 10.3322/caac.21387. PubMed PMID: 28055103.
5. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, Bernstein L, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol. 2016;45(3):916-28. doi: 10.1093/ije/dyv156. PubMed PMID: 26320033; PubMed Central PMCID: PMC5005939.
6. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Family history and risk of breast cancer: an analysis accounting for family structure. Breast Cancer Res Treat. 2017;165(1):193-200. doi: 10.1007/s10549-017-4325-2. PubMed PMID: 28578505; PubMed Central PMCID: PMC5511313.
7. Wörmann B. Breast cancer: basics, screening, diagnostics and treatment. Medizinische Monatsschrift fur Pharmazeuten. 2017;40(2):55-64. Epub 2017/02/01. PubMed PMID: 29952495.
8. Brandt J, Garne JP, Tengrup I, Manjer J. Age at diagnosis in relation to survival following breast cancer: a cohort study. World journal of surgical oncology. 2015;13(1):1-11.
9. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer. 2005;93(9):1046-52. doi: 10.1038/sj.bjc.6602787. PubMed PMID: 16175185; PubMed Central PMCID: PMC2361680.
10. Luini A, Aguilar M, Gatti G, Fasani R, Botteri E, Brito JA, et al. Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the European Institute of Oncology and review of the literature. Breast Cancer Res Treat. 2007;101(3):349-53. doi: 10.1007/s10549-006-9301-1. PubMed PMID: 17009109.
11. Orvieto E, Maiorano E, Bottiglieri L, Maisonneuve P, Rotmensz N, Galimberti V, et al. Clinicopathologic characteristics of invasive lobular carcinoma of the breast: results of an analysis of 530 cases from a single institution. Cancer. 2008;113(7):1511-20. doi: 10.1002/cncr.23811. PubMed PMID: 18704988.
12. Ferlicot S, Vincent-Salomon A, Medioni J, Genin P, Rosty C, Sigal-Zafrani B, et al. Wide metastatic spreading in infiltrating lobular carcinoma of the breast. European journal of cancer (Oxford, England : 1990). 2004;40(3):336-41. PubMed PMID: 14746850.
13. Francis PA, Pagani O, Fleming GF, Walley BA, Colleoni M, Láng I, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. New England Journal of Medicine. 2018;379(2):122-37. doi: 10.1056/NEJMoa1803164. PubMed PMID: 29863451.
14. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet (London, England). 2013;381(9869):805-16. Epub 2012/12/12. doi: 10.1016/s0140-6736(12)61963-1. PubMed PMID: 23219286; PubMed Central PMCID: PMCPMC3596060.
15. Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. American Society of Clinical Oncology; 2013.
16. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. The Lancet Oncology. 2017;18(11):1502-11. Epub 2017/10/17. doi: 10.1016/s1470-2045(17)30600-9. PubMed PMID: 29031778.
17. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, Putter H, van den Bosch J, et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05). Journal of the National Cancer Institute. 2018;110(1). Epub 2017/09/20. doi: 10.1093/jnci/djx134. PubMed PMID: 28922787.
18. Mamby CC, Love RR, Heaney E. Metastatic breast cancer 39 years after primary treatment. Wisconsin medical journal. 1993;92(10):567-9.
19. Lakhani SR, Ellis IO, Schnitt S, Tan PH, van de Vijver M. WHO Classification of Tumours of the Breast. 2012.
20. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991;19(5):403-10. Epub 1991/11/01. doi: 10.1111/j.1365-2559.1991.tb00229.x. PubMed PMID: 1757079.
21. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(16):2784-95. Epub 2010/04/21. doi: 10.1200/jco.2009.25.6529. PubMed PMID: 20404251; PubMed Central PMCID: PMCPMC2881855 are found at the end of this article.
22. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(8):1533-46. Epub 2015/05/06. doi: 10.1093/annonc/mdv221. PubMed PMID: 25939896; PubMed Central PMCID: PMCPMC4511219.
23. Pedersen RN, Esen BÖ, Mellemkjær L, Christiansen P, Ejlertsen B, Lash TL, et al. The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis. JNCI: Journal of the National Cancer Institute. 2021;114(3):391-9. doi: 10.1093/jnci/djab202.
24. Derks MG, Blok EJ, Seynaeve C, Nortier JW, Kranenbarg EM-K, Liefers G-J, et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2017;18(9):1211-20. doi: 10.1016/S1470-2045(17)30419-9
25. Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens JW, et al. Factors predicting late recurrence for estrogen receptor–positive breast cancer. Journal of the National Cancer Institute. 2013;105(19):1504-11. doi: 10.1093/jnci/djt244
26. Soni A, Ren Z, Hameed O, Chanda D, Morgan CJ, Siegal GP, et al. Breast Cancer Subtypes Predispose the Site of Distant Metastases. American Journal of Clinical Pathology. 2015;143(4):471-8. doi: 10.1309/ajcpyo5fsv3upexs.
27. Xiao W, Zheng S, Yang A, Zhang X, Zou Y, Tang H, et al. Breast cancer subtypes and the risk of distant metastasis at initial diagnosis: a population-based study. Cancer management and research. 2018;10:5329-38. Epub 2018/11/23. doi: 10.2147/cmar.s176763. PubMed PMID: 30464629; PubMed Central PMCID: PMCPMC6225920.
28. Chen W, Hoffmann AD, Liu H, Liu X. Organotropism: new insights into molecular mechanisms of breast cancer metastasis. npj Precision Oncology. 2018;2(1):4. doi: 10.1038/s41698-018-0047-0.
29. Wyld L, Gutteridge E, Pinder S, James J, Chan S, Cheung K, et al. Prognostic factors for patients with hepatic metastases from breast cancer. British journal of cancer. 2003;89(2):284-90. doi: 10.1038/sj.bjc.6601038.