ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Clinical and Pathological Predictors of Recurrent Breast Cancer

Khadija AlMusalhi[1]* and Salim Al Rahbi[2]

[1]General Surgery Residency Training Program, Oman Medical Specialty Board, Muscat, Oman

[2]Breast Surgery Department, Royal hospital, Muscat, Oman

ABSTRACT

Objectives: Recurrence of breast cancer is common. There are reported risk factors for recurrence which are patient age, tumor size, tumor grade, (lymph vascular invasion (LVI), extensive intraductal component (EIC), and margin status. Nodal involvement also contributes to the recurrence rate as well as hormonal status, and if the patient receives neoadjuvant/adjuvant therapy or not. The aim of this study is to look for the clinical and pathological predictors of patients who have recurrent breast cancer after surgical treatment.

Methods: We conducted a retrospective cohort study at one center (Royal hospital) between 2010 to 2020 for patients who were treated surgically for non-metastatic breast cancer. We collected the clinical which was mainly the age at the diagnosis and pathological predictors (final histopathology report of the surgical specimen) from the medical records system of the hospital after obtaining the ethical approval. Total sample size was 270 Omani patients. The primary endpoint was the time to locoregional recurrence or systemic recurrence as the first event. A multivariate analysis of the predictors was carried and a P-value of < 0.05 was considered statistically significant with 95% CI.

Results: Out of 270 patients with breast cancer who were surgically treated, 113 had recurrence and 157 had no recurrence. There were 104 patients with recurrence have invasive ductal carcinoma (IDC) and 9 patients with high-grade ductal carcinoma in situ (DCIS). The Mean age of patients with recurrence was 44.0 while in patients without recurrence was 48.3. The difference in age between the two groups is not statistically significant in predicting the recurrence (p = 0.816). **ER, LVI, EIC, nodal involvement, grade, margin, and type of tumor** were the significant predictors of recurrence by bivariate analysis. However, **High grade** (Hazard **ratio** (**HR**) = **3.823, 95% CI: 1.104-13.240; p = 0.034**), **EIC (HR = 17.407, 95% CI: 1.538-196.999; p = 0.021), and nodal involvement (HR = 2.314, 95% CI: 1.123-4.767; p = 0.023)** remain the significant predictors for recurrent breast cancer in the multivariate Cox regression analysis. By using Kaplan-Meier, the median survival time was 132 months and the recurrence-free survival at two years was 88.0% (The recurrence rate = 12.0%).

Conclusions: High grade, extensive intraductal component, and nodal involvement are significant predictors for breast cancer recurrence. The recurrence-free survival at 2 years is 88.0%. Our recommendation is a close follow-up for patients with these predictors.

***Corresponding author**

Khadija AlMusalhi, General Surgery Residency Training Program, Oman Medical Specialty Board, Muscat, Oman.

Received: May 04, 2024; **Accepted:** May 09, 2024; **Published:** May 16, 2024

Introduction

Recurrence of breast cancer is a common concern, with the 10-year incidence ranging around 12-13% following different treatment approaches. The majority of breast cancer recurrences occur within the first five years after diagnosis, particularly in cases with hormone receptor-negative disease [1]. There are studied predictors which showed a higher risk of recurrence. Age has been studied as a potential predictor of recurrence, and it was found that women aged 45 to 49 years tend to have the best prognosis, with higher relative survival rates compared to younger patients. However, relative survival declines significantly after the age of 49, particularly in women aged 50 to 59, and the oldest women (greater than 75) have the worst recurrence rates [2]. However, contemporary studies suggest that recurrences among young women diagnosed with breast cancer have become less frequent over time [3]. However, age is not considered as independent risk factor for recurrence.

Tumor size defined as the largest diameter of the primary breast tumor, was recognized early as an important prognostic factor in breast cancer [4]. Another risk factor of recurrence is nodal involvement. Among women with no evidence of metastatic disease (M0), the five-year survival rate for those who present with localized (i.e breast only) versus regional disease (ie, pathologic node involvement) is 99 and 85 percent, respectively [5]. In a study including over 2200 operable breast cancer cases, there was a correlation between histologic grade and worsened outcomes, with an HR for worsened breast cancer-specific survival (BCSS) of 1.6 for grade 2 versus 1 cancers (95% CI 1.1-2.5) and 3.9 for grade 3 versus grade 1 cancers (95% CI 2.6-5.8) [6]. The presence of lympho-vascular invasion appears to be a poor prognostic indicator, particularly in higher-grade tumors. This was shown in a cohort study of 1704 patients with operable breast cancer, that did not receive any systemic adjuvant therapy. Vascular invasion was of independent prognostic significance for both survival and for local recurrence of tumor [7]. In another retrospective analysis

of 2754 patients treated in two adjuvant therapy trials, PLVI was associated with worse disease free survival, but its prognostic value was abrogated by adjuvant endocrine therapy [8]. Margin status is an important predictor of recurrence as many studies stated so. in this prospective study it was concluded that patients with close margins and those with negative margins both had a rate of local recurrence (LR) of 7%. Patients with extensively positive margins had an LR rate of 27%, whereas patients with focally positive margins had an intermediate rate of LR of 14% [9]. In another prospective study followed patients after breast conserving surgery it was found that positive margin (p 5 0.02), IDC/DCIS (p 5 0.04) and age (0.0006) as significantly associated with local recurrence [10]. Never the less local recurrence doesn't only depend on a positive or a negative margin, but has other multiple predictors, including: presence of LVI, presence of EIC, and number of margins which are involved [11]. In addition, immunohistochemistry panel of the tumor and hormonal status are considered in evaluation patient with high risk of recurrence. Ki-67 was studied, heterogenous results are published, however the large studies concluded that Ki-67 is a poor prognostic factor [12]. ER, PR status play a major role in classifying patient into high risk for relapse or low risk. They are generally associated with improved breast cancer outcomes, at least over the short term [13,14]. In general, tumors that are singly hormone receptor positive (ie, ER positive and PR negative, or PR positive and ER negative) appear to have a worse prognosis than those that are ER positive and PR positive. This was shown in a cohort study of over 820,000 patients with hormone receptor-positive breast cancer, in which patients with single hormone receptor-positive subtypes had worse breast cancer-specific survival than patients with double hormone receptor-positive subtypes, over a median follow-up of almost six years (ER-positive/PR-negative tumors, HR 1.36, 95% CI 1.34-1.38; ER-negative/PR-positive tumors, HR 1.61, 95% CI 1.55-1.67) [15].

Breast cancer in Oman is most common cancer among Omani women, however we do not have a clear statistic about the recurrence rate and no previous studies in Oman or the gulf region about the recurrent breast cancer and its predictors. The aim of this study is to look for the clinical and pathological predictors of patients who have recurrent breast cancer after surgical treatment.

Methodology

We conducted a retrospective cohort study at one center (Royal hospital) between 2010 to 2020 for patients who were treated surgically for non-metastatic breast cancer. Inclusion criteria were: Women with breast cancer (Invasive ductal carcinoma /high grade DCIS) who developed recurrence after surgical treatment, no distal metastasis at the time of presentation, and recurrence was proven radiologically. Sample size was calculated using nMaster 2.0. Based on the expected recurrence prevalence of 20%, precision of 3% with desired confidence level of 95% with the expected population size of 120, need to study minimum of 102 samples. We collected the clinical which was mainly the age at the diagnosis and pathological predictors (final histopathology report of the surgical specimen) from the medical records system of the hospital after obtaining the ethical approval (Ethical approval was obtained from Centre of Studies and Research in MOH (code: MoH/CSR/22/25646). Total sample size was 270 Omani patients. The primary endpoint was the time to locoregional recurrence or systemic recurrence as the first event. A multivariate analysis of the predictors was carried and a P-value of < 0.05 was considered statistically significant with 95% CI. Data was analyzed using IBM SPSS Statistics 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.) Categorical variables were presented with frequency and percentages and compared using chi-square test. Continuous variables were presented with mean, standard deviation or median and compared using independent t-test. Kaplan-Meier survival curves were used to assess the recurrence free survival. Cox proportional hazard model was done to adjust the factors associated with recurrence. P-value of <0.05 was considered statistically significant.

Results

Total of 270 patients with breast cancer who were surgically treated were included between the period of 2010 to 2020. However, these are not the total patient who were treated in Royal hospital. These patients were followed up retrospectively after the surgery.113 had recurrence and 157 had no recurrence.104 patients with recurrence have IDC and 9 patients with high grade DCIS.

Bivariate Analysis of characteristics

by using Mann-Whitney test for both age at the diagnosis and size of the tumor the results showed the mean age at diagnosis for the group with recurrence was 44.08 years, while the mean age for the group without recurrence was 48.37 years, the p-value 0.006 which is statistically significant. The mean size of the tumor for the group with recurrence was 37.6559 mm, while the mean size for the group without recurrence was 31.8677 mm, the p-value for tumor size was 0.002 which is also statistically significant.

Table 1	Recurrence	Mean	Standard Deviation	P-Value
Age at Diagnosis	Yes	44.08	12.618	0.006
	No	48.37	12.382	
Size of the Tumor (mm)	Yes	37.6559	22.74313	0.002*
	No	31.8677	31.33379	

Other characteristics include ER, PR, Her-2, LVI, EIC, neoadjuvant chemotherapy, chemotherapy, radiotherapy, Herceptin (Trastuzumab), type of breast surgery: mastectomy vs. breast conserving surgery, nodal involvement, grade, margin, and type of tumor. The table (2) shows the number of patients (N) for each predictor, the recurrence rates for patients with and without the predictor, and the corresponding p-values by using chi-square test. The data reveals that patients with ER had a statistically significant difference in recurrence rates with 64.10% of patients without ER experiencing recurrence compared to 35.90% of patients with ER ($p = 0.011$). In contrast, patients with PR and Her-2 did not show significant differences in recurrence rates ($p = 0.171$ and $p = 0.702$, respectively). Patients with LVI had a significantly higher recurrence rate of 50.70% compared to 49.30% for patients without LVI ($p = 0.001$). Similarly, patients with EIC had a significantly higher recurrence rate of 51.70% compared to 48.30% for patients without EIC ($p < 0.001$).

Regarding treatment, patients who received neoadjuvant chemotherapy, chemotherapy, radiotherapy, and Herceptin (Trastuzumab) did not show significant differences in recurrence rates ($p = 0.263$, $p = 0.681$, $p = 0.555$, and $p = 0.788$, respectively). Patients who underwent breast surgery had a 56.20% recurrence rate with no significant differences between mastectomy and breast-conserving surgery ($p = 0.9$). Patients with nodal involvement had a much higher recurrence rate of 59.70% compared to 40.30% for patients without nodal involvement ($p < 0.001$).

Grade, margin, and type of tumor also showed significant associations with recurrence rates. Patients with high-grade tumors had a significantly higher recurrence rate than those with low-grade tumors ($p < 0.001$). Patients with close or positive margins also had a higher recurrence rate compared to patients with negative margins ($p = 0.018$). Patients with invasive ductal or high-grade DCIS tumors had significantly higher recurrence rates than patients with other types of tumors ($p = 0.006$).

Table 2 Predictor	N	Recurrence		P-Value
		No	Yes	
ER	270	64.10%	35.90%	0.011
PR	269	62.10%	37.90%	0.171
Her-2	270	59.80%	40.20%	0.702
LVI	263	49.30%	50.70%	0.001
EIC	60	48.30%	51.70%	<0.001
Neoadjuvant Chemotherapy	270	62.40%	37.60%	0.263
Chemotherapy	270	57.20%	42.80%	0.681
Radiotherapy	270	56.90%	43.10%	0.555
Herceptin (Trastuzumab)	269	56.80%	43.20%	0.788
Breast Surgery	258	56.20%	43.80%	0.9
Mastectomy	139	56.80%	43.20%	
Breast Conserving Surgery	119	55.50%	44.50%	
Nodal Involvement	231	40.30%	59.70%	<0.001
Grade	252	59.10%	40.90%	<0.001
1		85.00%	15.00%	
2		58.80%	41.20%	
3		46.90%	53.10%	
Margin	268	58.60%	41.40%	0.018
Negative	156	53.20%	46.80%	
Close	91	70.30%	29.70%	
Positive	21	47.60%	52.40%	
Type of Tumor	270	58.10%	41.90%	0.006
Invasive Ductal	229	54.60%	45.40%	
High Grade DCIS	41	78.00%	22.00%	

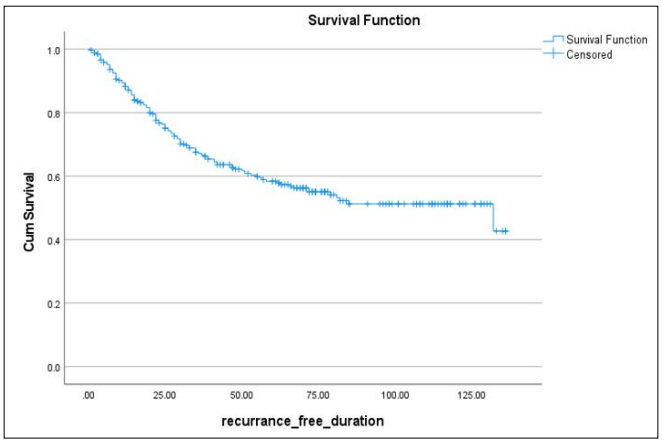
Multivariate Analysis: "Cox Regression"

The results indicate that several predictors are significantly associated with recurrence. Patients with extensive intraductal component (EIC) had a hazard ratio of 17.41 (CI 1.54-197.00, $p = 0.021$), indicating a significantly higher risk of recurrence. Similarly, patients with nodal involvement had a hazard ratio of 2.31 (CI 1.12-4.77, $p = 0.023$) compared to patients without nodal involvement. Patients with high-grade tumors (grade 2 and 3) also had a significantly higher risk of recurrence compared to patients with low-grade tumors, with hazard ratios of 3.44 (CI 0.98-12.08, $p = 0.053$) and 3.82 (CI 1.10-13.24, $p = 0.034$), respectively.

In contrast, age at diagnosis, size of the tumor, ER and PR receptor status, type of tumor, and margin status were not found to be significantly associated with recurrence in this analysis as shown in Table 3

Table 3 Predictor	P-Value	Cox Regression Hazard Ratio	95.0% CI	
			Lower	Upper
Age at Diagnosis	0.816	0.997	0.976	1.019
Size of the Tumor in (mm)	0.464	0.997	0.988	1.006
Receptors Status - ER	0.349	1.708	0.556	5.245
Receptors Status - PR	0.627	1.259	0.497	3.192
Lympho- Vascular Invasion	0.092	1.684	0.918	3.089
EIC	0.021	17.407	1.538	196.999
Grade	0.106			
Grade2	0.053	3.443	0.982	12.075
Grade3	0.034	3.823	1.104	13.24
Type of Tumor	0.965	0	0	0
Nodal Involvement	0.023	2.314	1.123	4.767
Margin	0.348			
Margin (Close)	0.291	0.76	0.456	1.265
Margin (Positive)	0.253	0.584	0.232	1.469

The median survival time is estimated to be 132 months, with a 95% confidence interval ranging from 40.555 to 211.488 months. Recurrence free survival at two years is 88% (12% recurrence rate). Graph 1



Median for Survival Time			
Estimate	**Std. Error**	**95% Confidence Interval**	
		Lower Bound	Upper Bound
132.000	40.555	52.512	211.488

Discussion

The present study analyzed the outcomes of 270 patients with breast cancer who underwent surgical treatment between the period of 2010 to 2020. It is important to note that these patients were followed up retrospectively after the surgery, and this sample does not represent all the patients treated in Royal Hospital during this period. Among these patients, 113 had recurrence, while 157 had no recurrence.

The mean age at diagnosis for the group with recurrence was 44.08 years, which was significantly younger than the mean age for the group without recurrence (48.37 years), as indicated by the p-value of 0.006. This finding suggests that younger patients may be at a higher risk for breast cancer recurrence than older patients. It is important to note, however, that the standard deviation for both groups was relatively high, indicating a wide range of ages within each group. Second, the mean size of the tumor for the group with recurrence was significantly larger than the mean size for the group without recurrence, as indicated by the p-value of 0.002. This finding suggests that tumor size may be an important factor in predicting breast cancer recurrence. However, it is important to note that the standard deviation for tumor size was also relatively high in both groups, indicating variability in tumor size within each group. However, the results of the Cox regression analysis indicate that after adjusting for other potential confounding variables, neither age at diagnosis ($p = 0.816$) nor tumor size ($p = 0.464$) were significant predictors of breast cancer recurrence. These results suggest that after controlling for other potential confounding variables, age and tumor size may not be independent predictors of breast cancer recurrence. These results do not match other studies results which found that age and tumor size are independent risk factors. This could be explained by the fact that mean age of diagnosis in both groups (recurrent vs. non-recurrent) is above 40 years of age which is considered as age of best survival [16,17].

In the bivariate analysis, several predictors were found to be significantly associated with breast cancer recurrence, including ER status, LVI, EIC, nodal involvement, grade, margin, and type of tumor. Patients with ER-positive tumors had a significantly lower risk of recurrence compared to patients with ER-negative tumors. Patients with LVI and EIC had significantly higher recurrence rates, highlighting the importance of these features in predicting patient outcomes. Nodal involvement, grade, margin, and type of tumor were also found to be significant predictors of recurrence in the bivariate analysis.

The multivariate analysis, which used Cox regression, revealed that only EIC, nodal involvement, and grade remained significant predictors of recurrence after adjusting for other potential confounding factors. Patients with EIC had a hazard ratio of 17.41, indicating a significantly higher risk of recurrence compared to patients without EIC. Nodal involvement was also found to be a significant predictor of recurrence, with a hazard ratio of 2.31. Patients with high-grade tumors had a significantly higher risk of recurrence compared to patients with low-grade tumors.

The study did not find significant differences in recurrence rates based on treatment modalities, including neoadjuvant chemotherapy, chemotherapy, radiotherapy, and Herceptin (Trastuzumab). This may indicate that the treatment modalities themselves do not significantly impact recurrence rates, but rather the underlying characteristics of the tumor and patient play a more significant role. However, it is important to notice that some patients did not complete full treatment and some of them lost follow up, therefore these factors could impact the results.

Interestingly, some predictors that were significant in the bivariate analysis, such as ER status and margin status, were not significant in the multivariate analysis. This may be due to the fact that these predictors are strongly correlated with other predictors in the model, and the effects of these other predictors may have overshadowed their individual effects.

However, our study cannot prove that hormonal status (ER, PR & HER-2 status) do not play role in recurrence rate because in this study we did not study the hormonal status of the tumor after recurrence which could be change from primary tumor as there is discordance in hormonal status between primary and recurrent tumor [18].

The study's findings regarding the lack of impact of positive margin on recurrence rate seem to contradict previous research, where it has been shown that positive or close margins can affect the distal and local recurrence rate, However, several factors might explain this discrepancy. It is possible that the recurrence rate is influenced by a combination of various factors, and margin status alone may not be a strong predictor. Additionally, the presence of other influential factors might overshadow the isolated effect of margin status on recurrence.

Moreover, the study has limitations that could have influenced the results. Being retrospective, the study might have introduced biases, and the presence of confounding factors and missing data could have affected the overall analysis. Furthermore, the study included different tumor types and various surgical management approaches, making it challenging to draw a definitive conclusion regarding the significance of margin status as a predictor of recurrence rate [19,20].

In light of these limitations, it would be premature to conclude that margin status is not a significant predictor in recurrence rate. Further research, with a prospective design and careful control of confounding factors, is necessary to gain a more comprehensive understanding of the relationship between margin status and recurrence rate.

The two-year recurrence-free survival rate in our study was 88%, indicating a 12% recurrence rate, which aligns with findings from other studies. However, our research revealed a noteworthy trend of increasing recurrence rates after the initial two years, with rates reaching as high as 40-50%, surpassing the rates reported in comparable studies. Several factors may account for this observation.

Firstly, it is possible that some patients who experienced recurrence were initially lost to follow-up, leading to delayed detection of the recurrence later on. Additionally, some individuals might not have completed their prescribed therapy, which could have contributed to the higher recurrence rates observed beyond the two-year mark.

Furthermore, a notable proportion of patients refused to adhere to the recommended management plan, choosing breast-conserving therapy despite its unsuitability for their specific case. For instance, some patients declined mastectomy, which could have potentially provided a more effective treatment option for their condition.

These findings emphasize the critical role of appropriate counseling for patients, ensuring they comprehend the significance of adhering to the proposed management plan. Timely follow-up and completion of the prescribed therapy can greatly impact long-term outcomes and reduce the risk of recurrence.

In conclusion, while the two-year recurrence-free survival rate may appear promising, our study highlights the importance of vigilance beyond this period, as recurrence rates tend to increase significantly over time. Addressing issues like patient follow-up, therapy adherence, and appropriate management plans can play a crucial role in mitigating recurrence risk and improving overall treatment outcomes.

Overall, the results of these analyses suggest that certain clinicopathological factors, including EIC, nodal involvement, and grade, are strong predictors of breast cancer recurrence in this dataset. These findings may have important implications for patient care and management, and can help guide treatment decisions and follow-up protocols. However, it is important to note that these results are based on a specific dataset and may not be generalizable to all breast cancer patients. Further research is needed to confirm these findings and explore the relationships between different predictors of recurrence in more details.

Conclusion

ER, LVI, EIC, Nodal Involvement, Grade, Margin, and Type of Tumor were significant predictors of recurrence by bivariate analysis. However **High grade, EIC, and Nodal Involvement** remain significant predictors for recurrent breast cancer in multivariate analysis. Recurrence free survival at two years is 88% (12% recurrence rate). However, it declines with time. In summary, the current study identified several predictors associated with an increased risk of recurrence, including EIC, nodal involvement, and high-grade tumors. The findings suggest that patients with these characteristics may benefit from more aggressive treatment strategies to reduce the risk of recurrence.

Study Limitation

It is important to note that this study has some limitations, including its retrospective design and the fact that it was conducted at a single institution. Further research with larger sample sizes and more diverse patient populations is necessary to confirm these findings and develop more effective strategies for managing breast cancer recurrence.

References

1. Colleoni M, Sun Z, Price KN, Karlsson P, Forbes JF, et al. (2016) Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results from the International Breast Cancer Study Group Trials I to V. J Clin Oncol Off J Am Soc Clin Oncol 20: 927-9535.
2. Adami HO, Malker B, Holmberg L, Persson I, Stone B (1986) The relation between survival and age at diagnosis in breast cancer. N Engl J Med 28: 559-563.
3. Aalders KC, Postma EL, Strobbe LJ (2016) van der Heiden-van der Loo M, Sonke GS, Boersma LJ, et al. Contemporary Locoregional Recurrence Rates in Young Patients with Early-Stage Breast Cancer. J Clin Oncol Off J Am Soc Clin Oncol 20: 2107-2114.
4. Carter CL, Allen C, Henson DE (1989) Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1: 181-187.
5. Siegel RL, Miller KD, Jemal A (2017) Cancer Statistics, 2017. CA Cancer J Clin 67: 7-30.
6. Rakha EA, El-Sayed ME, Lee AHS, Elston CW, Grainge MJ, et al. (2008) Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. J Clin Oncol Off J Am Soc Clin Oncol 26: 3153-3158.
7. Pinder SE, Ellis IO, Galea M, O'Rouke S, Blamey RW, et al. (1994) Pathological prognostic factors in breast cancer. III. Vascular invasion: relationship with recurrence and survival in a large study with long-term follow-up. Histopathology 24: 41-47.
8. Viale G, Giobbie-Hurder A, Gusterson BA, Maiorano E, Mastropasqua MG, et al. (2010) Adverse prognostic value of peritumoral vascular invasion: is it abrogated by adequate endocrine adjuvant therapy? Results from two International Breast Cancer Study Group randomized trials of chemoendocrine adjuvant therapy for early breast cancer. Ann Oncol Off J Eur Soc Med Oncol 21: 245-254.
9. Park CC, Mitsumori M, Nixon A, Recht A, Connolly J, et al. (2000) Outcome at 8 Years After Breast-Conserving Surgery and Radiation Therapy for Invasive Breast Cancer: Influence of Margin Status and Systemic Therapy on Local Recurrence. J Clin Oncol 18: 1668-1675.
10. Wazer DE, Schmidt-Ullrich RK, Ruthazer R, Schmid CH, Graham R, et al. (1998) Factors Determining Outcome for Breast-Conserving Irradiation with Margin-Directed Dose Escalation to the Tumor Bed. Int J Radiat Oncol 40: 851-858.
11. Alrahbi S, Chan PMY, Ho BCS, Seah MDW, Chen JJC, et al. (2015) Extent of Margin Involvement, Lymphovascular Invasion, and Extensive Intraductal Component Predict for Residual Disease After Wide Local Excision for Breast Cancer. Clin Breast Cancer 15: 219-226.
12. De Azambuja E, Cardoso F, De Castro G, Colozza M, Mano MS, et al. (2007) Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 96: 1504-1513.
13. Harvey JM, Clark GM, Osborne CK, Allred DC (1999) Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol Off J Am Soc Clin Oncol 17: 1474-1481.
14. Pertschuk LP, Kim DS, Nayer K, Feldman JG, Eisenberg KB, et al. (1990) Immunocytochemical estrogen and progestin receptor assays in breast cancer with monoclonal antibodies. Histopathologic, demographic, and biochemical correlations and relationship to endocrine response and survival. Cancer 66: 1663-1670.
15. Li Y, Yang D, Yin X, Zhang X, Huang J, et al. (2020) Clinicopathological Characteristics and Breast Cancer-Specific Survival of Patients with Single Hormone Receptor-Positive Breast Cancer. JAMA Netw Open 3: e1918160
16. Billena C, Wilgucki M, Flynn J, Modlin L, Tadros A, et al. (2021) 10-year Breast Cancer Outcomes in Women ≤ 35 Years of Age. Int J Radiat Oncol Biol Phys 109: 1007-1018.
17. Phung MT, Tin Tin S, Elwood JM (2019) Prognostic models for breast cancer: a systematic review. BMC Cancer 19: 230.
18. Liedtke C, Broglio K, Moulder S, Hsu L, Kau SW, et al. (2009) Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Ann Oncol 20: 1953-1958.

19. Maishman T, Cutress RI, Hernandez A, Gerty S, Copson ER, et al. (2017) Local Recurrence and Breast Oncological Surgery in Young Women with Breast Cancer: The POSH Observational Cohort Study. Ann Surg 66: 165-172.

20. Bundred JR, Michael S, Stuart B, Cutress RI, Beckmann K, et al. (2022) Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. BMJ 378: e070346.