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ORIGINAL RESEARCH

Correlation of Histopathological and Radiological Response Patterns and Their Prognostic Implications in Breast Cancer After Neoadjuvant Chemotherapy

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Purpose: In breast cancer (BC), neoadjuvant chemotherapy (NAC) responses can be categorized as concentric shrinkage (CS), non-concentric shrinkage (non-CS), and complete response, influencing surgical planning and survival. This study evaluates the correlation between histopathological and radiological response patterns in BC patients after NAC and their impact on overall survival (OS) and disease-free survival (DFS).

Patients and Methods: This retrospective study analyzed 168 BC patients who received NAC between 2018 and 2022. Tumor response was evaluated radiologically using MRI and histopathologically after surgery. Radiological response patterns were categorized into CS, non-CS, and radiological complete response (rCR). Histopathologically, patients were classified into CS, non-CS, and pathological complete response (pCR). Concordance between radiological and histopathological classifications was assessed using the kappa statistic. Survival outcomes, including OS and DFS, were analyzed using Kaplan-Meier methods.

Results: Histopathological response patterns were distributed as CS (31.5%), non-CS (34.5%), and pCR (34%). Moderate agreement was observed between radiological and histopathological assessments (κ: 0.439, $p < 0.001$). Radiological evaluation identified 64% of CS, 50% of non-CS, and 74% of pCR cases accurately. Tumor molecular subtypes significantly correlated with both radiologic and histopathologic response patterns ($p < 0.001$). Subtype analysis revealed higher pCR rates in TN, HER2-enriched, and Luminal B-HER2(+) tumors, while non-CS was predominant in Luminal A tumors. No significant correlation was observed between histopathological or radiological patterns and OS (p: 0.291, p: 0.515) or DFS (p: 0.599, p: 0.899). However, patients achieving pCR tended to have better survival outcomes.

Conclusion: We observed moderate concordance between histopathological and radiological response patterns in BC patients after NAC, but discrepancies highlight the limitations of radiological evaluation alone. These patterns did not significantly correlate with prognosis. Higher pCR rates were associated with better outcomes, but response patterns alone may not predict survival, warranting further research in larger cohorts.

Keywords: breast cancer, neoadjuvant chemotherapy, tumor shrinkage patterns, survival outcomes, radiologic response

Introduction

Neoadjuvant chemotherapy (NAC) has become the standard of care for breast cancer (BC) due to several key benefits. It facilitates breast-conserving surgery, potentially avoids axillary dissection by shrinking tumors, enables in vivo assessment of tumor response to adjust ineffective treatments, and provides prognostic information, as improved responses are correlated with better survival outcomes.[1,2]

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The superiority of magnetic resonance imaging (MRI) in evaluating the response to NAC has been established through meta-analyses.[3] However, challenges remain in assessing treatment response, particularly due to false positives and negatives. Residual tumors that are too small for MRI to detect, or heterogeneity in the tumor bed due to treatment, can complicate this evaluation. Tumors can exhibit various response patterns to NAC, including complete response, concentric shrinkage (CS), and non-concentric shrinkage (non-CS). CS is characterized by the absence of non-mass enhancement around the shrinking mass, while non-CS (such as crumbling patterns or multinodular lesions) represents other types of shrinkage patterns.[4]

In BC, response patterns to NAC, specifically CS and non-CS, have significant implications for treatment outcomes and patient management. These patterns can predict treatment efficacy and may correlate with histopathological findings. CS is generally associated with higher tumor regression, whereas non-CS may indicate partial response or resistance to therapy. General cellularity loss after treatment does not always correlate with a decrease in tumor size, highlighting the significance of residual tumor cellularity in evaluating response.[5,6] Additionally, the type of shrinkage pattern directly impacts surgical decisions. CS often facilitates breast-conserving surgeries, while non-CS may necessitate more extensive surgical interventions to ensure complete tumor removal.[7,8]

The integration of histopathological and radiological response patterns after NAC holds the potential to enhance the surgical decision-making process and improve treatment individualization. Tumor shrinkage patterns, such as concentric or non-concentric, may have significant implications for margin evaluation and local recurrence risk following breast-conserving surgery (BCS). At the 2017 St. Gallen International Expert Consensus Conference on primary therapy for early breast cancer, experts agreed that surgical strategies should be tailored based on the mode of tumor shrinkage.[9]

In this context, the relationship between molecular subtypes and response patterns is also crucial. A meta-analysis found that the incidence of concentric shrinkage mode after NAC in breast cancer was associated with hormonal receptor status. Patients with triple-negative (TN) breast cancer exhibited the highest rates of concentric shrinkage mode post-NAC.[10] It has been suggested that greater attention should be given to selecting patients with luminal subtypes for breast-conserving treatment during NAC.

After NAC, changes such as necrosis, fibrosis, and inflammatory reactions occur in the tumor bed. These changes exhibit distinct characteristics depending on tumor size and cellularity, leading to various patterns of tumor shrinkage. Although studies have been conducted on the molecular subtypes of tumors and their relationships with shrinkage patterns, there is limited research on the radiological and histopathological correlation of these patterns and their effects on survival.[10] Fukada et al[4] studied 183 patients with low-grade luminal BC who received NAC. In their study, CS observed on MRI was associated with improved disease-free survival (DFS) and overall survival (OS), while another study similarly found non-CS to be a recurrence risk factor.[11]

The aim of this study is to evaluate these response patterns both histopathologically and radiologically, and to examine their correlation. Additionally, the study seeks to elucidate the association between these response patterns and survival outcomes, specifically OS and DFS. By integrating histopathological and radiologic data, this research aims to enhance the predictive value of response assessments and contribute to the optimization of therapeutic strategies for BC.

Material and Methods

Study Design and Patient Selection

This retrospective, single-center study was performed following approval from the Ethics Committee of the University of Health Sciences at Izmir Bozyaka Education and Research Hospital, Turkey (approval number: 2023/117, dated 16.08.2023) and in compliance with the Declaration of Helsinki. The study included patients diagnosed with BC who received NAC between 2018 and 2022 at our hospital. All patients had pre- and post-treatment breast MRI imaging available, and surgical outcomes were obtained at our hospital following NAC.

Patients who did not have appropriate imaging protocols or had imaging artifacts that rendered the assessment non-evaluable (2 patients), those who were non-responsive to NAC based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines[12] (progressive or stable disease) (4 patients), confirmed histopathologically as non-responsive, those who had metastatic disease at initial diagnosis (4 patients), and those who did not complete the

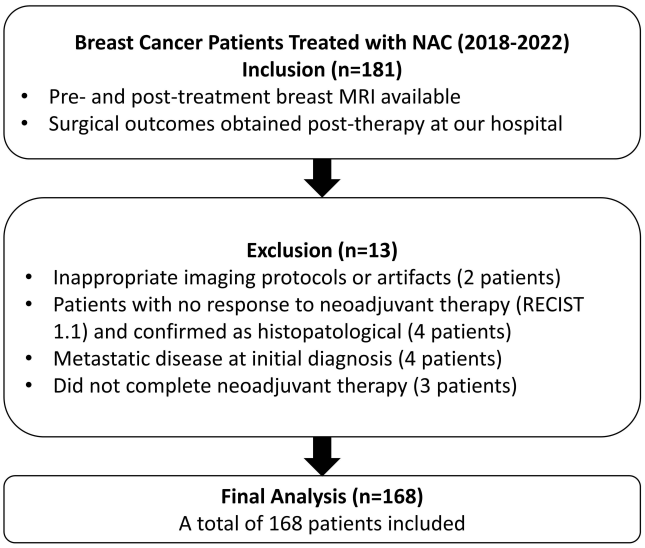

Figure 1 Patient Selection Flowchart.

NAC protocol (3 patients) were excluded from the study. In total, 168 patients were ultimately included in the analysis (Figure 1). All patients provided informed consent prior to surgery.

Histopathological Evaluation

Breast tumor samples obtained through tru-cut biopsy were classified into five molecular subgroups, primarily based on immunohistochemical evaluations: Luminal A (LA; Estrogen receptor ≥ 70% positive, progesterone receptor ≥ 20% positive, HER2 negative, and Ki-67 less than 14%), Luminal B-HER2 negative (LB-HER2 -; other HER2-negative and hormone-positive cancers), LB-HER2(+), HER2-enriched, and TN. A tumor was considered hormone receptor-positive if either the estrogen or progesterone receptor exhibited 1% or greater positivity according to IHC analysis.

Sections of post-treatment surgical specimens were re-evaluated. In cases where no macroscopic tumor nodule was detected, the tumor bed was extensively sampled. The response to therapy was assessed on hematoxylin and eosin (HE)-stained slides according to the Miller-Payne grading system (Grade 1–5).[13] Cases with no malignant cells observed in the tumor bed samples, where therapy-induced changes such as macrophage infiltration and hyalinization were noted in the stroma, were classified as having achieved a pathological complete response (pCR) (Grade 5). The presence of ductal carcinoma in situ (DCIS) was excluded from the pCR classification. The histopathological status of axillary lymph nodes was not considered in the definition of pCR. Cases with a reduction in tumor cells but the presence of residual malignant cells were categorized as having a partial response. This partial response group was further subdivided: those with a single, confined residual carcinoma nodule or residual tumor separated into small nests by fibrosis, confined to a limited area of the tumor bed, were classified as having a CS; those with residual tumor cells scattered as small nests or individual cells within a broad area of fibrosis were classified as having a non-CS. Cases with no response or progressive disease were excluded from the study (Grade 1, 2).

Chemotherapy Regimens

All patients completed the prescribed systemic NAC and subsequently underwent surgery. NAC regimens were categorized into three distinct groups: anthracycline-based regimens (doxorubicin or epirubicin), taxane-based regimens (docetaxel or paclitaxel), and sequential chemotherapy regimens (combining both anthracyclines and taxanes).

MRI Technique

MRI was performed with a 1.5T scanner (Siemens Healthineers, Magnetom Aera, Germany). The breast MRI protocol employed at our hospital is as follows: Axial T1-weighted (T1W) fatsat (TR/TE: 476/11 ms, FoV: 260 mm read, 112.5%

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phase, slice thickness: 4.0 mm), axial turbo inversion recovery magnitude (TIRM) (TR/TE: 2250/56 ms, FoV: 300 mm read, 100% phase, slice thickness: 4.0 mm), axial T1W Dixon (TR/TE: 449/11 ms, FoV: 320 mm read, 100% phase, slice thickness: 4.0 mm), axial T2-weighted (T2W) (TR/TE: 6240/76 ms, FoV: 320 mm read, 100% phase, slice thickness: 4.0 mm), echo planar imaging diffusion-weighted imaging (DWI) (TR/TE: 6900/66 ms, FoV: 360 mm read, 46.4% phase, slice thickness: 4.0 mm, b-values: 50, 500, and 800 s/mm²), and axial 3D fat-saturated T1W gradient echo (GRE) dynamic contrast-enhanced (DCE) (TR/TE: 4.53/1.82 ms, FoV: 300 mm read, 89.4% phase, slice thickness: 2.0 mm; subtraction images were obtained). In the axial plane, dynamic imaging was initiated before and 45 seconds after the intravenous administration of 0.1 mmol/kg gadobutrol (Gadovist™, Bayer AG, Berlin, Germany) at a rate of 3 mL/s. This was succeeded by five consecutive post-contrast scans and a 20 mL saline flush given at the same rate. All participants gave informed consent before undergoing imaging.

Radiologic Response Evaluation

Two radiologists, with 8 and 9 years of experience respectively, independently analyzed all images without knowledge of the patients' pathological outcomes. The evaluations were conducted on workstations (Siemens Healthineers). In cases of disagreement, the decision was made in consultation with a senior breast radiologist with 25 years of experience. The radiologic response to NAC was assessed according to the RECIST 1.1 guidelines. For multifocal or multicentric BC, up to two lesions, preferably the largest ones, were measured and designated as target lesions for follow-up imaging. Other enhancing lesions in the breast were considered non-target lesions and were evaluated but not measured in follow-up imaging.

Radiologic complete response (rCR) was characterized by the absence of all detectable lesions and a lack of residual enhancement. A radiologic partial response was characterized by a reduction of at least 30% in the total diameter of the target lesions. Stable disease was identified when the reduction was insufficient to be classified as a partial response, and the increase was not enough to be categorized as progressive disease. Progressive disease was defined by an increase of at least 20% in the total diameter of the target lesions or the emergence of new lesions. Patients with stable or progressive disease, confirmed histopathologically, were excluded from the study (n:4).

Patients showing a radiologic partial response were classified into two groups based on the pattern of shrinkage: radiologic CS and non-CS. Kim et al's[14] four shrinkage patterns were simplified into these two categories. CS was defined as a uniform reduction in tumor size from the periphery towards the center, maintaining a roughly spherical shape without surrounding lesions. Shrinkage patterns not meeting these criteria were classified as non-CS (Figure 2).

Statistical Analysis

The data analysis was performed with SPSS version 26 (IBM Corp., Armonk, NY, USA). Categorical independent variables were presented as frequencies and percentages with cross-tabulations, and their distributions were compared using the Chi-Square test. OS and DFS analyses were performed using the Kaplan-Meier method, with comparisons made using Log Rank tests. Hazard Ratios (HRs) were calculated as well. The agreement between radiologic and histopathological response patterns was evaluated using the Kappa statistic. A type I error rate of α: 0.05 was set for statistical tests, and two-tailed tests were applied.

Results

The study included 168 female patients, with a mean age of 52 years (standard deviation [SD] ± 10). The majority of patients had invasive ductal carcinoma (90%) and cT2 tumors (68%). When categorized by breast cancer molecular subtypes, 16 patients (9.5%) were LA, 79 patients (47%) were LB-HER2(-), 34 patients (20.2%) were LB-HER2(+), 15 patients (8.9%) were HER2-enriched, and 24 patients (14.3%) were TN. Most patients (87.5%) received sequential anthracycline and taxane-based chemotherapy (Table 1). The most common neoadjuvant regimen was dose-dense AC (adriamycin and cyclophosphamide), followed by weekly paclitaxel (50.6%). HER2(+) patients also received either single-agent trastuzumab or dual anti-HER2 treatments with chemotherapy (Table 2).

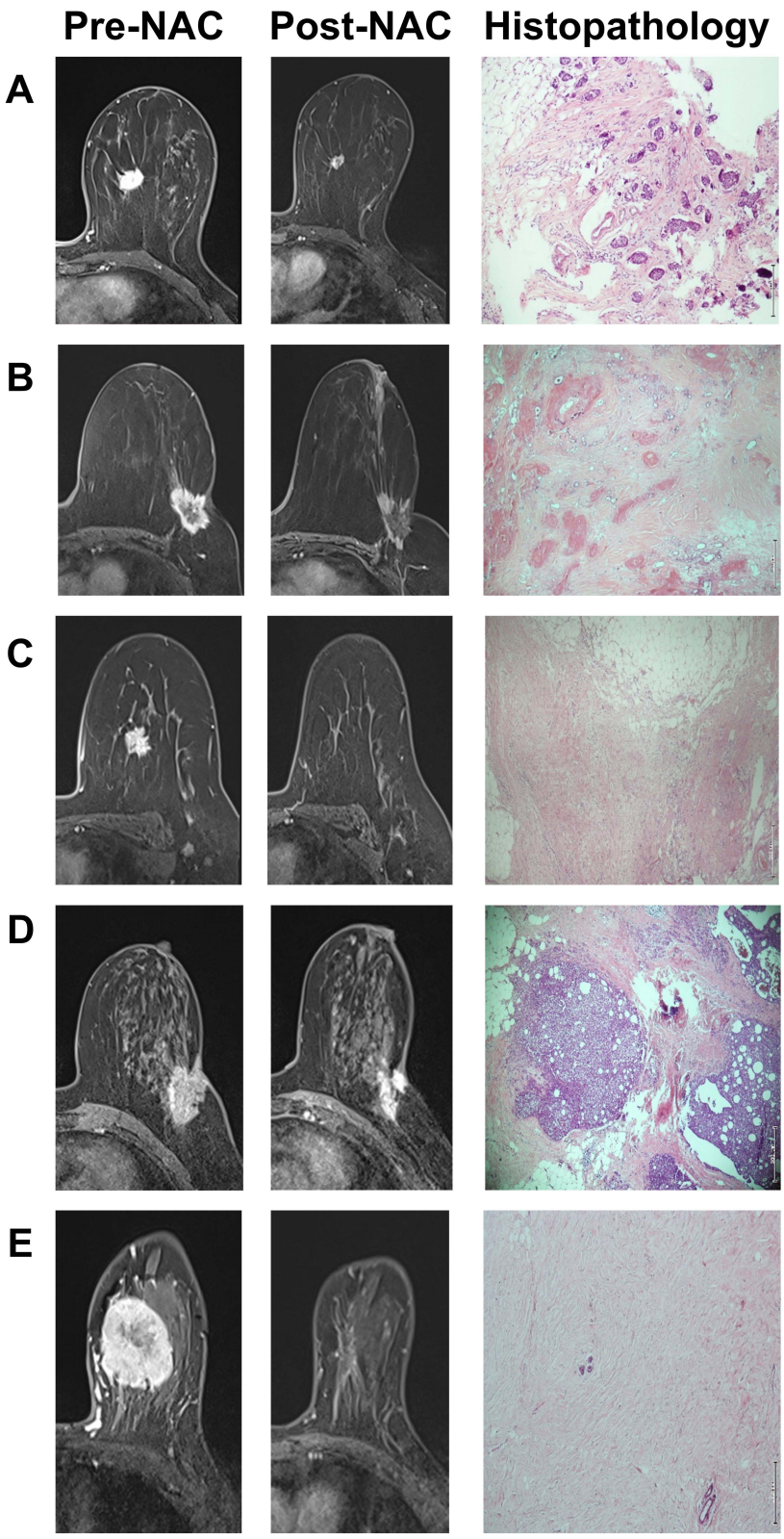

Figure 2 Patient Examples of Radiological and Histopathological Response Patterns This figure presents examples using Pre-NAC (Neoadjuvant Chemotherapy) and Post-NAC MRI (Magnetic Resonance Imaging) alongside histopathological microscopic images. (**A**) shows both radiological and histopathological concentric shrinkage (CS). (**B**) displays a non-CS pattern in both assessments. (**C**) illustrates a case with radiological complete response (RCR) and pathological complete response (pCR). (**D**) presents a patient initially interpreted as non-CS radiologically, but classified as CS histopathologically. (**E**) depicts a case where radiology incorrectly interpreted a non-CS pattern, but pathology confirmed pCR. (a: x100, b–e: x40, all stained with Hematoxylin and Eosin).

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Table 1 Demographic and Clinico-Pathological Variables of the Patients

Category	Subgroups	N	%
Age (years)	Mean ± SD (range)	52 ± 10	(27–75)
Histology	Invasive ductal	151	89.9
	Invasive lobular	9	5.4
	Other	8	4.8
Clinical stage	Local (early)	83	49.4
	Locally Advanced	85	50.6
CT	T1	21	12.5
	T2	114	67.9
	T3	14	8.3
	T4	19	11.3
CN-axilla	N0	5	3.0
	N1	95	56.5
	N2	56	33.3
	N3	12	7.1
Molecular subtype	Luminal A	16	9.5
	LB-HER2(-)	79	47.0
	LB HER2(+)	34	20.2
	HER2-enriched	15	8.9
	Triple-negative	24	14.3
ER status	Positive	124	73.8
	Negative	44	26.2
PR status	Positive	114	73.8
	Negative	54	26.2
HER2 status	Positive	49	29.2
	Negative	119	70.8
Tumor grade	I	8	4.8
	II	80	47.6
	III	80	47.6
Ki-67, %	Mean ± SD (range)	37 ± 22	(5–90)
	< 14	20	11.9
	14–20	23	13.7
	> 20	125	74.4

Abbreviations: SD, Standard Deviation; LB, Luminal B; cT, clinical Tumor Stage; cN, clinical Lymph Node Stage; ER, Estrogen Receptor; PR, Progesterone Receptor; HER2, Human epidermal growth factor receptor 2.

Histopathological analysis revealed that among these patients, 53 (31.5%) exhibited a CS pattern, 58 (34.5%) showed a non-CS pattern, and 57 (34%) achieved a pCR (Table 3).

Concordance analysis between histopathological and radiologic response patterns produced a kappa (κ) value of +0.439, indicating a moderate level of agreement with statistical significance ($p < 0.001$) (Table 3).

Table 2 Neoadjuvant Chemotherapy Regimens of the Patients

Category	n	%
Neoadjuvant chemotherapy regimens		
DD AC (q14d) - wPtx	85	50.6
DD AC (q14d) - Dtx (q21d)	42	25.0
EC (q21d) - wPtx	9	5.4
Only taxane (T) based	13	7.7
Only anthracycline (A) based	8	4.8
Other regimens (contains A plus T)	11	6.5
Neoadjuvant chemotherapy type		
Sequential A + T based	147	87.5
Only A based	8	4.8
Only T based	13	7.7
Anti-HER2 drug(s) for HER2(+) disease (n= 49)		
Trastuzumab	13	26.5
Trastuzumab + Pertuzumab	36	73.5

Abbreviations: DD, Dose Dense; AC, Doxorubicin + Cyclophosphamide, wPtx, Weekly Paclitaxel; Dtx, Docetaxel; EC, Epirubicin + Cyclophosphamide; q14d, every 14 days; q21d, every 21 days; T, Taxane; A, Anthracycline.

Table 3 Concordance Analysis Between Histopathological and Radiologic Response Patterns

			Histopathological Response Pattern			**Total**
			CS	***Non-CS***	***pCR***	
Radiologic Response Pattern	*CS*	Count	**34**	**19**	**11**	**64**
		% Row	53%	30%	17%	100%
		% Col.	64%	33%	19%	38%
		% Tot	20%	11%	7%	38%
	Non-CS	Count	**13**	**29**	**4**	**46**
		% Row	28%	63%	9%	100%
		% Col.	25%	50%	7%	27%
		% Tot	8%	17%	2%	27%
	rCR	Count	**6**	**10**	**42**	**58**
		% Row	10%	17%	72%	100%
		% Col.	11%	17%	74%	35%
		% Tot	4%	6%	25%	35%
Total		Count	**53**	**58**	**57**	**168**
		% Row	31.5%	35%	34%	100%
		% Col.	100%	100%	100%	100%
		% Tot	31%	35%	34%	100%

Notes: *Kappa (κ) = 0.439, indicating moderate agreement (p < 0.001).*
Abbreviations: CS, Concentric Shrinkage; Non-CS, Non-Concentric Shrinkage; pCR, Pathologic Complete Response; rCR, Radiologic Complete Response.

Of the 53 patients with a histopathologically confirmed CS pattern, 34 (64%) were accurately identified as having CS through radiologic evaluation. For the 58 patients with a non-CS histopathological pattern, 29 (50%) were correctly classified as non-CS based on radiologic assessment. Furthermore, 42 out of 57 patients (74%) who achieved a pCR were correctly identified through rCR (Table 3).

A statistically significant relationship was observed between histopathological and radiologic response patterns and tumor molecular subtypes ($p < 0.001$) (Tables 4 and 5), suggesting that integrating molecular subtype data with response

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Table 4 Association Between Tumor Subtypes and Histopathological Response Patterns

Molecular Sub-Type	*Histopathological Response Pattern*						*Total*		p*
	CS		*Non-CS*		*pCR*				
	N	%	**N**	%	**N**	%	**N**	%	
Luminal A	6	11%	10	17%	0	0%	16	10%	<0.001
LB-HER2(-)	33	62%	34	59%	12	21%	79	47%	
LB-HER2(+)	5	9%	7	12%	22	39%	34	20%	
HER2 Enriched	2	4%	1	2%	12	21%	15	9%	
Triple Negative	7	13%	6	10%	11	19%	24	14%	
Total	53	100%	58	100%	57	100%	168	100%	

Notes: *Pearson Chi-Square Test.
Abbreviations: CS, Concentric Shrinkage; Non-CS, Non-Concentric Shrinkage; pCR, Pathologic Complete Response; LB-HER2(-), Luminal B HER2-Negative; LB-HER2(+), Luminal B HER2-Positive.

Table 5 Association Between Tumor Subtypes and Radiologic Response Patterns

Molecular Sub-Type	*Radiologic Response Pattern*						*Total*		p*
	CS		*Non-CS*		*rCR*				
	N	%	**N**	%	**N**	%	**N**	%	
Luminal A	7	11%	8	17%	1	2%	16	10%	<0.001
LB-HER2(-)	36	56%	26	57%	17	29%	79	47%	
LB-HER2(+)	7	11%	7	15%	20	34%	34	20%	
HER2 Enriched	4	6%	0	0%	11	19%	15	9%	
Triple Negative	10	16%	5	11%	9	16%	24	14%	
Total	64	100%	46	100%	58	100%	168	100%	

Notes: *Pearson Chi-Square Test.
Abbreviations: CS, Concentric Shrinkage; Non-CS, Non-Concentric Shrinkage; rCR, Radiologic Complete Response; LB-HER2(-), Luminal B HER2-Negative; LB-HER2(+), Luminal B HER2-Positive.

pattern assessments may improve the interpretative value of radiological and histopathological evaluations, given their moderate concordance.

The relationship between histopathological response patterns and tumor molecular subtypes shows the following (Table 4):

- LA tumors: Predominantly non-concentric response (10/16 cases, 62.5%).
- LB-HER2(-) tumors: Non-concentric response was most common (34/79 cases, 43%), with concentric shrinkage closely following (33/79 cases, 42%).
- LB-HER2(+) tumors: pCR was the most frequent response (22/34 cases, 65%).
- HER2 Enriched tumors: Primarily pCR (12/15 cases, 80%).
- TN tumors: The most common response was pCR (11/24 cases, 46%), followed by concentric shrinkage (7/24 cases, 29%).

The relationship between radiologic response patterns and tumor molecular subtypes is as follows (Table 5):

- LA tumors: Predominantly non-concentric response (8/16 cases, 50%), followed by concentric response (7/16 cases, 44%).
- LB-HER2(-) tumors: Mostly concentric response (36/79 cases, 46%).

- LB-HER2(+) tumors: High rate of radiologic complete response (rCR) (20/34 cases, 58%).
- HER2 Enriched tumors: Dominantly rCR (11/15 cases, 73%).
- TN tumors: Primarily concentric response (10/24 cases, 42%), followed by rCR (9/24 cases, 37%).

The data show that for OS, 19 patients (11%) died due to BC, with a mean follow-up time of 44.4 months (SD: 16.7 months). For DFS, defined as the time from surgery to the first occurrence of either local recurrence and/or distant organ metastasis, 20 patients (12%) experienced disease recurrence, with a mean follow-up time of 43.3 months (SD: 16.5 months).

Tables 6 and 7 present the relationship between histopathological and radiologic response patterns with OS and DFS. The data indicate that no significant correlation was found between the histopathological response patterns (CS, non-CS, and pCR) and OS (p: 0.291) or DFS (p: 0.599) (Figure 3). Specifically, for histopathological response patterns, the mean OS ranged from 66 to 69 months, and the mean DFS was consistently around 67 months across different response groups. Similarly, radiologic response patterns (CS, non-CS, and rCR) also showed no significant correlation with OS (p: 0.515) or DFS (p: 0.899), with mean survival times ranging from 65 to 71 months (Figure 4). These findings suggest that the type of histopathological or radiologic response pattern does not significantly impact survival outcomes in this cohort.

Table 6 Association Between Histopathological Response Patterns and Survival Outcomes (OS and DFS)

Histopathological Response Pattern		Events	Estimate Time	p*
		N(%)	Mean (months)	
DFS	CS Non-CS pCR	8 (15%) 7 (12%) 5 (9%)	67 (61–73) 67 (62–72) 67 (64–71)	0.599
	Overall	20 (12%)	69 (66–72)	
OS	CS Non-CS pCR	7 (13%) 9 (16%) 3 (5%)	69 (64–74) 66 (61–71) 69 (66–72)	0.291
	Overall	19 (11%)	69 (67–72)	

Notes: *Kaplan-Meier survival analysis Logrank test.
Abbreviations: CS, Concentric Shrinkage; Non-CS, Non-Concentric Shrinkage; pCR, Pathologic Complete Response; DFS, Disease-Free Survival; OS, Overall Survival.

Table 7 Association Between Radiologic Response Patterns and Survival Outcomes (OS and DFS)

Radiologic Response Pattern		Events	Estimate Time	p*
		N(%)	Mean (months)	
DFS	CS Non-CS rCR	7 (11%) 6 (13%) 7 (12%)	70 (65–74) 66 (61–72) 65 (61–70)	0.899
	Overall	20 (12%)	69 (66–72)	
OS	CS Non-CS rCR	9 (14%) 6 (13%) 4 (7%)	68 (64–73) 66 (61–72) 71 (67–75)	0.515
	Overall	19 (11%)	69 (67–72)	

Notes: *Kaplan-Meier survival analysis Logrank test.
Abbreviations: CS, Concentric Shrinkage; Non-CS, Non-Concentric Shrinkage; rCR, Radiologic Complete Response; DFS, Disease-Free Survival; OS, Overall Survival.

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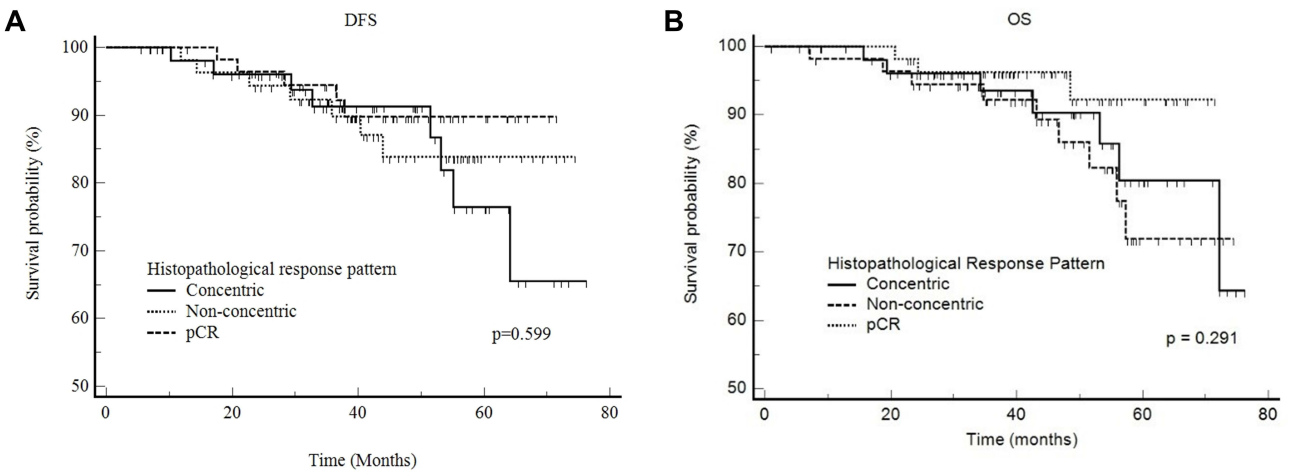

Figure 3 Kaplan-Meier Survival Curves for Histopathological Response Patterns in Predicting (**A**) Disease-Free Survival (DFS) and (**B**) Overall Survival (OS). The curves illustrate the survival probabilities for the concentric shrinkage (CS), non-concentric shrinkage (non-CS), and pathologic complete response (pCR) groups. No significant correlation was found between histopathological response patterns and either OS (p: 0.291) or DFS (p: 0.599).

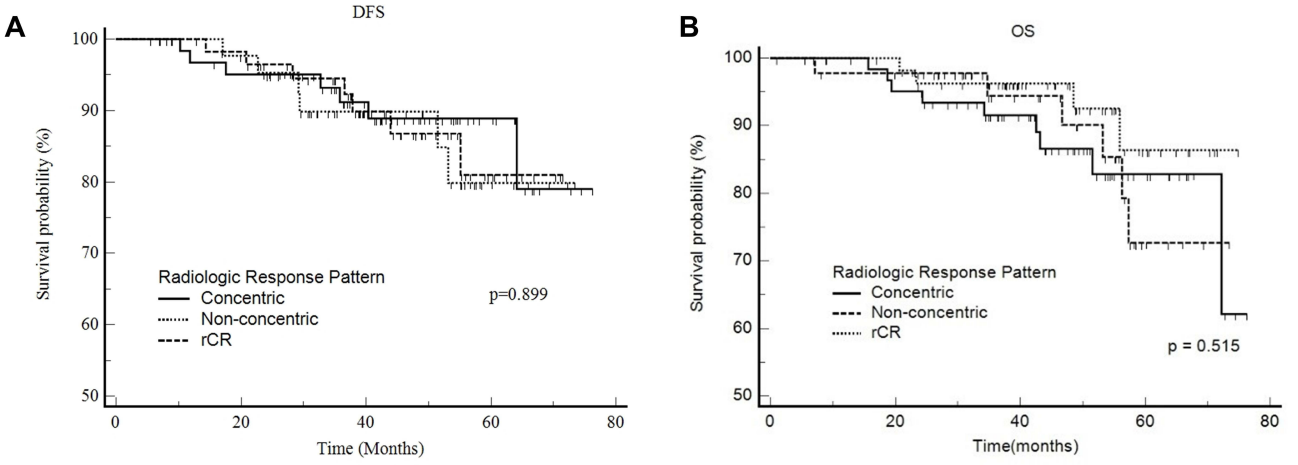

Figure 4 Kaplan-Meier Survival Curves for Radiologic Response Patterns in Predicting (**A**) Disease-Free Survival (DFS) and (**B**) Overall Survival (OS). The curves compare survival probabilities for concentric shrinkage (CS), non-concentric shrinkage (non-CS), and radiologic complete response (rCR) groups. Similar to histopathological findings, no significant association was observed between radiologic response patterns and OS (p: 0.515) or DFS (p: 0.899).

Discussion

Advancements in chemotherapy and targeted therapies for breast cancer have significantly improved treatment response rates. According to the literature, the pCR rates vary among different subtypes, with LA tumors exhibiting the lowest pCR rate at 0.3%, while HER2(+) tumors demonstrate the highest pCR rate at 38.7%.[15] Additionally, the same study reports that 19% of patients, irrespective of subtype, achieved pCR.[15] In our study, we observed an overall pCR rate of 34%, with a distribution across subtypes that aligns with the findings reported in the literatüre.[15,16]

As the possibility of omitting surgery in patients who achieve a pCR is increasingly considered,[17] accurate prediction of this response becomes critically important. The concept of "exceptional response" has emerged, emphasizing the significance of identifying patients who achieve pCR and could potentially be monitored without surgery.

Breast MRI is considered the most reliable imaging method for evaluating response both during and after NAC, with meta-analyses showing pooled sensitivities between 0.65 and 0.91, and pooled specificities between 0.81 and 0.88 for predicting pCR.[18,19] However, despite its accuracy, MRI can still overestimate the extent of disease in 6% to 19% of cases and underestimate it in 7% to 28% of cases.[20] Therefore, in patients monitored without surgery who exhibit a complete response, vacuum-assisted core biopsy techniques are often employed to confirm this response; however, due

to the limitations in needle thickness, there remains a risk of false negatives,[21] making surgery the gold standard for definitively determining the presence of complete response within the tumor bed.

Evaluating CS and non-CS patterns is essential for understanding treatment efficacy and tumor biology. Accurate assessment of these patterns is critical for surgical planning. CS, indicating homogeneous tumor reduction, facilitates clearer surgical margins. In contrast, non-CS requires careful evaluation during surgery due to potential treatment-resistant areas. Additionally, these patterns provide insights into the responses of different molecular subtypes. In our study, LA and LB-HER2(-) tumors predominantly showed a non-CS. Conversely, LB-HER2(+), HER2 Enriched, and TN tumors most frequently exhibited a pCR. A meta-analysis found that 56.6% of patients undergoing NAC were likely to achieve a CS pattern, with hormone receptor-negative subtypes having a 2.32 times higher likelihood than hormone receptor-positive subtypes. The highest rates of CS were observed in TN subtypes.[10] Consistent with these findings, our study revealed that in HER2 Enriched and TN tumors, the second most common response after pCR was CS, indicating that these subtypes may be more responsive to treatment, which is critical for treatment planning.

In previous studies, shrinkage patterns were predominantly determined based on MRI findings, with limited histopathological confirmation.[10] In our study, the radiopathological correlation was moderate, particularly for CS and non-CS patterns (κ: 0.439), with the lowest concordance observed in the non-CS pattern. In contrast, radiopathological concordance for pCR was higher. These findings suggest that although response patterns identified by radiologic and histopathologic assessments show moderate agreement, they are not entirely congruent. This highlights the limitations of relying solely on radiologic assessments and underscores the value of incorporating histopathological confirmation. Clinically, these findings support the complementary nature of radiologic and histopathologic evaluations; however, radiologic evaluation alone may be insufficient for comprehensive assessment. Future studies with larger, multicenter cohorts could further validate these observations and investigate the role of molecular subtype-specific response patterns.

The discordance observed in non-CS patterns following radiologic response assessment should be taken into account during surgical planning. Some patients identified radiologically as non-CS may actually have CS, and a small portion may even achieve pCR. The 2017 St. Gallen International Expert Consensus Conference emphasized the need to adapt surgical strategies based on tumor shrinkage patterns.[9] Therefore, accurately identifying and evaluating response patterns and their concordance holds significance in clinical decision-making.

In the study by Yoshikawa et al[22] involving 34 TN BC patients, a 41.2% agreement between MRI-based and histopathological shrinkage patterns was observed. They found that CS without surrounding lesions was the most common histopathological response pattern, with pCR being the second most frequent. In their study, 8 out of 13 patients exhibited a radiological CS pattern (sensitivity 61%). Furthermore, among the 11 patients with pCR, six were diagnosed with rCR (sensitivity 54.5%). Additionally, three of the 23 patients with residual disease did not exhibit contrast-enhanced lesions on MRI (with a specificity of 87.0%). In our study, the most frequent histopathological response pattern in TN tumors was pCR, followed by a CS pattern. Among the 11 patients with pCR, 9 were also found to have rCR, showing a higher sensitivity of 82%.

To our knowledge, there are few studies that investigate the radiopathological correlation of shrinkage patterns independent of molecular subtype. Therefore, our study may serve as a valuable reference for future research. The low degree of radiopathological concordance in shrinkage patterns also suggests that pathology should be considered the gold standard in studies evaluating post-treatment shrinkage patterns.

Recent studies have found that the neoadjuvant response pattern may play a significant role in determining patient prognosis.[23,24] In a meta-analysis by Spring et al[25] achieving pCR following NAT was significantly linked to better event-free survival (EFS) and OS, particularly in TN and HER2(+) BC.

In our study, no statistically significant association was identified between histopathological response patterns and OS (p: 0.291) or DFS (p: 0.599), regardless of subtype. However, a trend was observed toward better OS and DFS in patients who achieved pCR, indicating a potential association with improved prognosis. Similarly, a study involving 142 hER2(+) patients found no significant correlation between pCR and OS or DFS after NAC, though there was a trend toward improved DFS and OS in those who achieved pCR.[26] Villarreal-Garza et al[27] found that pCR did not improve prognosis in BC patients under 40 years of age. These findings suggest that while pCR may be important at the individual patient level, it may not be sufficient to compare outcomes between treatment groups.

In a retrospective study by Fukada et al[4] involving 183 patients with low-grade luminal BC who received NAC, it was found that CS observed on MRI was significantly associated with improved DFS and OS. Similarly, Sun et al[11] identified non-CS during post-NAC as a risk factor for recurrence in luminal BC. However, our study revealed no statistically significant correlation between histopathological and radiological response patterns and OS or DFS, potentially due to factors such as sample size, patient heterogeneity, and follow-up duration. This discrepancy may also suggest that the correlation between shrinkage pattern and prognosis is not as robust as previously assumed. Consequently, while response patterns alone may not significantly impact survival outcomes, these findings underscore the importance of considering potential confounders, such as molecular subtype variations. This highlights the need for further investigation into how subtype-specific responses may interact with survival outcomes.

This study has several limitations that should be acknowledged. Firstly, the retrospective design may introduce selection bias, as patient data were collected from a single center, potentially limiting the generalizability of the findings. Additionally, the classification of histopathological response patterns into CS and non-CS categories was based on subjective assessment, which, despite being conducted by experienced pathologists, may introduce variability and affect reproducibility. The reliance on MRI for determining radiologic response patterns is also constrained by the potential for both false positives and false negatives, particularly in detecting minimal residual disease or in cases where the tumor bed becomes heterogeneous after NAC. This limitation is critical given the moderate concordance observed between radiologic and histopathological assessments in this study. Furthermore, the sample size, while adequate for preliminary analysis, may not have been large enough to detect subtle differences in OS and DFS between different response patterns. Future studies with larger, multicentric cohorts and standardized assessment criteria could provide more definitive insights into the correlation between response patterns and survival outcomes. Additionally, incorporating molecular subtyping and exploring its relationship with response patterns may help identify patient subgroups that could benefit from tailored therapeutic strategies.

Conclusion

In this study, we assessed the correlation between histopathological and radiological response patterns following NAC and their relationship with survival outcomes. While a moderate concordance was observed between radiological and histopathological evaluations, the discordance, particularly in the non-CS pattern, should be considered in surgical planning. The 2017 St. Gallen International Expert Consensus Conference emphasized that surgical strategies should be tailored according to the tumor's shrinkage pattern. Therefore, determining and aligning response patterns is crucial for making informed surgical decisions. Although our study did not reveal a significant correlation between response patterns and survival outcomes, a trend toward improved survival was observed in patients who achieved pCR. Higher pCR rates were particularly noted in LB-HER2(+), HER2 Enriched, and TN molecular subtypes. These findings suggest that while response patterns following NAC may be relevant for surgical planning and treatment strategies, they may not independently predict survival outcomes. Future research, involving larger, multicenter cohorts and focusing on molecular subtype analysis, could provide further insights into how these response patterns might optimize therapeutic approaches and improve clinical practice.

Disclosure

The authors report no conflicts of interest in this work.

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