



Patterns of Regression in Breast Cancer after Primary Systemic Treatment

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Abstract

Despite national guidelines, the evaluation of effects of primary systemic treatment (PST) in breast cancer is a complex challenge. Our aims were to evaluate the response patterns focusing on correlations of radiological and pathological tumor size, regression heterogeneity in different molecular subtypes, cellularity changes and the incidence of enlarged, multinucleated neoplastic cells related to therapy. Slides of pretreatment biopsies and resection specimens of consecutive cases were reevaluated focusing on heterogeneity of regression per whole slide, and 40x or 100x magnification fields. Alteration in cellularity and the presence of multinucleated tumor giant cells were noted. The correlation of pathological and radiological sizes and their alterations were analyzed by Spearman rank correlation. The present study included 106 tumors. A decrease in size (84.9%) and cellularity (76.4%) was noted in all molecular subtypes. Inhomogeneous regression was found in 45.3%, with minor inhomogeneity in the majority. Scatter pattern regression was seen only in 8 cases (7.5%). Significant correlations were found between the pathological and radiological sizes ($p = 0.02$), and between the alterations of cellularity and pathological and radiological size ($p = 0.04$; $p = 0.03$, respectively). Multinucleated tumor giant cells were noted in 17.9% ($n = 19$), nearly exclusively in cases treated with PST including taxanes. Regression inhomogeneity following PST is present in about half of the cases, and is not related to molecular subtypes. The evaluation of the maximum area of the tumor bed is recommended for the proper evaluation of regression. Multinucleated tumor giant cells are related to PST including taxane derivate, and may cause upgrading.

Keywords Primary systemic therapy · Breast cancer · Regression pattern · Molecular subtypes

A 40-year-old woman with a cT2(34 mm)N0 M0 grade 3 estrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) negative breast cancer of no special type (Fig. 1a) received 6 cycles of docetaxel, epirubicin and cyclophosphamide as primary systemic treatment (PST), showed substantial regression on imaging, and underwent breast conserving surgery with sentinel node biopsy. The localization metal clip was not included in the first excision and a re-excision was needed to remove the clip, too. The first surgical specimen included an empty tumor bed area with 11.4 mm greatest dimension, but the empty tumor bed was in the margin (Fig. 1b). The second specimen sent for

histology also included the localization clip and a tumor bed area harboring both ductal carcinoma in situ and a 6 mm-large residual grade 3 invasive carcinoma (ypT1b) (Fig. 1c, d). The cited introductory example highlights that tumor regression may be misleadingly inhomogeneous, and this may lead to the false impression of complete regression on one end and lack of regression on the other end of the spectrum unless the full tumor bed is investigated.

PST of breast cancer has become more frequent recently. This approach to systemic treatment is currently applied in bulky (>2 cm) tumors or locally advanced cancers [1]. The radiologic and pathologic interpretation of regression is sometimes controversial due to some mismatch between the entities used for assessment. There is no internationally agreed consensus on how different imaging modalities should be prioritized and specimen handling is also rather heterogeneous.

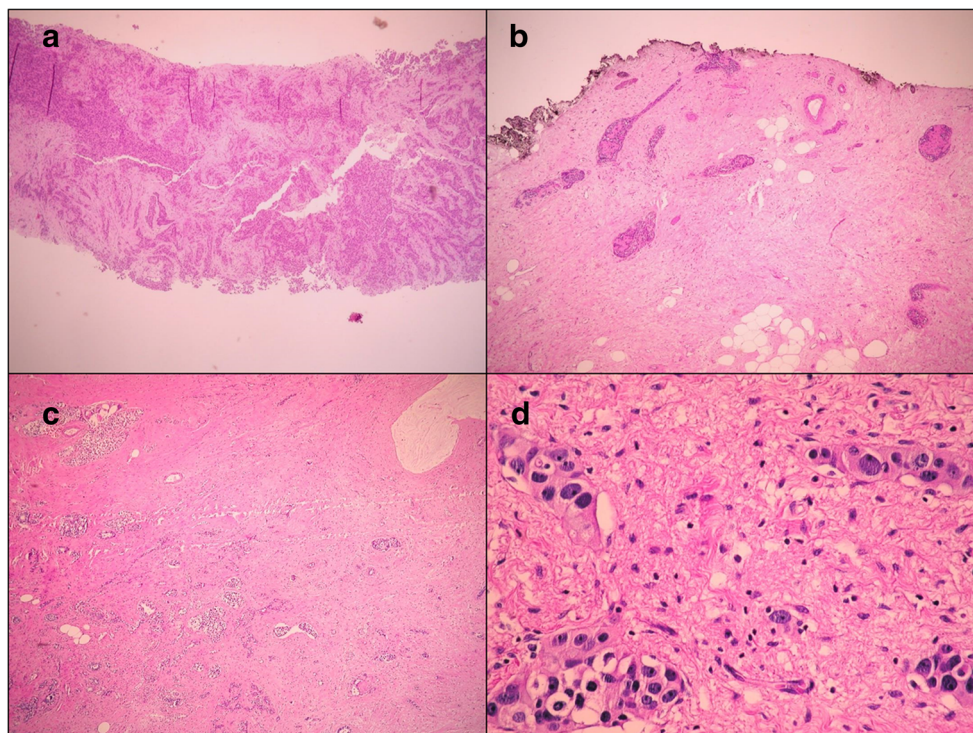
The presence or absence of regression is evaluated by radiologic modalities, namely ultrasonography (US), mammography and magnetic resonance imaging (MRI). This examination influences the continuation, shift or termination of PST and the multidisciplinary decision about surgical treatment.

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Fig. 1 Example case with inhomogeneous (scatter pattern) regression. **a** Cellular tumor on core needle biopsy (HE, 40x). **b** Empty tumor bed with remnants of an intraductal papilloma in the firstly excised surgical specimen. No margin labeling ink on tumor (free margin?), but ink on the empty tumor bed. (HE, 40x). **c** Second surgical specimen included both areas of empty tumor bed (top right third) and residual invasive carcinoma (HE, 40x). **d** Higher magnification of part C, with residual invasive tumor cell clusters (HE, 400x)



After the operation, the pathological examination reveals the degree of regression: pathological complete regression (pCR) on one end, and the complete lack of regression on the other end of the spectrum. The scale of regression affects further treatment decisions. Therefore, a standard approach to the evaluation of the breast specimen is crucial. To reach this aim, national guidelines have been developed in individual countries like Australia [2], Belgium [3], Germany [4], the United Kingdom [5], the Netherlands [6], the United States [7] and Hungary [8].

Despite these guidelines or reviews [9, 10] aiming at some uniformity in breast cancer reporting, there are several inconsistencies, namely in specimen work-up, definition of pCR, patterns and grades of regression.

After PST, the identification of the tumor bed may be difficult because the tumor may have become less firm, and less well circumscribed. Therefore, gross examination must be correlated with the clinical and especially radiological localization to ensure that the correct area is sampled. Systematic sampling should include the grossly visible tumor bed or the location of clip markers and neighboring areas to incorporate the area involved by carcinoma before treatment [10]. Digital photos, specimen mammography images or drawings should be taken for helping the comparison between clinical and morphological findings. Histopathological evaluation is based on sampling: representative areas are chosen for tissue blocks during grossing, and a tissue section represents about one thousandth of the whole thickness of the tissue block. It is

obvious, that the more thorough the sampling, the more details one can discover under the microscope, especially in non-homogeneous lesions exemplified in the first paragraph and Fig. 1.

In case of inhomogeneous, scattered focal regression, the assessment of tumor size may be problematic, as well. The dimension of the largest invasive focus may deviate from the largest dimension of the residual tumor affected area in the tumor bed (i.e. the extent) [11].

According to the United States' Food and Drug Administration (FDA), 'Pathological complete response is defined as the absence of residual invasive cancer (ypT0ypN0 or ypT0isypN0) on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy' [12]. The AJCC has endorsed the same definition [13]. This recommendation is based on the findings of the Collaborative Trials in Neoadjuvant Breast Cancer project. In this study, there was no difference in event-free and overall survival of patients having ypT0ypN0 or ypTisypN0 breast cancer [14]. On the contrary, the German and Austrian Breast Groups demonstrated significant worsening in event-free survival of ypTisypN0 versus ypT0ypN0 breast cancer cases [15]. Therefore, an alternative definition of complete response was proposed by this group, which excludes both residual ductal carcinoma in situ (DCIS) and invasive carcinoma in the breast (ypT0ypN0 only).

Regression and its scale can be characterized by different parameters, like the size of residual invasive carcinoma, lymph node status, tumor cellularity, tumor grade, proportion

of tumor remaining in breast (%) and finally the size of tumor bed in two dimensions. Several regression grading systems based on these parameters have been introduced and validated, including those described by Miller and Payne [16], Pinder [17], Denkert and Sinn [18] and Sataloff [19].

Another feature of response to neoadjuvant therapy is homogeneity or heterogeneity of the regression. According to Provenzano and coworkers, the patterns of residual disease are the following: homogenous regression (cellularity decreased, size unchanged), inhomogeneous regression (cellularity decreased, size variable, small areas without residual disease), “scatter pattern” (cellularity decreased, size variable, tumor bed slides without residual disease) and “concentric shrinkage” (CS) (size decreased, cellularity similar) [10]. Especially the “scatter pattern” may lead to diagnostic pitfalls if not systematically sampled.

Not only the size and cellularity change following PST, but grade may also be altered. After PST, bizarre and/or macronucleated neoplastic giant cells may sometimes be found in the tumor bed. These cells are generally attributed to the effects of chemotherapy. The presence of these bizarre cells may increase the posttreatment grade, whereas a reduction in the proliferating cells may decrease it.

The aims of the present study were to evaluate the response patterns in breast cancers after PST, focusing on correlations of radiological and pathological tumor sizes, regression heterogeneity in the tumor bed and in the axilla in different molecular subtypes of breast cancer, cellularity changes between biopsy and resection specimen, correlation between cellularity and size alterations and the incidence of macronucleated, bizarre neoplastic cells related to therapy.

Materials and Methods

Consecutive invasive breast carcinomas treated with PST and operated on at the Bács-Kiskun County Teaching Hospital, Kecskemét or at the Department of Surgery, University of Szeged from 2015 through February 2018 and from 2013 through May 2018, respectively were included. Additionally some earlier cases (from between 2010 and 2014) collected for a previous study on PST ($n = 8$) were also included. Exclusion criteria were unavailability of slides of either the biopsy or the excision specimen and primary endocrine therapy.

Clinical data, namely age, gender, laterality, type of surgery, pre- and posttreatment size determined by US, mammography and MRI (as available), primary systemic therapy were collected from medical charts. Pathological data including ER, progesterone receptor (PR) and HER-2 status, ypT and ypN categories [13], TR and NR tumor and node regression categories [20], pre- and posttreatment histological grade, pathological size (both the largest invasive focus and extent of

the area involved by tumor, either invasive or in situ) were obtained from the histopathology reports. The immunohistochemical surrogate classification of molecular subtypes of breast carcinomas was utilized according to the St. Gallen Consensus Conference [21]. The latest recommendations of American Society of Clinical Oncology were applied for the evaluation of HER-2 immunohistochemical staining [22].

Both departments have used the same work-up methodology recommended by the 3rd Hungarian Consensus Conference on Breast Cancer [8] including radiological localization, systematic sampling and clinical-pathological correlation on multidisciplinary meetings.

All hematoxyline-eosin stained tumor (bed) containing slides of biopsy and excision specimens were analyzed. The cellularity was estimated by two pathologists (TZ & GC) both on biopsy and excision specimens. Consensus was always reached.

The tumor bed areas showing complete regression or the absence of any regression pattern were evaluated on low (4x) and medium (10x) power fields (field areas: 0.24 mm² and 0.005 mm², respectively). The presence of whole slides, any low power field or any medium power field showing complete response or the lack of any response were noted. Homogenous regression was defined as pCR (Fig. 2a), absence of regression on all slides (Fig. 2b) and uniform degree of regression on all slides (Fig. 2c). Any other pattern was perceived as inhomogeneous response (Fig. 2e–g). The latter included the so called “scatter pattern” [17], the CS [17], which was identified in case of reduction of tumor size with similar cellularity (Fig. 2d).

The cells having enlarged cytoplasm, multiple and/or enlarged bizarre hyperchromatic nuclei with different size and shape were labelled as “monster cells” for the purpose of this study (Fig. 2h, i).

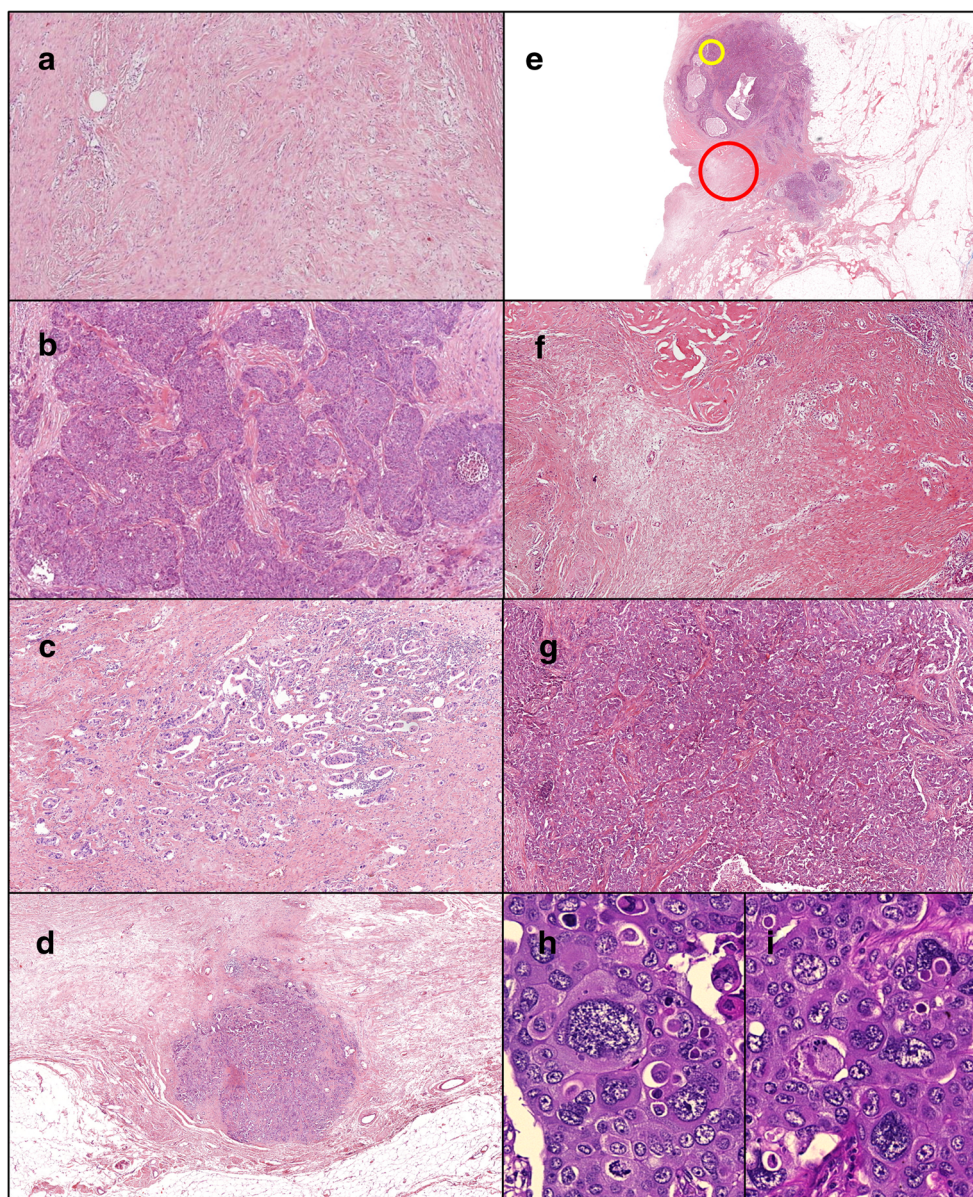
The slides of axillary sentinel lymph node excisions and/or axillary lymph node dissections were reevaluated and the presence or absence of metastasis and regression were documented. If metastatic nodes were seen with and without regression, inhomogeneous axillary response was identified.

The alteration of pre- and posttreatment cellularity and size; and the correlation between radiological (exclusively uniformly available US data) and pathological size were analyzed by the Spearman rank model. All statistical tests were one-sided, and $p < 0.05$ values were considered statistically significant. We utilized the SPSS Statistics software (IBM, SPSS 22.0, Armonk, NY USA).

Results

In this series, 106 cases were included: 56 and 50 patients from the University of Szeged and the Bács-Kiskun County Teaching Hospital, respectively. The basic clinical

Fig. 2 Patterns of regression and peculiar cellular changes (monster cells) in post-treatment specimens. **a** Complete pathological regression (HE,40x). **b** Absence of any regression in the tumor bed (HE, 40x). **c** Homogenous regression (HE, 40x). **d** Concentric shrinkage pattern (HE, 40x). **e** Inhomogenous regression in a tumor bed. Big red circle and small yellow circle display 40x and 100x field area, respectively. (HE, 1x). **f** 40x field area of tumor bed on “E” slide shows complete response (HE, 40x). **g** 10x field area of tumor bed on “E” slide lacks any regression (HE, 100x). **h** and **i** bizarre macronucleated “monster” cells (HE, 400x)



characteristics of these cases, namely age, type of surgery, histological type of tumor, ypT, ypN categories, pretreatment grade and therapy received are summarized in Table 1. Seven patients having stage IV disease defined by distant metastasis received palliative chemotherapy before surgery.

The morphological parameters evaluated are displayed in Table 2. In all IHC approached molecular subtypes defined by the St. Gallen Consensus Conference in 2013, diminution was the most frequent size alteration after PST. The Spearman rank correlation revealed that the concordance between post-treatment pathological size and radiological size (defined by US examination) was high ($p = 0.002$).

Regarding the homogeneity of regression, the luminal A, HER-2 and triple negative breast cancers (TNBCs) showed more homogeneity, whereas luminal B cases demonstrated more inhomogeneity. Unfortunately, statistical analysis could

not been applied due to the low case number in the groups. Lack of any regression, uniform degree of regression and pCR were observed in 7.5%, 18.8% and 28.3% of all cases, respectively. The vast majority of inhomogeneous regression was minor inhomogeneity (36.7% of all cases). The scatter pattern was identified in only 8 cases (7.5%), while CS was the rarest ($n = 2$; 1.8%). The regression inhomogeneity is demonstrated in Table 3 displaying the distribution of complete regression and the lack of any regression patterns at the different magnifications evaluated. In the lymph node specimens, homogeneity was more frequent (homogeneity: 45.3% versus inhomogeneity: 23.5% of all cases). In cases having neither metastasis nor regression in the lymph nodes, homogeneity of regression or its lack could not be evaluated (31.2%).

Cellularity changes reflected decrease in most cases (two thirds of all patients) but an increase was recorded in a

Table 1 Clinical characteristics of patients

Clinical parameters	
Age (year)	
Range	32–77
mean / median	54.5 / 55
Type of surgery (n; (%))	
Mastectomy	71 (66.9)
breast conserving surgery	35 (33.1)
Type of lymphadenectomy (n; (%))	
SLND	35 (33.1)
ALND	80 (75.4)
SLND+ALND	10 (9.4)
None	1 (0.9)
Histological type of tumor (n; (%))	
NST	100 (94.5)
Lobular	4 (3.7)
Other	2 (1.8)
ypT (n; (%))	
ypT0	25 (23.6)
ypTis	5 (4.7)
ypT1a	8 (7.5)
ypT1b	9 (8.6)
ypT1c	18 (16.9)
ypT2	30 (28.3)
ypT3	9 (8.6)
ypT4	2 (1.8)
ypN (n; (%))	
ypN0	55 (51.8)
ypN1	26 (24.5)
ypN2	12 (11.3)
ypN3	11 (10.3)
no data	2 (1.8)
Grade on core needle biopsy (n; (%))	
1	6 (5.6)
2	41 (38.7)
3	59 (55.7)
Treatment (n; (%))	
anthracycline ± targeted therapy	9 (8.6)
taxane ± platinum derivatives	27 (25.4)
anthracycline + taxane	70 (66.0)

(SLND: sentinel lymph node dissection, ALND: axillary lymph node dissection, NST: breast carcinoma of no special type, ypT and ypN: categories defined by the 8th edition of Cancer staging manual introduced by AJCC [13:AJCC])

significant minority (15.1%). The correlation between changes in cellularity and the alterations of post-treatment pathological and radiological tumor sizes compared to the pretreatment US size were significant ($p = 0.04$ and $p = 0.03$, respectively). After exclusion of cases showing pCR following PST (where grade alteration was not interpretable) the grade of tumors was

unchanged in 72.4%. Upgrading and downgrading were detected in 10 and 10 cases (13.8% and 13.8%), respectively. The latter was not seen among patients having TNBC.

“Monster” cells were seen in 17.9% ($n = 19$) of all cases. They were present in pre- and posttreatment grade 2 and 3 tumors exclusively. Their possible influence on grade alteration and association with PST are demonstrated in Table 4. Among these findings, the following are underlined: in 5 cases, upgrading (grade 2 to post-treatment y-grade 3) was detected in presence of “monster” cells and the monster cells were present only (all but one case) in patients who received PST including a taxane.

No correlation was found between the molecular subtypes and treatment related alteration in (pathological) size, cellularity, grade, the homogeneity of regression in lymph node specimens and presence of “monster” cells.

Discussion

The concepts of PST were developed in the last years and offer an alternative option for patients having primary breast cancer. The aims of PST are combination of systemic treatment and surgical treatment in order to eliminate all tumor cells, down staging breast cancers to make them operable by breast conserving options, and enabling the assessment of regression by pathological means [23–25]. In PST studies, the pathological diagnosis is the most important parameter for the generation of study endpoints [26]. The histopathological changes after PST are complex, therefore careful systematic analysis of the specimen is required for accurate diagnosis and treatment. The standardization of specimen handling and histological interpretation is essential for approaching pCR as an indicator in PST studies, or for measuring residual disease [10].

Although one of the most cardinal features of residual disease is the tumor size, it is often difficult to determine after PST. Besides the hardships of systematic sampling of the tumor bed, residual tumor may be present as multiple, small scattered foci. In the latter case, the size of the largest invasive focus determines the ypT category according to the 8th edition of the AJCC staging system [13], while the extent defined by the largest dimension inclusive of all independent invasive foci may be better for comparison with radiologic size [12]. Our findings have demonstrated, that pathological tumor size correlates with radiological (US) size, and the alteration of pathological size is in keeping with radiological findings [27, 28].

Primary chemotherapy selectively eliminates the proliferating cells, therefore the mitotic activity and the cellularity may decrease. Though, the change in cellularity is one of the most representative features of PST [29], it is not recorded routinely in the histopathological reports, because it is not easy to assess, lacks standardization and is an important

Table 2 Morphological features of cases evaluated, displayed according to the molecular subtypes of breast cancer [20]

Morphological variable	Luminal A n (%) 20 (100)	Luminal B n (%) 29 (100)	HER-2 n (%) 26 (100)	TNBC n (%) 31 (100)
Radiological size alteration				
shrinkage	15 (75)	26 (89)	24 (92.4)	25 (80.6)
growth	2 (10)	0 (0)	2 (7.6)	4 (12.9)
unchanged	2 (10)	3 (11)	0 (0)	2 (6.5)
no data	1 (5)	0 (0)	0 (0)	0 (0)
Regression pattern in the resection specimen				
Homogeneous	14 (70)	10 (34.4)	15 (57.6)	19 (61.3)
pCR	0 (0)	6 (20.7)	12 (46.2)	12 (38.7)
uniform degree of regression	11 (55)	3 (10.3)	2 (7.6)	4 (12.9)
lack of any regression	3 (15)	1 (3.4)	1 (3.8)	3 (9.6)
Inhomogeneous	6 (30)	19 (65.6)	11 (42.3)	12 (38.7)
minor inhomogeneity	5 (25)	17 (58.8)	9 (34.7)	8 (25.9)
"scatter pattern"	1 (5)	2 (6.8)	1 (3.8)	3 (9.6)
concentric shrinkage	0 (0)	0 (0)	1 (3.8)	1 (3.2)
Regression pattern in the lymph node specimen				
homogeneous	9 (45)	12 (41.4)	13 (50)	14 (45.2)
inhomogeneous	7 (35)	10 (34.5)	4 (15.4)	4 (12.9)
not applicable	4 (20)	7 (24.2)	9 (34.6)	13 (41.9)
Change in cellularity				
decreased	15 (75)	23 (79.5)	21 (80.8)	22 (70.9)
increased	2 (10)	3 (10.3)	4 (15.4)	7 (22.6)
unchanged	3 (15)	1 (3.4)	1 (3.8)	2 (6.5)
no data	0 (0)	2 (6.8)	0 (0)	0 (0)
Change in grade				
decreased	4 (20)	3 (10.3)	3 (11.5)	0 (0)
increased	2 (10)	5 (17.3)	0 (0)	3 (9.6)
unchanged	14 (70)	12 (41.4)	11 (42.3)	15 (48.3)
no data	0 (0)	9 (31.0)	12 (46.2)	13 (41.9)
Presence of "monster" cells				
present	5 (25)	6 (20.6)	3 (11.5)	5 (16.1)
absent	15 (75)	23 (79.4)	23 (88.4)	26 (83.9)

(HER-2: human epidermal growth factor receptor-2; TNBC: triple negative breast cancer, pCR: pathological complete regression)

parameter in only some tumor-response systems [16, 30] while it is not one in others [31–33]. Cellularity is utilized in two regression grading systems: in the Miller-Payne and in the Residual Cancer Burden system (RCB). Regarding the five-tiered Miller-Payne system, the pre- and post PST cellularity are compared, and the presence of invasive carcinoma is considered [16]. The four-tiered RCB is based on the size of the tumor bed in two dimensions, tumor cellularity in the post-treatment specimen, the proportion of DCIS in residual cancer, the number of lymph nodes with residual metastasis and the size of the largest lymph node metastasis [30]. In the present series, biopsies taken before PST and resection specimen were evaluated for cellularity changes. In the vast majority of the cases, cellularity has declined and a

significant correlation was detected between alterations of cellularity and (pathological) size.

Our findings suggest that homogeneity and inhomogeneity of regression are not associated with any molecular subtypes, and both are present approximately in half of the cases. The majority of inhomogeneous regression represented minor inhomogeneity seen in differences between one and the other medium or low power field, while the scatter pattern and CS were exceptionally rare. Although, the most remarkable pattern is the scatter pattern regarding the problems of tumor bed sampling (Fig. 1 and introductory example), where complete slides may be present without residual cancer, minor heterogeneity may also cause diagnostic controversy if only core biopsy is taken after PST.

Table 3 Morphological characteristics of regression patters

Patterns of inhomogeneity	Complete regression pattern at magnification of/on				Lack of any regression pattern at magnification of/on				
	40x	100x	Whole slide	Absent	40x	100x	Whole slide	Absent	
Minor inhomogeneity	39	19 (48.7)	14 (35.8)	0	6 (15.5)	15 (35.5)	9 (23)	3 (7.8)	12 (30.7)
Scatter pattern	7	0	0	7 (100)	0	2 (28.5)	3 (43)	0	2 (28.5)
Concentric shrinkage	2	2 (100)	0	0	0	1 (50)	0	0	1 (50)

When a pattern was present on the whole slide, it was also present in a medium power (10x) and low power field, too; but the numbers in the table reflect only the largest of the three areas assessed

Several ongoing or completed studies on PST feature post-PST biopsies as parts of the design [34–38]. By taking interim or final biopsies, pathological response and the effects of treatment can be characterized. Tumor heterogeneity, especially the scatter pattern of regression may have an impact on these studies. Limited sampling by biopsies may be the source of misinterpretations, if the biopsy is taken from the part of tumor bed showing complete response, or another part lacking any response. To avoid these diagnostic pitfalls, generous sampling by multiple biopsies is recommended for cases showing the extremes on the scale of regression, if the assessment of the complete tumor bed is not feasible. The results may also have an impact on the management of cases similar to the introductory example: an empty tumor bed with tumor bed on the inked margin may not be a perfect evidence of pCR or complete tumor resection.

Histological grade of breast cancer is one of the most established traditional prognostic factors. Honkoop and co-workers have found significant decline in mitotic activity following PST [39], while Sharkey et al. have identified significant increase of nuclear pleomorphism [40]. While the decline of mitotic count can lead to “downgrading”, more severe nuclear atypia could result in “upgrading”. The result of these contradirectional changes may alter the posttreatment histological grade. We have demonstrated that up-

and downgrading are rare, especially because the majority of PST case belong to grade 3. In half of the cases with upgrading, monster cells were present.

The monster cells (Fig. 2h, i) are giant tumor cells often having hyperchromatic macronuclei or multilobated or multiple nuclei and they are associated with effects of PST [40]. The presence of these cells was associated with taxane treatment. The principal effect of taxanes is the disruption of microtubule function, including the blockage of the mitotic spindle. Microtubules are essential to cell division, and taxanes stabilize GDP-bound tubulin in the microtubule, thereby inhibiting the process of cell division as depolymerization is prevented. The tumor cells are not able to divide after the duplication of their chromatin content, and the result may be the formation of macronucleated “monster” cells. Our findings suggest that the presence of these monster cells may increase nuclear atypia and therefore it may lead to upgrading following PST. Due to polyploidization, such cells are also expected to show an increased copy number of many genes, including HER2, leading to a post-treatment positive status of questionable therapeutic significance in these cells [41].

Limitations of the present study could be the low number of cases and the exclusion of patients receiving primary hormone therapy (PHT). Fukada and coworkers have reported that CS is significantly more frequent in luminal breast cancers following PHT, and these patients had significantly better outcome than patients having other patterns [42]. In contrast, there was no significant correlation between regression patterns and molecular subtypes in present work. This discrepancy may be explained by the exclusion of cases with PHT.

To our knowledge, this is the first study describing the distribution of regression heterogeneity according to molecular subtypes. Our findings suggest that regression may be inhomogeneous in half of the cases, and it does not seem to be related to any molecular subtype, therefore the evaluation of the whole tumor bed is recommended for the best assessment of regression. The “monster” cells are related to PST including taxane derivate, and may cause upgrading in tumors with non-high grade nuclei at the start of PST.

Table 4 Relation between alterations of grade, therapy received and “monster” cells, respectively

Alteration of grade	Monster cells	
	Present	Absent
Increased	5	5
Decreased	1	9
Unchanged	11	41
No data	2	32
Therapy		
anthracycline ± targeted therapy	1	8
taxane ± platinum derivatives	4	23
anthracycline + taxane	15	55

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Compliance with Ethical Standards

Conflicts of Interest No editorial or financial conflicts of interest exist for this submission.

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