RESEARCH ARTICLE

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Stromal Tumor Infiltrating Lymphocytes (sTIL) as an Independent Predictor of Pathologic Response to Neadjuvant Chemotherapy in Breast Cancer in Indonesia: A Hospital-based Study

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Abstract

Objective: We aim to describe the sTIL profiles of Indonesian breast cancer patient and its role in predicting neoadjuvant chemotherapy response. **Method:** This retrospective cohort study used secondary data from the archive of Anatomic Pathology Department FMUI/CMH. We did total sampling of 62 cases of locally advanced breast cancer cases that were biopsied, had neoadjuvant chemotherapy, and operated on from 2015 to 2020. We collected the clinicopathological data of each sample, measured the sTIL intensity in the biopsy specimen and evaluated the chemotherapy response from the mastectomy specimen using residual cancer burden (RCB) scoring method. Multivariate linear regression determined the independent predictors of RCB score. **Result:** There were 62 female patients, 45.2% were Luminal-HER2-, 43.5% were HER2+, and 11.3% were triple negative (TN). Most sTIL intensity (59.7%) were low (median 10%; 1%-60%). Moderate-high sTIL intensity was associated with HER2+ type, while low sTIL was with luminal-HER2- (p=0.038). Only 8.1% patients achieved pCR. Statistically different median sTIL intensity in minimal, moderate, and extensive burden group were 28%, 20%, and 8%, respectively (p=0.002). sTIL was an independent predictor for better response (lower RCB score), which were 0.07 (95% CI 0.04-0.09) lower for every 1% increase in sTIL intensity.**Conclusion:** sTIL intensity was mostly low in Indonesian breast cancer patient. However, it can predict neoadjuvant chemotherapy response, with 0.07 lower RCB score for every 1% increase of sTIL intensity.

Keywords: Breast cancer, *stromal tumor infiltrating lymphocytes*/sTIL, neoadjuvant chemotherapy response

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Introduction

Breast cancer is still the most commonly diagnosed cancer in the world, including in Indonesia. It was the second most contributor of cancer death in Indonesia (9.6%) after lung cancer in 2020 (GLOBOCAN, 2020). There were 722 cases of breast cancer studied in Anatomic Pathology Department, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital (FMUI/CMH) in 2019. Most cases (80%) in Indonesia were diagnosed at an advanced stage. In CMH, 42.7% cases came with a locally advanced stage (Yang and Yulian, 2022). Neoadjuvant chemotherapy is administered before definitive surgery in such cases to downstage, shrink the tumor, and decrease distant recurrence risk. Pathologic response to neoadjuvant chemotherapy correlates well with survival and prognosis. The preferred method of its evaluation is with residual cancer burden score (Symmans et al., 2017).

The pathological complete response (pCR) of breast cancer to neoadjuvant chemotherapy was very low in Indonesia (Shintia et al., 2016), which necessitates research for its predictors. The pCR rate in Indonesia was once reported to be only 4.76%, compared with 19% overseas (Spring et al., 2020). Partial tumor reduction was reported in 40.48% of patients, minimal tumor reduction in 19.05% patients, and no tumor reduction in 35.71% patients (Shintia et al., 2016). The cause of high neoadjuvant chemotherapy failure rate has not been studied to date . Stromal tumor infiltrating lymphocytes (sTIL) intensity, which can be counted in simple routine pathology examination, has been reported to be associated with pCR, albeit with conflicting results in luminal-HER2-type (Denkert et al., 2018; Gao et al., 2020). Higher sTIL intensity was more frequently found in younger breast cancer patients (Takada et al., 2022). The median age of breast cancer diagnosis in Indonesia was 48 years old (Anwar et al., 2019), which was much younger than in Europe and USA (68 and 62 years old, respectively) (Bidoli et al., 2019). However, the sTIL profile of these

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relatively younger Indonesian breast cancer patients and its role in predicting neoadjuvant chemotherapy response in various molecular types of breast cancer has not been studied.

Materials and Methods

This was a retrospective cohort study, which used secondary data from the archive of Anatomic Pathology Department, FMUI/CMH and electronic health record (EHR) of CMH. All breast cancer cases refered from 1 January 2015 to 31 December 2020, to our hospital were included. The inclusion criteria were locally advanced breast cancer cases (stage IIB-III) which underwent histopathologic biopsy examination and immunohistochemical examination to determine their molecular type, had neoadjuvant chemotherapy, and underwent mastectomy in CMH. The exclusion criteria were cases with incomplete clinicopathologic data and unavailable histopathology specimen in our archive.

Clinicopathologic data collected were age, sex, histologic type, Nottingham histologic tumor grade, lymphovascular invasion, molecular type, type of neoadjuvant chemotherapy (anthracycline based/first line drug or taxane based/second line drug), completeness of the neoadjuvant chemotherapy regimen, sTIL intensity, and residual cancer burden (RCB) score and class. Molecular type of breast cancer were classified as luminal-HER2 (hormone receptor positive/HER2 negative), HER2+ (hormone receptor positive/HER2+ or hormone receptor negative/HER2+), and triple negative (TN). Intensity of sTIL was assessed on simple routine histopathologic examination (with hematoxylin & eosin/H&E staining) according to International TILs Working Group guidelines (Salgado et al., 2014), and was reported numerically in percentage (continuous scale). The intensity of sTIL was considered low if ≤10%, moderate if 11-59%, and high if ≥60. Residual cancer burden score and class was determined from the mastectomy specimen, and calculated using the residual cancer burden calculator from MD Anderson Cancer Center, available online. The RCB score calculation involved primary tumor bed area, overall cancer cellulalrity, percentage of cancer that is in situ disease, number of positive lymph nodes, diameter of largest metastasis. Score 0 is classified as pathological complete response/RCB class 0, score >0-1.36 is minimal burden/residual disease/RCB class I, score >1.36-3.28 is moderate burden/residual disease, and score >3.28 is extensive burden/residual disease.

Statistical analysis was done using IBM SPSS® Statistics 26.0. Univariate analysis was done using Pearson or Spearman correlation test for numeric variables; chi-square, Mann-Whitney U, or Kruskal-Wallis test for categorical variables. Multivariate analysis was done with multiple linear regression to determine independent predictors for the RCB score.

Results

There were 62 females, median age of whom was 46 years old (range: 28-71 years old). Most of them (88.7%) had invasive carcinoma of no special type (NST). Almost 60% of them had intermediate Nottingham histologic grade. Lymphovascular invasion was noted in more than half of the sample (51.6%). Only 11.3% of the samples were triple negative breast cancer. The rest were almost equally divided into luminal-HER2- type (45.2%) and HER2+ type (43.5%). More than half of the patients (58.1%) had taxane-based neoadjuvant chemotherapy. Half of the patient had complete chemotherapy regimen. The median sTIL intensity was 10% (range: 1%-60%). Most patients (59.7%) had low sTIL intensity. Only 8.1% patients achieved pCR. Most patients (51.6%) still had extensive residual burden (RCB class III) after neoadjuvant chemotherapy. The complete clinicopathologic characteristics of the samples were described in Table 1.

Table 1. Clinicopathological Features of the Patients

Parameter	N (%)	Median (Min-Max)
Age (years old)		46 (28-71)
Gender		
Female	62 (100)	
Male	0 (0)	
Histologic type		
No special yype (NST)	55 (88.7)	
Special type	6 (9.7)	
Mixed type	1 (1.6)	
Tumor Nottingham grade		
1	11 (17.7)	
2	37 (59.7)	
3	14 (22.6)	
Lymphovascular invasion		
Absent	32 (51.6)	
Present	30 (48.4)	
Molecular type		
Luminal-HER2-	28 (45.2)	
HER2+	27 (43.5)	
TNBC	7 (11.3)	
Chemotherapy regimen		
Taxane-based	36 (58.1)	
Non-taxane-based	26 (41.9)	
Chemotherapy cycles		
Complete	31 (50)	
Incomplete	31 (50)	
sTIL (%)		10 (1-60)
sTIL category		
Low	37 (59.7)	
Intermediate-high	25 (40.3)	
RCB score		3.359 (0-5.328)
RCB class		
pCR	5 (8.1)	
I/minimal burden	1 (1.6)	
II/moderate burden	24 (38.7)	
III/extensive burden	32 (51.6)	

Table 2. Clinicopathologic Characteristics of the Sample Based on sTIL Intensity

Parameter	sTIL group (mean ± SD or n (%))		p value
	Low	Intermediate-high	
Age (years old)	48 ± 10	47 ± 12	0.722
Histologic type			0.691
NST	32 (58.2)	23 (41.8)	
Non-NST	5 (71.4)	2 (28.6)	
Tumor Nottingham grade			0.731
1	6 (54.5)	5 (45.4)	
2	24 (64.9)	13 (35.1)	
3	7 (50.0)	7 (50.0)	
Lymphovascular invasion			0.408
Absent	17 (53.1)	15 (46.9)	
Present	20 (66.7)	10 (33.3)	
Molecular type			0,038*
Luminal-HER2-	22 (78.6)	6 (21.4)	
HER2+	10 (37.0)	17 (63.0)	
TNBC	5 (71.4)	2 (28.6)	
Chemotherapy cycles			1
Complete	19 (61.3)	12 (38.7)	
Incomplete	18 (58.1)	13 (41.9)	
Chemotherapy regimen			0.594
Taxane-based	14 (53.8)	12 (46.2)	
Non-taxane-based	23 (63.9)	13 (36.1)	
RCB class			0,002*
pCR-Minimal burden (0-I)	2 (33.3)	4 (66.7)	
Moderate burden (II)	10 (41.7)	14 (58.3)	
Extensive burden (III)	25 (78.1)	7 (21.9)	

*p<0.05, significant

Table 2 showed the clinicopathologic characteristics of the samples based on sTIL intensity (low vs intermediate-high). Intermediate-high sTIL intensity was associated with HER2+ molecular type, while low sTIL intensity was associated with luminal-HER2- type and TNBC. No significant difference was noted in age, histologic type, Nottingham histologic grade, lymphovascular invasion, completeness of chemotherapy regimen, and type of chemotherapy between the two groups of sTIL intensity.

The intensity of sTIL were statistically different in various RCB classes (p=0.002, Figure 1) . Intermediate-high sTIL intensity was more frequently found in RCB class 0-II. Low sTIL intensity was more frequently found in RCB class III. Median sTIL intensity in pCR-RCB class I, RCB class II, and RCB class III was 28%, 20% and 8%, respectively.

To determine the independent predictor for RCB score, we did multiple linear regression analysis (Table 3). In bivariate analysis, the significant predictors were age, lymphovascular invasion, chemotherapy regimen, and sTIL intensity. Younger age, no lymphovascular invasion, taxane-based chemotherapy, and higher sTIL intensity predicted lower RCB score/better response to neoadjuvant chemotherapy. Every 1 year decrease in age, absence of lymphovascular invasion, taxane-based neoadjuvant chemotherapy, and every 1% increase in sTIL intensity is predicted to reduce RCB score by 0.03 (95% CI 0.002-0.06), 0.77 (95% CI 0.09-1.46), 0.69 (95% CI 0.001-1.4) and 0.07 (95% CI 0.05-0.09), respectively. In multivariate analysis, the only independent predictor was sTIL intensity. Every 1% increase in sTIL intensity is predicted to reduce RCB score by 0.07 (95% CI 0.04-0.09).

In subgroup analysis (Table 4), the independent predictors of RCB score in luminal-HER2- type were age, lymphovascular invasion, and sTIL. Every 1 year

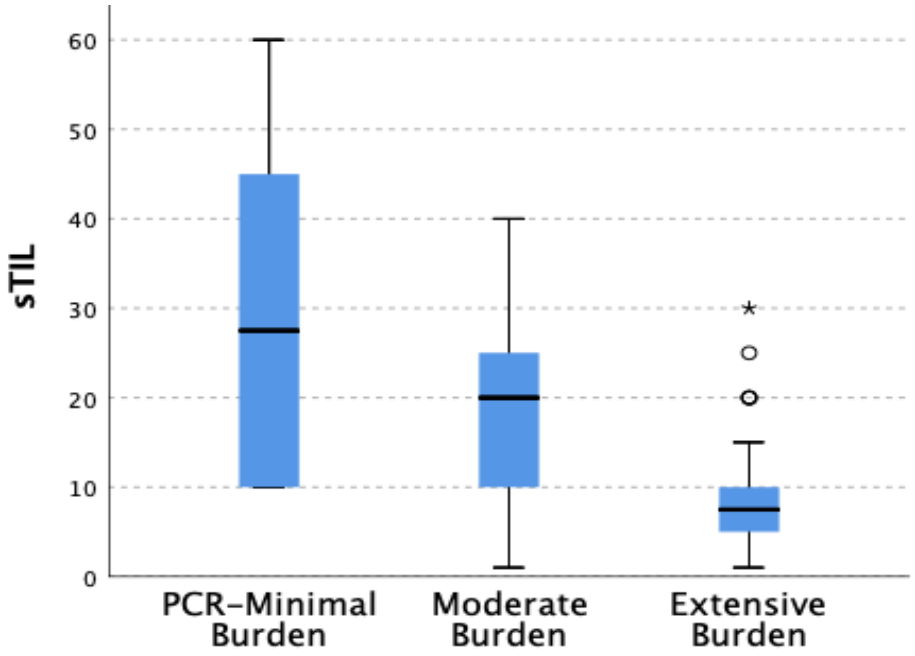

Figure 1. The Median sTIL Intensity in Various RCB Classes. There were significant difference in sTIL intensity between RCB class III (extensive residual burden) and RCB class II (moderate residual burden), as well as between RCB class III (extensive residual burden) and class 0-I (pCR-minimal residual burden).

Table 3. Adjusted and Unadjusted Multiple Linear Regression to Predict RCB Score

Independent variables	Unadjusted β coefficient (CI 95%)		Adjusted β coefficient (CI 95%) (Full model, Adjusted R2 0.392)		Adjusted β coefficient (CI 95%) (Final model, Adjusted R2 0.436)	
Age	0.03*	(0.002 – 0.06)	0:03	(-0.001 – 0.06)	0:02	(-0.001 – 0.05)
Lymphovascular invasion						
Present	1:00		1:00		1:00	
Absent	-0.77*	(-1.46 – -0.09)	-0.52	(-1.13 – 0.08)	-0.54	(-1.08 – 0.01)
Chemotherapy regimen						
Taxane-based	1:00		1:00		1:00	
Non-taxane-based	0.69*	(0.001 – 1.40)	0:52	(-0.16 – 1.20)	0:43	(-0.12 – 0.97)
sTIL intensity	-0.07*	(-0.09 – -0.05)	-0.07*	(-0.09 – -0.04)	-0.07*	(-0.09 – -0.04)
Chemotherapy cycles						
Complete	1:00		1:00			
Incomplete	-0.22	(-0.93 – 0.49)	-0.05	(-0.70 – 0.61)		
Molecular type						
Luminal-HER2-	1:00		1:00			
HER2-	-0.44	(-1.19 – 0.32)	-0.37	(-0.29 – 1.03)		
TNBC	-0.18	(-1.36 – 1.00)	-0.26	(-0.78 – 1.30)		
Tumor Nottingham grade						
1	1:00		1:00			
2	0:01	(-0.96 – 0.98)	-0.34	(-1.13 – 0.46)		
3	-0.14	(-1.28 – 1.00)	-0.33	(-1.30 – 0.64)		

*p<0.05. CI, confidence interval; From the final model, we can estimate the RCB score = 2.954 + 0.25 (age) + 0.427 (chemotherapy regimen) – 0.537 (lymhovascular invasion) – 0.066 (sTIL intensity). For the chemotherapy regimen, insert 0 for taxane-based chemotherapy, insert 1 for non-taxane-based chemotherapy. For lymphovascular invasion, insert 0 if lymphovascular invasion is present, insert 1 if lymphovascular invasion is absent.

decrease in age, absence of lymphovascular invasion, and every 1% increase in sTIL intensity were predicted to lower RCB score by 0.044, 1.187, and 0.047. The independent predictors of RCB score in HER2+ type were sTIL intensity and tumor Nottingham grade. Every 1% increase in sTIL intensity and grade 2 tumor were predicted to lower RCB score by 0.1 and 1.805. Subgroup analysis of the TNBC type could not be done as the sample size in the group was limited.

Table 4. Subgroup Analysis of luminal-HER2- type and HER2+ type. Adjusted multiple linear regression to predict RCB score.

Independent variables	Luminal-HER2- Adjusted β coefficient (Final model, Adjusted R^2 0.520)	HER2+ Adjusted β coefficient (Final model, Adjusted R^2 0.572)
Age	0.044* (p=0.021)	
Lymphovascular invasion	-1.187* (p=0.03)	-0.755 (p=0.103)
sTIL intensity	-0.047* (p=0.029)	-0.100* (p<0.001)
Tumor Nottingham grade		
1	1	1
2	0.706 (p=0.20)	-1.805* (p=0.01)
3	-	-0.848 (p=0.159)
Chemotherapy regimen		
Taxane-based	1	
Non-taxane-based	0.793 (p=0.1)	

*p<0.05; In luminal-HER2- type, we can estimate RCB score = 1.272 + 0.044 (age) – 1.187 (lymphovascular invasion) – 0.047 (sTIL intensity) + 0.706 (tumor Nottingham grade) + 0.793 (chemotherapy regimen). For lymphovascular invasion, insert 0 if lymphovascular invasion is present, insert 1 if lymphovascular invasion is absent. For tumor Nottingham grade, insert 0 for tumor Notthingham grade 1, insert 1 for tumor Nottingham grade 2, and insert 0 for tumor Nottingham grade 3. For neoadjuvant chemotherapy regimen, insert 0 if it is taxane-based, insert 1 if it is non-taxane-based; In HER2+ type, we can estimate RCB score = 6.416 – 0.1 (sTIL intensity) – 1.805 (tumor grade 2) – 0.848 (tumor grade 3) – 0.755 (lymphovascular invasion). For tumor Nottingham grade 1, insert 0 in tumor grade 2 variable and tumor grade 3 variable. For tumor Nottingham grade 2, insert 1 in tumor grade 2 variable and insert 0 in tumor grade 3 variable. For tumor Nottingham grade 3, insert 0 in tumor grade 2 variable and insert 1 in tumor grade 3 variable. For lymphovascular invasion, insert 0 if lymphovascular invasion is present, insert 1 if lymphovascular invasion is absent.

Discussion

Breast cancer is composed not only of neoplastic cells, but also its microenvironment (tumor microenvironment/ TME), which plays a role in tumor growth, spread, and treatment response. TME comprises cellular, soluble, and physical component. The cellular component includes fibroblasts, leucocytes, adipocytes, myoepithelial cells, and endothelial cells. The soluble component is consisted of cytokines, hormones, growth factors, and enzymes. Physical components includes extracellular matrix and pH. The leukocytes infiltrating the tumor and its stroma can be of any type, including lymphocytes, plasma cells, dendritic cells, macrophages, and neutrophils. The predominant leukocyte in breast cancer is the T lymphocyte (Soysal et al., 2015; Li et al., 2021).

To date, there has not been any cutoff for sTIL intensity that is clinically relevant. The concept lymphocyte predominant breast cancer (LPBC) is used in various research for breast cancer with sTIL intensity of 50%-60%, as is used to classify high sTIL intensity in this study (Salgado et al., 2015). LPBC with HER2+ type and TNBC more frequently achieved pCR after neoadjuvant chemotherapy with better prognosis (Mao et al., 2014). The incidence of LPBC is relatively low (11%, range 5%-26%). LPBC was reported to be highest in TNBC (20%, range 4%-37%), HER2+ (16%, range 11%-24%), and lowest in luminal-HER2- (6%, range 3%-12%) (Stanton et al., 2016). We found that the number of LPBC cases were particularly low in Indonesia. Overall, there was only 1 of 62 cases (1.6%) with LPBC (sTIL 60%) in this study. We found that age, histologic type, tumor Nottingham grade, and lymphovascular invasion did not affect sTIL intensity. However, the intensity of sTIL differed in various molecular types of breast cancer.

Intermediate-high sTIL intensity was more frequently found in HER2+ type compared to luminal-HER2- type (63,0% vs 21,4%, p=0,002), in agreement with meta analysis by Denkert (2018), He (2020), and Stanton (2016). In TNBC type, only 2 out of 7 patients (28.6%) had intermediate-high sTIL intensity. It was inconsistent with various studies that found higher sTIL intensity in TNBC and HER2+ type (Salgado et al., 2014; Soysal et al., 2015; Yee et al., 2020). The limited sample size in TNBC precluded its generalization to populations.

TNBC and HER2+ type are more potent inducer of type 1 immunity, particularly CD8+ T lymphocyte, compared to luminal-HER2- type. The CD8+ T lymphocyte is the most important effector cell involved in tumor destruction (Stanton et al., 2016). Some factors contributed to the higher sTIL intensity in HER2+ type and TNBC. Both types of breast cancer have more instable chromosomes and genomes which cause more mutations and produce novel proteins. The new proteins attract more sTIL to the tumor as they are recognized as foreign antigens by the host's immune system. The EGFR, MET, and PI3K signaling pathway often undergoes aberration in TNBC. The aberrant phosphorylated proteins induce new phosphopeptide formations which are immunogenic, hence the denser sTIL (Li et al., 2021).

The intensity of sTIL was an independent predictor of the overall RCB score. In this study, age, tumor Nottingham grade, lymphovascular invasion, molecular type, chemotherapy regimen, chemotherapy cycles completeness could not predict neoadjuvant chemotherapy response. Every 1% increase in sTIL intensity was predicted to decrease the RCB score by 0.07, adjusted for other variables. It was consistent with the study by Denkert (2018) which proved that high sTIL intensity associated with pCR in all molecular types of breast cancer. Gao (2020) only found the association in HER2+ type and TNBC, but not in luminal-HER2- type. He (2020) found that pCR frequency increased with every 10% increase in breast cancer sTIL in HER2+ type and TNBC. In luminal-HER2-, the association was only found in cases with >50% sTIL intensity.

The chemotherapy effect seemed to be augmented in tumors with higher sTIL intensity. Chemotherapy causes not only direct cancer cell death, but also immunogenic cell death by cytotoxic T lymphocyte. The damaged cancer cells release damage-associated molecular patterns (DAMPs), which will activate dendritic cells, the most potent antigen presenting cells (APCs). The activated APCs will present the tumor antigens to T lymphocytes, activating them, which in turn will attack the cancer cells. In addition, drugs such as taxane, anthracycline, and anti-HER2 monoclonal antibody can also cause cancer cell killing effect through dendritic cell activation. Thus, tumors with higher sTIL intensity before neoadjuvant chemotherapy is hypothesized to experience amplified chemotherapy effect compared with tumors with lower sTIL intensity (Li et al., 2021).

Subgroup analysis of the HER2+ type showed that the host immune response (depicted in the sTIL intensity) and tumor grade were the independent predictors of neoadjuvant chemotherapy response. Nottingham grade 1 tumors did not respond as well as grade 2 or 3 to neoadjuvant chemotherapy. It was consistent with reports finding better neoadjuvant chemotherapy response in higher grade tumors (Petit et al., 2004; Lin et al., 2013; Li et al., 2016). HER2+ type and TNBC associated with better neoadjuvant chemotherapy response (Yee et al., 2020; Asaoka et al., 2019; Nekljudova et al., 2018). However, the response may not be as good if the grade is low.

In luminal-HER2- type, prediction of neoadjuvant chemotherapy response needed combination of more variables (age and lymphovascular invasion) than just sTIL intensity. Age and lymphovascular invasion were reported in previous reports to associate with pCR, particularly in HER2- tumors (Häberle et al., 2018; Samanci et al., 2021). In luminal-HER2 type, we also found a trend of higher pCR in higher grade tumors. The frequency of pCR in grade 3, grade 2, and grade 1 tumors were 14%, 6%, and 0%, respectively. Statistical significance was not achieved probably because of the small sample size in this subtype.

Some caveats were noted in this study. The limited sample size particularly in TNBC precludes its subgroup analysis and generalization of the findings in this type to populations. The determination of RCB score in this study was done retrospectively, which may affect the accuracy

of the tumor bed area measurement as we rely only on the pathology and radiology report.

In conclusion, the sTIL intensity are lower in Indonesian breast cancer patients (median 10%, range 1%-60%) despite the relatively younger age compared to overseas patients. Intermediate-high sTIL intensity associated with HER2+ type, while lower sTIL intensity associated with luminal-HER2-. Only few patients (8.1%) achieved pCR after neoadjuvant chemotherapy. Most patients (51.6%) still had extensive residual disease (RCB class III). Overall, higher sTIL intensity was an independent predictor of lower RCB score. Every 1% increase in sTIL intensity was predicted to lower RCB score by 0.07.

Author Contribution Statement

All authors contributed equally in this study.

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