

The Gulf Journal of Oncology



Indexed By PubMed and Medline Database

Issue 42, May 2023
ISSN No. 2078-2101



*8th Gulf Week for
Cancer Awareness,
1-7 February 2023*

The Official Journal of the Gulf Federation For Cancer Control

Table of Contents

Original Articles

Identification of the Physiological Dimension and Self-Concept among Husbands of Iranian Women with Mastectomy; a Directed Content Analysis.....	06
Marzieh Beigom Bigdeli Shamloo, Nasrin Elahi, Marziyeh Asadi Zaker, Kourosh Zarea, Armin Zareyan	
Tumor–Stroma Ratio in ER+/HER2– Breast Cancer: Is it a Tool for Treatment Decision?.....	14
Choukri ELMHADI, Mohammed Allaoui, Meryem Zerrik, Mohammed Oukabli, Rachid Tanz, Mohammed Ichou	
Prevalence of BRCA1 and BRCA2 Mutations Among High–risk Bahraini Patients with Breast Cancer.....	22
Zain Bukamal, Amal AlRayes	
Survival Outcomes of Post–mastectomy Breast Cancer Patients Treated with Hypofractionated Radiation Treatment Compared to Conventional Fractionation –a Retrospective Cohort Study.....	26
Ciniraj Raveendran, Suma Susan Meloot, I Yadev	
Variants of Human Mucin Genes in Clear Cell Renal Cell Carcinoma and their Potential Prognostic and Predictive Values.....	35
Jamal Zekri, Mohammed A. Baghdadi, Abdelrazak Meliti, Turki M. Sobahy, Saba Imtiaz	
Study of Efficacy and Toxicity of Capecitabine Maintenance After Response to Docetaxel, Cisplatin, and 5–Fluoracil–Based Chemotherapy in Advanced Carcinoma Stomach.....	40
Udip Maheshwari, Pankaj Goyal, Varun Goel, Nivedita Patnaik, Venkata Pradeep babu koyyala, Krushna Chaudhari, DC Doval, Vineet Talwar	
EGFR Expression in Gallbladder Carcinoma in North Indian Population.....	47
Vikash, Vikas Kailashiya, Mohan Kumar, Puneet	
Does the Nightmare of Distressing Complications of Groin Dissection Over with “River Flow” Incision? – Experience of 240 Dissections from Tertiary Referral Oncology Centre,India.....	53
M D Ray, J R Jeena Josephin, Premanand N	

Review Article

Peptic Ulcer Disease and its Treatments and Risk of Pancreatic Cancer: a Meta–analysis.....	61
Nasser Alkhashaym, Goot Albuainain, Tuqa A AbuShaheen, Mohammed Y. Alshami, Ali S Almutairi, Ayman Ahmed Sakr, Ayat S Almuhayshi	

Case Reports

Treatment Process of Primary Prostate Leiomyosarcoma: A Rare Case Report.....	70
Denis Cetin, Mustafa Murat Mdk, Mustafa Mustafayev, Burcak Karaca	
Metastatic Small Cell Carcinoma of a Male Breast: A Case Report and Review of the Literature.....	74
Nadin Shawar Al Tamimi, Yousra Bennouna, Mohammed El Fadli, Rhizlane Belbaraka	
A Rare Tumor in Adulthood: Extrapneumatic Pancreatoblastoma.....	79
Ugur Topal, Begm alm Grbz, Hasan Bektas	

Conference Highlights/Scientific Contributions

News Notes.....	84
Advertisements.....	86
Scientific events in the GCC and the Arab World for 2023.....	87



Tumor–Stroma Ratio in ER+/HER2– Breast Cancer: Is it a Tool for Treatment Decision?

Choukri ELMHADI^{1,2}, Mohammed Allaoui³, Meryem Zerrik⁴, Mohammed Oukabli³, Rachid Tanz¹, Mohammed Ichou¹

¹ Department of Medical Oncology, Mohammed V Military Teaching Hospital of Rabat, Morocco

² School of Medicine and Pharmacy, University Hassan II, Casablanca, Morocco

³ Department of Pathology, Mohammed V Military Teaching Hospital of Rabat, Morocco

⁴ Department of Internal Medicine Mohammed V Military Teaching Hospital of Rabat, Morocco

Abstract

Purpose: The primary aim of this study is to determine the relationship between tumor–stroma ratio (TSR) and traditional prognostic factors in luminal early breast cancer in women treated at the medical oncology department of the military hospital of Rabat in Morocco.

Methods: A retrospective study was performed on primary invasive ER+/HER2– breast cancer in the period from January 1st, 2019 to December 31st, 2019. Prognostic factors included age, tumour size, lymph nodes status, Scarff–Bloom–Richardson grading, lymphovascular invasion (LVI), Ki67 and the stage of the disease. The type of Adjuvant systemic therapy was also reported. Two independent pathologists have assessed TSR by microscopic evaluation of haematoxylin and eosin tumor slides. Patients with less than 50% stroma were classified as low–stroma, the others are classified as high–stroma.

Results: Of 53 ER+/HER2– operable breast cancer, 41.5% patients had low–stroma and 58.5% patients had high stroma–tumour. High stroma was significantly associated with more stage III ($p=0.041$), more LVI (0.034), high Ki–67 ($p=0.002$) and more luminal B disease ($p=0.001$). Also, high stroma received more adjuvant chemotherapy ($p=0.005$). The results are maintained in univariate analysis

Conclusions: Data suggest that TSR can be used to guide decisions on adjuvant systemic therapy for ER+/HER2– breast cancer. The integration in routine of this simple and reproducible parameter requires a homogenization of the techniques as well as a prospective validation.

Keywords: breast cancer, luminal, tumor–stroma ratio, decision–support tool

Introduction

Breast cancer, in women, is the most commonly diagnosed cancer in the vast majority regions worldwide^[1]. It is also the most frequent cause of death from cancer in eleven regions of the world^[1]. Nearly 90% of women will be diagnosed as having early–stage disease–cancer that is confined to the breast or extends locally into the axillary lymph nodes for which surgery is the only curative treatment. However, almost 30% of women with cancer confined to the breast and 75% of women with nodal involvement will ultimately have a recurrence^[2]. This fact suggests the presence of micrometastases, considered to be clinically occult tumors lingering after surgery, endowed a potential to metastasize and increase both morbidity and mortality. Because of this, an adjuvant systemic treatment is given to reduce the risk of relapse. The treatment may include cytotoxic chemotherapy, endocrine therapy or target

therapy according to the molecular subtype.

Breast tumors are very heterogeneous and can be classified into three main groups based on their molecular profile: luminal cancers that express estrogen and/or progesterone receptors; HER2–positive cancers that express the tyrosine kinase receptor ERBB2; and triple negative (TN) cancers in which none of these receptors

Corresponding Author: Choukri ELMHADI, médical oncologist, Department of Medical Oncology, Mohammed V Military Teaching Hospitalhayriad, Rabat, Morocco. Zip code 10100, Telephone 00212613144918, Email address : dr.choukrielmhadi@gmail.com

are detected [3]. Luminal breast account for 70 to 80% of all breast cancers. It includes a heterogeneous population of tumors, differing by their clinical course, histopathological aspects, phenotypes and molecular features [3]. Recently, therapeutic de-escalation by sparing chemotherapy is the trend in patients with luminal breast. In addition, 50% of these tumors are associated with a very good prognosis (so-called luminal A tumors with regard to the intrinsic molecular classification). Only 20% of luminal tumors display a poor clinical outcome (so-called luminal B tumors). The remaining tumors match to intermediate lesions that are difficult to classify. As a result, luminal A tumors are best treated by endocrine therapy, while additional adjuvant chemotherapy will be proposed to patients with luminal B breast cancer [3].

Traditional prognostic factors such as tumor size, lymph node involvement, histological grade, patients' age, expression of estrogen receptors (ER) and progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2 or c-erbB2) status, continue to be of importance to guide the choice of adjuvant treatments, but may have limitations for an individualized approach for treatment [4]. A report from the St Gallen International Expert Consensus recommends the use of proliferation markers (eg, Ki67 index and mitosis) and multigene assays when choosing the appropriate systemic treatment [5].

New and sophisticated genomic tools (such as OncotypeDx® and Mammaprint®) are henceforth available and may improve ability to select patients [6]. Nonetheless, their routine use in developing countries is limited by their cost.

Tumourstroma includes several cell types like myoepithelial cells, fibroblasts, endothelial cells, inflammatory cells, and bone-marrow-derived. These cells variety interact with the extracellular matrix (ECM), extracellular molecules, cancerous cells and other host cells to create a tumor-permissive microenvironment able to provide continuous support for tumor growth, progression, angiogenesis, invasion, and metastasis [7]. Tumourstroma is thought to promote tumorigenesis by different mechanisms including remodelling of the extracellular matrix, suppression of immune reaction and damages in stromal regulatory pathways affecting the motility and aggressiveness of cancer cells [8].

Recently, tumourstroma emerges fastly as a significant prognostic indicator in patients with colorectal cancers [9], lung cancer [10], prostate cancer and stomach cancer [11]. Also, the tumor-stroma ratio (TSR) has been recently reported to have prognostic value in patients with triple negative cancer for which studies were largely focused [12, 13-14].

The purpose of this study was to determine the relationship between the amount of tumour-associated stroma and traditional prognostic factors in luminal early breast cancer in a Moroccan population.

Materials & Methods

Study design

This is a retrospective study over a period of one year (from 1 January 2019 to 31 December 2019) including patients with primary operable invasive breast cancer of no special type at the medical oncology department of the military hospital in Rabat in Morocco. Expression of oestrogen (ER), progesterone (PR) and human epidermal growth factor receptor 2 gene (HER2) were pre-determined by immunohistochemistry on formalin-fixed paraffin-embedded tumour material according to standard diagnostic procedure. Estrogen and /or progesterone receptors must be equal or more than 10% positive cells. HER-2/neu testing should be scored 0, 1+ or 2+ without gene amplification in fluorescence in situ hybridization.

Radiological staging including chest x-rays, liver ultrasound, bone scintigraphy or chest-abdomen-pelvis computed tomography should be normal. Patients should not have a history of breast cancer; they should not receive any neoadjuvant therapy.

Data collection

Data on clinical and histological features were collected using the clinical files in all cases with determination of the age, tumour size, lymph nodes status, Scarff-Bloom-Richardson (SBR) grading, the extent of lymphovascular invasion, Ki67, stage of disease and type of adjuvant systemic therapy.

The tumor size is classified in pT1 (the tumor is 2 cm or less across in greatest dimension), pT2 (the tumor is larger than 2 cm but less than 5 cm across) or pT3 (the tumor is larger than 5 cm across but does not grow into the chest wall or skin). Lymph node invasion is classified as pN0 (no regional lymph node metastasis identified histologically), pN1 (micrometastases or metastases in one-three axillary lymph nodes), pN2 (metastases in four-nine axillary lymph nodes) or pN3 (metastases in ten or more axillary lymph nodes). Tumors are graded as I, II, or III according to SBR grading. A 20 % Ki67 cut-off was admitted to define high proliferation.

Staging is done according to the TNM classification in stage I, stage II or stage III [15]. Patients were also assigned into two groups according to type of adjuvant systemic therapy (chemotherapy and/or hormonal therapy).

Measurement of stromal density

The histological sections are made from the paraffin blocks of the tumor taken from the mastectomy surgical specimens and are stained with Hematéine–Eosine (H.E.). All histopathological specimens were evaluated independently by two pathologists. The amount of stroma was quantified using a 50x objective lens to select the most invasive part of the tumour, then the 100x objective lens was used to score. The fields that we rescored are the ones where both stroma and tumour cells were present, tumour cells had to be seen on all sides of the microscopic image field. The tumor–stroma ratio was visually estimated in a blinded manner and scored per tenfold percentage (10, 20, 30% etc.). In case of tumourheterogeneity, those areas with the highest stromal percentage were decisive. Patients with more than 50% intra–tumor stroma were quantified as stroma–high and patients with less than 50% as stroma–low.

Statistical analysis

All analyses were performed with SPSS 18 software. The number of patients and the corresponding percentages were given for categorical variables, mean \pm standard deviation were reported to describe the normally distributed continuous variables, and medians with interquartile ranges were reported for continuous variables with skewed distributions. The Kolmogorov–Smirnov test was performed on all measures to assess data normality. Chi–square or Fisher’s exact test were used to compare the categorical variables as appropriate. Means were compared using the Student’s t–test and medians were compared using the Mann whitney test. Univariate logistic regression analysis was conducted to compare several toxicities between the original drug and generics. A p value < 0.05 was considered statistically significant.

Results

Fifty–three consecutive luminal breast cancer patients were selected for this study. The mean age of patients at the time of surgery was 49years (range 23–68). Lymphovascularinvasion (LVI) were present in 39.6% of cases. The tumors were T2 in 43.4% of cases and had grade II SBR in 55.3%. The absence of lymph node invasion (N0) was seen in 49.1% and stage II was the most represented (44%). The median of Ki67 was 20 (range 6–24) and a total of 59% had luminal B disease. The table 1 shows clinicopathological characteristics of patients.

22 (41.5%) patients had low stroma ($<50\%$ stroma) (figure1, 2–3) and 31 (58.5%) patients had high stroma ($\geq 50\%$ stroma) (figure 4).

High stromal content was significantly associated

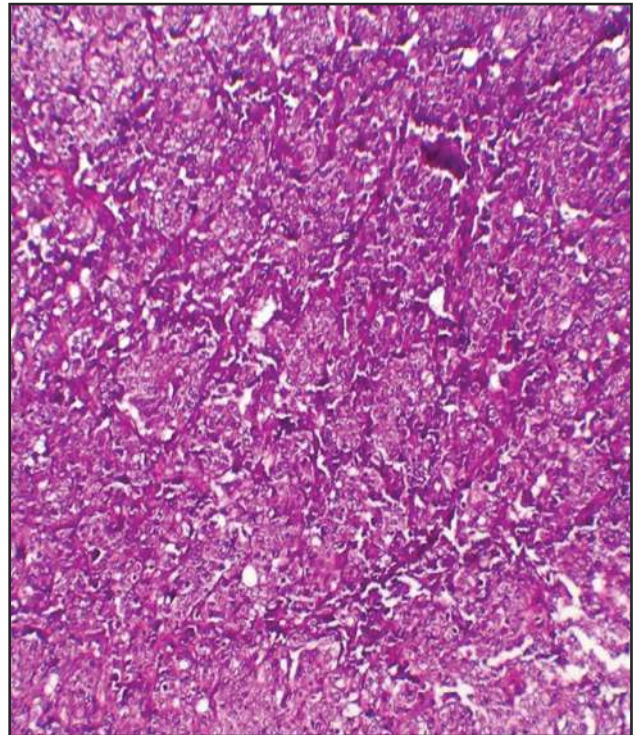


Figure 1. Haematoxylin and eosin–stained sections of invasive ductal breast tumours : Tumour with low stroma (1%). Magnification x100 objective

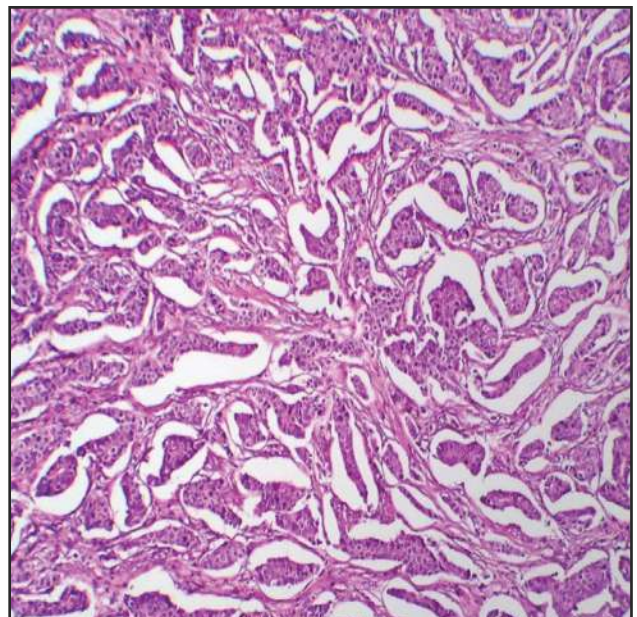


Figure 2. Haematoxylin and eosin–stained sections of invasive ductal breast tumours : Tumour with low stroma (10%). Magnification x100 objective

with more stage III ($p=0.041$), more LVI (0.034), high Ki–67 proliferative index ($p=0.002$) and more luminal B disease ($p=0.001$). Also, tumors with high stroma received more adjuvant chemotherapy ($p=0.005$). The results are maintained in univariate analysis (table 3).

Furthermore, low stromal content received more exclusive hormonotherapy ($p=0.005$).



Figure 3. Haematoxylin and eosin–stained sections of invasive ductal breast tumours: Tumour with low stroma (30%). Magnification x100 objective
S: stroma
T: tumor

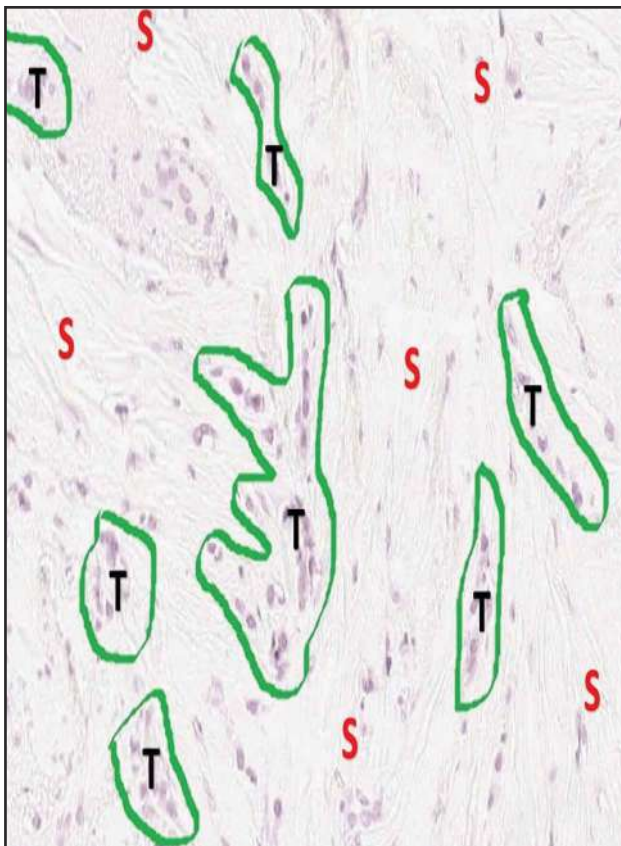


Figure 4. Haematoxylin and eosin–stained sections of invasive ductal breast tumours: tumour with high stroma (70%). Magnification x100 objective
S: stroma
T: tumor

Number of patients	53
Age*	49,31 ± 9
Ki 67 §	19 [6–24]
LVI	
+	39.6%
–	60.4%
SBR	
I	21.3%
II	55.3%
III	23.4%
T	
T1	30.2%
T2	43.4%
T3	26.4%
N	
N0	49.1%
N1	22.6%
N2	15.1%
N3	13.2%
Stage	21%
II	44%
III	35%
Subtype	
Luminal A	41%
Luminal B	59%

Table 1. The clinicopathological characteristics of patients with early breast cancer
 * means ± standard deviation
 §median [interquartile range]

	Low stroma < 50% (n= 22)	High stroma ≥ 50% (n= 31)	P
Age (ans) M ± ET	46,8 ± 9,3	50,9 ± 8,8	0,15
Stage III	18,2%	45,2%	0,041
LVI	22,7%	51,6%	0,034
Ki 67 M(IQ)	8 (5 ; 19,25)	20 (12 ; 30)	0,002
Luminal B	31,8%	77,4%	0,001
Adjuvant chemotherapy	31,8%	71%	0,005
Exclusive hormonotherapy	62,7%	37,5%	0,005

Table 2. The inter–relationship between clinicopathological characteristics and tumourstroma percentage
 LVI: lymphovascular invasion

	Low stroma < 50% (n= 22)	High stroma ≥ 50% (n= 31)	P
Age (ans) M ± ET	46,8 ± 9,3	50,9 ± 8,8	0,15
Stage III	18,2%	45,2%	0,034
LVI	22,7%	51,6%	0,001
Ki 67 M(IQ)	8 (5 ; 19,25)	20 (12 ; 30)	0,005
Luminal B	31,8%	77,4%	0,001
Adjuvant chemotherapy	31,8%	71%	0,005
Exclusive hormonotherapy	62,7%	37,5%	0,005

Table 3 .The inter–relationship between clinicopathological characteristics and tumourstroma percentage: univariate analysis LVI: *lymphovascular invasion*

Discussion

Our study shows that in luminal early breast cancer, tumors with high stroma are consistently associated with a high tumor volume with more stage III and commonness of LVI. The median of Ki67 was 20 suggesting highly proliferating tumors. Also, patients with high stromal content often received adjuvant chemotherapy. This data indicate that the TSR can be used in combination with other prognostics factors to guide decisions on adjuvant systemic therapy. Many investigations support the notion that tumor stroma plays a major role in tumor initiation, progression and dissemination based on the assumption that tumors are composed of tumor parenchyma and stroma two distinct but interactive parts that crosstalk to promote tumor growth [16].

In breast cancer, attention has initially focused on the “quality” of the of tumour–associated stroma (the composition of the tumor stroma). Cancer–associated fibroblasts have been demonstrated to serve a crucial role in cancer pathogenesis and therapeutic resistance through paracrine factors and/or direct cell–cell crosstalk [17]. Endothelial cells are involved in angiogenic switch which might lead to the vascularization of the growing tumor [18]. Cancer–associated adipocytes are able to cause a modification in the phenotype of cancer cells, and, as such, favor metastasis behavior and this contribution in breast cancer progression may elucidate why obesity is a negative prognosis factor [19]. Tumour–infiltrating lymphocytes reflect the intensity and the quality of the immune reaction to breast cancer. Their density and phenotypic profile have been demonstrated to be predictive of response to neoadjuvant treatment and of patient outcome and could be used as biomarker with the potential to predict response to immunotherapy [20]. All of these elements are embedded in an extracellular matrix, involved in the generation of a significant drug concentration gradient, metabolic changes, and increased interstitial fluid pressure, all of which can

significantly enhance the resistance of tumor cells to chemotherapeutics [21].

Recently attention has focused on the potential prognostic value of TSR in different types of cancer. Current literature describes conflicting results, especially in breast, and seemingly dependent on hormone status.

In the first study published by De Kruijf et al, TSR was identified as an independent prognostic factor for relapse–free period in 574 breast cancer patients without distant metastasis (pT1–4, pN0–3, M0 [14]. Stroma–rich tumors had a shorter relapse–free period and overall survival compared to stroma–poor tumors for all subgroups [14]. Other series support this data. Dekker et al have highlighted TSR as an independent prognostic parameter for disease–free survival (DFS) in favour of stroma–low tumours, in 403 premenopausal node–negative breast cancer patients and limit statistical significance for OS [22]. In the Gujam et al study, stroma–high tumours defined as more than 30% is correlated with a poor 15–year cancer–specific survival in multivariate survival analysis in 361 patients with invasive carcinoma of no special type (NST) (T1–3, N0–>3, grade I–III,) [23]. Moreover, in 737 patients with primary operable invasive breast cancer, Roeke et al. corroborate that a high stromal content was a prognostic factor for short OS, distant metastasis–free survival (DMFS) and RFS [24].

Subgroup analysis of these trials confirms the prognostic value of TSR in triple negative tumors in two of the four studies previously cited [14–22]. In the Kruijf study, in the 81 patients with triple–negative breast cancer, tumors with high stroma had a significantly shorter overall survival and relapse–free period compared to those with low stroma. The 5–year RFP were 56% versus 81%, respectively [14]. 69 patients were diagnosed with TNBC in the cohort of Dekker, again Stroma–high tumours had a 2.71 greater risk of developing a recurrence compared to patients with stroma–low tumours [22]. These results do not show up in the two cohorts of Gujam and Roeke probably

because of reduced number of stroma—high tumours in the TNBC subgroup [23–24]. Although the Moorman cohort, dedicated exclusively to women with TNBC independently of the tumor size, lymphatic invasion or the SBR grade, attests after a multivariate analysis the prognostic value of TSR for both of RFS and OS to the disadvantage of patients with stroma—high tumours with 45% and 65% five—year RFS and OS respectively [12]. Following these five studies, we can conclude with some confidence that the amount of the stroma can be used to predict disease progression and patient prognosis especially in TNBC [25]. These data are weighted with the molecular heterogeneity of TNBC and the vast differences in stromal composition of these tumours [26]. Thus, predominantly lymphocytic stroma type might have a favourable prognosis compared to fibroblast or collagen type [27]. Considering aggressive nature of TNBC, implication of TSR to predict the efficacy of adjuvant chemotherapy would be unlikely. Further research should investigate the potential value of this ratio in predicting the efficacy of neoadjuvant chemotherapy.

The RH + HER2— subgroup remains the most common subtype of breast cancer, again the major challenge is the identification of the patients subgroups that will derive clinical benefit from therapeutic. According to the American Society of Clinical Oncology Clinical Practice guideline, many prognostic gene expression signatures are currently validated into routine clinical practice in order to reduce the administration of adjuvant chemotherapy and prevent overtreatment. However, their cost limits their introduction into care programs in developing countries like our country [28]. Also, the stromal component known as an important factor affecting the natural history of tumour is not taken into account these molecular [16].

In addition, another study of ER—positive breast cancers demonstrated that a high TSR was related to better survival across genders in ER—positive disease [23]. These results contradictory with data in triple—negative breast cancer, and own work on ER—positive cases in two studies [14–24] can be explained by several elements: first the inclusion of patients of both sexes, then the threshold of positivity of the hormonal receptors which is not defined (1% or 10%) and finally the course of this study between 1988 And 2005 when the determination of the status of HER2 was not a standard.

Despite the prognostic value of HER2 in breast cancer [25]. There are no studies on the evaluation of TSR in this molecular subtype. However, patients with high TSR had more Her—2—positive tumours [22].

In the stroma—high group statistically significant more patients had a large tumor volume recognized as an unfavorable prognostic factor and often associated with the prescription of adjuvant chemotherapy. These

results are consistent with those objectified in other series suggesting potential interactions between high stroma, tumor size and lymph node invasion [12–13]. Assessing the TSR on tumor—positive lymph nodes can provide additional prognostic information for patients with node—negative disease or with one—three invaded nodes in order to refine the indications for adjuvant chemotherapy in this subgroup of patients and to be able to supplant the genomic signatures in this case [22,29–5]. Also, the evaluation of this ratio in the lymph nodes in combination with that of the mammary tumor could bring strong additional prognostic information [29].

More recently Ki67 determination is principally used for estimation of prognosis and guiding the decision on adjuvant treatment choice, also for prediction of response to neoadjuvant treatment in ER+/HER2— breast cancer [30]. Our study demonstrates that a high stroma tumor was associated with high Ki—67 expression suggesting that a combined analysis of these two parameters would help in the choice of adjuvant treatments.

The present study has some methodological limitations. One aspect concerns the small sample and the retrospective nature of the study. In addition, the determination of the tumor stroma ratio is highly pathologist—dependent. Also, cutoff at 50% was not adopted by all studies. These factors should be considered in future studies.

Conclusions

TSR can be used as a tool for decision support in ER+/HER2— Breast Cancer treatment. It is easy to determine, reproduce, and it is quickly performed. This parameter requires a homogenization of the techniques used and a standardization of its cutoff as well as a prospective evaluation notably in a neoadjuvant situation to be able to serve as a surrogate marker for conventional clinicopathological factors.

Acknowledgements

The authors wish to thank Prof. Salma Seffar for her proof—reading and assistance in helping improve the language and style of this article.

Conflict of Interest

The authors declare that they have no competing interests

References

1. Ferlay J , Colombet M, Soerjomataram I , et al.: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer.* 144:1941–1953. 10.1002/ijc.31937

2. Chew HK. *West J Med: Adjuvant therapy for breast cancer: who should get what?*. 2001 Apr, 174:284–7. 10.1136/ewjm.174.4.284
3. Franchet C, Duprez–Paumier R, Lacroix–Triki M: *Molecular taxonomy of luminal breast cancer in 2015*. *Bull. Cancer*. 2015 Jun, 102:34–46. 10.1016/S0007–4551(15)31216–9
4. López–Tarruella S, Martín M: *Recent advances in systemic therapy: advances in adjuvant systemic chemotherapy of early breast cancer*. *Breast. Cancer Res*. 2009:204. 10.1186/bcr2226
5. Balic M, Thomssen C, Würstlein R, Gnant M, Harbeck N: *St: Gallen/Vienna 2019: a brief summary of the consensus discussion on the optimal primary breast cancer treatment*. *Breast Care*. 2019, 1–8. 10.1159/000499931
6. Markopoulos C, van de Velde C, Zarca D, Ozmen V, Masetti R: *Clinical evidence supporting genomic tests in early breast cancer. Do all genomic tests provide the same information?* *Eur J SurgOncol*. 2016 Aug, 31:10.1016/j.ejso.2016.08.012
7. Khamis ZI, Sahab ZJ: *Byers SW, SangQX. Novel stromal biomarkers in human breast. cancer tissues provide evidence for the more malignant phenotype of estrogen receptor–negative tumors*. *Journal of Biomedicine and Biotechnology*. 2011, 723650. 10.1155/2011/723650
8. Kim JB, Stein R: *O’Hare MJ. Tumour–stromal interactions in breast cancer: the role of stroma in tumorigenesis*. *Tumour Biol*. 2005 Jul–Aug, 26:173–85. 10.1159/000086950
9. West NP, Dattani M, McShane P, et al.: *The proportion of tumour cells is an independent predictor for survival in colorectal cancer patients*. *Br J Cancer*. 2010 May, 11:1519–23. 10.1038/sj.bjc.6605674
10. Maeshima AM, Niki T, Maeshima A, Yamada T, Kondo H: *Matsuno Y. Modified scar grade. A prognostic indicator in small peripheral lung adenocarcinoma*. *Cancer*. 2002 Dec, 15:2546–54. 10.1002/cncr.11006
11. Yanagisawa N, Li R, Rowley D, et al.: *Stromogenic prostatic carcinoma pattern (carcinomas with reactive stromal grade 3) in needle biopsies predicts biochemical recurrence–free survival in patients after radical prostatectomy*. *Hum. Pathol*. 2007 Nov, 38:1611–20. 10.1016/j.humpath.2007.04.008
12. Moorman AM, Vink R, Heijmans HJ, van der Palen J: *Kouwenhoven EA. The prognostic value of tumour–stroma ratio in triple–negative breast cancer*. *Eur J SurgOncol*. 2012 Apr, 38:307–13. 10.1016/j.ejso.2012.01.002
13. Gujam FJ, Edwards J, Mohammed ZM, Going JJ: *McMillan DC. The relationship between the tumour stroma percentage, clinicopathological characteristics and outcome in patients with operable ductal breast cancer*. *Br J Cancer*. 2014 Jul, 1:157–65. 10.1038/bjc.2014.279
14. de Kruijf EM, van Nes JG, van de Velde CJ, Putter H, Smit VT: *Liefers GJ. Tumour stroma ratio in the primary tumor is a prognostic factor in early breast cancer patients, especially in triple–negative carcinoma patients*. *Breast Cancer Res Treat*. 2011 Feb, 125:687–96. 10.1007/s10549–010–0855–6
15. Edge SB, Compton CC: *The American Joint Committee on Cancer: the of the AJCC cancer staging manual and the future of TNM*. *Ann SurgOncol*. 2010, 1471:4. 10.1245/s10434–010–0985–4
16. Hanahan D. & Weinberg R. A: *Hallmarks of cancer: the next generation*. *Cell*. 144–646. 10.1016/j.cell.2011.02.013
17. Mao Y., Keller E. T., Garfield D. H., Shen K. & Wang J: *Stromal cells in tumor microenvironment and breast cancer*. *Cancer Metastasis Rev*. 32:10–1007. 10.1007/s10555–012–9415–3
18. M.R. Junttila, F: *J.de Sauvage, Influence of: tumour micro–environment heterogeneity on therapeutic response*. *Nature*. 2013, 501:346. 10.1038/nature12626
19. Dirat B, Bochet L, Dabek M, et al.: *Cancer–Associated Adipocytes Exhibit an Activated Phenotype and Contribute to Breast Cancer Invasion*. *Cancer Res*. 2011, 71:2455. 10.1158/0008–5472
20. Stanton SE: *Disis ML. Clinical significance of tumor–infiltrating lymphocytes in breast cancer*. *J. Immunother Cancer*. 2016 Oct, 18:4. 10.1186/s40425–016–0165–6
21. Majidinia M: *Yousefi B. Breast tumor stroma: A driving force in the development of resistance to therapies*. *Chem Biol Drug Des*. 2017 Jan 2. DOI, 10.1111/cbdd.12893
22. Dekker TJ, van de Velde CJ, van Pelt GW, Kroep JR, Julien JP, Smit VT et al: *Prognostic significance of the tumor–stroma ratio: validation study in node–negative premenopausal breast cancer patients from the EORTC perioperative chemotherapy. POP) trial (10854)*. *Breast. Cancer Res Treat*. 2013 Jun, 139:371–9. 10.1007/s10549–013–2571–5
23. Gujam FJ, McMillan DC, Mohammed ZM, Edwards J, Going JJ: *The relationship between tumour budding, the tumour microenvironment and survival in patients with invasive ductal breast cancer*. *Br. J Cancer*. 2015 Sep, 7:1066–74. 10.1038/bjc.2015.287
24. Roewe T, Sobral–Leite M, Dekker TJA, et al.: *The prognostic value of the tumour–stroma ratio in primary operable invasive cancer of the breast: a validation study*. *Breast Cancer Res Treat*. 166:435–445. 0.1007/s10549–017–4445–8

-
25. Kramer CJH, Vangangelt KMH, van Pelt GW, Dekker TJA, Tollenaar RAEM: MeskerWE. The prognostic value of tumour–stroma ratio in primary breast cancer with special attention to triple–negative tumours: a review. *Breast. Cancer Res Treat.* 2019 Jan, 173:55–64. 10.1007/s10549–018–4987–4
 26. Lehmann BD, Bauer JA, Chen X, Sanders ME: Chakravarthy AB, Shyr Y: PietenpolJA. Identification of human triple–negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest.* 2011 Jul, 121:2750–67. 10.1172/JCI45014
 27. Ahn S, Cho J, Sung J, et al.: The prognostic significance of tumor–associated stroma in invasive breast carcinoma. *TumourBiol.* 33:1573–1580. 10.1007/s13277–012–0411–6
 28. Krop I, Ismaila N, Andre F, et al.: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early–stage invasive breast cancer. American Society of Clinical Oncology. clinical practice guideline focused update. *J Clin Oncol.* 35:2838–2847. 10.1200/JCO.2017.74.0472
 29. Vangangelt K.M.H , Tollenaar L.S.A, van Pelt G.W , de Kruijff E.M, Dekker T.J.A: Kuppen P.J.K: et al. The prognostic value of tumor–stroma ratio in tumor–positive axillary lymph nodes of breast cancer patients. *Int J Cancer.* 2018 Dec, 12:3194–3200. 10.1002/ijc.31658
 30. Penault–Llorca F, Radošević–Robin N: Ki67 assessment in breast cancer: an update. *Pathology.* 2017 Feb, 49:166–171. 10.1016/j.pathol.2016.11.006