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: Immunoscore; CD3; CD8; erapeutic response; Rectal cancer; Neoadjuvant treatment

Tumor microenvironment is an extrinsic factor that modi es the behavior of the tumor cell [1]. e understanding of the tumoral properties leads to appreciate the in uence of the peripheral and intratumoral immune component on the prognosis and the evolution of the cancer [2]. e immune system alone is able to recognize and eliminate precancerous cells that are undergoing cancer transformation [3]. e concept of “immune surveillance of cancer” is currently demonstrated and validated, and has been de ned as a new vision of “immunoediting of cancer” [4,5]. In Addition, the tumor immune in ltrate consists of adaptive immune cells such as B and T-lymphocytes presenting a speci c antigen receptor, and which are responsible for the immune memory function. Furthermore innate immune system cells are part of the tumor in ltration [2]. e “immunoscore” method has been designed by several authors to focus on the concept of the tumor microenvironment, as well as to explore and quanti es the immune in ltrate characters in solid tumors [2,5]. e European Hospital of Georg Pmpridus (EHGP)19(un)4(e sysm)19(p)2(n)8(s)t2(r)63(, a)8.9g a steocmaonstrated0.181 Tw 0 -1.2 TD[(micr) ex5(tl)-5(l)3(s (t)0.6((n)4(cep

In all, 54 patients diagnosed with adenocarcinoma at HASSAN II University Hospital Center of Fez were included in this study. Patients received neoadjuvant treatment followed by surgical procedure. We followed the methods of Otmani [13]. Samples collected and selected for Immunohistochemistry (IHC) were Formalin-Fixed-Para n-Embedded (FFPE) pre-therapeutic biopsies.

Histological slides based on a hematoxylin and eosin-stained slide were evaluated by a gastrointestinal pathologist. Histological parameters were investigated and performed according to the staging criteria of the American Joint Committee on Cancer, 7th edition (AJCC) (histological type, tumor di erentiation, tumor regression grade with the Dworak Grading, post-neoadjuvant treatment TNM stage (ypTNM), lymph node status. And other clinic pathological characteristics). Data registered include demographic details, neoadjuvant treatment details, type and results of surgery, pathology reports, and cancer outcome.

e total density of cytotoxic CD3$^+$ and CD8$^+$ T lymphocytes were evaluated by immunohistochemistry and quanti ed by simple optical microscope analysis for 54 tumor biopsies taken before neoadjuvant

L	15 (27.8)
M	12 (22.2)
H	27 (50)
L	27 (50)
H	27 (50)
<50%	19 (35.2)
Ó 50%	35 (64.8)
Incomplete response	45 (83.3)
Complete response	9 (16.7)
1	7 (13)
2	19 (35.2)
3	19 (35.2)
4	9 (16.7)
Presence	6 (11.1)
Absence	48 (88.9)
Presence	4 (7.4)
Absence	50 (92.6)
N0	36 (66.7)
N1	13 (24.1)
N2	5 (9.3)
T0	9 (16.7)
T1	2 (3.7)
T2	20 (37)
T3	22 (40.7)
T4	1 (1.9)
CT: Core of tumor; IM: Invasive margin; Ld: Low density; Md: Moderate density; Hd: High density; L: Low; M: moderate; H: high	

: Description analysis of clinicopathologica data.

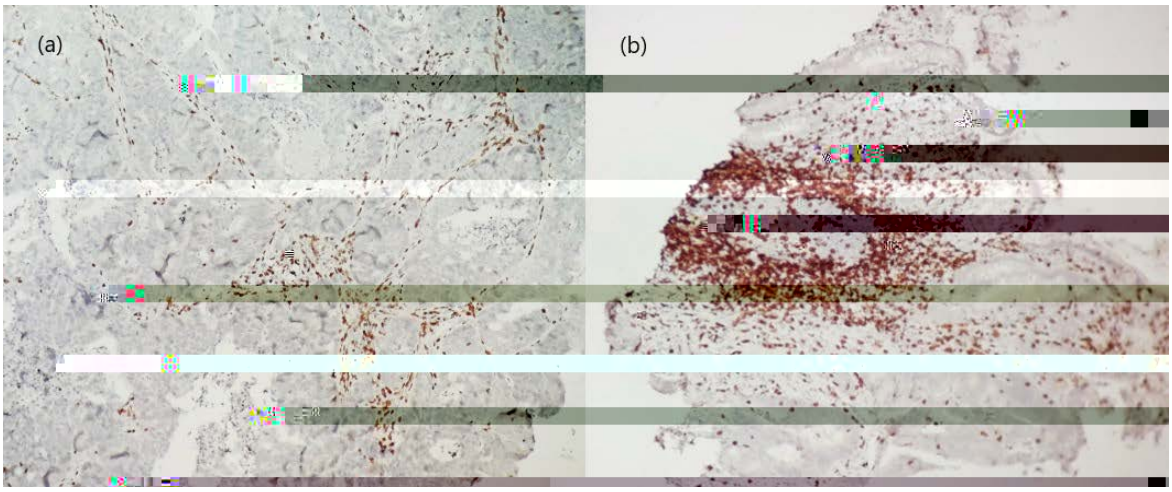
We analyzed immune in ltration using immunoscore grouped into 3 methods; 5 groups, 3 groups and 2 groups. e 3 methods were correlated with clinic pathological characteristics of pre-treated rectal cancer biopsies and post therapeutic resected specimens. High immunoscore (I4) was signi cantly associated with complete response (p=0.003) as shown in Table 3. In addition there was signi cant association between high immunoscore (I4) and lower ypT stage (p=0.008), as shown in Tables 3-5. Moreover, signi cant association was founded between 5 groups of immunoscore and lymph node status, low immune in ltration (I0, I1 I2) was associated presence of metastasis lymph node (N1)(p=0.039).

In contrast when dividing patients into 3 and 2 groups of immunoscore, as shown in no other signi cant association was observed between clinicopathological parameters and Immune in ltration (Tables 4 and 5).

Considering analysis according to one marker of CD3 and CD8. Density evaluated in combined CT and IM tumor region associated with clinicopathological features was illustrated in Table 6.

Signi cant association was found between density of CD3 and sex, 43.8% of women had a high density in ltration compared to only 36.4 of men with a proportion of 36.4% in high score in ltration. Both CD3 and CD8 showed association with pathologic response to neoadjuvant treatment. We observed that 88.9% and 100% of CD3 and CD8, respectively, of patients who expressed high density had a complete response (p=0.008, p=0.002). Moreover, 64.5% of patients who had a T0, T1 and T3 stage was classed in High score of density in ltration of CD8 (p=0.016).

e correlation between survival analysis and immunoscore was investigated in rectal cancer. e e ect of T-cell density was correlated to immune in ltration classi ed on 3 groups as showed in Figures 3a and 3b, a signi cantly association was found between OS and high expression of immunoscore (p=0.45), while RFS was not associated with immune density in di erent region of two markers. Patient's



Immunohistochemistry showing nuclear staining. (a) Core of tumor region of CD3 (magniýcation x 200), (b) Invasive margin region of CD8 (magniýcation x200).

0.36S277404.4 83.3

Male	1 (4.5)	13 (59.1)	8 (36.4)	0.031	5 (22.7)	7 (31.8)	10 (45.5)	0.077
Female	9 (28.1)	9 (28.1)	14 (43.8)		9 (28.1)	7 (21.9)	16 (50)	
<50	4 (18.2)	9 (40.9)	9 (40.9)	1	8 (36.4)	5 (22.7)	9 (40.9)	0.375
Ó 50	6 (18.8)	13 (40.6)	13 (40.6)		6 (18.8)	9 (28.1)	17 (53.1)	
Adenocarcinoma	9 (17.6)	21 (41.2)	21 (41.2)	1	13 (25.5)	13 (25.5)	25 (49)	1
Mucinous carcinoma/signet ring carcinoma	1 (33.3)	1 (33.3)	1 (1)		1 (33.3)	1 (33.3)	1 (33.3)	
Well	5 (18.5)	12 (44.4)	10 (37)	0.898	6 (22.2)	11 (40.7)	10 (37)	0.147
Moderate	5 (20.8)	9 (37.5)	10 (41.7)		7 (29.2)	3 (12.5)	14 (58.3)	
poor/undifferentiated	0 (0)	1 (33.3)	2 (66.7)		1 (33.3)	0 (0)	2 (66.7)	
<50%	3 (15.8)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

survival curves according to density of each marker of CD3 and CD8 did not show signi cance as describe in Figures 3-5.

e interaction between immune system cells and cancer cells is part of the mechanisms of "immunosurveillance" [14]. In a global way, a new type of biomarker can de ne the intratumoral component in immune cells. is biomarker may be complementary to other biomarkers linked directly to the tumor cell [3]. e technological revolution, which concerned nanotechnologies, the calculation and imaging system as well as digital pathology, made it possible to better characterize and identify the component of the tumor cell with great precision and robustness. is has created a favourable ground for research and development of new biomarkers [15]. Also allowed to understand the role that the immune system plays in the dynamics of cancer and to develop an original method called "Immunoscore" [5,6]. Studies have shown that in most solid tumours such as colorectal cancer, a strong immune in ltration in the tumor has been associated with prolonged survival [9].

Our study was conducted to evaluate relationships between immune in ltration using Immunoscore test, and therapeutic response, clinicopathological features and survival outcomes of patients. We here in demonstrate that high score of immune cells in ltration in pre-treated tumours is associated with a complete pathologic response a er neoadjuvant therapy. As a result, we demonstrate the importance role of densities of CD3 and CD8 in both CT and IM in therapy sensitivity.

e high level expression of immune cells of CD3 and CD8 proved necessary to ensure a complete response. is result is in accordance with publication of several studies [10,16] in which they report a signi cant

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