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Expression of Stem Cell Markers Cd133 and OCT-4 in Rectosigmoid Adenocarcinoma and their Predictive Significance of Response to Chemoradiotherapy

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Abstract

Colorectal carcinoma (CRC) is one of the most common cancers in the world. Preoperative radiation with concurrent chemotherapy and subsequent surgery is the standard treatment for locally advanced rectal cancer. However, the tumor response to preoperative chemoradiotherapy (pCRT) varies significantly. CSCs have been found in many human malignant tumors including rectal cancer. Several markers for CSCs have been proposed in CRC, OCT-4 and CD133 have been the most frequently researched.

This study was targeted to evaluate the immunohistochemical expression of stem cell markers OCT-4 & CD133 in rectosigmoid adenocarcinomas and correlate their expressions with the grade, stage, and response of the tumor to CRT.

The present study comprised 30 specimens of rectosigmoid adenocarcinoma. The primary antibodies used were: OCT-4 antibody, clone PA5-27438, and CD133 antibody, clone144305. Positive OCT-4 expression was observed in 12/30 cases. A significant relationship was found between OCT-4 expression and tumor stage and sex of the patients. No statistically significant relation was found between OCT-4 expression and age of the patients, tumor grade, lymph node stage, pathological response to CRT, OS, or the expression of CD133.

20/30 cases were positively stained for CD133, no significant correlation between CD133 expression and any of the clinicopathological parameters.

OCT-4 was expressed in 40% and CD133 in 66% of rectosigmoid cancers studied, so they might be involved in the development of CRC. New therapeutic perspectives based on the selective targeting of the specific population of cells expressing one of those CSCs. OCT-4 expression might be a bad prognostic indicator in rectosigmoid cancer.

Keywords: Stem cell markers; Adenocarcinoma; Radiotherapy

Abbreviations: CEA: Carcinoembryonic antigen; FOLFOX: FOL– Folinic acid (leucovorin), F– Fluorouracil (5-FU), OX-Oxaliplatin (Eloxatin); AJCC: American Joint Committee on Cancer; TNM: Tumor Node Metastasis

Introduction

Rectal cancer is the third most common cancer after lung and prostate cancers in males and breast and lung cancers in females worldwide [1]. Pre-operative radio chemotherapy (pRCT) is currently the standard treatment for locally advanced rectal cancer [2-5]. Approximately 40% of patients show poor or no response to pRCT, while a pathologic complete response (pCR) has been reported in approximately 40% of cases [5]. The objective of neoadjuvant treatment is down-staging of disease, sphincter preservation for surgically unresectable tumors, and increased disease-free survival rate of 30% at 5 years.

However, the response to pCRT in locally advanced rectal cancer varies among patients. While ~40% of patients have a partial response (PR) and 8%-20% of patients achieve a pCR at the time of surgery, a subset of tumors (~20%) exhibit resistance to pCRT, demonstrating either progression or only minimal regression to stable disease [6]. These different responses to pCRT are associated with long-term outcomes including disease-free survival (DFS) and 10-year cumulative incidence of distant metastasis. In addition, given the observation of pCR in a significant proportion of patients undergoing pCRT and the adverse effects of surgery (bowel, urinary and sexual dysfunctions), alternative approaches, such as the "wait-and-see" policy or trans anal local excision, have been suggested. On the other hand, patients exhibiting resistance to pCRT need more successful treatment approaches earlier in their management. Therefore, there is a critical need of biomarkers predicting response to pCRT at an early time point, allowing selecting rectal cancer patients who would or would not have a benefit from pCRT, to reduce toxicity associated with ineffective pCRT, and to provide adequate treatment option [7].

Several clinicopathologic and treatment-related factors were independently associated with pCR: Lower tumor grade, lower clinical

T and N stage, higher radiation dose, and delaying surgery by more than 6-8 weeks after the end of radiation were associated with higher odds of pCR. Numerous retrospective cohort studies have identified a variety of disease-related variables as potential predictors of pCR. These include low pre-therapy CEA, low CEA after nCRT, small pre- and post-treatment tumor size, pre-treatment tumor 'movability', low N category, low tumor grade, shorter distance from the anal verge, smaller circumferential tumor extent, and low neutrophil to lymphocyte ratio. Identification and awareness of these factors may help to predict which patients are more likely to achieve pCR with neoadjuvant treatment, and may be used to counsel patients more accurately regarding their prognosis and treatment options. It is interesting that several of these factors are also those that make a rectal tumor more suitable for trans anal excision; thus, patients with tumors that exhibit most or all of these features may potentially be identified as safe candidates for less radical surgery following neoadjuvant therapy [8,9].

According to the CSC hypothesis, these stem-like cells play a pivotal role in tumor genesis, metastasis and relapse. Previous work showed that only CSCs could reconstitute tumors with similar histopathological characteristics to the primary cancer, whereas non-stem cancer cells failed to effect tumor initiation [10]. The identification of normal and malignant colorectal stem cells has always been difficult. Only recently, new methods have been developed to aid in their identification and isolation. At this stage, the most important of these has been the identification of surface markers by immunohistochemical analysis. Several markers have been identified as solid CSC markers, CD133, and OCT4 [11].

Octamer 4 (OCT-4), is a member of the POU domain transcription factor family, normally expressed in both adult and embryonic stem cells [12]. Extensive investigations have revealed that OCT-4 is expressed in some cancer cell types, such as breast, prostate, hypopharyngeal, bladder, lung, esophageal, and hepatocellular cancer. Recent reports have demonstrated that OCT-4 is not only involved in controlling the maintenance of stem cell pluripotency, but is also responsible for the unlimited proliferative potential of stem cells, suggesting that OCT-4 serves as a master switch during differentiation of human somatic cells. Moreover, overexpression of OCT-4 increases the malignant potential of tumors, and downregulation of OCT-4 in tumor cells inhibits tumor growth, suggesting that OCT-4 might contribute on maintaining the survival of cancer cells [13].

CD133 is a five-transmembrane glycoprotein that was first found to be expressed in hematopoietic stem and progenitor cells [14]. The exploration of CD133 as a surface marker of colon cancer stem cells is still in progress. O'Brien et al and Ricci et al. found that CD133 (+) cells in colon cancers had the ability to initiate tumor growth. The colon cancer-initiating cells (CC-ICs) represented enrichment in CD133 (+) populations. These two studies strongly support CD133 as a marker of Colon CSCs based on the evidence that CD133 (+) cells could produce tumors with preserved self-renewal and differentiation capabilities and without phenotypic alterations after serial transplantation [15].

Material and Methods

A total of 30 retrospective cases of rectosigmoid adenocarcinoma were chosen from the archive of the pathology & oncology departments, Alexandria Faculty of medicine, because they received the following management protocol:

Preoperative radiation therapy of 45 GY in 25 fractions (1.8 GY per-day) was delivered to the whole pelvis over the course of 5 weeks. A 5.4 GY boost in three fractions was subsequently delivered to the primary tumor.

Concurrent oral capecitabine was given at a dose of 825mg/m^2 twice daily during radiotherapy.

Surgery was done 6 to 8 weeks after end of chemo radiotherapy.

Adjuvant FOLFOX for 4 cycles was considered.

Collection of clinical data

The clinical data obtained included: age, sex, clinical presentation, treatment received and follow up.

Pathological examination of colonoscopic biopsy before the treatment

For each case, 5 micron thick sections were cut from the formalin-fixed, paraffin-embedded blocks of the tumor, one for H&E (hematoxylin and eosin staining) and 2 sections on coated slides for immunohistochemical staining.

H&E sections were examined under light microscopy for determination of:

Histological type of the tumor (adenocarcinoma, mucinous adenocarcinoma, signet ring adenocarcinoma). According to the WHO classification (16,17).

Histologic grade was done according to the most recent WHO series on tumors of the digestive system using the two tiered grading system (low versus high grade) in grading colorectal cancer (18).

Low-grade (well-differentiated ≥ 95% gland forming and moderately differentiated=50%-95% gland forming).

High-grade (poorly-differentiated=0%-49% gland forming and undifferentiated).

Pathological examination of rectosigmoidectomy specimen after the neoadjuvant treatment

All microscopic slides of each case were reviewed and the most representative section for the tumor was selected. Pathological grading of primary tumor regression was performed semi quantitatively by determining the amount of residual tumor cells compared with the desmoplastic response. The 4 AJCC TRG classification groups were as follows: TRG0, no residual tumor cells; TRG1, single cells or small groups of cells; TRG2, residual cancer with desmoplastic response; and TRG3, minimal evidence of tumor response.

Evaluation of immunohistochemical staining

Evaluation of OCT-4 and CD133 IHC was done on all 30 colonoscopic biopsies.

OCT-4 immunostaining:

Positive staining for OCT-4 was detected as brown staining of the nuclei. Cytoplasmic staining was considered negative.

A semi-quantitative evaluation system was employed to obtain the staining scores.

The staining intensity was classified into four grades: 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining.

The percentages of stained cells were classified as: 0, no stained tumor cells; 1, staining of <10% tumor cells; 2, 10%-50% stained tumor cells; and 3, >50% stained tumor cells.

The final score was calculated by adding the percentage score to the intensity score: scores <4 were defined as negative staining, and scores ≥ 4 were defined as positive staining.

CD133 immunostaining: Positive staining for CD133 was detected as a cytoplasmic staining pattern of tumor cells.

The percentages of stained cells were categorized into:

Score 0=Negative staining in all tumor cells.

Score 1=positivity in <50% of tumor cells (low positive).

Score 2=positivity in ≥ 50% of tumor cells (high positive).

Results

The present study included 30 patients with rectosigmoid adenocarcinoma. All of them received neoadjuvant chemoradiotherapy. Fifteen patients were females (50%) and 15 were males (50%). Their age ranged from 20 to 73 years with a mean of 46.5 years. Eighteen patients were ≥ 50 years (60%) and 12 were >50 years (40%). All the cases were adenocarcinoma. Two cases were diagnosed as adenocarcinoma with mucin differentiation. The tumors were graded into low grade and high grade. Out of the 30 cases, 27 were low grade adenocarcinomas; while 3 were high grade adenocarcinoma.

According to TNM staging of colorectal carcinoma (18), 3 cases were pT2, 15 cases were pT3, and 12 cases were pT4. According to TNM staging of colorectal carcinoma (18), 14 cases were N0, 9 cases were N1, and 7 cases were N2. According to AJCC tumor regression grading system, 15 cases were TRG1 (Figure 1), 7 cases were TRG2 (Figure 2), and 8 cases were TRG3 (Figure 3).

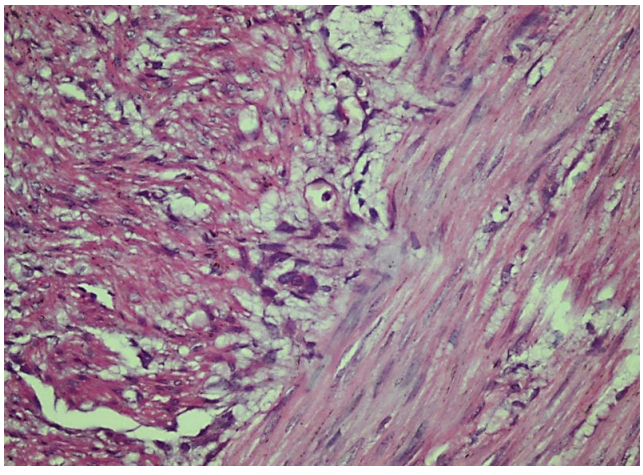

Figure 1: TRG1 (Near complete response) (H&E 400).

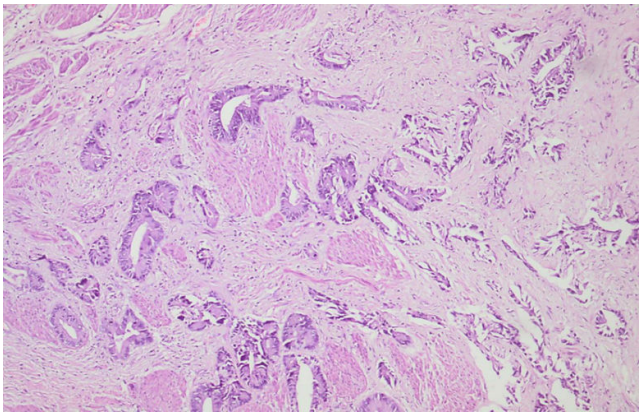

Figure 2: TRG2 (minimal response) (H&E 100).

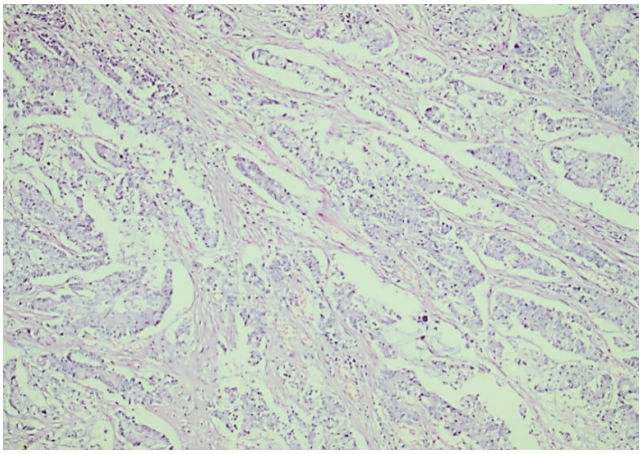

Figure 3: TRG3 (poor response) (H&E 100).

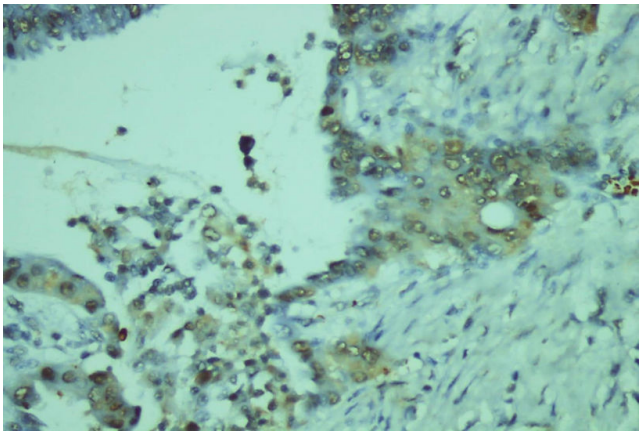

Figure 4: Positive OCT-4 nuclear expression in a moderately differentiated adenocarcinoma (IHC 400).

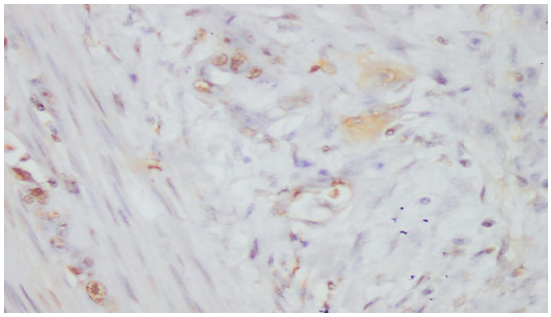

Figure 5: Positive OCT-4 nuclear expression in a poorly differentiated adenocarcinoma (IHC ⊠ 400).

Tumor stage	OCT-04				χ^2	MCp
	Negative staining (n=18)		Positive staining (n=12)			
	No.	%	No.	%		
pT1	0	0	0	0	5.992*	0.036*
pT2	3	16.7	0	0		
pT3	11	61.1	4	33.3		
pT4	4	22.2	8	66.7		

χ^2, p: χ^2 and p values for Chi square test; ^{MC}p: p value for Monte Carlo for Chi square test; *: Statistically significant at $p \leq 0.05$

Table 1: Relation between OCT-4 and tumor stage.

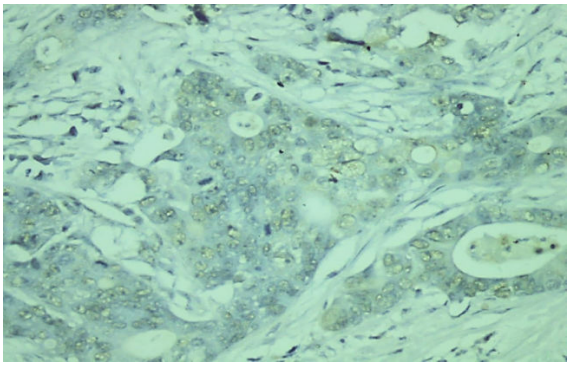

Figure 6: Negative OCT-4 nuclear staining (score <4) in a moderately differentiated adenocarcinoma (IHC 400).

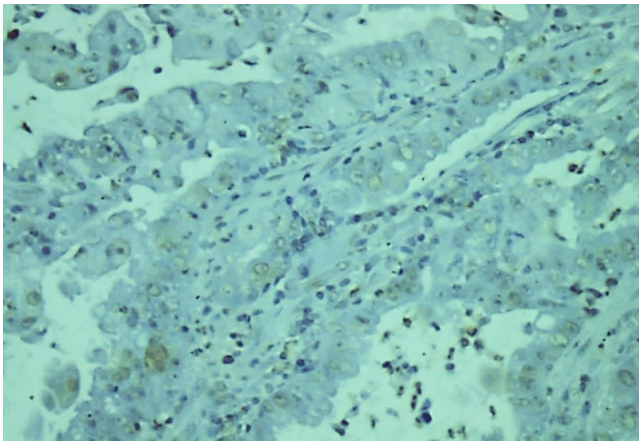

Figure 7: Negative OCT-4 nuclear staining (score <4) in a well differentiated adenocarcinoma (IHC ⊠ 400).

Positive OCT-4 expression (scores equal to or more than 4) was observed in 12 cases. (Figures 4 and 5). Negative OCT-4 expression (scores less than 4) was noted in 18 cases. (Figures 6 and 7).

No statistically significant relation was found between OCT-4 expression and age of the patients, tumor grade, pathological response and nodal status. A significant positive relationship was found between OCT-4 expression and tumor stage (p=0.036) (Table 1).

Expression and localization of CD133

Twenty cases showed positive staining while the remaining 10 were negative. (Figures 8-11). Positively stained samples were further classified into high expression (8 specimens) and low expression (12 specimens).

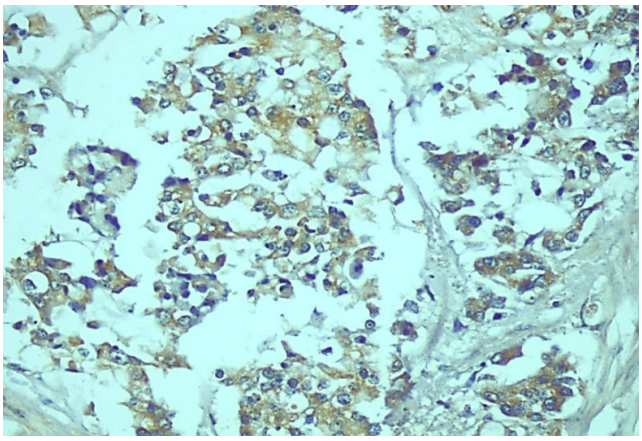

Figure 8: Positive CD133 cytoplasmic immunostaining (score 2) in a poorly differentiated adenocarcinoma (400).

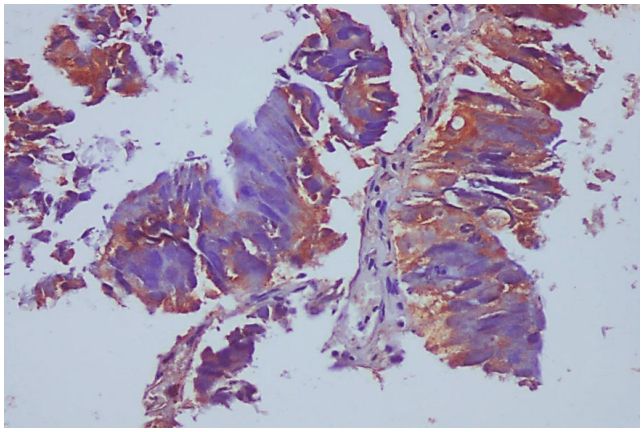

Figure 9: Positive CD133 cytoplasmic immunostaining (score 2) in a moderately differentiated adenocarcinoma (400).

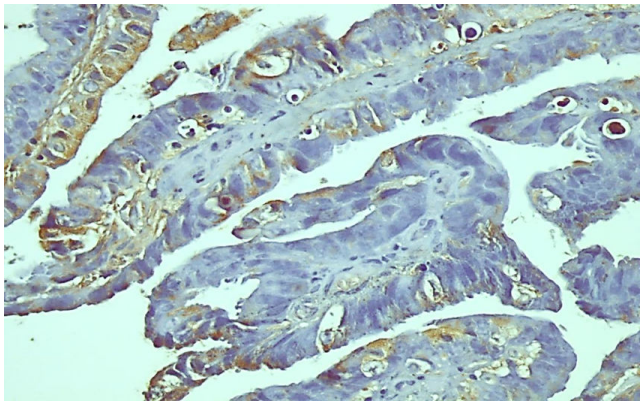

Figure 10: Positive CD133 cytoplasmic immunostaining (score 1) in a moderately differentiated adenocarcinoma (400).

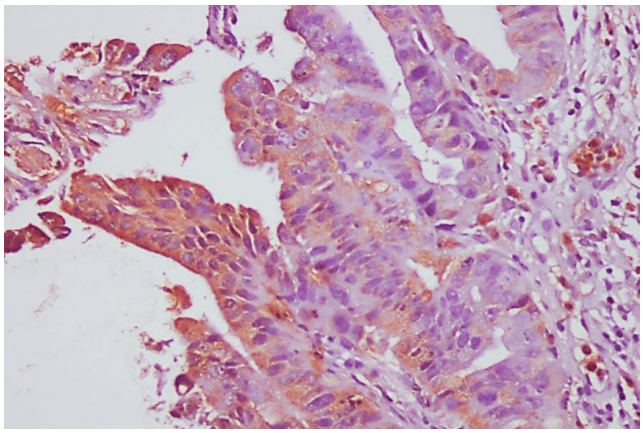

Figure 11: Positive CD133 cytoplasmic immunostaining (score 1) in a moderately differentiated adenocarcinoma (400).

No significant relation was found between the expression of CD133 and either the patient's age or tumor grade or stage, nodal status or pathological response. No statistically significant relationship was found between the expression of the two stem cell markers OCT-4 and CD133. The mean OS was 21.4 months, and the 2 year survival was 76.7% in these patients (Figure 12).

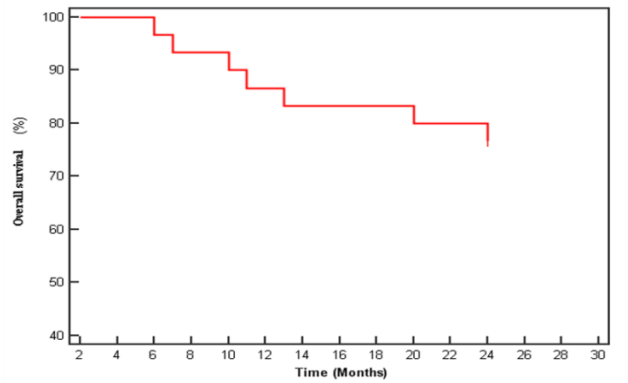

Figure 12: Kaplan-Meier survival curve for overall survival.

No statistically significant relationship was found between OS and either OCT-4 or CD133 expression.

Discussion

Colorectal cancer (CRC) is the third most common cancer affecting males and females in most countries and is a leading cause of cancer related deaths [19]. In Egypt, colorectal cancer occupies first rank among digestive system malignancies and fifth rank among total cancers [20].

Despite the great improvement in early diagnosis, operative treatment, adjuvant therapies (such as chemotherapy, and radiotherapy) and integrated patients' care, the prognosis of rectal cancer patients remains far from satisfaction [21].

In an attempt to further identify predictors of response to CRT, several studies have reported that colorectal cancers positive for some cancer stem cells (CSCs) markers might be more resistant to therapy [22]. CSCs are a special kind of cancer cells that have the ability of self-renewal and differentiation to other cells. They have been found in many human malignant tumors including rectal cancer [23].

Several markers for CSCs have been investigated and proposed in colorectal cancer. Of those, OCT-4 and CD133 have been the most frequently researched and are thought to be the most likely markers for colorectal CSCs [11].

Therefore, in the present work immunohistochemical expression of stem cell markers OCT4 and CD133 was investigated on 30 formalin fixed paraffin-embedded colonoscopic specimens of rectosigmoid adenocarcinoma to determine if there is correlation between their expressions and different clinicopathological parameters of the tumors and treatment outcomes.

In the present study, 60% of the patients were ≤ 50 years of age whereas 40% were >50 years, with a mean of 46.5 years. In the study by Hu et al. from China, the mean CRC patients age was 57 years, and in the study by Kojima et al. from Japan, the mean age was 55.9 years

(24,25). In the United States and European Union, only about 2%-8% of CRC occur in individuals under 40 years of age [1]. In accordance with our results, Abou-Zeid et al. found that 38% of Egyptian CRC patients in their study were under 40 years of age [26]. This indicates that the mean age for CRC is younger in the Egyptian population.

In the present work, 40% of the specimens were positively stained with OCT-4 and 60% were negatively stained. Similarly Zhou et al. in their study on 158 CRC found that 42.41% of specimens were positively stained by OCT-4 [27]. Hu et al. found that 50/143 (35%) of the specimens were positively stained by OCT-4 [24].

No significant relation was found between OCT-4 immunostaining and the grade of the tumor in the present study. Similarly Hu et al. did not identify statistical relations between OCT-4 expression and the extent of tumor differentiation [24]. Contradictory results have been reported by Shaheen et al. and You et al. who found that OCT-4 expression was significantly associated with high-grade adenocarcinoma [11,21]. The minority of higher grade specimens in the present work may explain this discordance.

In the present study, a statistically significant positive relationship was found between OCT-4 immunoexpression and stage of the tumor. This is concordant with Zhou et al. [27] and Xing et al. who showed that positive expression of OCT-4 is associated with a higher T stage [28].

In the present work, no relationship was found between OCT-4 and pathological response to preoperative chemoradiotherapy by using AJCC grading system. This is the first study to correlate OCT-4 expression with the pathological response by using AJCC grading system.

In the present study, no significant relation was found between OCT-4 immunostaining and OS of the patients. This is contradictory to Zhou et al. who reported that OCT4 positive cases had a significantly shorter survival time compared with OCT4 negative cases [27]. Short term follow-up in the present study may explain our inability to find such a relationship.

Regarding CD133 immunostaining, 20 specimens (66.7%) were positively stained (12 of them showing low expression; and the remaining 8 showing high expression) and 10 specimens (33.3%) were negatively stained. Hongo et al. found that CD133 expression was positively stained in 93 of the 225 specimens (41.3%) [29].

In the current study, the relation between CD133 immunostaining and grade of the tumor was statistically insignificant. Similarly, Wang et al. found that CD133 expression was not correlated with the degree of tumor differentiation [30]. Contradictory results have been reported by Hongo et al. who found that CD133 is highly expressed in well/moderately differentiated, but not in poorly differentiated tumors [29].

In the present study no relationship was found between CD133 immunostaining and T stage of the tumor. Similarly, Wang et al. found that CD133 immunostaining was not associated with depth of infiltration [30]. Contradictory results have been reported by Choi et al. and Chen et al. who found that there was a relation between CD133 expression and depth of invasion. Reasons for the discrepancies with other studies, may be the differences in sample size, the genotype of studied specimens as well as the differences in methodology (tissue microarray *vs.* whole tissue sections), and certainly in the choice of cutoff scores for the definition of positive staining [31,32].

In the present work, no relationship was found between CD133 immunostaining and the OS. This is contradictory to Ong et al. who found that overexpression of CD133 associated with poorer OS [33]. In 2012 and 2013, two meta-analysis reports suggested that CD133 expression is significantly related to shorter overall survival, and may play an important role in the progression of colorectal cancer [32,33]. Short term follow up in the present study may explain our inability to find such a relationship.

In the present study, the relationship between CD133 immunostaining and pathological response to preoperative CRT was statistically insignificant by using the AJCC TRG system. Huang et al. found an association between CD133 expression in rectal cancer and CRT effect (23). CD133 positive rate was lower in CRT responsive patients, which could be used to predict the curative effect, so as to reduce patient's burden. These contradictory results may be explained by: higher tumor stages in the present study (50% of cases were stage T3 and 40% were stage T4), different criteria used to classify positive staining, and different cutoff values used to discriminate low and high scores of IHC.

In the present work, no significant relationship was found between OCT-4 and CD133 expression. Similarly Saigusa et al. and Shaheen et al. didn't find a correlation between CD133 and OCT-4 expression in CRC specimens [11,34].

Conclusion and Recommendations

The mean age for development of CRC was found to be lower in our series of Egyptian patients than series from the Far East, United States and European Union. This indicates that screening for high risk people must start 10 years earlier in Egypt.

OCT-4 was expressed in 40% and CD133 in 66% of rectosigmoid cancers studied, indicating that they might be involved in the development of CRC. This could open new therapeutic perspectives based on the selective targeting of the specific population of cells expressing one of those CSCs.

A significant positive relationship was found between OCT-4 expression and tumor stage. This indicates that OCT-4 expression might be a bad prognostic indicator in rectosigmoid cancer and makes OCT-4 an important therapeutic target.

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