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Immunoexpression of DEK and Phospho-P38 proteins in rectal cancer before chemoradiation therapy

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ABSTRACT – Background – Colorectal cancer is the third cause of cancer worldwide and a quarter of them are in the rectum. DEK oncogene is involved in several nuclear processes and can accelerate tumorigenesis. **Objective –** This study aims to evaluate the immunoexpression of DEK and Phospho-P38 proteins before neoadjuvant therapy in patients with rectum adenocarcinoma and correlate it with a clinical response and survival. **Methods –** Patients with adenocarcinoma of the middle and low rectum who underwent chemotherapy and radiotherapy followed by surgical tumor resection were included. The expression and quantification were studied by immunohistochemistry in the tumor biopsy tissues using a HScore system. Score ≥4 were considered positive and those with <4 negative. **Results –** 22 patients were included with a mean age of 63.55 years (SD: ±13.49). The clinical-stage before treatment was T3 on 72.7%, T4 on 18.2%, 31.8% were N1, 50% N0 and all M0. After chemo and radiotherapy, 54.6% were T3; 22.7% were classified as T2; 9.1% as T1, and 13.6% were T0. Among the tumors, 22.7% were positive for DEK and 63.6% positive for Phospho-P38. There was a positive correlation between DEK protein before treatment and pTNM stage (P=0.011). Phospho-P38 protein showed no correlation with these parameters. Patients with a negative HScore had a mean survival of 141.33 months (95%CI: 112.41–170.25) and those with a positive HSscore had a mean survival of 25.10 months (95%CI: 17.36–32.84; P<0.001). **Conclusion –** A higher expression of DEK was observed in advanced stages. Patients who presented DEK expression <4 had a higher survival, being a factor of worst prognosis.

Keywords – Rectal cancer; immunohistochemistry; proto-oncogene DEK; Phospho-P38; prognosis; neoadjuvancy; chemoradiation.

INTRODUCTION

Colorectal cancer (CRC) is the third cause of cancer and the fourth leading cause of cancer-related mortality in both sexes worldwide. Up to a quarter of these cases are in the rectum, representing between 27% and 58% of all cases of CRC[1-3].

The mainstay of treatment for locally advanced rectal cancer (T3-4 or TxN+ - any T with positive lymph nodes) in the middle and lower portion of the rectum was neoadjuvant chemoradiation (nQRT) followed by surgical resection of the tumor and adjuvant therapy[4,5]. According to the literature, around 40–60% of patients who receive nQRT reach any degree of pathological response (complete, partial, or minimal response). Currently, there is still no effective method to predict which patients will or will not respond to neoadjuvant therapy. In this context, the study of potential biomarkers is extremely promising. Nowadays the total neoadjuvant treatment must be considered in these patients[6].

The DEK proto-oncogene (D6S231E) is involved in several fundamental nuclear processes, and scientific evidence proves that this gene is related to neoplastic progression, contributing to the tumorigenesis process. Studies that associated the expression of this biomarker with the pathological response in rectal adenocarcinoma, furthermore, DEK was described as having a high statistical power to predict pathological complete response to neoadjuvant chemotherapy in breast cancer, for example[7]. The P38 protein, on the other hand, is an important component of the mitogen-activated protein kinases (MAPK) family. Its active form, Phospho-P38 or PP38 (phosphorylated protein 38), plays a central role in cell proliferation and apoptosis in multiple neoplasms[7]. Recently disease response after chemotherapy treatment in CRC has been associated with the DEK expression, supporting a possible highly robust predictive model of cell death[8,9,10].

This study aimed to analyze the immunoexpression of DEK and Phospho-P38 proteins in cancer biopsy of the middle and lower rectum, before chemoradiotherapy and correlate these data to the clinical stage and survival.

METHODS

This is a retrospective longitudinal study, in a cohort of patients with medium and low rectal adenocarcinoma undergoing neoadjuvant treatment and follow-up at the Gastro-Oncology Outpatient Clinic in Hospital São Paulo - Brazil. Patients were selected through a survey and evaluation of medical records

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from the Gastro-Oncology Outpatient Clinic (Discipline of Gastroenterology-UNIFESP/EPM), according to the established inclusion criteria. All radiological, imaging, pathological diagnosis and clinical follow up in the medical records were reviewed and confirmed.

Ethics approval and consent to participate

The study was conducted in accordance with the World Medical Association (WMA) and the Declaration of Helsinki. Ethical approval for this study was obtained from the Ethics and Clinical Research Committee *Coordenadoria de Ensino e Pesquisa do Hospital* São Paulo-HU/UNIFESP. CAAE: 01059018.2.0000.5505. Patients provided written informed consent.

Immunohistochemistry and semi-quantification analysis

The antigen recovery, deparaffinization, and rehydration were performed in all silanized slides containing the histopathological material (3-µm sections of paraffin blocks), using the Target Retrieval Solution High pH – EnVision Flex DAKO for 20 minutes at 90^{0}C in a steamer. The slides were submitted to 4 baths of 5 minutes each with hydrogen peroxide to block endogenous peroxidase (Peroxidase Block – Novacastra Leica) and one bath of 5 minutes to block nonspecific proteins (Protein Block – Novocastra Leica). Incubation with primary antibody as executed with the Primary Antibody Diluent-Scytek, and the dilutions established were: DEK 1:300 (Thermo Fischer, #PA5-62975) and PP38 1:200 (Santa Cruz, Biotechnology Inc., Thr 180/Tyr 182, p38α-R, sc-17852-R). For the secondary antibody the Polymer Detection System Novolink – Leica kit was used, followed by incubation of the preparative solution (Post Primary – Novocastra Leica) for 30 minutes in a humid chamber and after, for revelation the chromogen (DAB Chromogen – Novocastra Leica). Finally, counterstaining with Hematoxylin was performed and the slide was mounted and the immunoexpression of the markers was evaluated by a pathologist from the Laboratory of Molecular and Experimental Pathology. The following criteria were considered: cell compartment (nuclear expression); percentage/extension of the reaction (%); intensity (0: unmarked; 1: weak; 2: moderate and 3 strong). In addition, the HScore system was applied for semi-quantitative analysis, based on the multiplication of the intensity of the reaction and the extent of staining. The extension of the positive area was rated on a scale from 0 to 3 (0: 0–10%; 1: 11–25%; 2: 26–50% and 3:>51% of the neoplastic cells stained). Reactions with a score greater than or equal to 4 were considered positive and those with a score less than 4, negative.

Statistical analysis

To analyze the behavior of continuous variables, descriptive statistics, histogram, and boxplot graphics and the specific test for the theoretical assumption of normality Shapiro-Wilk were done. Comparison between the two groups was performed using the Mann-Whitney test for numerical variables and Fisher's exact test for categorical variables; for three groups the Kruskal-Wallis test was used. Correlation analysis between numerical or ordinal variables was performed using Spearman's correlation coefficient. Survival analysis was performed using the Kaplan-Meier method and comparisons between groups were performed using the Mantel log-rank test[11]. Statistical analysis was performed using the IBM-SPSS Statistics version 27 software (IBM Corporation, NY, USA). *P* values <0.05 were considered significant.

RESULTS

Patients features

The study sample consisted of 22 patients diagnosed with adenocarcinoma of the middle and lower rectum undergoing neoadjuvant chemotherapy based on fluoropirimidine and local radiotherapy (45 GY in 25 fractions, 5 days a week) followed by surgery that included total mesorectal resection. The mean age of the patients included was 63.55 years (SD: ±13.49), with a predominance of females (63.60%).

A little more than half of the cases (59.1%) were in the lower rectum and the most frequent type of surgical resection was abdominoperineal amputation, in 59.2% of cases. Seventeen of the twenty-two patients (77.3%) had a tumor 4.0 cm in the largest diameter, and 8 (81.8%) were diagnosed with a moderately differentiated tumor. Half of the patients underwent adjuvant therapy based on fluoropirimidine and oxaliplatin. At the end of this study, 68.2% of the patients were alive and 18.2% developed metastatic disease. The others (31.8%) died (TABLE 1).

TABLE 1. Characteristics related to the tumor.

Characteristics	N (%) 22
Site, N (%)	
Medium rectum	6 (27.3)
Lower rectum	16 (72.7)
Type of resection, N (%)	
Abdominoperineal amputation	13 (59.2)
Rectosigmoidectomy	5 (22.7)
Local resection	3 (13.6)
Partial colectomy	1 (4.5)
Size of the tumor, N (%)	
<4cm	17 (77.3)
≥4cm	5 (22.7)
Differentiation grade, N (%)	
Well differentiated	4 (18.2)
Moderately differentiated	18 (81.8)
Adjuvant therapy, N (%)	
No	11 (50)
Yes	11 (50)
Outcome, N (%)	
Alive with disease	4 (18.2)
Alive without disease	11 (50)
Death	7 (31.8)

Categorical variables are described in number (percentage).

In the clinical TNM stage most cases were IIA (36.35%) and IIIB (36.35%). Before neoadjuvant treatment, most cases (72.7%) were T3, 8.2% were T4, and the others T2. Half of the patients in the study did not have lymph nodes invasion (N0) and 31.8% were N1. After surgical resection, 77.3% of patients were IIA, 13.6% had a complete response, and 27.3% had a tumor stage I (TABLE 2).

TABLE 2. TMN clinical stage (before therapy) and TNM pathological stage (after neoadjuvant treatment).

Clinical stage TNM	N=22
Tumor	N (%)
T0	–
T1	–
T2	2(9.1)
T3	16(72.7)
T4	4(18.2)
Lymph nodes	N (%)
N0	11(50)
N1	7(31.8)
N2	1(4.5)
N2a	1(4.5)
N2b	1(4.5)
Nx	1(4.5)
Pathological stage TNM	
Tumor	
T0	3(13.6)
T1	2(9.1)
T2	5(22.7)
T3	12(54.6)
T4	–
Lymph nodes	
N0	17(77.4)
N1	3(13.6)
N2	1(4.5)
N2a	1(4.5)
N2b	–
Nx	–

Categorical variables are equal in number (percentage). cTNM: clinical (pre-neoadjuvant); pTNM: pathological (post neoadjuvant); T: pre neoadjuvant; T post neoadjuvant.
†Fisher's Exact Test.

TABLE 3. Immunoexpression of DEK and Phospho-P38 proteins.

Characteristics	Protein	
	DEK N (%)	Fosfo-P38 N (%)
Extension scores of the positive expression area, N (%)		
0–10%	14 (63.7)	4 (18.2)
11–25%	3 (13.6)	2 (9.1)
26–50%	2 (9.1)	2 (9.1)
≥51%	3 (13.6)	14 (63.6)
Cell compartment, N (%)		
Negative nucleus	7 (31.8)	5 (22.7)
Positive nucleus	15 (68.2)	17 (77.3)
Intensity, N (%)		
Unmarked	7 (31.8)	3 (13.6)
Weak	7 (31.8)	3 (13.6)
Moderate	6 (27.3)	8 (36.4)
Strong	2 (9.1)	8 (36.4)
HScore, N (%)		
Negative <4	17 (77.3)	8 (36.4)
Positive ≥4	5 (22.7)	14 (63.6)

Hscore: extension score of the positive expression area multiplied by intensity where: 0, no marking; 1 weak; 2 moderate; 3 strong.

TABLE 4. Correlation between DEK protein expression (%) and age, clinical and pathological (after) TNM stage, N=22.

	DEK (expression %)		
	r_s	CI (95%)	Value *P*
Age	0.37	-0.07; 0.69	0.089
Stage			
cTNM	0.41	-0.01; 0.72	0.053
pTNM	0.52	0.12; 0.78	0.011

r_s: Spearman's correlation coefficient.; CI: confidence interval; cTNM: clinical (pre-neoadjuvant); pTNM: pathological (post neoadjuvant).

Immunoexpression of DEK and Phospho-P38

When analyzing the data related to DEK and Phospho-P38 proteins (TABLE 3), it is observed that the majority (63.7%) presented up to 10% of the extension score of the positive area marked for DEK. For Phospho-P38, the majority (63.6%) had ≥51% of positively marked area. Regarding the intensity of labeling in DEK immunoexpression, 63.6% were weak or unmarked, 27.3% moderate intensity, and 9.1% strong. In Phospho-P38, 72.8% of the cases had moderate and strong immunoexpression, and 27.2% had weak or no labeling. Interestingly, for the HScore of both proteins (score used to assess the markers, as explained above in the Method chapter), this pattern observed in each one was maintained. The majority, 77.3% of the DEK HScore was negative (<4) and 63.6% of the Phospho-P38 HScore was classified as ≥4 positives.

According to the correlation coefficient, there was a positive correlation between the DEK expression (%) and the pathological TNM stage (*P*=0.011) (TABLE 4).

Between the three patients with tumor complete response, two had no immunoexpression of the protein and 11 had 25%, all were considered negative for HScore. Advanced pTNM tumors, had a higher expression of DEK (%). Between the five patients with stage III disease, three had a positive DEK HScore. On the other hand, the Phospho-P38 expression (%), as well as its HScore, had no correlation with clinical or pathological variables.

Survival

The average in months of the overall cumulative was 124.6 months (95%CI 94.16: 155.13) (FIGURE 1A). The cumulative survival according to the HScore for DEK had a mean of 141.33 months (95%CI 112.41; 170.25) and a mean of 25.10 months (95%CI 17.36; 32 .84) for patients with HScore negative (<4) and HScore positive (≥4), respectively (*P*-value <0.001 by Mantel's Log Rank test) (FIGURE 1B). In the cumulative survival curve according to the HScore for Phospho-P38, the mean number of

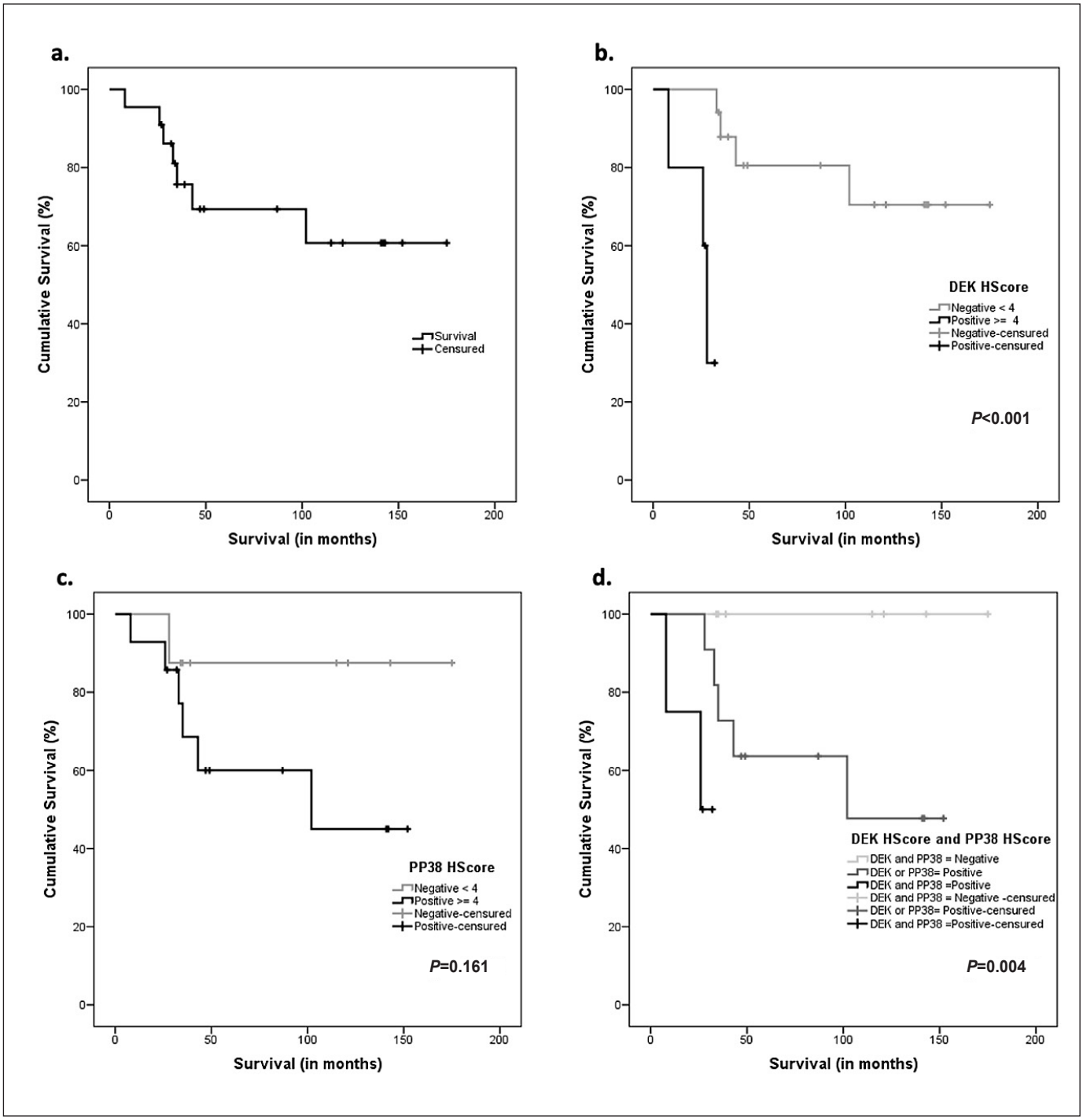

FIGURE 1. A) Overall cumulative survival curve (in months). **B)** Cumulative survival curve (in months) according to DEK HScore. **C)** Cumulative survival curve (in months) according to Phospho-P38 HScore (PP38). **D)** Cumulative survival curve (in months) according to Phospho-P38 (PP38) HScore matched in three combinations: both negative markers; one of the positive markers; both positive markers.

months was: 157.16 months (95%CI 123.54; 190.79) and 96.08 months (95%CI 63.26); 128.90) for patients with HSscore Negative (<4) and HSscore positive (≥4), respectively (*P*-value =0.161 by Mantel's Log Rank test) (FIGURE 1C).

Cumulative survival according to HScore of DEK and Phospho-P38 paired in the following combinations: two negative markers (mean 94.57 months and 95%CI 34;143), one of the positive markers (mean 78.09 months and 95%CI 28; 150), and two positive markers (mean 23.25 months and 95%CI 08;31). Through the Log Rank test, a significant difference was noted with *P*=0.004 (FIGURE 1D).

DISCUSSION

In this study, we found a predominance of females. Between the patients, 50% were alive without recurrence by the end of this study. The same percentage was also observed in a similar study by Martinez-Useros and collaborators[3]. Most of the patients had T3 tumors before treatment (72.7%), as described by Jia et al., Farhat et al., Ma et al., and Fokas et al.[12-15]. After neoadjuvant therapy, the percent of T3 tumors had a less frequency (54.6%), 13.6% were T0 and 9.1% T1. The percent of T2 that was 9.1% before CRT, rose to 22.7%. As observed in other studies[16-18], that 30% of the tumors had where it was described that although variable, around 25% of patients have a complete response to neoadjuvant chemoradiotherapy. Regarding the degree of differentiation, we mostly observed that 81.8% were classified as moderately differentiated, a finding that agrees with the study mentioned above, by Ma et al. (2019)[19].

We observed that tumors with higher DEK expression had a worse prognosis, in agreement with the meta-analysis performed by Liu et al. (2017), which described that DEK overexpression was significantly associated with poor overall survival in patients with solid tumors[20]. There was a positive correlation between pathological tumor stage and DEK immunoexpression: advanced pTNM had higher DEK expression. The cTNM had a marginal difference between stage and DEK immunoexpression (P=0.053). Overexpression of this protein was associated to the progression and aggressiveness of cancers in general. According to Yang et al. (2020)[21], the increased expression of DEK positively regulates the levels of active β catenin and Wnt target genes (cyclin D1, c Myc and MMP7), increasing the proliferative and invasive capacities of lung cancer cells[21]. In the study by Piao et al. (2014), the high level of DEK expression was a predictor of poor prognosis in patients with gastric cancer. In a later study, these authors observed that patients with early-stage gastric cancer and high DEK expression had the worst disease-free survival and overall survival[22].

In addition, to the HScore, we evaluated the cellular compartment of antibody stain. Some studies found that the expression of DEK had a nuclear pattern in gastric and colorectal cancers, both in the immunohistochemical and immunofluorescence techniques[23,24]. In the tumors analyzed in this study, for rectal adenocarcinoma, we observed that the majority (68.2%) had nuclear staining. Between the cases that presented a positive score, 1/3 (≅ 33.3%) were classified as HScore positive. Lin et al. (2013) found that DEK showed a strongly positive nuclear immunohistochemical staining pattern in 48.62% of cases of colorectal cancers, which was significantly higher than in the adjacent normal colon mucosa (9.17%) or in colorectal adenomas (13.46%)[23]. In 2014, the same group also studied the immunoexpression of the DEK protein in colorectal carcinoma. The data showed that the increase in its expression correlated with the antigen Ki-67 (Ki-67) proliferation index and the apoptotic index, suggesting that DEK promotes the growth and progression of CCR, and for this reason, it can be a therapeutic target[25].

According to the data collected in the present study, in adenocarcinomas of the rectum, no statistically significant difference was found concerning to sex, degree, of differentiation or part of the affected rectum. However, patients with advanced tumors had a higher expression of DEK. Most cases (77.3%) had a negative DEK HScore. The negative expression of this protein in tumor tissue correlated with greater survival. A group of Martinez-Useros et al., (2014), published a study revealing that the high expression of the DEK protein was described as an indicator for the aggressive phenotype of colorectal cancer[26]. The same group in 2018, did another study with DEK and colorectal cancer, and the results showed that 9 of 45 patients who had high DEK expression achieved a complete response, and among those with low expression, none had a complete pathological response, suggesting that low expression of this protein may predict a lower chance of complete response to neoadjuvant therapy. However, they did not correlate the immunoexpression of the protein with survival[3,27,28]. In the present study, three patients achieved a complete response, and all of them were classified as HScore DEK negative, in disagreement with the results discussed above.

It is important to note that, in the study by Martinez-Useros et al. (2018), pictured above, immunoreactivity was quantified from the percentage of positively stained cells over the total number of tumor cells. Positivity was defined as only medium to high levels of DEK expression and tissue microarray or Tissue Microarray Analysis (TMA) was performed to study the histopathological material. In the current study, we used the semi-quantitative scoring system. Another factor that may explain this discrepancy is that in our study we analyzed the protein immunoexpression in several areas of the tumor while, in the study previously mentioned, the expression was studied in TMA, an area that is representatively smaller, since this methodology uses a needle that has a diameter that can vary from 0.6 mm to 2 mm to remove the material from the block. Given these results, we hypothesized that the technique for analyzing the quantification of tissue DEK protein, through immunohistochemistry in rectal adenocarcinomas, needs to be better studied, as its standardization seems to have a direct relationship with the results.

As for the P38 protein, it showed a percentage of 63.6% of cases with a positive HScore (≥4). There was a predominance of the pattern of the intensity of moderate and strong marking. Despite this, the protein did not show statistical significance in the correlation with other variables such as sex, degree of differentiation, topography, and both clinical and pathological stage. According to the Atlas reference The Human Protein Atlas, MAPK14 (P38) is expressed in the cytoplasm or nucleus, depending on the tumor. In both normal colon and rectum tissues, expression is low[29]. Our findings demonstrate that 63.6% of cases were positive for the protein and most had a positive area marking extension ≥51%74. When analyzing survival according to the Phosfo-P38 HScore alone, there was no significant difference. However, for the analysis of paired markers, when both DEK and Phospho-P38 were negative, the survival was better. These results suggest that both proteins were involved in cancer agressivenes. According to the study by Martinez-Useros et al. (2018), Phospho-P38 alone also showed no association with the response to neoadjuvant therapy in rectal adenocarcinomas, but its high expression was directly associated with the high expression of DEK[3]. This possibly shows that as an isolated marker, perhaps the Phospho-P38 protein does not have a predictive function, but when associated with DEK, it shows promise. It is necessary to understand the connection between them, to establish which factors lead to the association of positivity and negativity of these markers. P38 signaling promotes cell death in some cell lines, in others P38 has been shown to increase cell survival, growth, and differentiation. Since the role of P38 in apoptosis varies according to cell type, in addition to being stimulus-dependent. It is worth mentioning that the regulation of the P38 pathway is not an isolated cascade and many different ascending signals can lead to protein activation[30].

The main limitation of the study was the small number of samples due to the difficulty in recovering the biopsy material for analysis before neoadjuvant treatment.

In conclusion, the highest expression of DEK protein was correlated with the T and N of the surgical specimen. Patients with negative DEK immunoexpression tumors (HScore <4) had increased survival. Overall, DEK protein immunoexpression may be a potential tissue biomarker of prognosis for patients with rectal adenocarcinoma, other studies are necessary to better elucidate the applicability of this protein.

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Authors' contribution

Tadokoro RB did the inclusion of the patients, performance of the Immunohistochemistry and written of the manuscript. Paiotti APR and Oshima CTF contributed to the interpretation of the results and performance of the immunohistochemistry. Cardili L Artigiani Neto R confirmed the diagnosis of rectal cancer and contributed to the Immunohistochemistry interpretation of the results. Forones NM contributed to the concept, design, and the finalization of the manuscript.

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RESUMO – Contexto – O câncer colorretal é mundialmente, a terceira causa de câncer e um quarto destes estão localizados no reto. O oncogene DEK está envolvido em vários processos nucleares e pode acelerar a tumorigênese. **Objetivo –** Este estudo tem como objetivo avaliar a imunoexpressão das proteínas DEK e Fosfo-P38 antes da terapia neoadjuvante em pacientes com adenocarcinoma de reto e correlacioná-la com resposta clínica e sobrevida. **Métodos –** Foram incluídos pacientes com adenocarcinoma de reto médio e baixo submetidos à quimio e radioterapia seguida de ressecção cirúrgica do tumor. A expressão e quantificação foram estudadas por imuno-histoquímica nos tecidos de biópsia tumoral utilizando um sistema HScore. Escores ≥4 foram considerados positivos e aqueles com <4 negativos. **Resultados –** Foram incluídos 22 pacientes com média de idade de 63,55 anos (DP: ±13,49). O estágio clínico antes do tratamento era T3 em 72,7%, T4 em 18,2%, 31,8% eram N1, 50% N0 e todos M0. Após a quimio e radioterapia, 54,6% eram T3; 22,7% eram T2; 9,1% eram T1 e 13,6% T0. Entre os tumores, 22,7% foram positivos para DEK e 63,6% positivos para Phospho-P38. Houve uma correlação positiva para a imunoexpressão da proteína DEK e o estágio pTNM (P=0,011). A proteína fosfo-P38 não apresentou correlação com esses parâmetros. Pacientes com HScore negativo para DEK tiveram sobrevida média de 141,33 meses (IC95%: 112,41–170,25) e aqueles com HScore positivo tiveram sobrevida média de 25,10 meses (IC95%: 17,36–32,84) (P<0,001). **Conclusão –** Observou-se maior expressão de DEK em estágios avançados. Os pacientes que apresentaram expressão de DEK <4 tiveram maior sobrevida, sendo um fator de pior prognóstico.

Palavras-chave – Câncer de reto; imuno-histoquímica; proto-oncogene DEK; Fosfo-P38; prognóstico; neoadjuvância; quimiorradiação.

REFERENCES

1. Dayde D, Tanaka I, Jain R, Tai MC, Taguchi A. Predictive and Prognostic Molecular Biomarkers for Response to Neoadjuvant Chemoradiation in Rectal Cancer. Int J Mol Sci. 2017;18:573.
2. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide. [Internet]. Available from: http://gco.iarc.fr
3. Martinez-Useros J, Moreno I, Fernandez-Aceñero MJ, Rodriguez-Remirez M, Borrero-Palacios A, Cebrian A, et al. The potential predictive value of DEK expression for neoadjuvant chemoradiotherapy response in locally advanced rectal cancer. BMC Cancer. 2018;18:1-11.
4. Zhu J, Yu K, Mello RA. In: Mello RA, Tavares A, Mountzios G. International Manual of Oncology Practice: (iMOP) - Principles of Medical Oncology. Switzerland: Springer; 2019;351-78.
5. Paquette IM, Atkinson SJ. In: Kwaan M, Zbar A. Comprehensive Rectal Cancer Care. Switzerland: Springer; 2019;3-16.
6. Berho M, Bejarano P. In: Kwaan M, Zbar A. Comprehensive Rectal Cancer Care: (Pathology of Rectal Cancer and Predictors of Response to Neoadjuvant Therapy). Switzerland: Springer; 2019;87-112.
7. Conde-Muíño R, Cuadros M, Zambudio N, Segura-Jiménez I, Cano C, Palma P. Predictive Biomarkers to Chemoradiation in Locally Advanced Rectal Cancer. Biomed Res Int. 2015;2015:921435.
8. Liu G, Xiong D, Zeng J, Xu G, Xiao R, Chen B et al. Prognostic role of DEK in human solid tumors: a meta-analysis. Oncotarget. 2017;8:1-8.
9. Witkiewicz AK, Balaji U, Knudsen E. Systematically defining single gene determinants of response to neoadjuvant chemotherapy reveals specific biomarkers. Clin Cancer Res. 2014;20:4837-48.
10. Pease NA, Wise-Draper T, Privette VL. Dissecting the Potential Interplay of DEK Functions in Inflammation and Cancer. J Oncol. 2015;2015:1-13.
11. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival Analysis Part I: Basic concepts and first analyses. Br J Cancer. 2003;89:232-8.
12. Jia AY, Narang A, Safar B, Zaheer A, Murphy A, Azad NS, et al. Sequential short-course radiation therapy and chemotherapy in the neoadjuvant treatment of rectal adenocarcinoma. Radiat Oncol. 2019;14:1-6.
13. Farhat W, Azzaza M, Mizouni A, Ammar H, Ltaifa MB, Lagha S, et al. Factors predicting recurrence after curative resection for rectal cancer: a 16-year study. World J Surg Oncol. 2019;17:1-10.
14. Ma X, Shen F, Jia Y, Xia Y, Li Q, Lu J. MRI-based radiomics of rectal cancer: preoperative assessment of the pathological features. BMC Med Imaging. 2019;19:1-7.

15. Fokas E, Allgäuer M, Polat B, Klautke G, Grabenbauer GG, Fietkau R, et al. Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12. J Clin Oncol. 2019;37:3212-22.
16. Lefevre JH, Rousseau A, Svrcek M, Parc Y, Simon T, Tiret E. French Research Group of Rectal Cancer Surgery (GRECCAR). A multicentric randomized controlled trial on the impact of lengthening the interval between neoadjuvant radiochemotherapy and surgery on complete pathological response in rectal cancer (GRECCAR-6 trial): rationale and design. BMC Cancer. 2013;13:1-8.
17. Glynne-Jones R, Hughes R. Complete response after chemoradiotherapy in rectal cancer (watch-and-wait): have we cracked the code? Clin Oncol (R Coll Radiol). 2016;28:152-60.
18. Wasmuth HH, Rekstad LC, Tranø G. The outcome and the frequency of pathological complete response after neoadjuvant radiotherapy in curative resections for advanced rectal cancer: a population-based study. Color Dis. 2016;18:67-72.
19. Ma X, Shen F, Jia Y, Xia Y, Li Q, Lu J. MRI-based radiomics of rectal cancer: preoperative assessment of the pathological features. BMC Med Imaging. 2019;19:1-7.
20. Liu G, Xiong D, Zeng J, Xu G, Xiao R, Chen B, Huang Z. Prognostic role of DEK in human solid tumors: a meta-analysis. Oncotarget. 2017;8:98985–92.
21. Yang M, Bai L, Lei L, Zheng Y, Wang Z, Li Z, et al. DEK promotes the proliferation and invasion of lung cancers and indicates poor prognosis in lung adenocarcinomas. Oncol Rep. 2020;43:1338-48.
22. Piao J, Shang Y, Liu S, Piao Y, Cui X, Li Y, Lin Z. High expression of DEK predicts poor prognosis of gastric adenocarcinoma. Diagn Pathol. 2014 20;9:1-7.
23. Lin L, Piao J, Gao W, Piao Y, Jin G, Ma Y, et al. DEK over expression as an independent biomarker for poor prognosis in colorectal cancer. BMC Cancer. 2013;13:366. doi:10.1186/1471-2407-13-366.
24. Piao J, Shang Y, Liu S, Piao Y, Cui X, Li Y, Lin Z. High expression of DEK predicts poor prognosis of gastric adenocarcinoma. Diagn Pathol. 2014;9:1-7.
25. Lin L, Piao J, Ma Y, Jin T, Quan C, Kong J, et al. Mechanisms Underlying Cancer Growth and Apoptosis by DEK Overexpression in Colorectal Cancer. PLoS One. 2014;9:1-12.
26. Martinez-Useros J, Rodriguez-Remirez M, Borrero-Palacios A, Moreno I, Cebrian A, Gomez del Pulgar T, et al. DEK is a potential marker for aggressive phenotype and irinotecan-based therapy response in metastatic colorectal cancer. BMC Cancer. 2014;14:1-10.
27. You S, Guan Y, Li W. Epithelialmesenchymal transition in colorectal carcinoma cells is mediated by DEK/IMP3. Mol Med Rep. 2018;17:1065-70.
28. Khodadoust MS, Verhaegen M, Kappes F, Riveiro-Falkenbach E, Cigudosa JC, Kim DS, et al. Melanoma proliferation and chemoresistance controlled by the DEK oncogene. Cancer Res. 2009;69:6405-13.
29. The Human Protein Atlas: MAPK14. [Internet]. Avaible from: https://www.proteinatlas.org/ENSG00000112062-MAPK14
30. Zarubin T, Han J. Activation and signaling of the p38 MAP kinase pathway. Cell Res. 2005;15:11-8.

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