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Original Article

Overexpression of integrin α7 correlates with advanced disease condition and poor prognosis in rectal cancer patients

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Abstract: The purpose of this study was to investigate the association of integrin α7 expression with clinicopathological features and disease-free survival (DFS) as well as overall survival (OS) in rectal cancer (RC) patients. 219 RC patients who underwent surgery were retrospectively reviewed in this study. Tumor tissues and paired adjacent tissues samples were collected. An immunofluorescence assay was preformed to detect integrin α7 expression. The median follow-up duration in this study was 70 months, and the last follow-up date was 2017/12/31. Integrin α7 was overexpressed in tumor tissues compared to paired adjacent tissues (P<0.001), and its high expression correlated with higher pathological grade (P<0.001), larger tumor size (≥5 cm) (P=0.018), advanced T stage (P=0.003), elevated N stage (P=0.003) and increased TNM stage (P=0.004). Kaplan-Meier curves disclosed that integrin α7 high expression was associated with shorter DFS (P<0.001) and worse OS (P<0.001) compared to low expression. A multivariate Cox's analysis revealed that integrin α7 high expression was an independent factor for unfavorable DFS (P<0.001) and OS (P<0.001) in RC patients. In conclusion, Integrin α7 is highly expressed in tumor tissues and positively correlates with advanced disease condition, and it serves as an independent factor for unfavorable prognosis in RC patients.

Keywords: Integrin α7, clinicopathological features, prognosis, rectal cancer

Introduction

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer-related death among all malignancies, with an estimated 1,360,600 new cases and 693,900 deaths occurring during 2012 worldwide [1, 2]. As a subtype of colorectal cancer, rectal cancer (RC) accounts for approximately 30% of all colorectal cancer cases, and its incidence presents with an increasing trend in China in recent decades, which severely threatens human health as well as directly decreases quality of life and even causes death [3-5]. Although disease management strategies, such as cancer screening and improved therapies (including total mesorectal excision (TME) and neoadjuvant chemoradiotherapy (nCRT)), have been effectively applied to reduce RC mortality rates, overall prognosis is still far from satisfactory [6, 7]. Therefore, exploring additional and accurate biomarkers should prove valuable in monitoring tumor progression and improving prognosis in RC patients.

Integrins, the large and complex transmembrane glycoproteins composed of an alpha (α) and a beta (β) subunit, belong to one family of cell adhesion molecules, which participate in various physiological and pathological processes by mediating cell-cell or cell-matrix adhesion [8, 9]. Integrin α7, localized on chromosome 12p13, consists of at least 27 exons spanning a region of about 22.5 kb, which was originally discovered on skeletal myoblasts and binds several laminin isoforms along with the integrin β1 [3, 10, 11]. According to several studies, integrin α7 is a potential cancer stem cells (CSCs) maker that functions in stemness regulation and CSCs maintenance. It acts as a critical promoter in tumor growth as well as malignant invasion, and its overexpression correlates with poor prognosis in several cancers such as oesophageal squamous cell carcinomas (OS-

Table 1. Baseline characteristics of rectal cancer patients

Items	Rectal cancer patients (N=219)
Age (years)	65.1±11.5
Gender (male/female)	118/101
Pathological grade (n/%)	
G1	38 (17.4)
G2	154 (70.3)
G3	27 (12.3)
Largest tumor size (cm)	4.6±1.2
T stage (n/%)	
T1	4 (1.8)
T2	27 (12.3)
T3	184 (84.0)
T4	4 (1.9)
N stage (n/%)	
N0	132 (60.2)
N1	63 (28.8)
N2	24 (11.0)
TNM stage (n/%)	
I	31 (14.2)
II	101 (46.1)
III	87 (39.7)

Data were presented as mean ± standard deviation or count (%).

CC), glioma, and glioblastoma (GBM) , while the role of integrin α7 in RC is still unclear [12-14]. Thus, the purpose of this study was to investigate the association of integrin α7 expression with clinicopathological features and disease-free survival (DFS) as well as overall survival (OS) in RC patients.

Patients and methods

Patients

219 rectal cancer patients underwent surgery at the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology between 2010/1/1 and 2012/12/31 and were retrospectively analyzed in this study. The inclusion criteria were: (1) Diagnosed as primary rectal cancer according to clinical and pathological findings. (2) Age above 18 years. (3) Paraffin-embedded tumor tissue and paired adjacent tissue samples were available from the specimen storehouse of The Central Hospital of Wuhan. (4) Tumor property information was accessible from the electronic medical record system of The Central Hospital of Wuhan including at least the pathological grade, tumor size, and TNM stage. (5) Patients with regular follow up and completed OS data. Patients who received neoadjuvant therapy, lost follow up, or had a history of other solid tumors or hematologic malignancies were excluded from the study. The Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology had approved the protocol of this study, and all the patients or their families signed the informed consents or orally agreed with the informed consents by a recorded telephone call.

Sample collection and immunofluorescence (IF) assay

Paraffin-embedded tumor tissue and paired adjacent tissue samples were obtained from specimen storehouse of The Central Hospital of Wuhan, which were acquired during the surgeries. An IF assay was used to determine Integrin α7 expression in tissues. In brief, each formalin-fixed, paraffin-embedded tissue section was deparaffined and dehydrated at 65°C for 4 h, and after being permeabilized in polybutylene terephthalate (PBST) (PBS, 1% Bull Serum Albumin (BSA), 0.1% Triton) overnight, the section was treated with methanol containing 0.3% hydrogen peroxide and autoclaved at 121°C for 10 minutes for antigen retrieval. Subsequently, each tissue section was blocked with 10% goat serum, and then incubated with mouse antibody against integrin α7 with dilution 1:1000 (Abcam, USA) at 4°C overnight. After being washed with PBS three times, each tissue section was incubated with an Alexa Fluor® 594 Conjugate labeled antibody against mouse IgG with dilution 1:500 (CST, USA) as a secondary antibody. After staining, the sections were counterstained with Hoechst 33342. As to the evaluation of staining intensity, the histological score (HSCORE) was used as follows [15]: HSCORE=$\sum$Pi (i+1), among which Pi stands for the percentage of stained epithelial cells for each intensity which scored from 0% to 100%, while i represents the intensity of staining with a value at 1, 2 or 3 (weak, moderate or strong, respectively), whereas 1 is a correction for optimal density. HSCORE=0.7 was considered as a threshold to distinguish the high expression and low expression of IF staining.

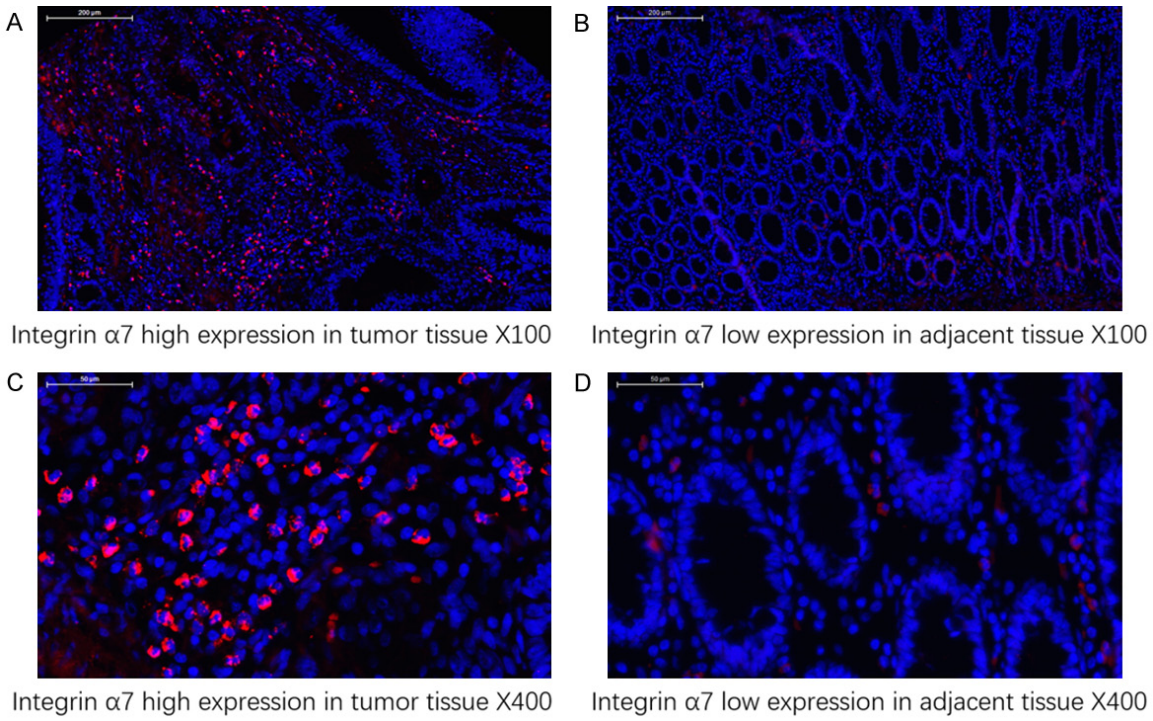

Figure 1. Integrin α7 expression in tumor tissues and paired adjacent tissues. Immunofluorescence assay revealed that integrin α7 was mainly expressed in cell membranes. A, C: Increased expression of integrin α7 in tumor tissue (original magnification: ×100, 400 respectively). B, D: Decreased expression of integrin α7 in adjacent tissues (original magnification: ×100, 400 respectively).

Table 2. Integrin α7 expression in tumor tissues and paired adjacent tissues

Items	Integrin α7	
	High expression	Low expression
Tumor tissue (n/%)	83 (37.9)	136 (62.1)
Paired adjacent tissue (n/%)	42 (19.2)	177 (80.8)
P value	<0.001	

Data were presented as counts (%). Comparison was determined by McNemar test. *P* value <0.05 was considered significant.

Data collection

Baseline characteristics of patients were retrieved and recorded, including age, gender, pathological grade, tumor size, and TNM stage. In this study, the TNM stage was evaluated according to the 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual.

Survival calculation

DFS was calculated from the date of surgery to the date of disease recurrence or death from any cause, and OS was calculated from the date of surgery to the date of death from any cause. The median follow-up duration in this study was 70 months, and the last follow-up date was 2017/12/31.

Statistical analysis

Statistical analysis was performed using SPSS software 21.0 (IBM, USA) and GraphPad Prism software 5.01 (GraphPad, USA). Data were mainly presented as mean ± standard deviation or count (percentage). The comparisons between the two groups were determined by Chi-square tests, McNemar tests, or Wilcoxon rank sum tests. The analysis of DFS and OS was determined by Kaplan-Meier (K-M) curves and a log-rank test. Baseline factors affecting DFS and OS were analyzed by univariate and multivariate Cox's proportional hazards regression. P<0.05 was considered as significant.

Results

Baseline characteristics

As listed in **Table 1**, the mean age was 65.1± 11.5 years in RC patients, and 118 males and 101 females were enrolled in this study. As to

Table 3. Correlation of integrin α7 expression and clinicopathologic characteristics in rectal cancer patients

Items	Integrin α7 high expression (N=83)	Integrin α7 low expression (N=136)	*P* value
Age (n/%)			0.110
<65 years	44 (43.6)	57 (56.4)	
≥65 years	39 (33.1)	79 (66.9)	
Gender (n/%)			0.140
Male	50 (42.4)	68 (57.6)	
Female	33 (32.7)	68 (67.3)	
Pathological grade (n/%)			<0.001
G1	7 (18.4)	31 (81.6)	
G2	56 (36.4)	98 (63.6)	
G3	20 (74.1)	7 (25.9)	
Largest tumor size (n/%)			
<5 cm	37 (30.8)	83 (69.2)	0.018
≥5 cm	46 (46.5)	53 (53.5)	
T stage (n/%)			0.003
T1	0 (0.0)	4 (100.0)	
T2	5 (18.5)	22 (81.5)	
T3	75 (40.8)	109 (59.2)	
T4	3 (75.0)	1 (25.0)	
N stage (n/%)			0.003
N0	42 (31.8)	90 (68.2)	
N1	23 (36.5)	40 (63.5)	
N2	18 (75.0)	6 (25.0)	
TNM stage (n/%)			0.004
I	5 (16.1)	26 (83.9)	
II	37 (36.6)	64 (63.4)	
III	41 (47.1)	46 (52.9)	

Data were presented as count (%). Comparison was determined by Chi-square test or Wilcoxon rank sum test. *P* value <0.05 was considered significant.

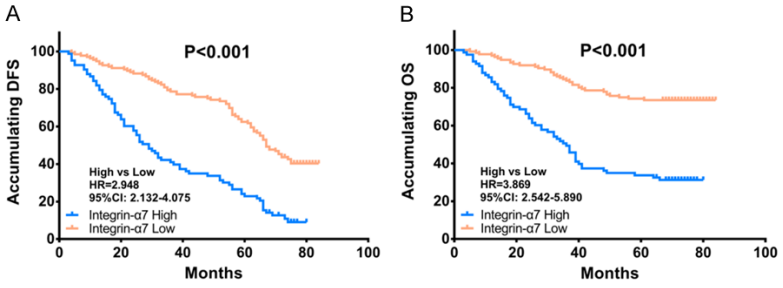

Figure 2. The correlations of integrin α7 expression with DFS and OS in RC patients. A: Integrin α7 high expression correlates with shorter DFS; B: Integrin α7 high expression correlates with worse OS. Kaplan-Meier curves and log-rank test were used to evaluate the correlations of integrin α7 expression with DFS and OS in RC patients. P<0.05 was considered as significant. DFS: disease-free survival; OS: overall survival.

pathological grade, 38 (17.4%), 154 (70.3%) and 27 (12.3%) patients were at G1, G2 and G3 respectively. Additionally, the mean value of largest tumor size was 4.6±1.2 cm. Also, there were 4 (1.8%), 27 (12.3%), 184 (84.0%) and 4 (1.9%) patients at the T1 stage, T2 stage, T3 stage, and T4 stage respectively. As for the N stage, the numbers of patients with N0 stage, N1 stage and N2 stage were 132 (60.2%), 63 (28.8%), 24 (11.0%) respectively. In addition, 31 (14.2%), 101 (46.1%) and 87 (39.7%) patients were at TNM stage I, TNM stage II, TNM stage III respectively.

Integrin α7 expression in tumor tissues and paired adjacent tissues

An immunofluorescence assay was performed to detect integrin α7 expression, which showed that integrin α7 was mainly expressed in the cell membranes (**Figure 1**). The numbers of patients with integrin α7 high expression in tumor tissues and adjacent tissues were 83 (37.9%) and 42 (19.2%) respectively, and integrin α7 was overexpressed in the tumor tissues compared to the paired adjacent tissues (P<0.001) (**Table 2**).

Correlation of integrin α7 expression and clinicopathologic characteristics in RC patients

Integrin α7 high expression correlated with higher pathological grade (P<0.001), larger tumor size (≥5 cm) (P=0.018), advanced T stage (P=0.003), elevated N stage (P=0.003), and worse TNM stage (P=0.004), but no correlation was found with integrin α7 expression and age (P=0.110) or gender (P=0.140) (**Table 3**).

Table 4. Cox's proportional hazards regression model analysis of factors affecting DFS

Parameters	Univariate Cox's regression				Multivariate Cox's regression			
	P value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Higher			Lower	Higher
Integrin-α7 high expression	<0.001	2.948	2.132	4.075	<0.001	2.465	1.710	3.554
Age (≥65 years)	0.121	1.290	0.935	1.779	0.210	1.342	0.847	2.126
Gender (male)	0.629	0.925	0.673	1.271	0.204	0.791	0.551	1.136
Higher pathological grade	<0.001	1.751	1.296	2.366	0.169	1.286	0.899	1.838
Largest tumor size (≥5 cm)	0.156	1.258	0.916	1.729	0.428	1.156	0.808	1.654
Higher T stage	0.158	1.284	0.907	1.817	0.188	1.636	0.786	3.406
Higher N stage	<0.001	1.558	1.223	1.984	0.025	1.835	1.078	3.123
Higher TNM stage	0.021	1.312	1.042	1.652	0.155	0.613	0.312	1.203

Data were presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). *P* value <0.05 was considered significant. Pathological grade was scored as 1-G1, 2-G2 and 3-G3; T stage was scored as 1-T1, 2-T2, 3-T3 and 4-T4; N stage was scored as 0-N0, 1-N1 and 2-N2; TNM stage was scored as 1-stage I, 2-stage II and 3-stage III; A Cox's proportional hazards analysis was performed based on these definitions. DFS: disease free survival.

Table 5. Cox's proportional hazards regression model analysis of factors affecting OS

Parameters	Univariate Cox's regression				Multivariate Cox's regression			
	P value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Higher			Lower	Higher
Integrin-α7 high expression	<0.001	3.869	2.542	5.890	<0.001	2.721	1.702	4.350
Age (≥65 years)	0.437	1.177	0.780	1.778	0.874	1.047	0.591	1.855
Gender (male)	0.152	1.351	0.895	2.040	0.671	1.110	0.686	1.798
Higher pathological grade	0.096	1.412	0.940	2.122	0.041	1.640	1.019	2.637
Largest tumor size (≥5 cm)	0.013	1.900	1.145	3.150	0.849	1.045	0.660	1.655
Higher T stage	<0.001	1.858	1.396	2.473	0.082	2.441	0.892	6.684
Higher N stage	0.002	1.635	1.199	2.228	0.043	1.944	1.023	3.697
Higher TNM stage	<0.001	3.869	2.542	5.890	0.169	0.535	0.219	1.304

Data were presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). *P* value <0.05 was considered significant. Pathological grade was scored as 1-G1, 2-G2 and 3-G3; T stage was scored as 1-T1, 2-T2, 3-T3 and 4-T4; N stage was scored as 0-N0, 1-N1 and 2-N2; TNM stage was scored as 1-stage I, 2-stage II and 3-stage III; A Cox's proportional hazards analysis was performed based on these definitions. OS: overall survival.

The correlation of integrin α7 expression with DFS and OS in RC patients

K-M curves and a log-rank test were used to evaluate the correlation of integrin α7 expression with DFS and OS in RC patients, which revealed that a high expression of integrin α7 was associated with shorter DFS (P<0.001, **Figure 2A**) and worse OS (P<0.001, **Figure 2B**) in RC patients.

Factors affecting DFS in RC patients

A univariate Cox's proportional hazards regression was used to evaluate factors influencing DFS in RC patients, as presented in **Table 4**, which indicated integrin α7 high expression (P<0.001) was associated with worse DFS, as well as higher pathological grade (P<0.001), higher N stage (P<0.001), and higher TNM stage (P=0.021). Further multivariate analysis revealed that integrin α7 high expression (P<0.001) and higher N stage (P=0.025) were independent factors for shorter DFS in RC patients.

Factors affecting OS in RC patients

A univariate Cox's analysis exhibited that Integrin α7 high expression (P<0.001), higher T stage (P<0.001), higher N stage (P=0.002), and higher TNM stage (P<0.001) were correlated with poor OS (**Table 5**). The further multivariate Cox's analysis showed that integrin α7 high

expression (P<0.001), higher pathological grade (P=0.041) and higher N stage (P=0.043) could independently predict shorter OS in RC patients.

Discussion

In this study, we observed that in RC patients: 1) integrin α7 was highly expressed in tumor tissues compared to adjacent tissues, and its high expression correlated with advanced disease severity; 2) integrin α7 high expression was an independent risk factor for worse DFS and shorter OS.

Integrins, belonging to transmembrane cell surface receptors, directly bind with components of the extracellular matrix (ECM) and contribute to various cellular processes, including cell proliferation, migration and invasion [8, 9]. A large number of previous studies have investigated the function of integrins in malignancy. For instance, one study found that integrin α6 contributes to the self-renewal, proliferation, and tumor formation capacity in glioblastoma stem cells (GSCs) [16]; and integrin α5 also has been shown to promote mesenchymal stem cell migration by activating PDGFR-b and potentiating growth factor signals [17]. As a common member of the integrin family, integrin α7 could act as a tumor promoter to regulate cell functions in several carcinomas, including OSCC, glioma and GBM [12-14]. A recent experiment conducted by Haas et al. explores the oncogenic function of integrin α7 and demonstrates that integrin α7 promotes cell proliferation, cell invasion and the clonogenic survival of glioblastoma stem cells (GSCs) through the activation of focal adhesion kinase (FAK), AKT (protein kinase) as well as Src, and represses cells apoptosis by activating the Wnt, mitogen-activated protein kinase (MAPK) and nuclear factor-kB (NF-kB) signaling pathway in GBM [12]. Another study discloses that integrin α7 promotes cell differentiation through regulating CSCs homeostasis by activating the FAK/MAPK/ERK (extracellular regulated protein kinases) signaling pathways, thereby increasing tumor invasion in OSCC [13]. Furthermore, integrin α7 is observed to interact with S100P to mediate the FAK/AKT signaling pathways, leading to accelerated cell migration in lung cancer as well [18]. Together, these previous studies suggest that integrin α7 acts as a promoter in tumor pathology.

A growing number of studies reveal that integrin α7 is highly expressed in several carcinomas, such as GBM, OSCC, and glioma [12-14, 19]. An interesting animal study builds OSCC xenograft mice models and demonstrates that integrin α7 is overexpressed in OSCC tissues, and its upregulation correlates with lymph node metastasis [13]. In addition, a previous clinical study shows that integrin α7 overexpression is associated with tumor aggressiveness in brain cancer patients [12]. Hence, these previous data indicate that integrin α7 serves an oncogenic role in some carcinomas. However, these previous studies focus on other carcinomas, but until now no data has been available about the role of integrin α7 in RC patients. In line with these studies, we found that integrin α7 was highly expressed in tumor tissues compared to adjacent tissues and its overexpression correlated with higher pathological grades, larger tumor size (≥5 cm) and advanced tumor stage in RC patients. The possible reason could be that integrin α7 mediates some genes or signaling pathways (such as AKT, Src, Wnt or the FAK/MAPK/ERK signaling pathways) to induce cell proliferation, invasion, migration and to inhibit cell apoptosis, thereby accelerating disease severity in RC patients.

Several previous studies investigated the predictive value for DFS and OS of integrin α7. In glioma patients, high integrin α7 expression correlates with poor OS [12]. As to GBM patients, integrin α7 expression is also negatively correlated with OS [14, 19]. However, little is known about the predictive value of integrin α7 for survival profiles in RC patients. In line with these previous studies, we observed that integrin α7 high expression was correlated with worse DFS as well as OS, and it could be an independent risk factor for prognosis in RC patients. The possible explanations are as follows: To begin with, integrin α7 might accelerate tumor progress, including cells proliferation, migration or invasion by upregulating several proteins and signaling pathways such as AKT, Src, Wnt or FAK/MAPK/ERK signaling pathways. Moreover, as a CSCs maker, integrin α7 plays a key role in promoting stemness, resulting in poor differentiation, advanced clinical stage and lymph node metastasis, which finally causes unfavorable effects on prognosis. Furthermore, integrin α7 might promote increased drug resistance, thereby decreasing treatment efficacy and leading to worse prognosis in RC patients.

Our study has several limitations. First, the sample size was relatively small, leading to

poor statistical power. Secondly, all patients were just from our hospital, so additional studies with more patients from other hospitals and regions are greatly needed.

In summary, integrin α7 is highly expressed in tumor tissues and positively correlates with advanced disease condition, and it serves as an independent factor for unfavorable prognosis in RC patients.

Disclosure of conflict of interest

None.

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