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Review Article

Clinical significance of ADAM10 and ADAM17 in gastric and colorectal cancers: a systematic review and meta-analysis

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Abstract: Background: The expression and prognostic value of ADAM10 and ADAM17 in gastric and colorectal cancers remained controversial. We performed a meta-analysis of cohort studies to evaluate the clinical significance of ADAM10 and ADAM17 in gastric and colorectal cancers. Materials and methods: PubMed, Embase, Cochrane library database, VIP and CNKI were systematically searched. Cohort studies assessing the expression and prognostic value of ADAM10 and ADAM17 in gastric and colorectal cancers were included. Meta-analysis was performed using random-effect model. Results: Five cohort studies involving 1150 participants were included in the meta-analysis. Overall, higher expression of ADAM10 and ADAM17 were found in T3-4 cancer than T1-2 cancer (OR=0.29; 95% CI=0.21 to 0.40; P<0.0001), N-positive cancer than N-negative cancer (OR=4.36; 95% CI=2.25 to 8.45; P<0.0001), cancer with distant metastasis than cancer without metastasis (OR=0.09; 95% CI=0.02 to 0.37; P=0.0008) in patients with gastric cancer, but the expression of ADAM10 and ADAM17 showed no relationship with cancer grade (G3 versus G1-2, OR=0.75; 95% CI=0.55 to 1.03; P=0.07). While in patient with colorectal cancer, ADAM10 and ADAM17 showed higher expression in patients with G3 compared to G1-2 (OR=0.30; 95% CI=0.15 to 0.62; P=0.001), N-positive cancer patients than N-negative cancer patients (OR=23.53; 95% CI=6.88 to 80.47; P<0.0001), cancer with distant metastasis than cancer without metastasis (OR=0.10; 95% CI=0.02 to 0.60; P=0.01), but the expression of ADAM10 and ADAM17 demonstrated no connection with T category (T3-4 cancer versus T1-2 cancer, OR=3.53; 95% CI=1.01 to 12.41; P=0.05). Conclusion: ADAM10 and ADAM10 were reliable for determining the T category, N category, distant metastasis and tumor grade of gastric cancer and colorectal cancer, and they hold some promise in identifying the prognosis of digestive cancers.

Keywords: ADAM10, ADAM17, gastric cancer, colorectal cancer, meta-analysis

Introduction

Although treatments of digestive cancers (e.g. pancreatic cancer, esophageal cancer, gastric cancer and colorectal cancer) have been developed rapidly, they still result in a high mortality [1-3]. It is widely accepted that two mechanisms mediating the migration of cancer cells in the body are invasion and metastasis, during which tumor cells have the ability to penetrate the walls of blood and lymphatic vessels and secondary tumors are formed following the transportation of primary tumor cells to other tissues [4]. It is valuable and urgent to explore sensitive and specific markers of carcinogenesis to assess diagnostic and prognostic digestive system cancers.

A disintegrin and metalloproteinase 10 (ADAM10) known as a member of the ADAM (a disintegrin and metalloproteinase) family of transmembrane metalloproteinases, is involved in the RIPing and shedding of dozens of substrates, and induces cancer progression and inflammatory diseases [5]. ADAM10 has some proteolytic activity [6]. ADAM10 and ADAM17 show some potential in the cleavage of transmembrane protein Klotho that is involved in aging process [7]. ADAM17, also called tumor necrosis factor-alpha-converting enzyme, is responsible for the inflammation, tumor growth, and angiogenesis [8]. ADAM17 was found to shed various proteins for regulating responses to tissue injury, inflammation, and carcinogenesis, and these proteins mainly include growth

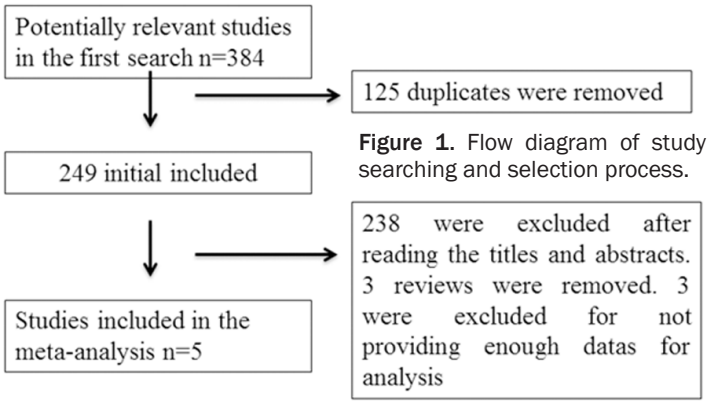

Figure 1. Flow diagram of study searching and selection process.

factors, receptors, and adhesion molecules [9, 10]. The unregulated expression of ADAM17 indicated a poor prognosis of various cancers and showed some association with tumor progression (e.g. breast, prostate, gastric, colorectal, hepatocellular, and ovarian cancer) [11].

Previous studies showed that ADAM10 and ADAM17 were found to be significantly increased in T3-4 category compared to T1-2 category for patients with gastric and colorectal cancers [12, 13]. Consistently, ADAM10 and ADAM17 expression of N-positive cancer patients was revealed to substantially be improved compared to that of N-negative cancer patients [12, 14].

In contrast to this promising finding, however, some relevant trials showed that ADAM10 and ADAM17 expression showed no association with T category, N category and tumor grade in gastric and colorectal cancers [12, 15, 16]. Considering these inconsistent results, we therefore conducted a systematic review and meta-analysis of cohort studies to evaluate the diagnostic and prognostic value of ADAM10 and ADAM17 in gastric and colorectal cancer.

Materials and methods

Search strategy

We performed this meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [17]. PubMed, Embase, Cochrane library database, VIP and CNKI from January 1980 to September 2016 were searched to identify relevant studies, without language restrictions. Search terms included “ADAM10” or “ADAM17”, and “gastric cancer” or “colorectal cancer” or “gastrointestinal cancer”. In addition, we reviewed the reference lists of retrieved papers and recent reviews to identify other potentially eligible studies that we had not searched.

Selection criteria

The inclusive selection criteria were as follows: (a) study design: cohort study; (b) study population: patients with gastric, or colorectal cancer; (c) comparison intervention: different TNM stages (Grade 1-2 versus Grade 3, T1-2 versus T3-4, N-positive versus N-negative, and M0 versus M1); and (d) outcome measure: expression of ADAM10 or ADAM17. In the case of duplicate data publication (studies with overlapping samples), we only included the most informative article or complete study to avoid duplication of information.

Data extraction and quality assessment

A standardized data collection form was used to extract the following information from each included article: first author, publication year, sample size, numbers, population characteristics, type of study design, T category, N category, distant metastasis and tumor grade. When necessary, we contacted the authors of included studies for additional information.

We assessed the methodological quality of each study on 8 items used in the Newcastle-Ottawa Scales (NOS) [18]. We assigned the risk of bias categories based on the number of NOS items judged inadequate in each study, as follows: low risk of bias (0-1 inadequate item); medium risk of bias (2-3 inadequate items); high risk of bias (over 3 inadequate items); very high risk of bias (no description of methods). Two investigators independently conducted the study selection, data extraction and quality assessment, and a third investigator was consulted to resolve any discrepancies.

Statistical analysis

Odd ratio (OR) was used as a common measure of the association between ADAM10 (or ADAM17) expression, and the TNM stages of gastric and colorectal cancers across studies. All meta-analyses were performed using random-effects models with DerSimonian and Laird

Table 1. Characteristics of included studies

NO.	Included studies	Study design	Biomarker	Number	Organ	Follow-up	T category (T1-2/3-4)	N category (P/N)	Distant metastasis (M0/M1)	Grade (1-2/3)
1	Zheng 2015	PC	ADAM10	158	Colorectal cancer	NA	52/5	46/3	17/24	35/19
2	Sun 2015	PC	ADAM17	60	Gastric cancer	NA	NA	28/17	30/17	NA
3	Yang 2012	PC	ADAM17	60	Colorectal cancer	NA	35/10	NA	19/26	32/13
4	Shou 2012	PC	ADAM17	436	Gastric Cancer	5 years	H (30/126) L (136/144)	H (135/21) L (135/145)	H (113/43) L (262/18)	H (44/112) L (97/183)
5	Wang 2011	PC	ADAM10	436	Gastric cancer	5 years	H (27/99) L (139/171)	H (106/20) L (164/146)	H (97/29) L (278/32)	H (34/92) L (107/201)

PC: prospective cohort, H: high expression, L: low expression, OS: overall survival, NA: not available.

Table 2. Methodological quality assessment (risk of bias) of included studies by Newcastle-Ottawa scales

Study	Selection				Comparability	Outcome			Total score
	Exposed Cohort	Nonexposed Cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Zheng 2015	*	*	*	*	**	*	-	-	7
Sun 2015	*	*	*	*	**	*	-	-	7
Yang 2012	*	*	*	*	**	*	-	-	7
Shou 2012	*	*	*	*	**	*	*	-	8
Wang 2011	*	*	*	*	**	*	*	-	8

*represents 1 scores, and **represents 2 scores.

weights. Heterogeneity was tested using the Cochran Q statistic (P<0.1) and quantified with the I^2 statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I^2 value greater than 50% indicated significant heterogeneity. To explore the possible source of heterogeneity and to examine the influence of various clinical factors on the overall risk estimate, we further carried out prior subgroup analyses according to gastric or colorectal cancer. We also investigated the influence of a single study on the overall pooled estimate by omitting one study in each turn. Owing to the limited number (<10) of included studies, publication bias was not assessed. P<0.05 in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search and study characteristics

Figure 1 showed the search strategy and selection process of this meta-analysis. In all, 384 studies in the first search seemed to be potentially relevant. 125 duplicates were removed. A total of 238 studies were excluded (irrelevant subjects) on the basis of initial screening of the titles and/or abstracts. And 3 reviews were removed and 3 studies were excluded for not providing enough data for analysis. The remaining 5 articles were included in the meta-analysis and there were two English papers and three Chinese papers [12-16].

Table 1 demonstrated the characteristics of the included studies. All of them were from China. Furthermore, 3 studies focused on colorectal cancer, and 2 focused on gastric cancer. A total of 1150 patients were included. The TNM stage and tumor grade was reported in 5 and 4 studies, respectively. Furthermore, high expression and low expression of ADAM were defined in 2 studies. In this paper, we defined the positive expression of ADAM as high expression in other 3 studies after carefully reading the original papers and thus take them for meta-analysis. There was just one paper reporting the overall survival of 5 years. The NOS score of the included studies ranged from 7 to 8, as shown in **Table 2**.

Primary outcome: correlation of ADAM10 or 17 and cancer grade (histologic differentiation, G1-2 vs G3)

This outcome data was analyzed with a random-effect model, the pooled estimate of the

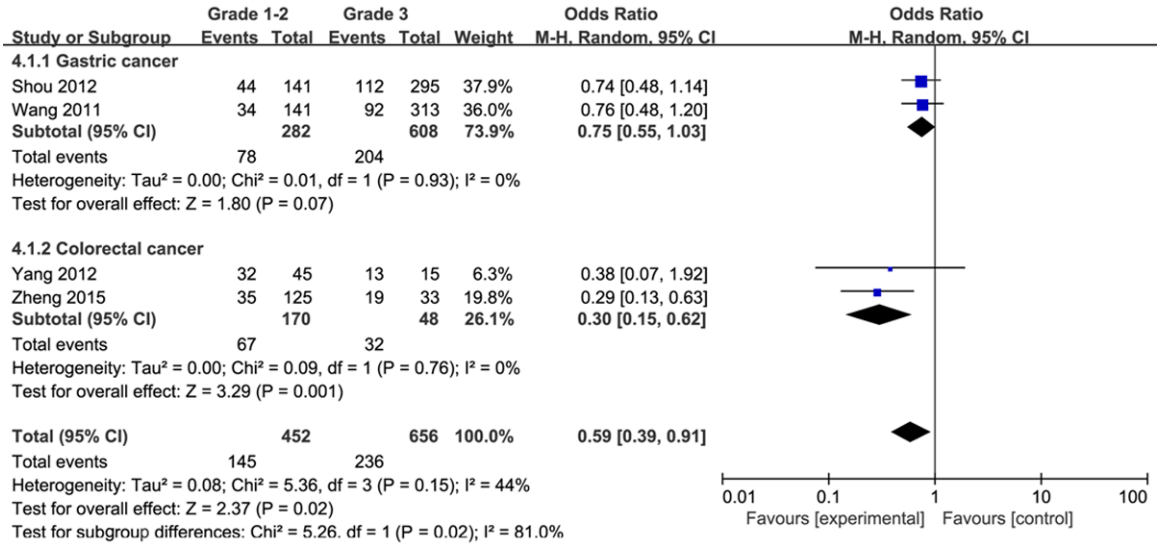

Figure 2. Forest plot showing the relationship of ADAM10 or 17 and cancer grade (G1-2 versus G3) and subgroup analysis is based on cancer classification.

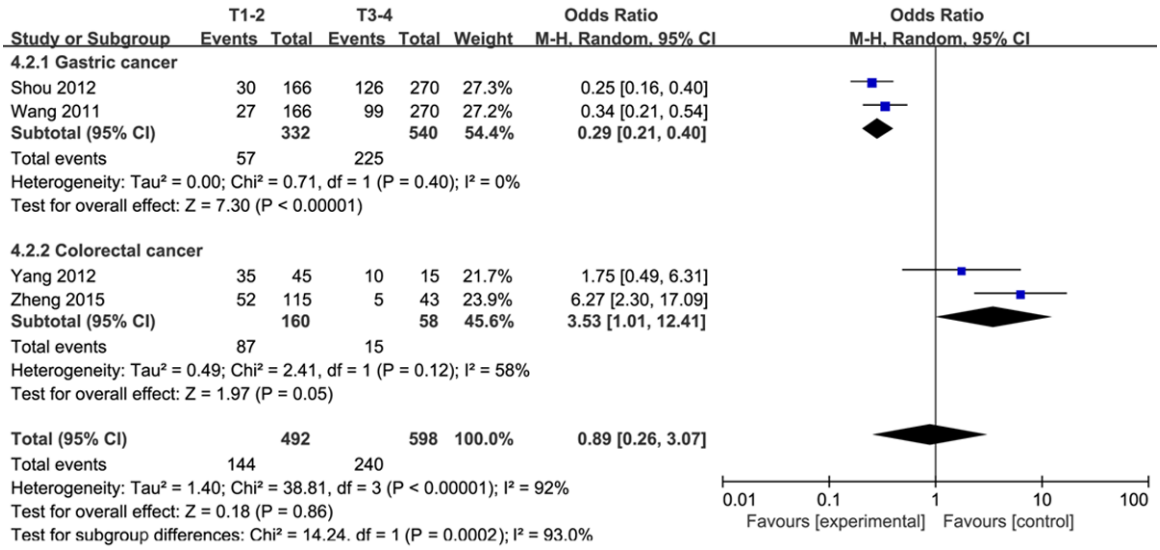

Figure 3. Forest plot showing the relationship of ADAM10 or 17 and T category (T1-2 versus T3-4) and subgroup analysis is based on cancer classification.

two included studies suggested that ADAM10 and ADAM17 showed no associated with increased cancer grade of gastric cancer (G3 versus G1-2, OR=0.75; 95% CI=0.55 to 1.03; P=0.07), with no heterogeneity among the studies (I^2=0%, heterogeneity P=0.93). In contrast, higher expression of ADAM10 and ADAM17 resulted in increased cancer grade of colorectal cancer after pooling the results of two included studies (OR=0.30; 95% CI=0.15 to 0.62; P=0.001), with no heterogeneity among the studies (I^2=0%, heterogeneity P=0.76, **Figure 2**).

Sensitivity analysis

No heterogeneity was observed among the included studies for the correlation of ADAM10 (or 17) and cancer grade after the subgroup analysis, as showed by both I^2=0. Thus, we did not perform sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

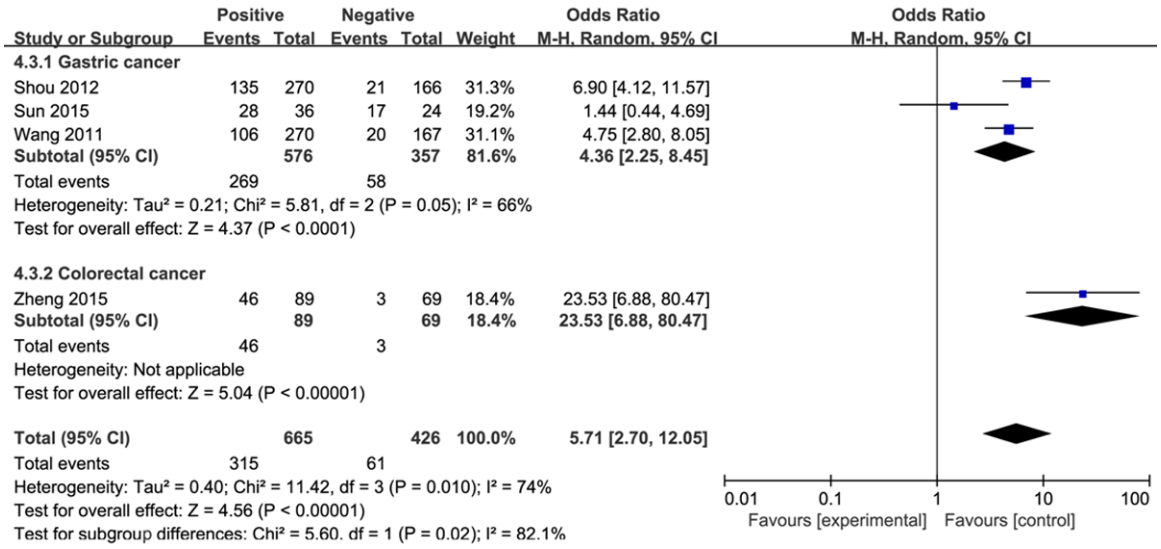

Figure 4. Forest plot showing the relationship of ADAM10 or 17 and N category (N-positive versus N-negative) and subgroup analysis is based on cancer classification.

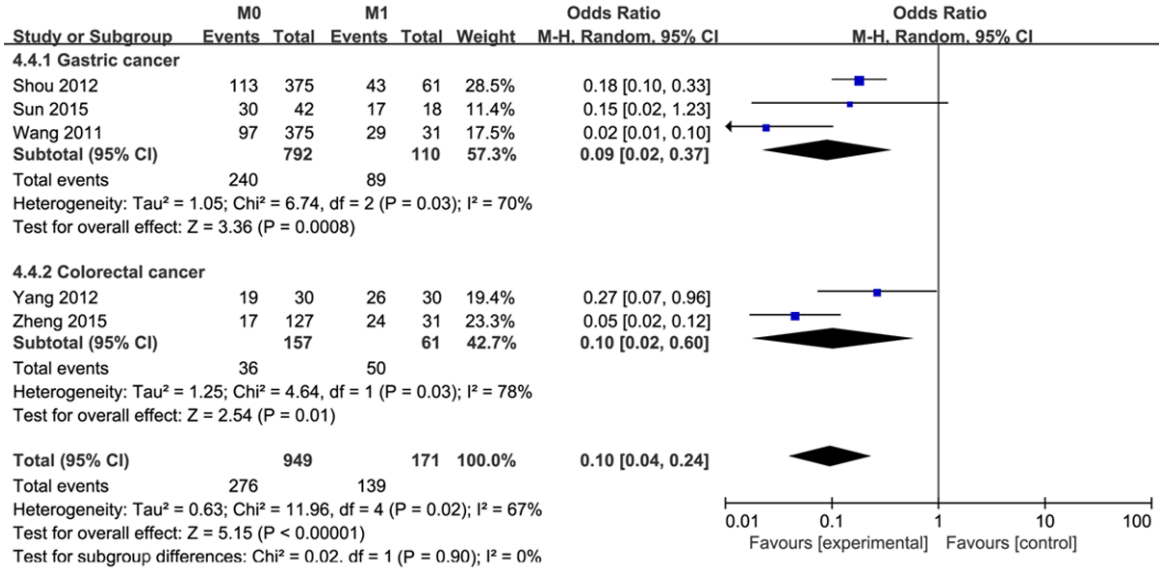

Figure 5. Forest plot showing the relationship of ADAM10 or 17 and Distant metastasis (M0 versus M1) and subgroup analysis is based on cancer classification.

Secondary outcomes

Compared with patients with T1-2, ADAM10 and ADAM17 were found to be expressed higher than patients with T3-4 of gastric cancer (OR=0.29; 95% CI=0.21 to 0.40; P<0.0001). However, their expression showed no significant difference in colorectal cancer comparing T1-2 and T3-4 (OR=3.53; 95% CI=1.01 to 12.41; P=0.05, **Figure 3**).

N-positive patients demonstrated increased expression of ADAM10 and ADAM17 for gastric cancer (OR=4.36; 95% CI=2.25 to 8.45; P<0.0001) and colorectal cancer (OR=23.53; 95% CI=6.88 to 80.47; P<0.0001, **Figure 4**).

Moreover, ADAM10 and ADAM17 were revealed to be associated with increased risk of distant metastasis (M0 versus M1) in gastric cancer (OR=0.09; 95% CI=0.02 to 0.37; P=0.0008),

and colorectal cancer (OR=0.10; 95% CI=0.02 to 0.60; P=0.01, **Figure 5**).

Discussion

To the best of our knowledge, this is the first meta-analysis to explore the association between ADAM10 (or ADAM17) and TNM stages in patients with gastric cancer and colorectal cancer. Our meta-analysis suggested ADAM10 and ADAM17 were found to be increased expression in patients with T3-4 than T1-2, N-positive patients than N-negative patients, patients with distant metastasis than patients without metastasis for gastric cancer. Except T category in colorectal cancer, ADAM10 and ADAM17 resulted in improved expression in patients with G3 than G1-2, N-positive patients than N-negative patients, patients with distant metastasis than patients without metastasis.

ADAM10 can cleave the extracellular domain of the neuronal cell adhesion molecule L1-CAM and is involved in beta-catenin-TCF signaling pathway. Previous studies revealed that ADAM10 overexpression was associated with digestive cancer (e.g. gastric cancer, colon cancer and liver cancer) and metastasis [19-21]. It is known that ADAM17 serves as an indispensable regulator of carcinogenesis and it sheds the growth factors responsible for tumor progression and growth [22]. These growth factors mainly included transforming growth factor-alpha, amphiregulin, heparin-binding epidermal growth factor-like growth factor and epiregulin [23, 24]. ADAM17 overexpression was found to have favorable influence on the progression of breast cancer, pancreatic ductal adenocarcinoma and gastric cancer etc [21, 25, 26].

TNM stage, and lymph node and distant metastasis were thought to be the important prognostic factors for gastrointestinal cancer [27]. The results of our meta-analysis strongly suggested that ADAM10 and ADAM17 could serve as independent and important prognostic factors for gastric and colorectal cancers. In addition, other factors significantly affecting the survival of the patients included age, tumor size, location, depth of invasion, TNM stage, vessel invasion and lymph node metastasis. Mean survival time of gastric cancer patients with low ADAM10 and ADAM17 expression was found to be longer than patients with their high expression [12, 13]. These results were consistent with previous studies that correlated elevated expression of ADAM17 with the poor prognosis in many tumors. ADAM17 showed significantly increased expression in high-grade tumors than low-grade tumors including breast cancer, gallbladder carcinoma and esophageal adenocarcinoma. And their high expression resulted in a significantly shorter overall survival time than the low expression [28-30].

Several limitations should be taken into account. Firstly, our analysis is based on only five cohort studies and two of them have a relatively small sample size (n<100). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Next, all the five studies were from China, and it was believed that there were distinct site differences. We tried to identify the relationship between the 5-year survival rate and ADAM expression, but only one study reported these datas. Finally, some unpublished and missing data might lead bias to the pooled effect.

Conclusions

ADAM10 and ADAM17 could serve as independent and significant prognostic factors for patients with gastric and colorectal cancers.

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Disclosure of conflict of interest

None.

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References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.

[2] Shi Q, De Gramont A, Grothey A, Zalcberg J, Chibaudel B, Schmoll HJ, Seymour MT, Adams R, Saltz L, Goldberg RM, Punt CJ, Douillard JY, Hoff PM, Hecht JR, Hurwitz H, Díaz-Rubio E, Porschen R, Tebbutt NC, Fuchs C, Souglakos J, Falcone A, Tournigand C, Kabbinavar FF, Heinemann V, Van Cutsem E, Bokemeyer C, Buyse M, Sargent DJ. Individual patient data analysis

of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. J Clin Oncol 2015; 33: 22-28.

[3] Ma G, Wang Q, Lv C, Qiang F, Hua Q, Chu H, Du M, Tong N, Jiang Y, Wang M, Zhang Z, Wang J, Gong W. The prognostic significance of HOTAIR for predicting clinical outcome in patients with digestive system tumors. J Canc Res Clin Oncol 2015; 141: 2139-2145.

[4] Walkiewicz K, Kozieł P, Bednarczyk M, Błażelonis A, Mazurek U and Muc-Wierzgoń M. Expression of migration-related genes in human colorectal cancer and activity of a disintegrin and metalloproteinase 17. Biomed Res Int 2016; 2016: 8208904.

[5] Crawford HC, Dempsey PJ, Brown G, Adam L and Moss ML. ADAM10 as a therapeutic target for cancer and inflammation. Curr Pharm Des 2009; 15: 2288-2299.

[6] Sahin U, Weskamp G, Kelly K, Zhou HM, Higashiyama S, Peschon J, Hartmann D, Saftig P and Blobel CP. Distinct roles for ADAM10 and ADAM17 in ectodomain shedding of six EGFR ligands. J Cell Biol 2004; 164: 769-779.

[7] Przemyslaw L, Boguslaw HA, Elzbieta S and Malgorzata SM. ADAM and ADAMTS family proteins and their role in the colorectal cancer etiopathogenesis. BMB Rep 2013; 46: 139-150.

[8] Blanchot-Jossic F, Jarry A, Masson D, Bach-Ngohou K, Paineau J, Denis MG, Laboisse CL and Mosnier JF. Up-regulated expression of ADAM17 in human colon carcinoma: co-expression with EGFR in neoplastic and endothelial cells. J Pathol 2005; 207: 156-163.

[9] Smalley DM and Ley K. L-selectin: mechanisms and physiological significance of ectodomain cleavage. J Cell Mol Med 2005; 9: 255-266.

[10] Hassemer EL, Endres B, Toonen JA, Ronchetti A, Dubielzig R and Sidjanin DJ. ADAM17 transactivates EGFR signaling during embryonic eyelid closure. Invest Ophthalmol Vis Sci 2013; 54: 132-140.

[11] McGowan PM, McKiernan E, Bolster F, Ryan BM, Hill AD, McDermott EW, Evoy D, O'Higgins N, Crown J and Duffy MJ. ADAM-17 predicts adverse outcome in patients with breast cancer. Ann Oncol 2008; 19: 1075-1081.

[12] Wang YY, Ye ZY, Li L, Zhao ZS, Shao QS and Tao HQ. ADAM 10 is associated with gastric cancer progression and prognosis of patients. J Surg Oncol 2011; 103: 116-123.

[13] Shou ZX, Jin X and Zhao ZS. Upregulated expression of ADAM17 is a prognostic marker for patients with gastric cancer. Ann Surg 2012; 256: 1014-1022.

[14] Zheng J, Sheng X, Wu J and Zhang Y. Expression and clinical significance of a disintegrin and metalloproteinase 10 (Adam10) in colorectal cancer. Zhejiang Clinical Medical Journal 2015; 17: 876-877.

[15] Yang l and Chen Z. Expression and significance of OPN and ADAM17 in colorectal cancer. Zhejiang Clinical Medical Journal 2012; 14: 1025-1027.

[16] Jin-bing S, Jian-long J, Kuang-yi L, Qiao C, Danhao T and Jian-qing M. Expression and significance of a disintegrin and metalloproteinase 17 (Adam17) in gastric cancer. Chin J Hemorh 2015; 2: 139-143.

[17] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-2012.

[18] Wells GA, Shea BJ, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis[J]. Appl Eng Agric 2000; 18: 727-734.

[19] Bai S, Nasser MW, Wang B, Hsu SH, Datta J, Kutay H, Yadav A, Nuovo G, Kumar P and Ghoshal K. MicroRNA-122 inhibits tumorigenic properties of hepatocellular carcinoma cells and sensitizes these cells to sorafenib. J Biol Chem 2009; 284: 32015-32027.

[20] Gavert N, Sheffer M, Raveh S, Spaderna S, Shtutman M, Brabletz T, Barany F, Paty P, Notterman D, Domany E and Ben-Ze'ev A. Expression of L1-CAM and ADAM10 in human colon cancer cells induces metastasis. Cancer Res 2007; 67: 7703-7712.

[21] Yoshimura T, Tomita T, Dixon MF, Axon AT, Robinson PA and Crabtree JE. ADAMs (a disintegrin and metalloproteinase) messenger RNA expression in Helicobacter pylori-infected, normal, and neoplastic gastric mucosa. J Infect Dis 2002; 185: 332-340.

[22] Gooz M. ADAM-17: the enzyme that does it all. Crit Rev Biochem Mol Biol 2010; 45: 146-169.

[23] Miyamoto S, Hirata M, Yamazaki A, Kageyama T, Hasuwa H, Mizushima H, Tanaka Y, Yagi H, Sonoda K and Kai M. Heparin-binding EGF-like growth factor is a promising target for ovarian cancer therapy. Cancer Res 2004; 64: 5720-5727.

[24] Zhuang S, Yan Y, Daubert RA and Schnellmann RG. Epiregulin promotes proliferation and migration of renal proximal tubular cells. Am J Physiol Renal Physiol 2007; 293: F219-F226.

[25] Ringel J, Jesnowski R, Moniaux N, Luttges J, Ringel J, Choudhury A, Batra SK, Kloppel G and Lohr M. Aberrant expression of a disintegrin and metalloproteinase 17/tumor necrosis fac-

tor-alpha converting enzyme increases the malignant potential in human pancreatic ductal adenocarcinoma. Cancer Res 2006; 66: 9045-9053.

[26] Zheng X, Jiang F, Katakowski M, Zhang ZG, Lu QE and Chopp M. ADAM17 promotes breast cancer cell malignant phenotype through EGFR-PI3K-AKT activation. Cancer Biol Ther 2009; 8: 1045-1054.

[27] Shiraishi N, Sato K, Yasuda K, Inomata M and Kitano S. Multivariate prognostic study on large gastric cancer. J Surg Oncol 2007; 96: 14-18.

[28] Kauttu T, Mustonen H, Vainionpaa S, Krogerus L, Ilonen I, Rasanen J, Salo J and Puolakkainen P. Disintegrin and metalloproteinases (ADAMs) expression in gastroesophageal reflux disease and in esophageal adenocarcinoma. Clin Transl Oncol 2016; 19: 58-66.

[29] Lee HS, Lee HK, Kim HS, Yang HK, Kim YI and Kim WH. MUC1, MUC2, MUC5AC, and MUC6 expressions in gastric carcinomas: their roles as prognostic indicators. Cancer 2001; 92: 1427-1434.

[30] Zhang D, Salto-Tellez M, Putti TC, Do E and Koay ES. Reliability of tissue microarrays in detecting protein expression and gene amplification in breast cancer. Mod Pathol 2003; 16: 79-84.