World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i12.3706

World J Gastroenterol 2015 March 28; 21(12): 3706-3710
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

Prognostic value of c-Met in colorectal cancer: A meta-analysis

Yan Liu, Xiao-Feng Yu, Jian Zou, Zi-Hua Luo

Yan Liu, Xiao-Feng Yu, Jian Zou, Zi-Hua Luo, Department of Gastroenterology, Huadong Hospital, Fudan University, Shanghai 200040, China
Author contributions: Liu Y and Yu XF conceived the study; Zou J and Luo ZF collected data and performed data analysis; Liu Y and Yu XF wrote the paper.

Correspondence to: Xiao-Feng Yu, Professor, Department of Gastroenterology, Huadong Hospital, Fudan University, 221 Yanan Xi Road, Shanghai 200040, China. yan_liu88@163.com
Telephone: +86-21-62484981
Fax: +86-21-62484981
Received: September 3, 2014
Peer-review started: September 4, 2014
First decision: October 14, 2014
Revised: October 31, 2014
Accepted: December 1, 2014
Article in press: December 1, 2014
Published online: March 28, 2015

Abstract

AIM: To assess the prognostic value of c-Met status in colorectal cancer.

METHODS: We conducted a search in PubMed, Web of Science, and the Cochrane Library covering all published papers up to July 2014. Only studies assessing survival in colorectal cancer by c-Met status were included. This meta-analysis was performed by using STATA11.0.

RESULTS: Ultimately, 11 studies were included in this analysis. Meta-analysis of the hazard ratios (HR) indicated that patients with high c-Met expression have a significantly poorer overall survival (OR) (HR = 1.33, 95%CI: 1.06-1.59) and progression-free survival (PFS) (HR = 1.47, 95%CI: 1.03-1.91). Subgroup analysis showed a significant association between high c-Met expression and poorer overall survival in the hazard ratio reported (HR = 1.41, 95%CI: 1.08-1.74).

CONCLUSION: The present meta-analysis indicated that high c-Met expression was associated with poor prognosis in patients with colorectal cancer.

Key words: Colorectal cancer; Prognosis; c-Met; Meta-analysis; Overall survival

Core tip: High c-Met expression was found in colorectal cancer and showed a positive relationship with early tumor invasion and metastasis. However, there still seems to be no consensus about the prognostic properties of c-Met status. In this paper, after combing the data from 11 retrospective studies with 1,895 patients, the authors found that high c-Met expression was associated with poor prognosis in patients with colorectal cancer.

Liu Y, Yu XF, Zou J, Luo ZH. Prognostic value of c-Met in colorectal cancer: A meta-analysis. *World J Gastroenterol* 2015; 21(12): 3706-3710 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i12/3706.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i12.3706

INTRODUCTION

Colorectal cancer (CRC) is one of the most common types of cancer worldwide. The 5-year survival rate of CRC is higher in the early stage due to radical surgical

resection. However, many patients who underwent resection for primary colorectal cancer developed local recurrences or distant metastases, and had a shorter survival[1]. Recent treatment options for patients with advanced colorectal cancer included combining anti- epidermal growth factor receptor (EGFR) or anti-vascular endothelial growth factor monoclonal antibodies with chemotherapy. Although many predictive markers have been identified[2-4], most of them are not commonly used in clinical practice. Identification of factors that can predict a more accurate prognosis is therefore required.

C-Met is a receptor tyrosine kinase encoded by the c-Met oncogene. High expression of c-Met has been found in different solid tumors and has a correlation with poor prognosis. In CRC, c-Met is considered to be related to tumor aggressiveness and invasiveness, as well as metastatic potential and poor prognosis[5-7]. In many tumors, the c-Met signaling pathway is activated aberrantly and represents one of the most important mechanisms of progression and invasiveness[8].

However, despite a large number of studies having researched the relationship between c-Met and survival in colorectal cancer, there still seems to be no consensus about the prognostic properties of c-Met status. It is for this reason that we performed this systematic review.

MATERIALS AND METHODS

Publication search

We searched PubMed, Web of Science, and the Cochrane Library with the following terms: (c-Met AND (colon or rectal or colorectal) AND (carcinoma or tumor or cancer) AND prognosis) from 1990 to July 2014. To expand our search, references of the retrieved articles were also screened for additional studies. The inclusion criteria for primary studies were as follows: (1) proven diagnosis of CRC in humans; (2) overall survival (OS) or progression-free survival (PFS) analyzed by c-Met level; and (3) c-Met evaluation using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) or immunohistochemistry (IHC). Data from abstracts, review articles, and letters were excluded.

Data abstraction

Relevant data were extracted from eligible studies by two researchers independently. The following information was extracted from each study: (1) basic information such as first author's name, country, and publication year of article; and (2) variables such as number of patients analyzed, disease stage, methods of c-Met analysis, and hazard ratio (HR) with 95%CI for progression-free survival (PFS) and overall survival (OS). When HRs and confidence intervals were not reported directly, we estimated them from the number of patients in each group and Kaplan-Meier curves by using the published methodology[9].

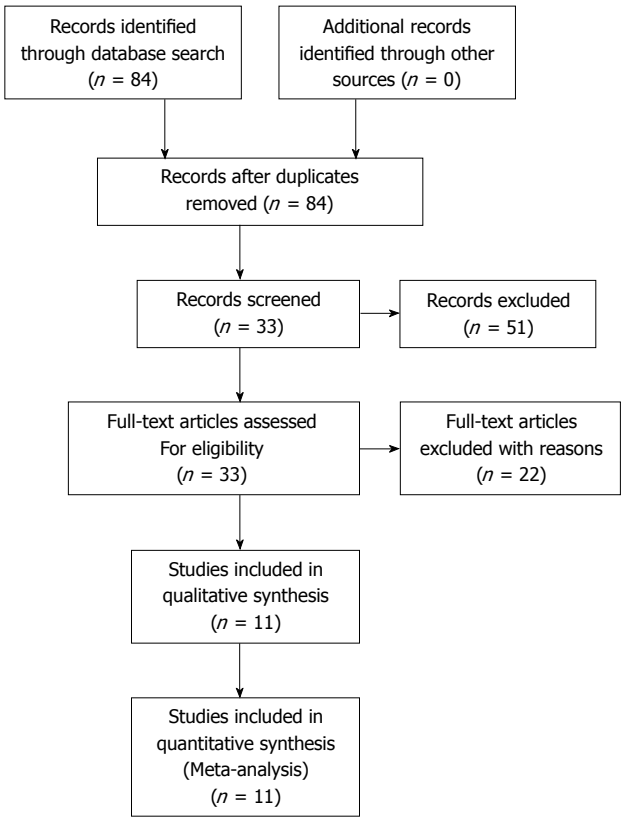

Figure 1 Flow chart of the meta-analysis.

Statistical analysis

We calculated HRs with their 95%CIs to evaluate the relationships between c-Met level and PFS or OS. Heterogeneity was defined as $I^2 > 50\%$. When heterogeneity was judged among primary studies, the random-effects model was used. Otherwise, the fixed-effects model was used. Publication bias was assessed using Egger's test. All statistical analysis was carried out with STATA 11.0.

RESULTS

Characteristics of included studies

The initial search yielded 84 articles, of which 51 were excluded after screening of their titles and abstracts. Following the evaluation of the full text, a total of 11 studies were ultimately included in our study. The selection process for the studies involved in this meta-analysis is shown in Figure 1. From the 11 studies that were included[10-20], a total of 1,895 patients were analyzed. The characteristics of the involved studies are showed in Table 1.

All of these studies were retrospective research. Of the 11 studies, two[11,13] included only patients with advanced disease (stage Ⅳ), while the remaining 9 studies[10,12,14-20] included patients with stage Ⅰ-Ⅳ. None of the patients received therapy before resection of the primary tumor. C-Met evaluation was performed by IHC or PCR. The rate of high c-Met level ranged

Table 1 Characteristics of the selected studies

Ref.	No. of patients	Country	Method to stratify c-Met status	Stage	Stage (Ⅰ, Ⅱ)	High c-Met expression	Survival	HR	95%CI
Zeng *et al*[17], 2008	247	United States	RT-qPCR	Ⅰ-Ⅳ	46%	29%	OS	2.08[1]	0.94-4.62
Voutsina *et al*[11], 2012	73	Greece	IHC	Ⅳ	NS	52%	OS	4.59	2.05-10.28
Resnick *et al*[19], 2004	134	Israel	IHC	Ⅰ-Ⅳ	NS	77%	PFS	0.81[1]	0.24-3.75
Garouniati *et al*[12], 2012	183	Greece	IHC	Ⅰ-Ⅳ	61%	72%	OS	1.02[1]	0.52-1.99
Inno *et al*[13], 2011	73	Italy	IHC	Ⅳ	NS	75%	PFS/OS	2.17/1.92	0.99-4.76/0.81-4.54
De Oliveira *et al*[14], 2009	286	Brazil	IHC	Ⅰ-Ⅳ	53%	79%	PFS/OS	1.65[1]/1.21[1]	0.56-4.21/0.85-2.06
Kishiki *et al*[10], 2014	75	Japan	IHC	Ⅰ-Ⅳ	NS	48%	PFS/OS	1.46/1.16	1.06-2.02/0.73-1.82
Ginty *et al*[16], 2008	583	United States	IHC	Ⅰ-Ⅳ	46%	62%	OS	1.45	1.06-1.96
Kammula *et al*[18], 2006	63	United States	RT-qPCR	Ⅰ-Ⅳ	39%	81%	OS	2.44	1.05-5.68
Lee *et al*[15], 2007	135	Taiwan	IHC	Ⅰ-Ⅳ	NS	72%	PFS/OS	10.05/3.93	2.54-43.84/1.40-10.99
Umeki *et al*[20], 1999	43	Japan	IHC/RT-qPCR	Ⅰ-Ⅳ	35%	30%/12%	OS	1.14[1]	0.78-3.45

[1]HR estimated, if the HRs were not directly given in the studies, we calculated them from the survival curves. RT-qPCR: Reverse transcriptase quantitative polymerase chain reaction; IHC: Immunohistochemistry; NS: Not shown.

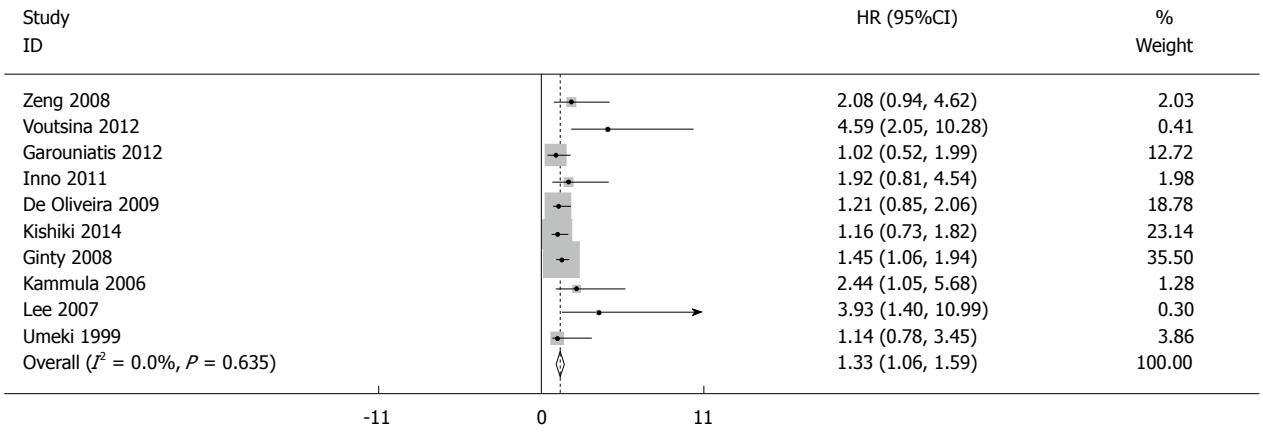

Figure 2 Fixed-effects model of hazard ratio of overall survival associated with c-Met overexpression.

from 12% to 81% (median, 61%). The median follow-up time was 80 months (range from 25 to 140 mo). In most of these studies, c-Met expression level was evaluated by cell percentage. High c-Met expression was defined as >50% positive cells. OS was presented in 10 studies, and PFS was reported in five studies. Six studies[10,12,13,15,16,18] presented data on HR, with 95% CI for PFS or OS directly. The remaining five studies did not present HRs and 95%CIs directly, so we estimated them from Kaplan-Meier curves.

Association between c-Met and OS

Forest plots for the relationships between c-Met level and overall survival are showed in Figure 2, with the results indicating a significant relationship between high c-Met expression and poorer OS (overall HR = 1.33, 95%CI: 1.06-1.59). No significant heterogeneity was found (P = 0.635, I^2 = 0.0%) and the HR for OS was assessed by using the fixed-effects model. There was no significant publication bias in this analysis of OS (Begg's test, P = 0.052; Egger's test, P = 0.094).

We also performed subgroup analysis in studies by HR reported. We found significant association between high c-Met expression and poorer overall survival in the hazard ratio reported (HR = 1.41, 95%CI: 1.08-1.74).

Association between c-Met and PFS

The pooled HR for PFS showed that patients with a high c-Met level had a significantly poorer PFS (HR = 1.47; 95%CI: 1.03-1.91). No significant heterogeneity was found (P = 0.778, I^2 = 0.0%), and the pooled HR for PFS was assessed by using the fixed-effects model (Figures 3 and 4). There was no significant publication bias in this analysis of PFS (Begg's test, P = 0.462; Egger's test, P = 0.548).

DISCUSSION

The main cause of CRC-related death is metastases. Identification of patients who are at risk of developing distant metastases is important to cancer treatment and prognosis. c-Met overexpression or genetic alteration has been proven to play an important role in the pathogenesis of many tumor types. In CRC, overexpression of c-Met has been found to be associated with tumor progression.

This systematic review is based on 11 studies

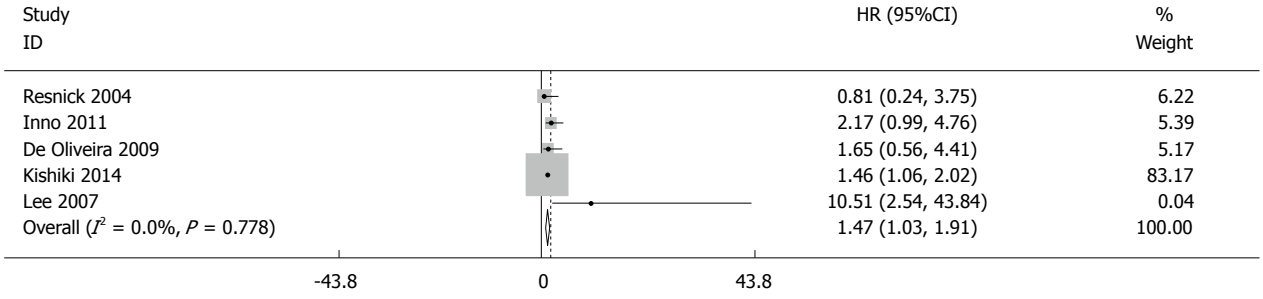

Figure 3 Fixed-effects model of hazard ratio of progression-free survival associated with c-Met overexpression.

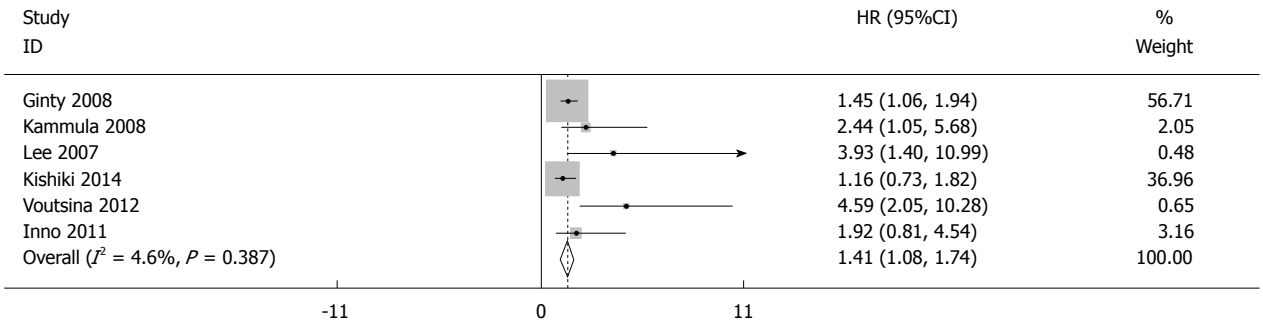

Figure 4 Forest plot showing the meta-analysis of hazard ratio reported for overall survival in patients.

and includes 1,895 patients with CRC. The results of this meta-analysis showed the prognostic value of c-Met expression level in CRC patients. High c-Met expression significantly predicted poor OS and PFS. We also performed subgroup analysis in studies by HR reported. There was a significant relationship between high c-Met expression and poorer overall survival in the hazard ratio reported.

A study conducted by Kishiki *et al*[10] showed that c-Met overexpression was associated with shorter PFS in metastasis colorectal cancer (mCRC) patients with wild-type *KRAS*. All patients received cetuximab- or panitumumab-based therapy. However, the study was conducted retrospectively in a relatively small and heterogeneous population. 90% of the patients were treated with two or more chemotherapy regimens before they were given anti-EGFR treatment. In addition, the anti-EGFR treatment protocols were also heterogeneous. Therefore their findings needed to be validated by more prospective studies. Zeng *et al*[17] found that amplification of c-Met gene is a relatively rare event (3.6%) in CRC, and that the majority of amplified cases occurred in patients with synchronous hepatic metastases (stage Ⅳ).

After identification of c-Met involvement in cancer progression and metastasis, many *in vitro* experimental studies have showed that c-Met plays a role in resistance to anti-EGFR therapy. Inno *et al*[13] retrospectively evaluated a cohort of 73 patients with mCRC treated with a cetuximab-containing regimen. They found an association of high c-Met level with shorter PFS and OS in patients with mCRC, and that the c-Met pathway may be involved in primary resistance to cetuximab. However, their study cannot ascertain whether c-Met is a predictive biomarker, because they assessed only patients treated with a cetuximab-containing regimen. In CRC, many studies have proved that KRAS mutations predict unresponsiveness to EGFR-targeted monoclonal antibody therapies; however, there still about 26% of patients who are not responsive to EGFR-targeted therapy that are a wild-type for KRAS. Therefore, we hypothesize resistance to EGFR-targeted therapies may be mediated by the activation of parallel pathways such as the c-Met signaling pathway. Therefore more prospective studies are needed to affirm the results.

c-Met as a biomarker might be used to select advanced colorectal cancer patients who could benefit from targeted therapies. A growing number of studies from *in vitro*, *in vivo*, and in various stages of clinical testing have shown that c-Met tyrosine kinase (TK) inhibitors can block c-Met signaling and arrest or reverse tumor growth in a subset of human cancers[21,22]. Recently a few studies have shown that c-Met amplification confers high sensitivity to a specific c-Met TK inhibitor in lung cancer and gastric cancer[23,24]. All of these findings indicate that amplified c-Met may serve as a biomarker for targeted therapy.

Some limitations to this meta-analysis require particular note: heterogeneity; differences in clinical treatment; and different criteria to stratify c-Met status.

In conclusion, our meta-analysis demonstrated a significant association between high c-Met expression and poor OS and PFS in CRC for the first time. However, further larger prospective studies are needed

to confirm these results.

COMMENTS

Background

High c-Met expression was found in colorectal cancer and showed a positive relationship with early tumor invasion and metastasis.

Research frontiers

There still seems to be no consensus about the prognostic properties of c-Met status.

Innovations and breakthroughs

This is the first known paper to conduct a comprehensive meta-analysis with the aim of investigating the relationship between c-Met and prognosis of colorectal cancer. The authors found that high c-Met expression was associated with poor prognosis in patients with colorectal cancer.

Applications

This study furthers the understanding of the association of c-Met with colorectal cancer prognosis.

Peer-review

This is a well-performed meta-analysis that aims to assess the prognostic value of c-Met status in colorectal cancer. Its findings are interesting.

REFERENCES

1 **Feezor RJ**, Copeland EM, Hochwald SN. Significance of micrometastases in colorectal cancer. *Ann Surg Oncol* 2002; **9**: 944-953 [PMID: 12464585]

2 **Itzkowitz SH**, Bloom EJ, Kokal WA, Modin G, Hakomori S, Kim YS. Sialosyl-Tn. A novel mucin antigen associated with prognosis in colorectal cancer patients. *Cancer* 1990; **66**: 1960-1966 [PMID: 2224793]

3 **Miyahara M**, Saito T, Kaketani K, Sato K, Kuwahara A, Shimoda K, Kobayashi M. Clinical significance of ras p21 overexpression for patients with an advanced colorectal cancer. *Dis Colon Rectum* 1991; **34**: 1097-1102 [PMID: 1959459]

4 **Leahy DT**, Mulcahy HE, O'Donoghue DP, Parfrey NA. bcl-2 protein expression is associated with better prognosis in colorectal cancer. *Histopathology* 1999; **35**: 360-367 [PMID: 10564391 DOI: 10.1046/j.1365-2559.1999.00743.x]

5 **Zeng Z**, Weiser MR, D'Alessio M, Grace A, Shia J, Paty PB. Immunoblot analysis of c-Met expression in human colorectal cancer: overexpression is associated with advanced stage cancer. *Clin Exp Metastasis* 2004; **21**: 409-417 [PMID: 15672865]

6 **Fujita S**, Sugano K. Expression of c-met proto-oncogene in primary colorectal cancer and liver metastases. *Jpn J Clin Oncol* 1997; **27**: 378-383 [PMID: 9437998 DOI: 10.1093/jjco/27.6.378]

7 **Shoji H**, Yamada Y, Taniguchi H, Nagashima K, Okita N, Takashima A, Honma Y, Iwasa S, Kato K, Hamaguchi T, Shimada Y. Clinical impact of c-MET expression and genetic mutational status in colorectal cancer patients after liver resection. *Cancer Sci* 2014; **105**: 1002-1007 [PMID: 24863535 DOI: 10.1111/cas.12453]

8 **Yi S**, Tsao MS. Activation of hepatocyte growth factor-met autocrine loop enhances tumorigenicity in a human lung adenocarcinoma cell line. *Neoplasia* 2000; **2**: 226-234 [PMID: 10935508]

9 **Parmar MK**, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998; **17**: 2815-2834 [PMID: 9921604 DOI: 10.1002/(SICI)1097-0258]

10 **Kishiki T**, Ohnishi H, Masaki T, Ohtsuka K, Ohkura Y, Furuse J, Watanabe T, Sugiyama M. Overexpression of MET is a new predictive marker for anti-EGFR therapy in metastatic colorectal cancer with wild-type KRAS. *Cancer Chemother Pharmacol* 2014; **73**: 749-757 [PMID: 24500024 DOI: 10.1007/s00280-014-2401-4]

11 **Voutsina A**, Tzardi M, Kalikaki A, Zafeiriou Z, Papadimitraki E, Papadakis M, Mavroudis D, Georgoulias V. Combined analysis of KRAS and PIK3CA mutations, MET and PTEN expression in primary tumors and corresponding metastases in colorectal cancer. *Mod Pathol* 2013; **26**: 302-313 [PMID: 22936063 DOI: 10.1038/modpathol]

12 **Garouniatis A**, Zizi-Sermpetzoglou A, Rizos S, Kostakis A, Nikiteas N, Papavassiliou AG. FAK, CD44v6, c-Met and EGFR in colorectal cancer parameters: tumour progression, metastasis, patient survival and receptor crosstalk. *Int J Colorectal Dis* 2013; **28**: 9-18 [PMID: 22733437 DOI: 10.1007/s00384-012-1520-9]

13 **Inno A**, Di Salvatore M, Cenci T, Martini M, Orlandi A, Strippoli A, Ferrara AM, Bagalà C, Cassano A, Larocca LM, Barone C. Is there a role for IGF1R and c-MET pathways in resistance to cetuximab in metastatic colorectal cancer? *Clin Colorectal Cancer* 2011; **10**: 325-332 [PMID: 21729677 DOI: 10.1016/j.clcc.2011.03.028]

14 **De Oliveira AT**, Matos D, Logullo AF, DA Silva SR, Neto RA, Filho AL, Saad SS. MET Is highly expressed in advanced stages of colorectal cancer and indicates worse prognosis and mortality. *Anticancer Res* 2009; **29**: 4807-4811 [PMID: 20032439]

15 **Lee CT**, Chow NH, Su PF, Lin SC, Lin PC, Lee JC. The prognostic significance of RON and MET receptor coexpression in patients with colorectal cancer. *Dis Colon Rectum* 2008; **51**: 1268-1274 [PMID: 18536971 DOI: 10.1007/s10350-008-9297-1]

16 **Ginty F**, Adak S, Can A, Gerdes M, Larsen M, Cline H, Filkins R, Pang Z, Li Q, Montalto MC. The relative distribution of membranous and cytoplasmic met is a prognostic indicator in stage I and II colon cancer. *Clin Cancer Res* 2008; **14**: 3814-3822 [PMID: 18559601 DOI: 10.1158/1078-0432.CCR-08-0180]

17 **Zeng ZS**, Weiser MR, Kuntz E, Chen CT, Khan SA, Forslund A, Nash GM, Gimbel M, Yamaguchi Y, Culliford AT, D'Alessio M, Barany F, Paty PB. c-Met gene amplification is associated with advanced stage colorectal cancer and liver metastases. *Cancer Lett* 2008; **265**: 258-269 [PMID: 18395971 DOI: 10.1016/j.canlet.2008.02.049]

18 **Kammula US**, Kuntz EJ, Francone TD, Zeng Z, Shia J, Landmann RG, Paty PB, Weiser MR. Molecular co-expression of the c-Met oncogene and hepatocyte growth factor in primary colon cancer predicts tumor stage and clinical outcome. *Cancer Lett* 2007; **248**: 219-228 [PMID: 16945480 DOI: 10.1016/j.canlet.2006.07.007]

19 **Resnick MB**, Routhier J, Konkin T, Sabo E, Pricolo VE. Epidermal growth factor receptor, c-MET, beta-catenin, and p53 expression as prognostic indicators in stage II colon cancer: a tissue microarray study. *Clin Cancer Res* 2004; **10**: 3069-3075 [PMID: 15131045 DOI: 10.1158/1078-0432.CCR-03-0462]

20 **Umeki K**, Shiota G, Kawasaki H. Clinical significance of c-met oncogene alterations in human colorectal cancer. *Oncology* 1999; **56**: 314-321 [PMID: 10343196 DOI: 10.1159/000011985]

21 **Kong-Beltran M**, Stamos J, Wickramasinghe D. The Sema domain of Met is necessary for receptor dimerization and activation. *Cancer Cell* 2004; **6**: 75-84 [PMID: 15261143]

22 **Kim SJ**, Johnson M, Koterba K, Herynk MH, Uehara H, Gallick GE. Reduced c-Met expression by an adenovirus expressing a c-Met ribozyme inhibits tumorigenic growth and lymph node metastases of PC3-LN4 prostate tumor cells in an orthotopic nude mouse model. *Clin Cancer Res* 2003; **9**: 5161-5170 [PMID: 14613995]

23 **Smolen GA**, Sordella R, Muir B, Mohapatra G, Barmettler A, Archibald H, Kim WJ, Okimoto RA, Bell DW, Sgroi DC, Christensen JG, Settleman J, Haber DA. Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. *Proc Natl Acad Sci USA* 2006; **103**: 2316-2321 [PMID: 16461907 DOI: 10.1073/pnas.0508776103]

24 **Mazzone M**, Comoglio PM. The Met pathway: master switch and drug target in cancer progression. *FASEB J* 2006; **20**: 1611-1621 [PMID: 16873884 DOI: 10.1096/fj.06-5947rev]

P- Reviewer: Falletto E, Hoensch HP, Tanyi M **S- Editor**: Ma YJ
L- Editor: Rutherford A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327