RESEARCH ARTICLE

Predictive and Prognostic Roles of Ribonucleotide Reductase M1 in Patients with Pancreatic Cancer Treated with Gemcitabine: A Meta-analysis

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Abstract

Increasing scientific evidence suggests that ribonucleotide reductase M1 (RRM1) may be a powerful predictor of survival in patients with pancreatic cancer treated with adjuvant gemcitabine-based chemotherapy after operative resection, but many existing studies have yielded inconclusive results. This meta-analysis aimed to assess the prognostic role of RRM1 in predicting survival in patients with pancreatic cancer treated with gemcitabine. An extensive literature search for relevant studies was conducted on PubMed, Embase, Web of Science, Cochrane Library, and CBM databases from their inception through May 1st, 2013. This meta-analysis was performed using the STATA 12.0 software and crude hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Eight clinical studies were included in this meta-analysis with a total of 665 pancreatic cancer patients treated with adjuvant gemcitabine-based chemotherapy, including 373 patients in the high RRM1 expression group and 292 patients in the low RRM1 expression group. Our meta-analysis revealed that high RRM1 expression was associated with improved overall survival (OS) of pancreatic cancer patients (HR=1.56, 95%CI=0.95-2.17, *P*<0.001). High RRM1 expression also was linked to longer disease-free survival (DFS) than low RRM1 expression (HR=1.37, 95%CI=0.25-2.48, *P*=0.016). In conclusion, our meta-analysis suggests that high RRM1 expression may be associated with improved OS and DFS of pancreatic cancer patients treated with adjuvant gemcitabine-based chemotherapy. Detection of RRM1 expression may be a promising biomarker for gemcitabine response and prognosis in pancreatic cancer patients.

Keywords: Pancreatic cancer - gemcitabine - ribonucleotide reductase M1 - meta-analysis

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Introduction

Pancreatic cancer is a highly aggressive cancer and the fourth leading cause of cancer death (Wang et al., 2009). In 2008, an estimated 278,684 new cases and 265,000 deaths as a result of pancreatic cancer occurred worldwide (Siegel et al., 2012). Indeed, even after surgical resection with curative intent, the actuarial 5-year survival rate has been reported to be less than 20% (Lau et al., 2010). Therefore, surgery alone is not a sufficient treatment for pancreatic cancer, and adjuvant chemoradiation following curative resection have an impact on long-term survival (Traverso, 2006; Hsu et al., 2010). Gemcitabine is a pyrimidine nucleoside analogue used for the treatment of a wide range of solid tumors, including pancreatic cancer (Wonganan et al., 2012). Previous studies have demonstrated that adjuvant chemoradiation with gemcitabine has a beneficial effect on prognosis in patients with pancreatic cancer after curative resection (Oettle et al., 2007; Van Laethem et al., 2010). Recently, it has been widely accepted that gemcitabine-based regimen is the first-line chemotherapy for patients with unresectable or resected pancreatic cancer (Kanai et al., 2011; Kim et al., 2011b).

Ribonucleotide reductase M1 (RRM1) is a multimeric enzyme that converts ribonucleotides to deoxyribonucleosides, both of which are required for DNA polymerization and repair (Kwon et al., 2006; Jordheim et al., 2011). It has been reported recently that RRM1 is predictive marker of response to adjuvant chemotherapy with gemcitabine (Ohtaka et al., 2008). Some studies also showed that high RRM1 gene expression was significantly associated with increased chemosensitivity to gemcitabine both in vitro and clinically (Bepler et al., 2006; Nakahira et al., 2007; Ueno et al., 2007). Several previous studies have indicated that high RRM1 protein/mRNA expression was associated with increased overall survival (OS) and disease-free survival (DFS) after gemcitabine-based chemotherapy (Nakahira et al., 2007; Akita et al., 2009; Fujita et al., 2010; Valsecchi et al., 2012; Nakagawa et al., 2013; Xie et al., 2013). However, there are also some contradictory data in the literatures concerning the prognostic value of RRM1 in predicting

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gemcitabine chemosensitivity for pancreatic cancer patients (Kim et al., 2011a; Marechal et al., 2012). The controversial findings are probably related to the effects from interacting with other genes, environmental effects on gene expression, different detection methods, sample sizes, and study design. Therefore, we attempt to perform a meta-analysis of all eligible studies to provide insights into the prognostic role of RRM1 expression in predicting survival in patients with pancreatic cancer treated with gemcitabine.

Materials and Methods

Search strategy

An extensive literature search for relevant studies was conducted on PubMed, Embase, Web of Science, Cochrane Library, and CBM databases from their inception through May 1st, 2013. We used the following keywords and MeSH terms: ["ribonucleotide reductase M1" or "ribonucleotide reductases" or "RRM1" or "RRM-1" or "RNR"] and ["pancreatic cancer" or "pancreatic neoplasm" or "pancreatic tumor" or "pancreatic carcinoma" or "pancreatic carcinogenesis"] and ["gemcitabine" or "GEM" or "deoxycytidine analog"]. There were no language restrictions. Manual search of reference lists from potentially relevant articles was also performed to identify other potential studies.

Selection criteria

To be included in the meta-analysis, these studies must meet the following criteria: (1) clinical studies focused on the prognostic role of RRM1 in predicting survival in patients with pancreatic cancer treated with gemcitabine; (2) all patients diagnosed with pancreatic cancer were confirmed through histopathologic examinations; (3) published data on DFS and OS estimates was sufficient. Studies were excluded if they did not meet all of the inclusion criteria. If more than one study by the same author using the same case series were published, either the study with the largest sample size or the most recent publication was included. Any disagreements were resolved through discussions and subsequent consensus.

Data extraction

Two authors independently extracted data from eligible studies using a standardized form. The following information were collected: surname of first author, year of publication, source of publication, country of origin, ethnicity, language of publication, study design, total number of cases, pathological subtype, detection method of RRM1 expression, etc. In cases of conflicting evaluations, disagreements on inconsistent data from the eligible studies were resolved through discussions and careful reexaminations of the full text by the authors.

Quality assessment

The quality of the included studies was assessed independently by two authors based on the Newcastle-Ottawa Scale (NOS) criteria for the assessment of the quality of nonrandomized studies (Stang, 2010). The NOS criteria use a "star" rating system to judge the methodological quality, which was based on three perspectives of the study: selection, comparability, and outcome. Scores ranged from 0 stars (worst) to 8 stars (best); a score equal to or greater than 7 indicates a generally good methodological quality. Disagreements on the quality assessment of the included studies were resolved through a comprehensive reassessment by the authors.

Statistical analysis

Crude hazard ratio (HR) with 95% confidence interval (CI) were calculated under a fixed or random effect model. The significance of the pooled HR was determined using the Z test. We estimated the degree of heterogeneity among studies using Cochran's Q-statistic, which is considered significant at $P<0.05$ (Jackson et al., 2012). The I^2 test was also conducted to quantify the heterogeneity (ranges from 0 to 100%) (Biggerstaff and Jackson, 2008). The random-effect model (DerSimonian Laird method) was conducted when there exists a significant Q-test with $P< 0.05$ or $I^2>50\%$. When there was no statistical heterogeneity, we used the fixed-effects model (Mantel-Haenszel method). In order to explore potential sources of heterogeneity, subgroup analyses were performed based on ethnicity and type of RRM1 expression. To evaluate the influence of single studies on the overall estimate, we conducted a sensitivity analysis by omitting each study in turn to assess the quality and consistency of the results. To investigate whether publication bias might have affected the validity of the estimates, funnel plots were constructed. The symmetry of the funnel plots was further evaluated by Egger's linear regression test (Peters et al., 2006). All tests were two-sided with a P value of <0.05 being considered statistically significant. All analyses were calculated using the STATA software, version 12.0 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics of included studies

A total of 73 articles relevant to the searched keywords were initially identified. Of these articles, 37 were excluded after a review of their titles and key words; then, abstracts

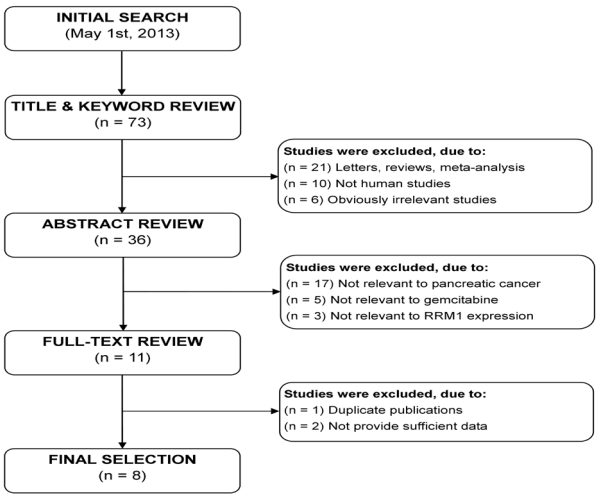

Figure 1. Flow Chart of the Literature Search and Study Selection

Table 1. Characteristics and Methodological Quality of the Included Studies

First author	Year	Country	Ethnicity	Case number		Expression	Detetion	Outcome	NOS
				High RRM1	Low RRM1	type	method		scale
Nakahira SS	2009	Japan	Asian	9	9	mRNA	qRT-PCR	OS	6/9
Akita HZ	2009	Japan	Asian	14	14	Protein	Immunohistochemistry	OS	7/9
Fujita H	2010	Japan	Asian	9	31	mRNA	qRT-PCR	OS	7/9
Kim R	2011	USA	Caucasian	28	28	mRNA	qRT-PCR	OS/DFS	6/9
Marechal R	2012	Belgium	Caucasian	207	30	Protein	Immunohistochemistry	OS	7/9
Valsecchi ME-1	2012	USA	Caucasian	32	61	Protein	Immunohistochemistry	OS	8/9
Valsecchi ME-2	2012	USA	Caucasian	10	39	mRNA	qRT-PCR	OS	8/9
Nakagawa N	2013	Japan	Asian	44	65	Protein	Immunohistochemistry	OS/DFS	8/9
Xie H-b	2013	USA	Caucasian	20	15	Protein	Immunohistochemistry	OS/DFS	7/9

RRM1, ribonucleotide reductase M1; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; OS, overall survival; DFS, disease-free survival; NOS, the Newcastle-Ottawa Scale criteria

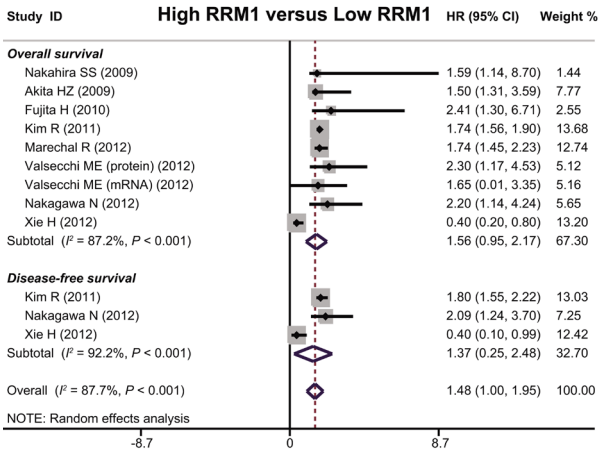

Figure 2. Forest Plots for the Associations between High RRM1 Expression and Improved Overall Survival and Disease-free Survival of Pancreatic Cancer Patients Treated with Adjuvant Gemcitabine-Based Chemotherapy. The squares and horizontal lines correspond to the study specific HR and 95% CI. The area of the squares reflects the weight. The diamond represents the summary HR and 95% CI

Table 2. Meta-analysis Findings for the Role of RRM1 Expression in Predicting Survival of Pancreatic Cancer Patients Treated with Adjuvant Gemcitabine-based Chemotherapy

Estimates	OS			DFS		
	HR	95%CI	*P*	HR	95%CI	*P*
Overall	1.56	[0.95, 2.17]	<0.001	1.37	[0.25, 2.48]	0.016
Ethnicity						
Caucasian	1.45	[0.70, 2.20]	<0.001	1.11	[0.26, 2.48]	0.013
Asian	1.8	[0.96, 2.65]	<0.001	2.09	[0.86, 3.32]	0.001
Type of RRM1 expression						
Protein	1.49	[0.60, 2.38]	0.001	1.14	[0.50, 2.79]	0.011
mRNA	1.74	[1.57, 1.91]	<0.001	1.8	[1.47, 2.14]	<0.001

RRM1, ribonucleotide reductase M1; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; 95%CI, 95% confidence interval

and full texts were reviewed, and another 28 papers were excluded. Eight clinical studies met our inclusion criteria for this meta-analysis (Nakahira et al., 2007; Akita et al., 2009; Fujita et al., 2010; Kim et al., 2011a; Marechal et al., 2012; Valsecchi et al., 2012; Nakagawa et al., 2013; Xie et al., 2013). The flow chart of the study selection process is shown in Figure 1. Publication years of the eligible studies ranged from 2009 to 2013. A total of 830 pancreatic cancer

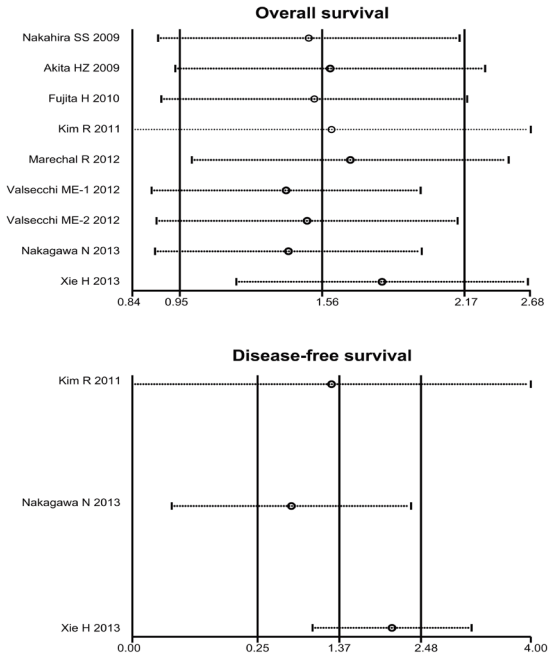

Figure 3. Sensitivity analysis of the Associations between High RRM1 Expression and Improved Overall Survival and Disease-free Survival of Pancreatic Cancer Patients Treated with Adjuvant Gemcitabine-based Chemotherapy. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95%CI

patients were involved in this meta-analysis, including 445 patients in the high RRM1 expression group and 385 patients in the low RRM1 expression group. Overall, four studies were conducted in Caucasian populations, and the other four studies in Asian populations. Detection methods include immunohistochemistry and quantitative reverse transcription-polymerase chain reaction (qRT-PCR). The characteristics and methodological quality of the included studies are summarized in Table 1.

Quantitative data synthesis

A summary of the meta-analysis findings for the role of the expression of RRM1 in predicting survival of pancreatic cancer patients treated with gemcitabine is provided in Table 2. Since heterogeneity obviously existed, which could be a result of differences in ethnicity, treatment regimen and type of RRM1 expression,

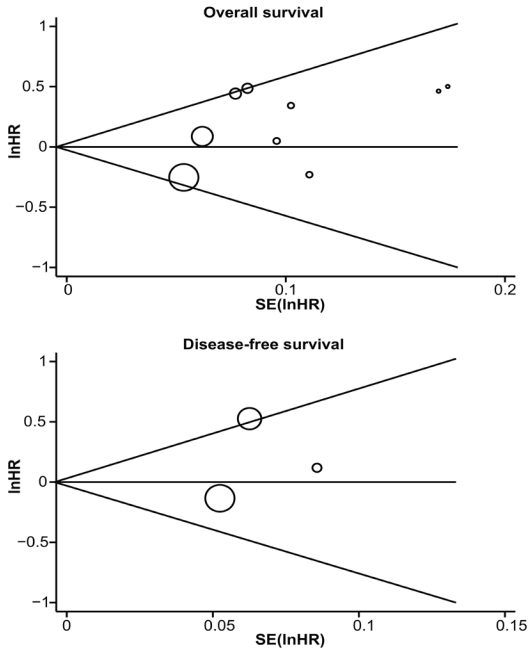

Figure 4. Funnel Plot of the Associations between High RRM1 Expression and Improved Overall Survival and Disease-free Survival of Pancreatic Cancer Patients Treated with Adjuvant Gemcitabine-Based Chemotherapy. Each point represents a separate study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line, mean magnitude of the effect

the random effects model was conducted. The meta-analysis results revealed that high RRM1 expression was associated with improved OS of pancreatic cancer patients (HR=1.56, 95%CI=0.95-2.17, $P<0.001$). Pancreatic cancer patients with high RRM1 expression also had a longer DFS than those with low RRM1 expression (HR=1.37, 95%CI=0.25-2.48, $P=0.016$) (Figure 2).

Subgroup analysis by ethnicity indicated that high RRM1 expression may improve OS and DFS of pancreatic cancer patients among Caucasian and Asian populations (all $P<0.05$). Further subgroup analysis based on type of RRM1 expression also showed that both high RRM1 protein and mRNA are associated with improved OS and DFS of pancreatic cancer patients treated with adjuvant gemcitabine-based chemotherapy (all $P<0.05$).

Evaluation of heterogeneity and publication bias

Sensitivity analysis was also performed to assess the influence of each individual study on the pooled HR by omitting each individual studies in turn to assess the quality and consistency of the results. The analysis results suggested that no individual studies significantly affected the pooled HRs (Figure 3). Funnel plots and Egger's linear regression test were used to assess potential publication bias in the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 4). Egger's test also did not display strong statistical evidence for publication bias (all $P>0.05$).

Discussion

Pancreatic cancer is one of the most lethal human cancers with an overall 5-year survival rate of less than 5% (Li et al., 2004; Neoptolemos et al., 2010). However, during the last decade, few successes have been archived in the treatment of pancreatic cancer (Choi et al., 2012). The most successful agent for pancreatic cancer treatment is gemcitabine, although the overall effect in terms of patient survival remains very poor (Kovacevic et al., 2011). Cellular uptake of the anticancer drug gemcitabine is mediated mainly by hENT1 and RRM1 (Mini et al., 2006; Ying et al., 2012). It has been hypothesized that deficiency of RRM1 may contribute to clinical gemcitabine resistance (Lai et al., 2008). Increasingly strong evidence suggests RRM1 is a prognostic biomarker in gemcitabine-treated pancreatic cancer, and may well be a predictive biomarker of gemcitabine efficacy (Giovannetti et al., 2006; Kim et al., 2011a). There is a compelling biological rationale for using the expression level of RRM1 to predict gemcitabine chemosensitivity and prognosis of pancreatic cancer patients.

Our meta-analysis suggested that high RRM1 expression was associated with improved OS and DFS of pancreatic cancer patients treated with gemcitabine-based regimens. These results indicated that the efficacy of adjuvant chemoradiation with gemcitabine is associated with the expression level of RRM1, which are consistent with previous studies. Fujita et al reported that RRM1 protein expression was associated with increased DFS and OS in pancreatic cancer patients who received gemcitabine, but not in those who received 5-fluorouracil (5-FU) (Fujita et al., 2010). Nakagawa et al demonstrated that the 1- year and 3- year OS rates were significantly greater in the high RRM1 expression group than in the low RRM1 expression group (Nakagawa et al., 2013). Other previous studies also indicated that the RRM1 expression was a significant and independent prognostic factor for OS (Nakahira et al., 2007; Akita et al., 2009; Valsecchi et al., 2012; Xie et al., 2013). In the current study, we also performed subgroup analyses based on ethnicity, treatment regimen and type of RRM1 expression to further evaluate the prognostic value of RRM1 expression for survival in pancreatic cancer patients who received gemcitabine. The results strongly suggested that detection of RRM1 expression may be a promising biomarker for gemcitabine response and prognosis in pancreatic cancer patients.

Our meta-analysis has several limitations that should be acknowledged. The first major limitation is the relatively small sample size of this meta-analysis, which may not have sufficient statistical power in estimating the prognostic role of RRM1 expression in pancreatic cancer. Therefore, more studies with larger sample size are still needed. On the other hand, as a type of a retrospective study, a meta-analysis of summary data from previously published studies may encounter recall or selection bias, thereby possibly influencing the reliability of the results. Most important of all, the lack of access to all the data from the original studies limited further evaluations of the potential values of RRM1 expression. However, despite these statistical limitations, our study is the first comprehensive meta-analysis of all eligible studies concerning the prognostic role of RRM1 expression in predicting survival in patients with pancreatic cancer treated with gemcitabine.

In conclusion, our meta-analysis indicates that high RRM1 expression may be associated with improved OS and DFS of pancreatic cancer patients treated with gemcitabine. Detection of RRM1 expression may be a promising biomarker for gemcitabine response and prognosis in pancreatic cancer patients. However, due to the limitations mentioned above, further detailed studies are still required to confirm our findings.

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