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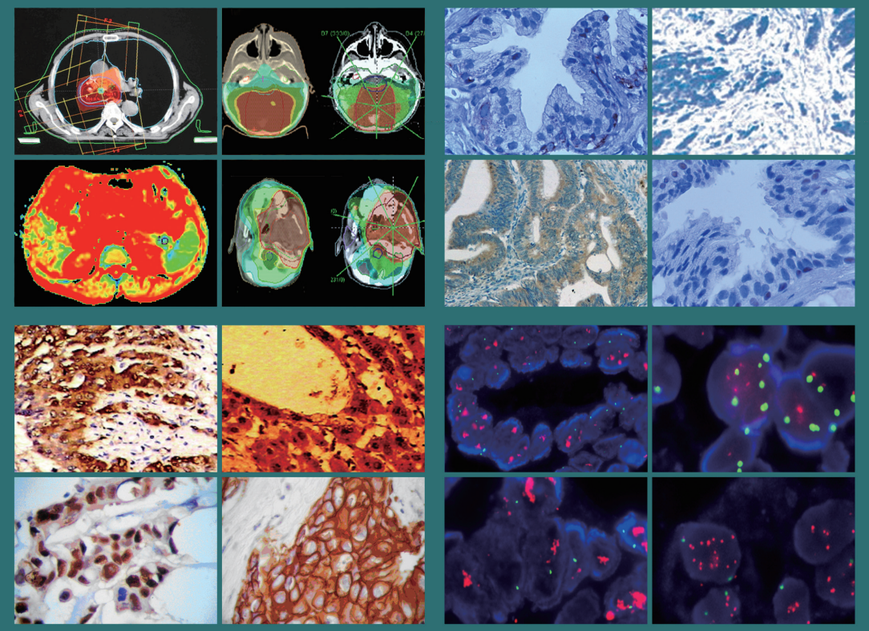

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Aims & Scope

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ORIGINAL ARTICLE

Association of genetic polymorphisms of GSTM1 and smoking status with lung cancer risk*

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Abstract

Objective Long-term cigarette smoke exposure damages the airway epithelium. However, the correlation among GSTM1 gene polymorphism, smoking status, and lung cancer susceptibility remains unclear. This study aimed to identify the genetic polymorphism of GSTM1 and examine the association of GSTM1 polymorphism and smoking history with lung cancer susceptibility.

Methods The genetic polymorphism of GSTM1 was genotyped by polymerase chain reaction (PCR) in 217 lung cancer patients and 198 controls. The demographic data and smoking history of the patients were collected. The age, sex, and residence of the two groups were also obtained.

Results Significant differences in GSTM1 polymorphism were observed between the case and control groups (P = 0.024). Smoking time and smoking index were significantly different between the case and control groups. With the increase in smoking time and smoking index, the differences became more obvious. There was a synergistic effect between GSTM1 and smoking (S = 3.35). The risk of developing lung cancer increased 4.82 fold in smokers carrying deficient-type GSTM1. Compared with patients carrying wild-type GSTM1, the risk of developing lung cancer was higher in those carrying deficient-type GSTM1 with the increase in smoking time and smoking index. In different pathological types, no significant differences were observed in GSTM1 polymorphism. In different pathological types, the proportions of patients increased with the increase in smoking time and smoking index, especially the proportion of patients with squamous cell carcinoma. Compared with wild-type GSTM1, the proportion of patients with deficient-type GSTM1 increased with the increase in smoking time and smoking index (P = 0.003 and 0.017). This trend was mainly observed in those with squamous cell carcinoma.

Conclusion GSTM1 mutation is associated with lung cancer susceptibility. Smokers carrying deficient-type GSTM1 are more likely to develop lung cancer. Compared with patients carrying wild-type GSTM1, smokers with deficient-type GSTM1 are more likely develop lung cancer when smoking time is more than 30 years and smoking index is more than 400. In patients carrying deficient-type GSTM1, the risk of developing squamous cell carcinoma increases with an increase in smoking time and smoking dose.

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Key words: GSTM1; genetic susceptibility; smoking; lung cancer

The occurrence of lung cancer is based on the interaction between genetic factors and the environment. Smoking is one of the major risk factors that causes lung cancer. Approximately 5 million people worldwide die each year because of smoking. However, only 10%–15% of smokers developed lung cancer. This finding suggests that except smoking, susceptibility to lung cancer may also be associated with genetic factors.

Previous studies showed that cigarette smoke contains 69 types of carcinogens, including polycyclic aromatic hydrocarbons (PAH), nitrosamines, benzo[a]pyrene, and aromatic amines [1]. Cigarette is a rich source of oxidants and reactive oxygen species (ROS) [2]. Smoking can not only result in directly take of exogenous ROS, but can also lead to the generation of endogenous ROS, which increases oxidativestress in tissues [3]. The increase of ROS during oxidative stress can break the balance between oxidation and antioxidation and lead to oxidative stress [4–6]. ROS can damage DNA, RNA, and protein, which causes chromosomal instability, gene mutation, or altered

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gene expression, and promotes tumor occurrence [7–8]. Long-term cigarette smoke exposure damages the airway epithelium, which induces the expression of related factors involved in oxidative stress. Therefore, polymorphisms of these genes associated with oxidative stress may be related to the susceptibility to lung cancer.

Glutathione-S-transferases (GSTs) belong to phase II metabolic enzymes, which are associated with the metabolism of carcinogens, drugs, and ROS. Therefore, GSTs protect DNAs against oxidative damage [9–10]. Among the GSTs, GSTM1 plays a key role in the detoxification of carcinogenic electrophiles of aflatoxin and PAHs in tobacco smoke [11–12]. Deletion of GSTM1 leads to loss of the enzyme's ability to detoxify carcinogens. Individuals with deficient-type GSTM1 are more likely to develop cancer, including lung cancer [13–15]. There is a synergistic effect between GSTM1 and smoking in lung cancer [15–17]. However, several studies have reported conflicting views [18–20].

In this study, we aimed to determine the potential link between GSTM1 polymorphism, smoking, and lung cancer. To further investigate the effect of smoking, smoking was graded according to smoking times and smoking doses. No previous studies have investigated the relationship between GSTM1 polymorphism and smoking time and dose.

Patients and methods

Patients

A total of 217 lung cancer patients from Beijing Chest Hospital, China and 198 healthy controls were enrolled between August 2005 and June 2006. These participants belonged to the Chinese Han ethnic group. The patients were pathologically diagnosed with lung cancer and did not undergo preoperative surgery, radiotherapy, chemotherapy, molecular targeted therapy, immunotherapy, etc. The patients had complete clinical information, basic data, and follow-up records. Patients with other malignancies were excluded. All healthy controls had no hereditary disorders or known medical illness. Patients' demographic data were accurately collected. Patients in the case group were aged 24–83 years [mean: (58.98 ± 11.33) years], while those in the control group were aged 26–88 years [mean: (53.39 ± 15.44) years]. The proportions of male and female were 68.2% and 31.8% in the case group and 64.7% and 35.3% in the control group. The distributions of age and sex were balanced in the two groups. This study was approved by the Ethical Committee of Beijing Chest Hospital, China.

Genotyping

Sodium citrate tube was used to collect peripheral blood from all participants. Serial phenol/chloroform extraction was used to extract genomic DNA.GSTM1 genotype was identified by polymerase chain reaction (PCR) using the following primer sequences:

P1: 5′–GAACTCCCTGAAAAGCTAAAGC–3′,
P2: 5′–GTTGGGCTCAAATATACGGTGG–3′,
β1: 5′–CAACTTCATCCACGTTCACC–3′, and
β2: 5′–GAAGAGCCAAGGACAGGTAC–3′.

The PCR amplification conditions used in this study were as follows: 94 °C for 7 minutes and 30 cycles (94 °C for 1 minute, 59 °C for 1 minute, and 72 °C for 1 minute) and 72 °C for 10 minutes. For better quality control, 80 samples were randomly selected for duplicate genotyping. The concordance rate was 100%.

Statistical analysis

Quantitative variables were compared using the one-way analysis of variance. Qualitative variables, genotype/allele frequency, and Hardy-Weinberg equilibrium of the polymorphism were tested using the χ^2 test. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression (LR) models adjusted for potential confounders. Unconditional logistic regression analyses were used to calculate gene-environment interaction. Statistical significance was assessed using a P-value of < 0.05. All tests were two-sided, and statistical analyses were conducted using SPSS statistics 17.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Patients' characteristics

Table 1 summarizes the characteristics of the patients in this study. A significant difference was observed between cases and controls in terms of smoking status ($P = 0.000$). Among male participants, the proportions of smokers and non-smokers were 75.7% and 24.3%, respectively. Among female participants, these proportions were 11.6% and 88.4%, respectively. Of the total participants, 29.5% had squamous carcinoma, 37.3% had adenocarcinoma, 17.1% had small cell carcinoma; and 16.1% had other types of cancer.

Correlation of GSTM1 and smoking with lung cancer risk

To evaluate the independent effect of GSTM1 and smoking on lung cancer susceptibility, we used unconditional LR models, as detailed in Tables 1 and 2. Deletion of GSTM1 was related to a 1.56-fold increase in lung cancer risk ($P = 0.024$). Smoking was related to a 2.59-fold increase in lung cancer risk ($P = 0.000$). OR values increased from 1.05 (95% CI = 0.49–2.21) to 3.62 (95% CI = 2.03–6.45) when smoking times were divided according to every 10 years. OR values increased from 2.64 (95% CI

Table 1 Controls and patients characteristics [*n* (%)]

Variables	Cases [*n* = 217 (%)]	Controls [*n* = 198 (%)]	*P* value
Age (years)			
Range	24–83	26–88	
Mean ± SD	58.98 ± 11.33	53.39 ± 15.44	0.305
Gender			
Male	148 (68.2)	128 (64.7)	0.443
Female	69 (31.8)	70 (35.3)	
Histology			
Squamous carcinoma	64 (29.5)		
Adenocarcinoma	81 (37.3)		
Small cell carcinoma	37 (17.1)		
Other	35 (16.1)		
Male			
Squamous carcinoma	58 (39.2)		
Adenocarcinoma	39 (26.4)		
Small cell carcinoma	27 (18.2)		
Other	24 (16.2)		
Female			
Squamous carcinoma	6 (8.7)		
Adenocarcinoma	42 (60.9)		
Small cell carcinoma	10 (14.5)		
Other	11 (15.9)		
Smoking history			
No smoking	97 (44.7)	134 (67.7)	0.000
Smoking	120 (55.3)	64 (32.3)	
Male			
No smoking	36 (24.3)	65 (50.8)	0.000
Smoking	112 (75.7)	63 (49.2)	
Female			
No smoking	61 (88.4)	69 (98.6)	0.017
Smoking	8 (11.6)	1 (1.4)	
Age starting smoking (years)			
Mean ± SD	27.69 ± 0.88	27.57 ± 1.42	0.862

= 1.17–5.96) to 3.43 (95% CI = 2.19–5.36) when smoking index increased from ≤ 200 to > 400. To analyze GSTM1-smoking interaction, LR model was used and showed a synergistic effect between smoking and GSTM1 (S = 3.35).

Relevance between GSTM1 polymorphism and smoking exposure

To further analyze GSTM1-smoking interaction, GSTM1 was layered to analyze. OR values were significantly different between wild-type and GSTM1 deletion when smoking time was analyzed (Table 3). OR values increased from 1.56 (95% CI = 0.37–6.59) to 2.84 (95% CI = 1.23–6.53) in smokers with wild-type GSTM1 and from 0.85 (95% CI = 0.23–3.14) to 4.51 (95% CI = 1.99–10.22) in smokers with GSTM1 deletion. Compared with non-smoker carrying wild-type GSTM1, smokers with GSTM1 deletion had a 5.55-fold increase in lung cancer risk when smoking time was equal or greater than 30 years. OR values were significantly different between wild-type and deletion GSTM1 when smoking index was analyzed (Table 4). OR values increased from 1.56 (95% CI = 0.37–6.59) to 2.56 (95% CI = 1.36–4.82) in smokers with wild-type GSTM1 and from 0.42 (95% CI = 0.04–4.17) to 4.75 (95% CI = 2.47–9.14) in smokers with GSTM1 deletion. Compared with non-smokers carrying wild-type GSTM1, smokers with GSTM1 deletion had a 5.85-fold increase in lung cancer risk when smoking index was more than 400.When smoking time and smoking index were the same, the risk of cancer in patients with mutated GSTM1 was doubled compared with that of patients with functional GSTM1.

Correlation between GSTM1 and smoking and pathological type

To evaluate the effect of GSTM1 and smoking on pathological type, we used unconditional LR models, as detailed in Table 5. There was no significant difference in GSTM1 polymorphism between different pathological types ($P = 0.932$). A significant difference was observed in smoking status between different pathological types ($P = 0.000$). Approximately 40.83% of smokers had squamous carcinoma, while 20% (17.5%–23.3%) had other types of cancer. In the squamous carcinoma group, the proportion of smokers was increased from 0% to 35.9% when smoking times changed from < 10 years to ≥ 30 years and from 0% to 67.2% when smoking index changed from ≤ 200 to > 400. In the adenocarcinoma group, the proportion of smokers increased from 8.6% to 12.3% when smoking times changed from < 10 years to ≥ 30 years and from 4.9% to 25.9% when smoking index changed from ≤ 200 to > 400.

Relevance of GSTM1 polymorphism and smoking exposure with pathological type

The results were shown in Table 6 when smoking exposure was analyzed in detail. The proportions of squamous carcinoma increased from 0% to 23.1% in smokers with wild-type GSTM1 and from 0% to 44.7% in smokers with GSTM1 deletion. There were considerable proportions of patients with other types of cancer who had wild-type GSTM1 and GSTM1 deletion. Table 7 shows the results of the analyses of smoking index. In wild-type GSTM1 smokers, the proportion of patients with squamous carcinoma increased from 0% to 61.5% and that of patients with adenocarcinoma increased from 8.6% to 25.7%. In deletion-type GSTM1 smokers, the proportion of patients with squamous carcinoma increased from 0% to 71.1% and that of patients with adenocarcinoma increased from 2.2% to 26.1%.

Table 2 Association between lung cancer risk, GSTM1 and smoking

Factors		Control [*n* (%)]	Case [*n* (%)]	Risk estimate OR* (95% CI)	*P* value**	S***
GSTM1	Wide-type	104 (52.5)	90 (41.5)	1.00 (Reference)		
	Deletion	94 (47.5)	127 (58.5)	1.56 (1.06–2.30)	0.024	
Smoking history	No smoking	134 (67.7)	97 (44.7)	1.00 (Reference)		
	Smoking	64 (32.3)	120 (55.3)	2.59 (1.74–3.87)	0.000	
Smoking time (years)	No smoking	134 (68.2)	97 (44.7)	1.00 (Reference)		
	< 10	10 (5.1)	8 (3.7)	1.05 (0.49–2.21)	0.919	
	10–	15 (7.6)	15 (6.9)	2.60 (1.08–6.28)	0.034	
	20–	18 (9.1)	45 (20.7)	3.25 (1.12–9.41)	0.030	
	30–	20 (10.1)	52 (24.0)	3.62 (2.03–6.45)	0.000	
Smoking index	No smoking	134 (67.2)	97 (55.2)	1.00 (Reference)		
	SI ≤ 200	18 (9.1)	6 (2.8)	2.64 (1.17–5.96)	0.019	
	SI (200–400)	7 (3.5)	16 (7.4)	3.44 (1.04–11.49)	0.044	
	SI > 400	40 (20.2)	99 (45.6)	3.43 (2.19–5.36)	0.000	
GSTM1						
Wide-type	No smoking	64 (32.3)	41 (18.9)			
Wide-type	Smoking	40 (20.2)	49 (22.6)	1.91 (1.08–3.39)	0.026	
Deletion	No smoking	71 (35.9)	56 (25.8)	1.23 (0.73–2.08)	0.438	
Deletion	Smoking	23 (11.6)	71 (32.7)	4.82 (2.61–8.89)	0.000	3.35

SI, smoking index, which is the number of cigarettes smoked per day × years of smoking; * Associations were determined using multivariate logistic regression models to estimate the risk of developing lung cancer using GSTM1 wild-type, and no smoking as the reference; ** Differences in the frequency of high-risk and low-risk groups between cases and controls were determined using the χ^2 test of association with a significance level of 0.05; *** S, synergy index = $(RR_{++} - 1.0) / (RRi - 1.0)$, RR: relative risk

Table 3 Association between lung cancer risk, GSTM1 and smoking time

GSTM1	Smoking time (years)	Control [*n* (%)]	Case [*n* (%)]	OR (95% CI)	*P* value**
Wide-type	No smoking	64 (61.5)	41 (45.6)		
	< 10	4 (3.8)	4 (4.4)	1.56 (0.37–6.59)	0.542
	10–	12 (11.5)	7 (7.8)	0.91 (0.33–2.50)	0.856
	20–	13 (12.5)	18 (20.0)	2.16 (0.96–4.88)	0.060
	30–	11 (10.6)	20 (22.2)	2.84 (1.23–6.53)	0.012
Deletion	No smoking	71 (75.5)	56 (44.1)		
	< 10	6 (6.4)	4 (3.1)	0.85 (0.23–3.14)	0.802
	10–	3 (3.2)	8 (6.3)	3.38 (0.86–13.34)	0.068
	20–	5 (5.3)	27 (21.3)	6.85 (2.48–18.92)	0.000
	30–	9 (9.6)	32 (25.2)	4.51 (1.99–10.22)	0.000
				5.55 (2.40–12.82)*	0.000

* OR values of smokers (smoking time was more than 30 years) with deletion type GSTM1 and no smokers with wide-type GSTM1; ** Differences in the frequency of high-risk and low-risk groups between cases and controls were determined using the χ^2 test of association with a significance level of 0.05

Discussion

Previous studies showed that 85%–90% of lung cancer patients are smoking [21–23]. In this study, 55.3% of patients in the case group were smokers, which is higher than that in the control group ($P = 0.000$). When smoking was analyzed according to smoking time and smoking dose, we found an increasing trend in the risk of developing cancer with the extension of smoking time and smoking dose. When smoking time is greater than or equal to 30 years, the risk of developing cancer increases by 3.62 times. When smoking index is more than 400, the hazard to lung cancer increases by 3.43 times. A multicenter study found that the risk of lung cancer was 11.95 times in heavy smokers [24]. This value is higher than that reported in our study. This may be related to the differences in patients' behavior. Among European patients, 44% of women were heavy smokers, whereas none of our study patients were heavy smokers. The kitchen fume is also a risk factor for lung cancer among Chinese women.

The pathological types of lung cancer have changed since the 1950s. The most common type of lung cancer is lung adenocarcinoma [25–28]. This may be related to the recent advancements in the production of cigarettes and

Table 4 Association between lung cancer risk, GSTM1 and smoking index

GSTM1	Smoking index	Control [*n* (%)]	Case [*n* (%)]	OR (95% CI)	*P* value**
Wide-type	No smoking	64 (61.5)	41 (45.6)		
	SI ≤ 200	4 (3.8)	4 (4.4)	1.56 (0.37–6.59)	0.542
	SI (200–400)	11 (10.6)	4 (4.4)	0.57 (0.17–1.90)	0.352
	SI > 400	25 (24.0)	41 (45.6)	2.56 (1.36–4.82)	0.003
Deletion	No smoking	71 (75.5)	56 (44.1)		
	SI ≤ 200	3 (3.2)	1 (0.8)	0.42 (0.04– 4.17)	0.448
	SI (200–400)	4 (4.3)	10 (7.9)	3.17 (0.94–10.64)	0.052
	SI > 400	16 (17.0)	60 (47.2)	4.75 (2.47– 9.14)	0.000
				5.85 (2.98–11.52)*	0.000

* OR values of smokers (smoking index was more than 400) with deletion GSTM1 and no smokers with wide-type GSTM1; ** Differences in the frequency of high-risk and low-risk groups between cases and controls were determined using the χ^2 test of association with a significance level of 0.05

Table 5 Association between pathological type, GSTM1 and smoking

Factors		Pathological type [*n* (%)]				χ^2 value	*P* value*
		Squamous carcinoma	Adenocarcinoma	Small cell carcinoma	Other		
GSTM1	Wide-type	26 (40.6)	35 (43.2)	16 (43.2)	13 (37.1)	0.44	0.932
	Deletion	38 (59.4)	46 (56.8)	21 (56.8)	22 (62.9)		
Smoking	No smoking	15 (23.4)	53 (65.4)	15 (40.5)	14 (40.0)	26.43	0.000
	Smoking	49 (76.6)	28 (34.6)	22 (59.5)	21 (60.0)		
Smoking time (years)	No smoking	15 (23.4)	53 (65.4)	15 (40.5)	14 (40.0)	44.13	0.000
	< 10	0 (0.0)	7 (8.6)	1 (2.7)	0 (0.0)		
	10–	6 (9.4)	2 (2.5)	3 (8.1)	4 (11.4)		
	20–	20 (31.2)	9 (11.1)	7 (18.9)	9 (25.7)		
	30–	23 (35.9)	10 (12.3)	11 (29.7)	8 (22.9)		
Smoking index	No smoking	15 (23.4)	53 (65.4)	15 (40.5)	14 (40.0)	35.05	0.000
	SI ≤ 200	0 (0.0)	4 (4.9)	1 (2.7)	0 (0.0)		
	SI (200–400)	6 (9.4)	3 (3.7)	3 (8.1)	2 (5.7)		
	SI > 400	43 (67.2)	21 (25.9)	18 (48.6)	19 (54.3)		

* χ^2 test

Table 6 Association between pathological type, GSTM1 and smoking time

GSTM1	Smoking time (years)	Pathological type [*n* (%)]				χ^2 value	*P* value*
		Squamous carcinoma	Adenocarcinoma	Small cell carcinoma	Other		
Wide-type	No smoking	7 (26.9)	23 (65.7)	6 (37.5)	5 (38.5)	21.16	0.048
	< 10	0 (0.0)	3 (8.6)	1 (6.2)	0 (0.0)		
	10–	3 (11.5)	1 (2.9)	1 (6.2)	2 (15.4)		
	20–	10 (38.5)	3 (8.6)	2 (12.5)	3 (23.1)		
	30–	6 (23.1)	5 (14.3)	6 (37.5)	3 (23.1)		
Deletion	No smoking	8 (21.1)	30 (65.2)	9 (42.9)	9 (40.9)	30.28	0.003
	< 10	0 (0.0)	4 (8.7)	0 (0.0)	0 (0.0)		
	10–	3 (7.9)	1 (2.2)	2 (9.5)	2 (9.1)		
	20–	10 (26.3)	6 (13.0)	5 (23.8)	6 (27.3)		
	30–	17 (44.7)	5 (10.9)	5 (23.8)	5 (22.7)		

* χ^2 test

the application of cigarette filter [29–30]. In this study, the number of adenocarcinoma cases was slightly higher than that of squamous carcinoma cases. However, the results were significantly different when patients were stratified by sex. The number of squamous carcinoma cases was obviously higher than that of adenocarcinoma cases in male patients, and lower in female patients. The difference may be related to the different proportions of

Table 7 Association between pathological type, GSTM1 and smoking index

GSTM1	Smoking index	Pathological type [*n* (%)]				χ^2 value	*P* value*
		Squamous carcinoma	Adenocarcinoma	Small cell carcinoma	Other		
Wide-type	No smoking	7 (26.9)	23 (65.7)	6 (37.5)	5 (38.5)	19.14	0.024
	SI ≤ 200	0 (0.0)	3 (8.6)	1 (6.2)	0 (0.0)		
	SI (200–400)	3 (11.5)	0 (0.0)	1 (6.2)	0 (0.0)		
	SI > 400	16 (61.5)	9 (25.7)	8 (50.0)	8 (61.5)		
Deletion	No smoking	8 (21.1)	30 (65.2)	9 (42.9)	9 (40.9)	20.22	0.017
	SI ≤ 200	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)		
	SI (200–400)	3 (7.9)	3 (6.5)	2 (9.5)	2 (9.1)		
	SI > 400	27 (71.1)	12 (26.1)	10 (47.6)	11 (50.0)		

* χ^2 test

male and female smokers. Approximately 75.7% of men were smokers, while only 11.6% of women were smokers. Approximately 66.3% of men were heavy smokers, in contrast to 0.0% of women who were heavy smokers. Smokers who smoked for more than 30 years accounted for approximately 45.7% of men and 3.6% of women subjects.

Heavy smoking has been strongly associated with the development of squamous carcinoma [31–33]. This explains our study results. In women, second-hand smoke and cooking oil fumes are the most important risk factors, mainly for lung adenocarcinomas [21, 30, 34–35].

Smoking is the known major cause of lung cancer, but only a small proportion of smokers develop lung cancer. This finding suggests the possible involvement of genetic factors. GSTM1 catalyzes the covalent binding of GSH to polycyclic aromatic hydrocarbons. A meta-analysis suggested that the presence of mutated GSTM1 increases the risk of lung cancer [12, 36–38]. However, other studies reported contrasting results [39–41]. This study found that the presence of mutated GSTM1 is associated with the risk of lung cancer. Long-term cigarette smoke exposure damages the airway epithelium, which induces the expression of related factors involved in oxidative stress. GSTM1 is involved in the metabolism of carcinogens, drugs, and ROS. This study reported a synergistic effect between GSTM1 and smoking. Smokers with mutated GSTM1 have a 4.82-fold increased risk of lung cancer compared with nonsmokers carrying functional GSTM1. To further investigate GSTM1 and smoking interaction, a stratified analysis of GSTM1 was conducted. Results showed that the risks of lung cancer increased in patients with both functional GSTM1 and mutated GSTM1 with the increase of smoking time and smoking index. If the smoking time and smoking index are the same, the risk of cancer in patients with mutated GSTM1 is doubled compared with that in patients with functional GSTM1. These results suggest that smokers with deficient-type GSTM1 are more likely to develop lung cancer. In particular, when smoking time is more than 30 years and smoking index is more than 400, the risk of lung cancer in patients with mutated GSTM1 is five times higher than their counterparts.

Several studies have shown that patients with GSTM1 are susceptible to SCLC and AC [23, 42–43]. However, some studies reported contradicting results [44–45]. In our study, GSTM1 is not related to the pathological type of lung cancer. This discrepancy may be relevant to different research populations. Cigarette is a rich source of oxidants and ROS. Deletion of GSTM1 leads to loss of the enzyme's ability to detoxify carcinogens. Hence, smoking, GSTM1, and pathological types were analyzed. After GSTM1 was layered, lung adenocarcinoma accounted for majority of non-smokers. In the smoking population, the proportions of patients with squamous carcinoma have an obvious increase in the number of mutated GSTM1 with the increase of smoking time and smoking index compared with those with functional GSTM1. When smoking time and smoking index are the same, the proportions of patients with squamous carcinoma carrying a mutated GSTM1 are higher than those with functional GSTM1. However, the proportion of patients with other pathological types had no obvious difference after GSTM1 was layered. In other words, the number of cases with mutated GSTM1 is equivalent to that of cases with functional GSTM1 when smoking time and smoking index are the same. This finding suggests that people with mutated GSTM1 are susceptible to squamous cell carcinoma when smoking time is greater than or equal to 30 years and smoking index is greater than 400.

In summary, mutated GSTM1 is associated with lung cancer susceptibility. In particular, smokers carrying deficient-type GSTM1 more easily develop lung cancer, because of the loss of the enzyme's ability to detoxify carcinogens. In addition, with the increase of smoking time and smoking index, respiratory epithelial cells are repeatedly stimulated by carcinogens and ROS produced by cigarettes and are damaged due to the inability to detoxify these carcinogens; hence, smokers with deficient-

type GSTM1 are more likely to develop lung cancer. This result indicates that the occurrence of lung cancer is related to respiratory inflammation.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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ORIGINAL ARTICLE

Vascular endothelial growth factor expression and significance in different grades of the Breast Imaging Reporting and Data System*

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Abstract

Objective Mammography is the only modality proven to reduce mortality in breast cancer, and ultrasonography is a well-known adjunct to mammography screening. The Breast Imaging Reporting and Data System (BI-RADS) classification is a practical tool and is correlated with histopathology and combined use with triple assessment (examination, imaging, and biopsy) of palpable diagnostic cases. This study aimed to investigate the relationship between vascular endothelial growth factor (VEGF) expression and different grades of BI-RADS in breast cancer.

Methods Ninety-six patients with breast carcinoma were evaluated using BI-RADS by ultrasonography, mammography, and a combination of both modalities. In the combined imaging assessment, BI-RADS 1–4a grade was considered when the score of ultrasonography and mammography was lower than 4a, and BI-RADS 4b–5a grade was considered when the score of ultrasonography and mammography was higher than 4a. Immunohistochemical Ultra Sensitive™ S-P method was employed to evaluate the expression of VEGF in 96 patients. Fifty patients with benign breast disease were selected as the control group. The relationship between VEGF expression and different grades of BI-RADS and that between VEGF expression and other standard prognostic parameters associated with invasive breast cancer, such as size, grade, cancer stage, and metastasis were analyzed.

Results The sensitivities of ultrasonography and mammography alone was 74.0% and 84.4%, respectively; However, the sensitivity of their combination increased to 90.6%. The positive rates of VEGF in invasive breast cancer BI-RADS 4b–5 (59/87, 67.8%) were higher than those in BI-RADS 4a (3/9, 33.3%, $P < 0.05$) and benign breast disease tissues (BI-RADS 1–4a, 11/50, 22.0%) ($P < 0.05$). There was a positive correlation between VEGF overexpression and BI-RADS 4b–5, histological grade (III), lymph node metastasis, and distant metastasis of invasive breast cancer. VEGF expression was not related to the age and size of the tumor in each group ($P > 0.05$).

Conclusion There was a positive correlation between VEGF overexpression and BI-RADS 4b–5 grade. The overexpression of VEGF might be an important biological marker for the invasion and metastasis of breast cancer.

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Key words: breast cancer; vascular endothelial growth factor (VEGF); BI-RADS; ultrasonography; mammography

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Breast cancer is the most common form of cancer in women and the second leading cause of death due to malignant disease in women, following lung cancer [1–2]. Recently, there has been an upward trend in the incidence of breast cancer in our country, and it tends to develop at a younger age [3–4]. Furthermore, breast cancer has become one of the most common malignant tumors in women and is therefore one of the most significant threats to a woman's health [3–4]. The American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) classification is a practical tool and has correlation with histopathology and combined uses with triple assessment (examination, imaging and biopsy) of palpable diagnostic cases. Mammography is widely used in the diagnosis and screening of breast cancer and the only modality that has been proven to reduce mortality in breast cancer, and with recent technological advancements, ultrasonography in breast examination plays an important role in breast cancer detection, diagnosis, needle biopsy, and operation method selection [5]. The development of ultrasonography has made the early detection of small lesions in the breast possible, which has been shown to reduce mortality in breast cancer [3, 5]. When the tumor diameter is > 2 mm, new vessels will be generated to provide essential oxygen and nutrition to the tumor [6–7]. New vessels that promote tumor growth and metastasis are controlled by several positive and negative factors [6]. The vascular endothelial growth factor (VEGF), which promotes angiogenesis and proliferation of endothelial cells, exerts an important effect in the genesis, development, metastasis, and recurrence of various tumors. To date, there are few studies on the relationship between VEGF expression and different grades of BI-RADS. This study aimed to evaluate the relationship between VEGF expression and different grades of BI-RADS in breast cancer.

Materials and methods

Patients

Ninety-six patients diagnosed with invasive breast carcinoma were evaluated using the BI-RADS by ultrasonography, mammography, and a combination of both modalities. Complete clinical and follow-up data were confirmed by surgery and pathology (Table 1). We excluded cases in which both ultrasonography and mammography were not performed. Preoperatively, the BI-RADS breast lesions detected by routine ultrasonography and mammography were analyzed. Postoperatively, the breast lesions were diagnosed as benign and malignant lesions according to the pathological results. The ages of the 96 patients diagnosed with breast carcinomas ranged from 28 to 74 years (mean, 46.8 years). All patients underwent excision surgery at Rizhao People's Hospital from January 2016 to December 2018 and were evaluated using BI-RADS by ultrasonography, mammography, and a combination of both modalities. Fifty patients with benign breast disease were included in the control group, with age ranging from 28 to 71 years (mean, 48.8 years).

Table 1 Clinicopathological factors of breast cancer (n = 96)

Clinicopathological factors	n
Age at diagnosis (years)	
≤ 50	39
> 50	57
Tumor size (cm)	
≤ 2	31
> 2	65
Histoligical grade	
I + II	67
III	29
Lymph node metastasis	
Present	61
Absent	35
Distant metastasis	
Present	25
Absent	71

Methods

All 96 patients with invasive breast carcinomas were evaluated using BI-RADS by ultrasonography, mammography, and a combination of both modalities. Patients were divided into two groups based on ultrasonography and mammography findings: ACR BI-RADS 1–4a and 4b–5 groups. If the patient underwent more than one imaging examination before tissue biopsy, the latest imaging result was analyzed. In patients with bilateral biopsies or more than one biopsy in one breast, the most serious result was considered. In the combined imaging assessment, BI-RADS 1–4a grade was considered when the score of ultrasonography and mammography was lower than 4a, and 4b–5 grade was considered the score of ultrasonography and mammography was higher than 4a. The relationship between VEGF expression and different grades of BI-RADS in breast cancer and that between VEGF expression and other standard prognostic parameters associated with invasive breast cancer, such as size, grade, cancer stage, and metastases, were analyzed.

Imaging protocols

Ultrasonograms and mammograms were interpreted by experienced technologists, and the findings were reported by two experienced radiologists based on ACR BI-RADS grades. All ultrasonography examinations included real-time bilateral whole-breast and power Doppler blood flow scans using ultrasound machines (IU Elite Medical System, Philips, USA), with linear probes

measuring 5–12 MHz. Diagnostic mammograms were obtained in standard craniocaudal and mediolateral oblique views by well-trained technologists using digital mammography machines with full-field digital mammograms (Senographe 2000D, GE, USA). Mammography and breast ultrasound findings were classified using the BI-RADS into five grades: BI-RADS 1, breasts where no pathological lesions are seen; BI-RADS 2, benign findings; BI-RADS 3, probably benign findings; BI-RADS 4, lesions suspicious for malignancy; BI-RADS 4, divided into three sublevels of 4a, 4b, and 4c; BI-RADS 5, lesions highly suspicious for malignancy or malignant lesion. A lesion graded lower than BI-RADS 4a is considered a benign lesion, while a lesion graded higher than 4a is considered a malignant lesion.

Pathology

Breast tissue samples were fixed in 10% neutral buffered formalin and embedded in paraffin at 4 °C for 24 h. Tissue sections of 5 μm thickness were deparaffinized and rehydrated using standard procedures. The specimens were examined under a binocular-dissecting microscope. The pathological diagnosis was independently verified by two pathologists using histological methods, and pathological grading was determined according to the current 2012 World Health Organization classification system (WHO 2012) [6]. Immunoreactions were processed to detect VEGF expression in 96 patients using the Ultra SensitiveTM S-P Kit (Maixin-Bio, China) according to the manufacturer's instructions, and signals were visualized using the DAB substrate, which stains the target protein yellow. Negative controls were used. The primary antibody was replaced with PBS containing 0.1% bovine serum albumin at the same concentration as the primary antibody. The positive controls were tissues known to express the antigen being studied. VEGF was localized in the cytoplasm and membrane. Cells were classified according to the positive rate and color intensity as follows: negative, number of positive cells < 25%; positive, brown particles, number of positive cells ≥ 25%. The pathological reading was determined for each biopsy slide with an overall pathological diagnosis determined for each subject. The tumor grade was determined according to the modified Bloom-Richardson score. Fifty patients with benign breast disease were included in the control group.

Statistical analysis

SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Enumeration data were analyzed using the chi squared (χ^2) test. A P value < 0.05 was considered statistically significant.

Table 2 Results of BI-RADS assessments of different breast cancer detection methods

BI-RADS assessment	No. of patient		Total
	1–4a	4b–5	
Mammography alone	15	81	96
Ultrasonography alone	25	71	96
Combination*	9	87	96

*Combined mammography and ultrasonography: BI-RADS 1–4a grade was considered when the score of mammography and ultrasonography was lower than 4a, and 4b–5a category was considered when the score of mammography and ultrasonography was higher than 4a

Results

BI-RADS finding

The sensitivity of ultrasonography alone was 74.0%, and that of mammography alone was 84.4%. However, the sensitivity of the combination of ultrasonography and mammography increased to 90.6% (Table 2). Factors such as tumor edge, contrast mode, lobular sign, prick sign, vascular distortion, skin thickening in areola area, and score of elastography were related to the benign and malignant features of breast lesions (Table 3). High BI-RADS grade on ultrasonography was often indicated by breast hypoechoic mass, heterogeneous internal echo, punctate calcification with strong echo and unclear boundary irregular margin, and lobular sign. Elastography showed that the tubercle was hard. Color Doppler flow imaging (CDFI) showed blood flow signal in the border area of the nodule or short rod blood flow signal in the mass (Fig. 1). High BI-RADS grade on mammography was indicated by breast mass, irregular margin, lobular sign, prick sign, vascular distortion, nipple depression, and skin thickening in areola area (Fig. 2).

VEGF expression in different BI-RADS grade groups

The positive rates of VEGF in invasive breast cancer BI-RADS 4b–5 (59/87, 67.8 %) were higher than those in breast cancer BI-RADS 4a (3/9, 33.3%) and benign breast disease tissues (BI-RADS 1–3, 11/50, 22.0%) (P < 0.05) (Table 4). There was a positive correlation between VEGF overexpression and BI-RADS 4b–5 (P < 0.05).

Relationship between VEGF expression and clinicopathological parameters

The positive rates of VEGF in invasive breast cancer were 64.6% (62/96), which were higher than those in benign lesion tissues (22.0%, 11/50) (P < 0.05) (Table 5). There were significant differences in the VEGF expression between histological invasive breast cancer groups with lymph node metastasis, distant metastasis, and recurrence and those without (P < 0.05). There was a positive correlation between VEGF overexpression and

Table 3 BI-RADS findings in patients with breast cancer (n = 96)

Groups	Total
Ultrasonography	
Mass Echo homogeneous	
Yes	23
No	73
Boundary clear	
Yes	52
No	44
Ring strong echo around the mass	
Yes	21
No	75
Edge regular	
Yes	29
No	67
Peripheral tissue echo slight	
Yes	31
No	65
CDFI short rod blood flow signal in the mass	
Yes	49
No	47
Elastic imaging showed that the tubercle was hard	
Yes	18
No	78
Mammography	
Breast mass	
Yes	77
No	19
Edge regular	
Yes	17
No	79
Margin clear	
Yes	23
No	73
Lobular sign	
Yes	47
No	49
Prick sign	
Yes	28
No	68
Vascular distortion	
Yes	34
No	62
Nipple depression	
Yes	31
No	65
Skin thickening in areola area	
Yes	28
No	68

histological grade III, lymph node metastasis, and distant metastasis in invasive breast cancer. However, there was no significant difference in VEGF expression with respect to age (≤ 50 years *vs* > 50 years) and tumor diameter (≤ 2 cm *vs* > 2 cm) (P > 0.05).

Discussion

Breast cancer is one of the most common malignant tumors, and its morbidity rate is increasing annually [8]. The overall BC incidence has been increasing in China, with an earlier age of onset compared with Western countries and a peak incidence rate at age 50 years [9]. Early detection, diagnosis, and treatment play an important role in the prognosis of breast cancer [10]. As a result, numerous studies worldwide have sought to determine the most effective strategies to conduct early diagnosis, treat breast cancer, assess therapeutic effects, correctly evaluate prognosis, and identify postoperative recurrence in patients. Imaging examination is important in the detection and diagnosis of breast cancer [11]. The ACR BI-RADS classification is a practical tool and has correlation with histopathology and combined uses with triple assessment (examination, imaging, and biopsy) of palpable diagnostic cases. The BI-RADS was established by the ACR to standardize mammographic reporting in 2003 [12]. Five levels are included in the BI-RADS, and level 4 is divided into three sublevels: 4a, 4b, and 4c. A lesion categorized as lower than 4a is considered a benign lesion, while a lesion categorized higher than 4a is considered a malignant lesion. The ACR BI-RADS provides standardized descriptors of imaging features of breast lesions, is helpful in predicting benign or malignant potential, and can be used globally. Mammography is an accurate, relatively inexpensive, and convenient technique; therefore, it is an important method used in the diagnosis of breast cancer. Mammography is the only modality that has been proven to reduce mortality in breast cancer [3], and ultrasonography is a well-known adjunct to mammography screening [5]. Routine mammography and sonographic manifestations of BI-RAD 4 breast lesions tend to have a certain degree of overlapping and are sometimes difficult to assess [13]. Thus, it is difficult to identify the nature of such lesions in the clinic. In our study, the sensitivity of detection using mammography was 84.4%, and that of ultrasonography was 74.0%; however, the sensitivity detection using the combination of ultrasonography and mammography increased to 90.6%. Our results reveal that the characteristics of irregular margin, lobular sign, prick sign, vascular distortion, nipple depression, and skin thickening in the areola area are important early signs of breast cancer and may sometimes be the sole sign of malignancy. Our study showed that the tufted apical calcification detection rate can be further improved by mammography than ultrasonography, and mammography is regarded the gold standard for the detection and characterization of microcalcifications. However, the marked improvement of current high-frequency transducer technology has yielded high spatial resolution, allowing better and

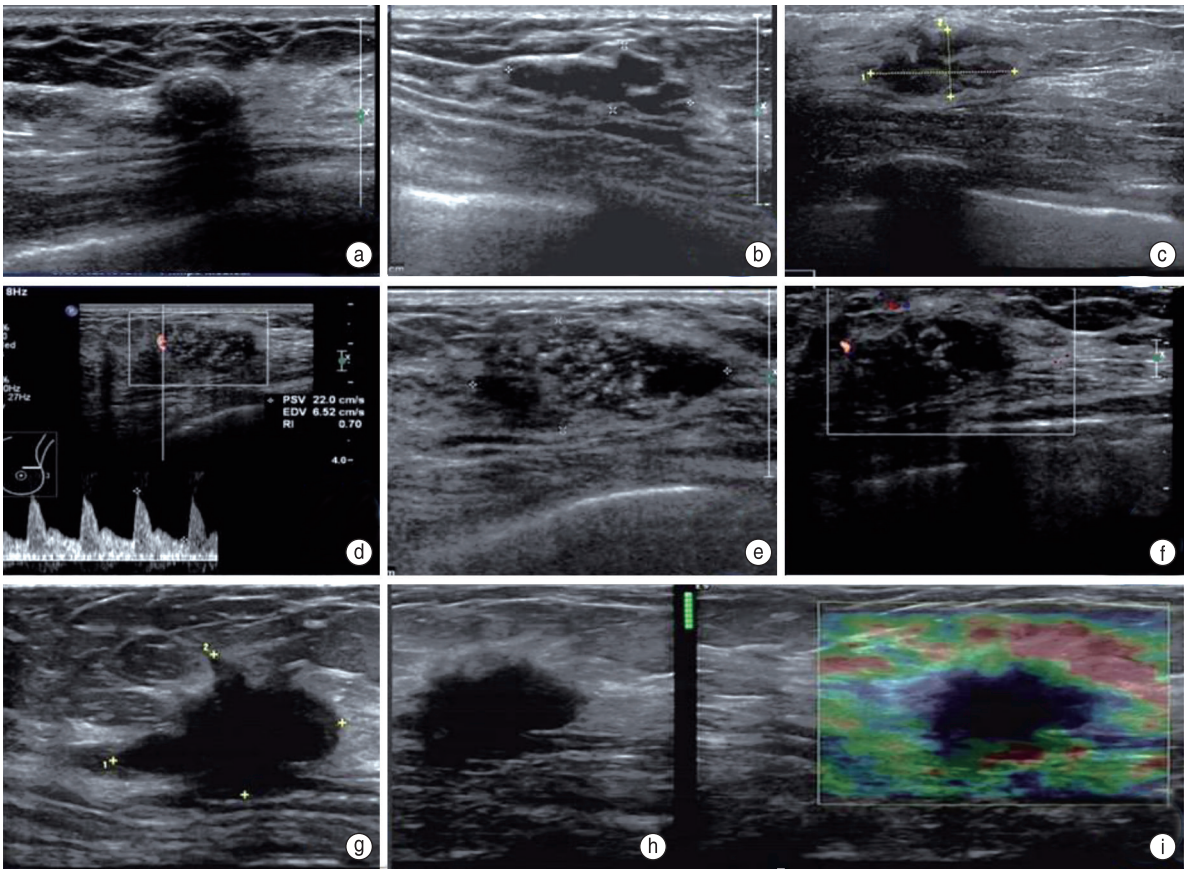

Fig. 1 BI-RADS on ultrasonography. (a) BI-RADS 3 (benign lesion). The echo inside the mass was not homogeneous, boundary was still clear, and ring echo around the mass was strong; (b) BI-RADS 4a (benign lesion). The internal echo of the mass was not homogeneous and the boundary was still clear, but the edge was irregular; (c) BI-RADS 4b (invasive ductal carcinoma II). The echo inside the mass was not homogeneous, boundary was not clear, edge was irregular, and echo behind the mass was weak; (d, e, and f) BI-RADS 4c (invasive ductal carcinoma III with ductal carcinoma in situ). Hypoechoic mass, heterogeneous internal echo, punctate calcification with strong echo, and unclear boundary were observed. CDFI showed short rod blood flow signal in the mass; (h and i) BI-RADS 5 (invasive ductal carcinoma II). The shape of the nodule was irregular, edge was not smooth, burr sign was visible, internal echo was weak, punctate strong echo was visible, signal behind the nodule was attenuated, and surrounding gland structure was twisted. Elastography showed that the tubercle was hard. CDFI showed the blood flow signal in the border area of the nodule

more frequent visualization of breast microcalcifications [3]. Calcification within the breast and simple clustered calcification are important early signs of breast cancer and may sometimes be the sole sign of malignancy [3]. In this study, high BI-RADS grade on ultrasonography was often indicated by breast hypoechoic mass, heterogeneous internal echo, punctate calcification with strong echo and unclear boundary irregular margin, and lobular sign. Elastography showed that the tubercle was hard. CDFI showed blood flow signal in the border area of the nodule or short rod blood flow signal in the mass.

However, even after curative resection, tumor recurrences are likely to assume different forms in various organs. The prediction of risks for recurrences and recurrence patterns after surgery could help the development of better follow-up programs and appropriate treatment strategies for patients with breast cancer. Additionally, the prognosis after resection has remained unsatisfactory due to a high incidence of cancer lymph node metastases and cancer recurrence. The identification of variables in breast tumor biology may lead to a more precise assessment of outcome and response to therapy. The development of prognostic markers that can accurately predict outcome is crucial in identifying patients who could benefit from aggressive therapy. VEGF, one of the key factors to promote tumor angiogenesis and with the strongest function and highest specificity, can not only promote the proliferation of endothelial cells but also regulate and participate in angiogenesis. Due to an intimate association with genesis, development, metastasis, and infiltration of breast cancer, it is an important indicator in evaluating metastasis and infiltration of breast cancer in the clinic.

In our study, the positive rates of VEGF in breast

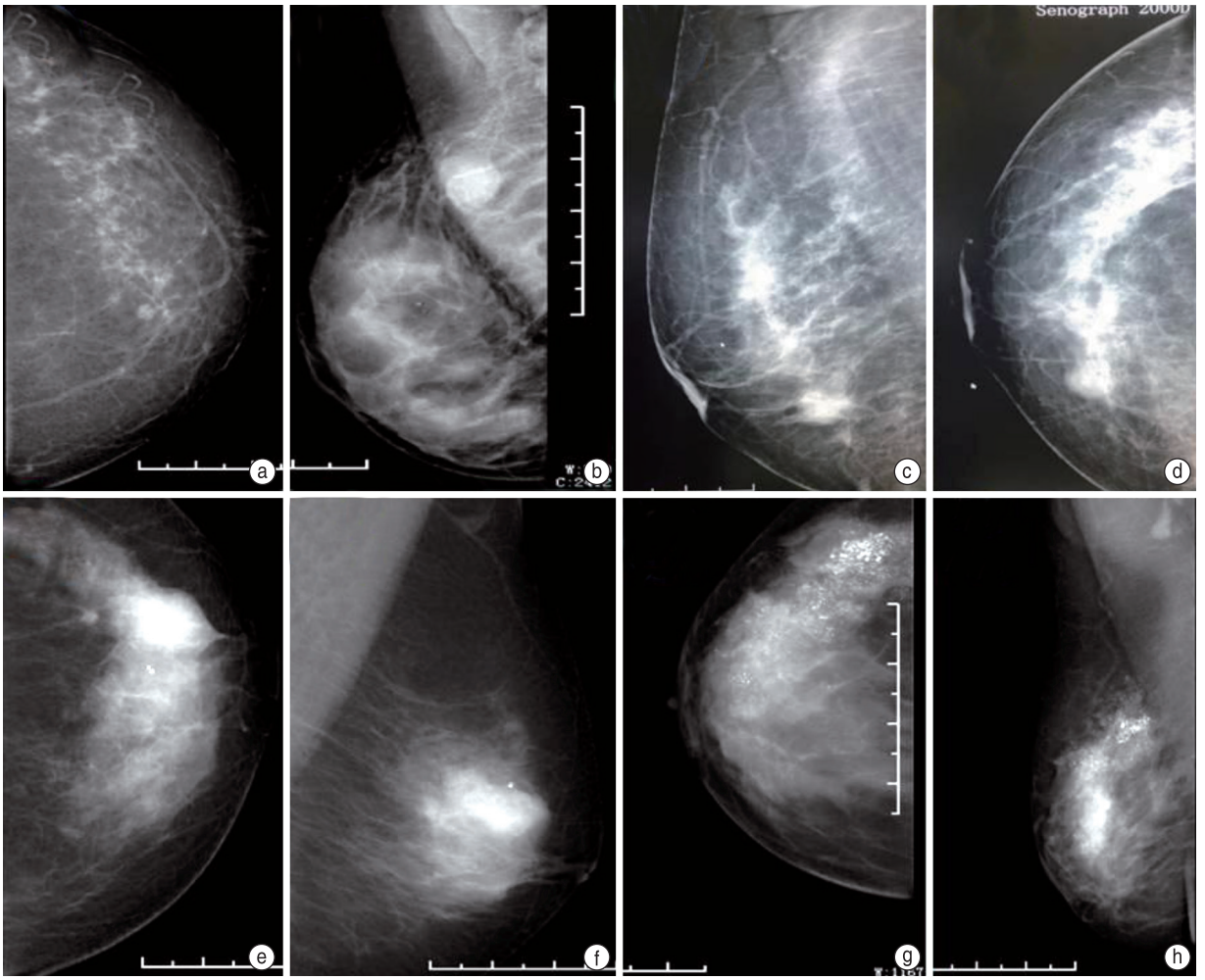

Fig. 2 BI-RADS on mammography. (a) BI-RADS 3 (benign lesion), CC, the boundary of the mass was clear; (b) BI-RADS 4a (benign lesion), MLO, there was a nodule near the pectoralis major muscle in the upper right breast with clear margin; (c and d) BI-RADS 4b (invasive ductal carcinoma II), (c) CC and (d) MLO. Inferior intramammary nodule, unclear margin, and lobular sign; (e and f) BI-RADS 4c (invasive ductal carcinoma II), (e) CC and (f) MLO. Left lateral superior breast nodule, uneven density, unclear margin, and visible lobular sign; (g and h) BI-RADS 5 (invasive ductal carcinoma III), (g) CC and (h) MLO. The density of the right breast was obviously increased, the margin was unclear, and there was scattered cluster needle tip calcification

Table 4 VEGF expression of in different BI-RADS groups (n = 96)

Pathologic diagnosis	BI-RADS groups	VEGF express		Total
		–	+	
Invasive carcinoma	4b–5	28	59	87
	4a	8	3	9
Benign leisions	1–3	39	11	50

Table 5 VEGF expression in different groups

Groups	VEGF express		Total
	–	+	
Breast carcinoma	34	62	96
Benign breast leisions	39	11	50

cancer were higher than those in benign lesion tissues, and there were significant differences in the VEGF expression between histological breast cancer groups with lymph node metastasis, distant metastasis, and recurrence and those without. These research results revealed that the VEGF expressions in the patients with lymph node metastasis were markedly higher than those without lymph node metastasis, and the difference was statistically significant. The results suggested that, with increasing pathological stage, the VEGF levels in the observation group gradually increased, and the statistical significance was remarkable. In the study, significantly higher VEGF expression was found in tumors with lymph node metastasis, advanced stage, and recurrence. When tumors were divided into grade I–II and grade III, high VEGF expressions were also significantly associated with advanced grade (III). However, there was no difference in the VEGF expressions with respect to age at diagnosis

(≤ 50 years *vs* > 50 years) and tumor size (≤ 2 cm *vs* > 2 cm). Additionally, our studies suggested that the positive rates of VEGF in invasive breast cancer BI-RADS 4b–5 were higher than those in breast cancer BI-RADS 4a and benign breast disease tissues (BI-RADS 1–3). There was a positive correlation between VEGF overexpression and BI-RADS 4b–5. VEGF that is capable of promoting angiogenesis exerts an important effect in the processes of genesis, development, metastasis, and recurrence of various tumors. In the process of tumor genesis and development, tumor regenerative capillaries capable of providing nutrients to tumor cells and favorable conditions for distal metastasis are the precondition to induce local growth, infiltration, and distal metastasis of malignant tumors; hence, how to inhibit tumor angiogenesis is a new research hotspot at present [14]. Due to the intimate association between genesis, development, metastasis, and infiltration of breast cancer, VEGF is an important indicator of metastasis and infiltration of breast cancer in the clinical setting. However, further study is needed to understand the exact pathogenic mechanism.

Conclusion

Our results reveal that there is a positive correlation between VEGF overexpression and BI-RADS 4b–5 in breast cancer. Increased VEGF expressions are associated with tumor progression, invasion, and metastasis. The overexpression of VEGF might be an important biological marker for invasion, metastasis, and poor differentiation, especially in higher-grade lesions and metastatic disease.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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ORIGINAL ARTICLE

The expression of miR-155 and miR-181 in gastric cancer and their effects on clinical parameters and prognostic value*

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Abstract

Objective The aim of this study was to investigate the expression and clinical significance of miR-155 and miR-181 in gastric cancer.

Methods Sixty-eight patients with gastric cancer and 80 healthy volunteers were selected as subjects. Serum samples of patients and volunteers were collected to detect miR-155 and miR-181 expression levels in serum and tumor tissues.

Results miR-155 and miR-181 serum levels were significantly higher in patients with gastric cancer than those in the control group ($P < 0.05$). miR-155 and miR-181 expression levels in gastric cancer tissues were 16.74 ± 4.29 and 12.17 ± 3.26, respectively and 3.42 ± 0.39) and 3.06 ± 0.69 in paracancerous tissues, respectively, and they were 1.22 ± 0.21 and 1.08 ± 0.35 in normal tissues, respectively. miR-155 and miR-181 expression levels in cancer tissues were significantly higher than adjacent tissues, and they were lowest in normal tissues ($P < 0.05$). High miR-155 and miR-181 expression had significant effects on differentiation, T stage, lymph node metastasis, and clinical stage ($P < 0.05$). Cox multivariate analysis showed that onset, T stage, clinical stage, differentiation degree, lymph node metastasis, miR-155, and miR-181 were independent risk factors for prognosis of patients with gastric cancer.

Conclusion Serum miR-155 and miR-181 have a diagnostic value in gastric cancer, and they are strong signals of poor prognosis.

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Key words: miR-155; miR-181; gastric cancer; tumor markers

China has one of the highest gastric cancer incidences in the world, with an average annual mortality of 150,000 people. Its overall 5-year survival rate is still unsatisfactory [1–2]. Until now, effective molecular markers for screening, early diagnosis, and prognosis judgment of the population at a high-risk for gastric cancer are still limited despite molecular biology studies that found a large number of abnormal molecular events during gastric carcinogenesis and progression [3]. miR-155 and miR-181 are highly conserved and widely distributed in many animals. Previous studies found that miR-155 and miR-181 play important roles in tumor and nervous system diseases [4]. There are few studies on the combined detection of miR-155 and miR-181 in gastric cancer patients. This study aimed to explore the expression of miR-155 and miR-181 in gastric cancer, their impact on clinical case parameters, and their prognostic value.

Materials and methods

Research subjects

Sixty-eight patients with gastric cancer admitted to our hospital were selected as the study subjects, including 43 males and 25 females aged between 42 and 76 years old. Inclusion criteria were as follows: (1) Gastric cancer was definitively diagnosed by pathology. (2) First diagnosis. (3) Preoperative treatment included radiotherapy and chemotherapy. (4) The clinical data and follow-up data are complete. Exclusion criteria were as follows: (1) Malignant tumors with other systems. (2) Compliance was poor, and the patients dropped out during follow-up. (3) Death in hospital. (4) The patient had received anti-tumor treatments such as radiotherapy or chemotherapy before surgery. Meanwhile, patient clinical data were

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collected and followed up. We collected samples from healthy check-up individuals in our hospital at the same time as the patients. After describing the purpose and significance of the study to the patients in detail, the volunteers gave blood samples with voluntary consent. A total of 80 volunteers were enrolled in the study, including 54 males and 26 females with an average age of 36 to 72 years.

Sample collection

(1) Gastric cancer tissue specimens: target tissue specimens included paracancerous tissue, non-necrotic cancer focus, and normal mucosal tissue. Samples were placed in an EP tube pre-loaded with RNA later™ solution and stored at -80 °C until later. (2) Peripheral blood samples: 4 mL peripheral blood samples were collected from patients with gastric cancer and healthy volunteers. The supernatant was centrifuged for 10 min at 3000 rpm at 4 °C. The supernatant was collected and stored in an EP tube without RNA enzyme. Patients did not receive radiotherapy or chemotherapy before tissue and blood samples were collected.

Detection of miR-155 and miR-181 expression levels

Trizol Reagent was purchased from Invitrogen (USA), and reverse transcription kits and eDNA amplification kits were purchased from MBI Fermentas. qRT-PCR reagents were purchased from BioRad Company (USA). Total RNA in serum and tissues was extracted according to the manufacturer's instructions. Cellular RNA was reverse transcribed into DNA and amplified in a qPCR reaction. All steps were performed strictly according to the reverse transcription kit and amplification kit instructions. The miR-155 primer sequences were as follows: 5'-CTGTAT-CAAAAGCCAACTGAA-3', downstream, 5'-GTGTCTATCCT-TATGAATCGCCA-3', upstream 5'-GGGGAAACTACTTGTCCTT-3', and downstream 5'-TCGTATCCAGTGCGTCGT-3', with GAPDH as an internal reference. All primers were synthesized by Shanghai Biotechnology Co. Ltd. (China). The reaction conditions of RT-PCR were as follows: pre-denaturation at 95 °C for 10 min, denaturation at 95 °C for 30 s, annealing at 50 °C for 30 s, and extension at 70 °C for 40 cycles, and a final extension at 70 °C for 10 min. The amplified products were measured using 1% agarose gel electrophoresis and gel imaging analysis system.

Follow-up

All patients with gastric cancer were followed up by telephone or outpatient follow-up to understand postoperative complications, recurrence, and survival. The follow-up deadline was January 2019, and the median follow-up time was 33 months (2–63 months). The end point for follow-up was death or deadline.

Statistical analysis

All data were processed using the SPSS20.0 software package. The counting data were expressed using frequency and rate, and statistical inferences were tested using a chi-square test. The measurement data were expressed using mean + SD, and statistical inferences were tested using a t test. The Cox risk model was used to analyze the risk factors affecting patient prognosis. The test level was $\alpha = 0.05$.

Results

Expression of miR-155 and miR-181 in serum

Compared with healthy volunteers, the levels of miR-155 and miR-181 in the serum samples of patients with gastric cancer were significantly higher ($P < 0.05$; Table 1).

Expression of miR-155, miR-181 in gastric cancer and paracancerous tissues

The expression levels of miR-155 and miR-181 in gastric cancer tissues were 16.74 ± 4.29 and 12.17 ± 3.26, respectively, 3.42 ± 0.39 and 3.06 ± 0.69 in paracancerous tissues, and 1.22 ± 0.21 and 1.08 ± 0.35 in normal tissues. miR-155 and miR-181 expression was significantly higher in cancerous tissues than in paracancerous tissues, and it was lowest in normal tissues ($P < 0.05$).

Influence of miR-155 and miR-181 expression

The patients were divided into the high expression group and low expression group based on the mean of miR-155 and miR-181 expression levels. The results showed that the high expression of miR-218 and miR-181 had significant effects on differentiation, T stage, lymph node metastasis, and clinical stage ($P < 0.05$; Table 2).

Analysis of risk factors affecting patient prognosis

Cox multivariate analysis found that T stage, clinical stage, degree of differentiation, lymph node metastasis, and high expression of miR-155 and miR-181 were independent risk factors for prognosis of patients (Table 3).

Table 1 Expression of miR-182, miR-618 and tumor markers in serum

Index	Esophageal cancer group (n = 68)	Volunteer group (n = 80)	t	P
miR-182	7.73 ± 11.58	1.04 ± 0.89	5.152	0.000
miR-618	5.69 ± 1.16	0.76 ± 0.92	28.821	0.000

Table 2 Effects of expression of miRNA-155 and miRNA-181 on clinicopathological parameters

Index	miR-155		χ^2	*P*	miR-181		χ^2	*P*
	Low expression (*n* = 32)	High expression (*n* = 36)			Low expression (*n* = 32)	High expression (*n* = 36)		
Gende			0.387	0.534			0.272	0.602
Female	19	24			20	23		
Male	13	12			10	15		
Age (years)			0.165	0.684			0.103	0.748
< 60	18	22			17	23		
≥ 60	14	14			13	15		
Tumor size (cm)			3.032	0.082			3.743	0.053
< 5	25	21			24	22		
≥ 5	7	15			6	16		
Differentiation degree			5.903	0.015			15.270	0.000
High and middle differentiation	21	13			23	11		
Poorly differentiated	11	23			7	27		
T stage			7.072	0.008			7.070	0.008
T1–2	21	12			20	13		
T3–4	11	24			10	25		
Lymphatic metastasis			9.894	0.002			7.070	0.008
No	22	11			20	13		
Yes	10	25			10	25		
Clinical stages								
I, II	26	15			24	17		
III, IV	6	21			6	21		

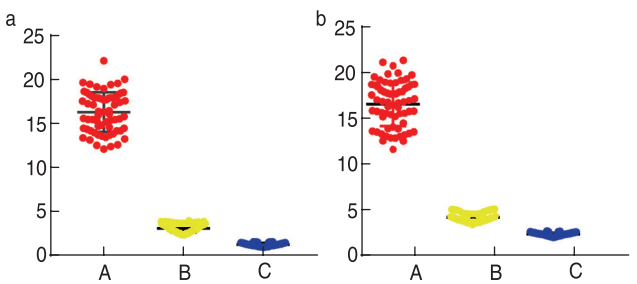

Fig. 1 (a) expression level of miR-155 in gastric cancer tissues and paracancerous tissues; (b) expression level of miR-181 in gastric cancer tissues and paracancerous tissues. A: gastric cancer tissue; B: paracancerous tissue; C: normal tissue.

Discussion

In recent years, increasing examples of abnormal miRNA expression have been found in gastric cancer. These include up-regulation of miRNAs such as miR-21, miR-192, and miR-106, which can promote the proliferation, invasion, and metastasis of cancer cells or down-regulation of miRNAs such as miR-375 and miR-203, which can inhibit the cell cycle and promote cancer cell apoptosis. However, there are few studies on the prognosis of gastric cancer using miR-155 and miR-181 [5–6]. miR-155 was shown to have a role in hematopoiesis based on the observation that it is overexpressed in some B-cell lymphomas [7]. Proviral integration by virus activates a gene called "BIC," or B-cell integration cluster, which encodes miR-155 in a gene that generates a fully spliced and polyadenylated transcript [8–9]. miRNA-181 is

Table 3 Analysis of risk factors affecting patient prognosis

Index	β	SE	Wald	*P*	RR	95.0% CI
Differentiation degree	0.573	0.389	2.175	0.140	1.774	0.828–3.799
T stage	0.832	0.377	4.876	0.027	2.297	1.098–4.805
lymphatic metastasis	0.775	0.360	4.624	0.032	2.170	1.071–4.397
clinical stages	0.588	0.242	5.907	0.015	1.800	1.120–2.891
miR-155	0.381	0.096	15.786	0.000	1.464	1.213–1.767
miR-181	0.684	0.219	9.785	0.002	1.982	1.291–3.042

an extremely conserved star molecule in evolution. miR-181 family members in the human genome include miR-181a-1, miR-181a-2, miR-181b-2, miR-181b-2, miR-181c, and miR-181d [10]. miR-181 was first discovered in mouse B lymphocytes, and it can regulate the formation of the early hematopoietic system. These characteristics have attracted research attention [11]. miR-181 is highly expressed in the mouse thymus, brain, lung, and other organs. Its presence was also detected in bone marrow and spleen, but its expression was low in hematopoietic progenitor cells [12]. Among them, miR-181a is considered to be involved in the differentiation and maturation of B cells.

In this study, we found that the serum levels of miR-155 and miR-181 were significantly higher in patients with gastric cancer than in normal controls. This indicates that there is an abnormality in serum miRNA levels in patients with gastric cancer, and this is also the basis for the early diagnosis using miRNAs such as miR-155 and miR-181. Further, we detected the expression of miR-155 and miR-181 in cancer tissues. The results showed that the expression levels of miR-155 and miR-181 were significantly higher in cancer tissues than in adjacent tissues, and they were lowest in normal tissues. This suggests that miR-155 and miR-181 may be involved in the occurrence and development of gastric cancer, and also indicates that miR-155 can act as an oncogene in gastric cancer. Since the mechanism of the action of miR is to inhibit their function by binding to the target RNA, the overall biological effects of miR depend on the sum of different genes regulated by miRNAs [13–14]. Therefore, the same miRNA can exert different biological effects in different tumors. In addition, the differences in detection methods and heterogeneity in cancer patients are also reasons for the different biological effects of miRNAs. Cox multivariate analysis showed that T stage, clinical stage, differentiation degree, lymph node metastasis, miR-155, and miR-181 were independent risk factors for prognosis of patients with gastric cancer. These results suggest that miR-155 and miR-181 have significant adverse effects on the prognosis of patients, and can be used as one of the indicators to judge the prognosis of patients.

In summary, in this study, we found that serum levels of miR-155 and miR-181 have a diagnostic value for gastric cancer. The expression of miR-155 and miR-181 in tumor tissues increased significantly, which is a strong signal of poor patient prognosis. However, the sample size of this study is small. In future, a multi-center study having a larger sample size will be carried out to obtain further evidence.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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ORIGINAL ARTICLE

Value of partial hepatectomy for the treatment of hilar cholangiocarcinoma: a Meta-analysis study*

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Abstract

Objective To discuss the value of partial hepatectomy in patients with hilar cholangiocarcinoma.

Methods English articles related to hilar cholangiocarcinoma were screened from January 1, 1990 to May 12, 2019 in the PubMed, MEDLINE, EMBASE, and Cochrane Library databases. Information on postoperative radical cure, survival, morbidity, and mortality after surgery were extracted from articles that met the inclusion criteria for the meta-analysis.

Results Twenty-two articles that met the inclusion criteria were classified into 4 study groups: the hepatectomy radical cure group (19 articles), the hepatectomy survival group (16 articles), the hepatectomy morbidity group (9 articles), and the hepatectomy mortality group (17 articles). We found that the rate of radical cure after partial hepatectomy (odds ratio [OR] 0.32, 95% confidence interval [CI] 0.20–0.51) and the survival rate (hazard ratio [HR] 0.67, 95% CI 0.58–0.79) were significantly higher than after simple bile duct resection, but that morbidity (OR 1.99, 95% CI 1.37–2.90) and mortality (OR 2.71, 95% CI 1.47–4.98) in patients within the partial hepatectomy group were also higher than in the simple bile duct resection group, taking into account the significant heterogeneity in the articles pertaining to the hepatectomy radical cure group (I^2 = 68.3%, P = 0.000), a sub-group analysis was subsequently conducted. Its results showed that when the branches of the secondary bile ducts were not involved during hilar cholangiocarcinoma, then a bile duct resection had a similar radical cure outcome as combined partial hepatectomy (OR 0.94, 95% CI 0.54–1.65).

Conclusion Partial hepatectomy can increase the proportion of radical cure in patients with hilar cholangiocarcinoma and extend the survival time after surgery. However, the morbidity and mortality after surgery are higher than those in simple bile duct resections. Therefore, simple bile duct resection is still a relevant and efficient tool in the treatment of Bismuth-Corlette Type I and II hilar cholangiocarcinomas.

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Key words: hilar cholangiocarcinoma; partial hepatectomy; prognosis; meta-analysis

Hilar cholangiocarcinoma (HCCA) is a malignant cancer that arises in the biliary confluence. These types of tumor were first described by Gerald Klatskin in 1965 [1] and designated as Klatskin tumors. Surgical resection of HCCA tumors remains a profound surgical challenge because of its biological characteristics and anatomical location. It is thought that the optimal surgical treatment for HCCA should not be limited to the reconstruction of the biliary drainage system, but also to completely excise the tumor, to minimize surgical trauma, reduce liver damage and incidence of postoperative complications and mortality. Combined hepatectomy can expand the scope of resection and increase the likelihood of complete tumor resection. However, it does have an associated risk of postoperative liver failure.

Due to the low incidence of HCCA and the challenges in its treatment, there is still a lack of large sample studies on the postoperative radical effects, long-term prognosis, postoperative complications, and surgical death after combined partial hepatectomy. Several issues remain unanswered such as whether the combination of partial liver resection prolongs the postoperative survival period and improves the postoperative radical cure rate or whether the surgical trauma increases postoperative

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complications and mortality.

The purpose of this study is to explore the effects of different surgical resections by analyzing all current available literature, and to provide evidence-based medical data on the effectiveness of surgical treatments for HCCA.

Methods

Literature search

Studies were identified through a search of PubMed, MEDLINE, EMBASE, and Cochrane Library databases using the following retrieval formula: "hilar cholangiocarcinoma" or "Klatskin tumor". The search included articles ranging from January 1st 1990 to May 12th 2019. The language of the articles was restricted to English. References and reviews were manually searched to detect additional studies.

Inclusion criteria

The systematic review generated a complete database from the published studies by analyzing the prognosis of patients with HCCA treated by bile duct resection with or without partial hepatectomy. Eligible studies met the following inclusion criteria: the subject of the study included patients with HCCA; all patients underwent surgical treatment; data included a prognosis analysis in patients with HCCA who underwent bile duct resection with or without combined partial hepatectomy (prognosis included at least one of four indexes: radical resection, long-term survival, postoperative complications and short-term mortality); hazard ratio (HR) and 95% confidence interval (CI) for survival were included according to patients' survival status, either reported or extrapolated from the original data; in the case of patient duplication, the most recent report or the most informative report was included; and, finally, study quality with > 5 stars were included, according to the Newcastle-Ottawa quality assessment scale [2].

The exclusion criteria were as follows: prognostic effects were evaluated by a recurrence rate; prognosis of a single surgical treatment was reported without the inclusion of a control group; or letters, reviews, case reports, conference abstracts, editorials, and expert opinions.

Data extraction

Two investigators (Liu JL and Yang M) reviewed all articles. Data were extracted independently by two investigators (Liu JL and Chen JH) using a data extraction sheet. Data included the name of the first author, year of publication, ethnic origin of patients, number of patients, bile duct resection with or without combined partial hepatectomy, Bismuth-Corlette classification of patients undergoing different surgical procedures, number of radical resections, survival data (HR and 95% CI), number of postoperative complications and postoperative short-term mortality. When data was conflicting, the two data extractors would jointly resolve the problem.

Assessment of study quality

Study quality was assessed independently by two investigators (Liu JL and Chen JH), according to the Newcastle-Ottawa quality assessment scale. Briefly, the overall star system assesses three main categories: selection of cohort, comparability of cohort, and ascertainment of outcome. A study is awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. The total number of stars was evaluated, with higher stars reflecting higher methodological quality. A single study can be awarded a maximum of nine stars.

Statistical analysis

In this study, the odds ratios (OR) and 95% confidence intervals (CI) were used to evaluate the outcomes of the different surgical procedures on radical resection, postoperative complications and short-term mortality in patients with HCCA. HR and 95% CI were used to estimate the impact of different surgical procedures on survival. A HR below 1 was attributed when the survival time for the combined hepatectomy group was longer than for the bile duct resection group. Otherwise, the HR value was calculated using the formula: exp (LN (HR)).

When data for HR and 95% CI was not available, an estimated value was derived indirectly from the Kaplan-Meier curves using the previously described method by Tierney *et al* [3]. Kaplan-Meier curves were analyzed using the Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) to retrieve the survival data, and the obtained values were entered in the spreadsheet appended in Tierney's publication [3]. This work was performed by two independent researchers to increase the accuracy of the extracted survival rates.

To assess heterogeneity among the studies, we used the Cochran Q and I^2 statistics. For the Q statistic, a P value < 0.10 was considered statistically significant [4]. The random effects model was calculated according to the DerSimonian-Laird method [5]. Otherwise, the fixed-effects model (Mantel-Haenszel method) was used. For I^2, a value > 50% was considered a measure of severe heterogeneity [6]. For groups presenting with high heterogeneity, the source of heterogeneity was analyzed by single factor meta-regression analysis, and the subgroup analysis was carried out according to the source of heterogeneity. The funnel plot and Egger test were used to evaluate publication bias. A significant two-

way P value for comparisons was defined as $P < 0.05$.

Literature Selection

A total of 1376 potentially relevant citations were retrieved after an initial database search. An additional 55 studies were found from the reference list of the articles and reviews or after a manual search of the journals. These were duplicates from the database search studies. Titles and abstracts of all relevant articles were read by two independent researchers (Liu JL and Yang M). One thousand and fourteen studies were excluded from the analysis after initial screening based on abstract or title, with a remaining 219 going through further full-text review. After applying the inclusion criteria, 197 studies were excluded. The final 22 studies fulfilled the inclusion criteria [7-28] and were subdivided into 4 study groups: the hepatectomy radical cure group (19 articles) [9–20, 22–28], the hepatectomy survival group (16 articles) [7–8, 10–13, 15–16, 19-21, 23-27], the hepatectomy morbidity group (9 articles) [9, 14–16, 19–20, 23, 26–27] and the hepatectomy mortality group (17 articles) [9,11–20, 22–24, 26–28] (Fig. 1).

Methodological quality of the studies

For all included studies, two researchers independently extracted the data and assessed the methodological quality using the Newcastle-Ottawa quality assessment scale. The scores are shown in Table 1. The studies included in our meta-analysis showed a high level of methodological quality (> 5 stars on the Newcastle-Ottawa scale).

Assessment of heterogeneity

The Q test and I^2 test were used to assess the heterogeneity between the study groups. We found that the hepatectomy survival group (I^2 = 41.7%, P = 0.041), the hepatectomy morbidity group (I^2 = 0.0%, P = 0.772), and the hepatectomy mortality group (I^2 = 0.0%, P = 0.979) did not show significant heterogeneity, unlike the hepatectomy radical cure group (I^2 = 68.3%, P = 0.000), which showed a significant heterogeneity.

Single factor meta-regression was used to investigate the source of heterogeneity in the hepatectomy radical cure group. Three factors were investigated: the ethnic origin of the patients (Asian or other), the year of publication (before or after 2005), and whether the indication of hepatectomy was explicitly outlined. Following single factor meta-regression analysis, we found that the indication of hepatectomy according to the Bismuth-Corlette classification was an important factor affecting heterogeneity (P = 0.007). According to these results, a subgroup analysis was further performed on the indications of hepatectomy.

Results

Meta-analysis for the hepatectomy radical cure group

In the 19 articles included in this group, a total of 2139 patients with HCCA were analyzed including 1648 patients who underwent combined partial hepatectomy

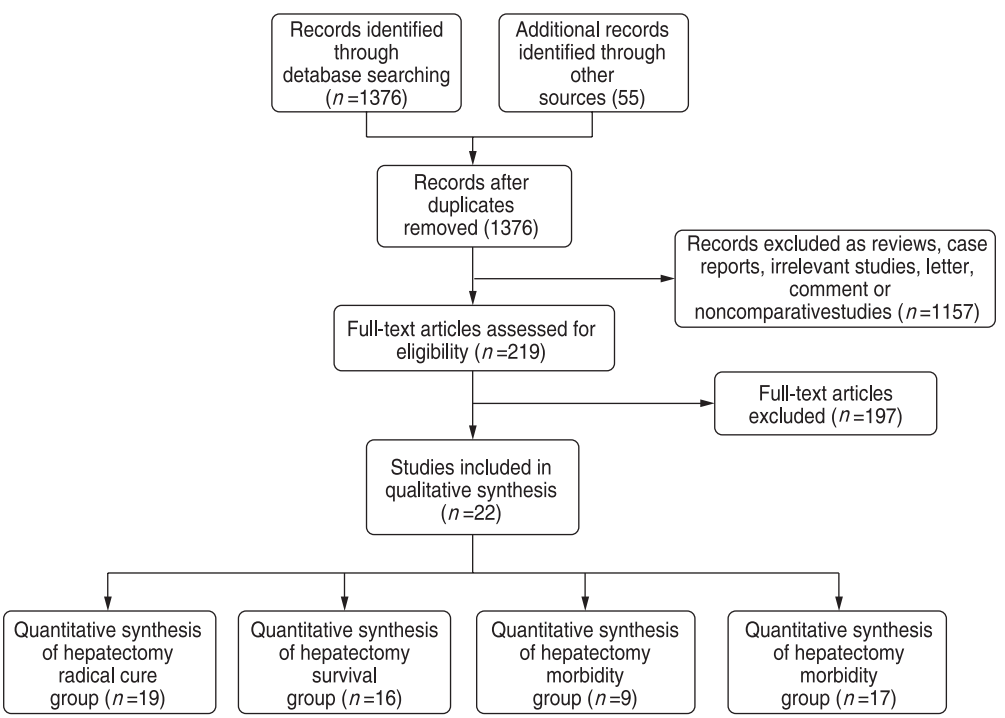

Fig. 1 Flow diagram representative of the study selection

Table 1 characteristics of include studies and the study groups belonged

First author	Newcastle-Ottawa Score	Publish year	Country	Study group
Capussotti L [8]	7	2002	Italy	2
Cho MS [10]	9	2012	South Korea	1, 2
de Jong MC [11]	7	2012	America	1, 2, 4
Hadjis NS [12]	7	1990	Britain	1, 2, 4
Jarnagin WR [15]	9	2001	America	1, 2, 3, 4
Klempnauer J [16]	7	1997	Germany	1, 2, 3, 4
Lim JH [19]	8	2013	South Korea	1, 2, 3, 4
Otani K [23]	8	2012	Japan	1, 2, 3, 4
Tabata M [26]	8	2000	Japan	1, 2, 3, 4
Lee SG [18]	7	2010	South Korea	1, 4
Ramesh H [24]	8	2004	India	1, 2, 4
Chen RF [9]	6	2007	China	1, 3, 4
Han SS [13]	7	2008	South Korea	1, 2, 4
Lee SG [17]	6	2000	South Korea	1, 4
Matsuo K [20]	8	2012	America	1, 2, 3, 4
Miyazaki M [21]	7	2007	Japan	2
Miyazaki M [22]	8	2010	Japan	1, 4
Song SC [25]	9	2013	South Korea	1, 2
Zervos EE [28]	6	2005	America	1, 4
Hirano S [14]	8	2010	Japan	1, 3, 4
Abd ElWahab [7]	7	2016	Egypt	2
Xiong J [27]	7	2015	China	1, 2, 3, 4

1, hepatectomy radical cure group; 2, hepatectomy survival group; 3, hepatectomy morbidity group; 4, hepatectomy morbidity group

and 491 patients who underwent simple bile duct resection. In the hepatectomy radical cure group, the collective radical cure rate was 76.09% (1254 / 1648) after combined partial hepatectomy, and the collective radical cure rate after simple bile duct resection was 51.93% (255 / 491). The radical resection rate in the combined partial hepatectomy group was significantly higher than in the simple bile duct resection group. The combined OR for the hepatectomy radical cure group was 0.32 (95% CI: 0.20–0.51) (Fig. 2). Out of the 19 articles, 6 reported surgical indications for different surgical procedures. One [23] reported combined hepatectomy for patients with Bismuth-Corlette III and IV HCCA, another article [24] reported simple bile duct resection for patients with Bismuth-Corlette I HCCA, and four articles [12, 14, 16, 28] reported simple bile duct resection for patients with Bismuth-Corlette I and II HCCA.

For the study group with high heterogeneity in the literature (I^2 = 68.3%, P = 0.000), we conducted a meta-regression analysis based on the ethnic origin of patients (Asian or other), the year of publication (before or after 2005), and whether the indication of hepatectomy was explicitly expressed. We found that the indication of hepatectomy is an important factor affecting heterogeneity (P = 0.006). Subsequently, we used this factor as a grouping basis for the subgroup analysis. Subgroup analysis revealed that the heterogeneity was

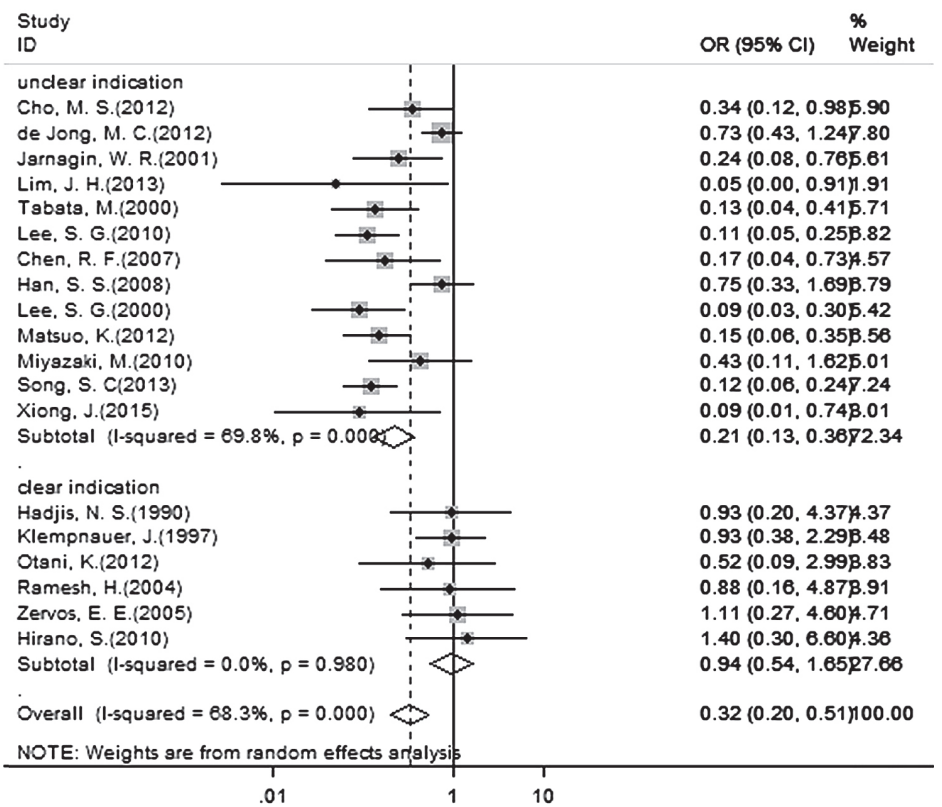

Fig. 2 Forest plot for the hepatectomy radical cure group Subgroup analysis according to the indication of hepatectomy is showed

significantly reduced when combining the articles for the indication of hepatectomy (I^2 = 0.0%, P = 0.980) (Fig. 2). The pooled OR values suggest that when simple bile duct resection was chosen for patients with type I and II HCCA, this would not reduce the probability of radical resection due to the extent of resection (OR 0.94, 95% CI 0.54–1.65) (Fig. 2).

Meta-analysis for the hepatectomy survival group

In the 16 articles included in this group, a total of 1680 patients with HCCA were analyzed including 1188 patients who underwent combined partial hepatectomy and 492 patients who underwent simple bile duct resection. The reported 3-year survival rate for HCCA patients was between 30.5% [26] and 42% [25], and the 5-year survival rate between 20.2%[11] and 33% [25]. Out of the 16 articles, 7 [7, 10–11, 15, 20–21, 25] presented a HR value with a 95% CI. In the remaining 9 [8, 12–13, 16, 19, 23–24, 26–27], we extrapolated the HR from the Kaplan-Meier curves using Tierney's method [3]. The collective HR from the 16 articles suggested that survival for HCCA patients after combined partial hepatectomy was significantly increased compared to that of patients who underwent simple bile duct resection (HR 0.67, 95% CI 0.58–0.79), (Fig. 3).

A subgroup analysis was subsequently performed according to the source of the HR. Following a Q test, the P value was lower than 0.10, therefore the fixed effect model was selected. Following the subgroup analysis, and regardless of whether HR were directly collected or extrapolated via indirect calculations, the collective HR suggested that survival for HCCA patients after partial hepatectomy was significantly increased compared to patients who underwent simple bile duct resection (Fig. 3).

Meta-analysis for the hepatectomy morbidity group

In the 9 included articles, a total of 782 patients with HCCA were analyzed including 583 patients who underwent combined partial hepatectomy and 199 patients who underwent simple bile duct resection. Reported complications from surgery for HCCA included liver abscess, abdominal abscess, postoperative liver dysfunction, hyperbilirubinemia, intraperitoneal hemorrhage, bile leakage, portal vein thrombosis and others. To determine whether combined partial hepatectomy increased the risk of surgical complications, nine articles in the hepatectomy morbidity group were collectively evaluated. Following this analysis we found

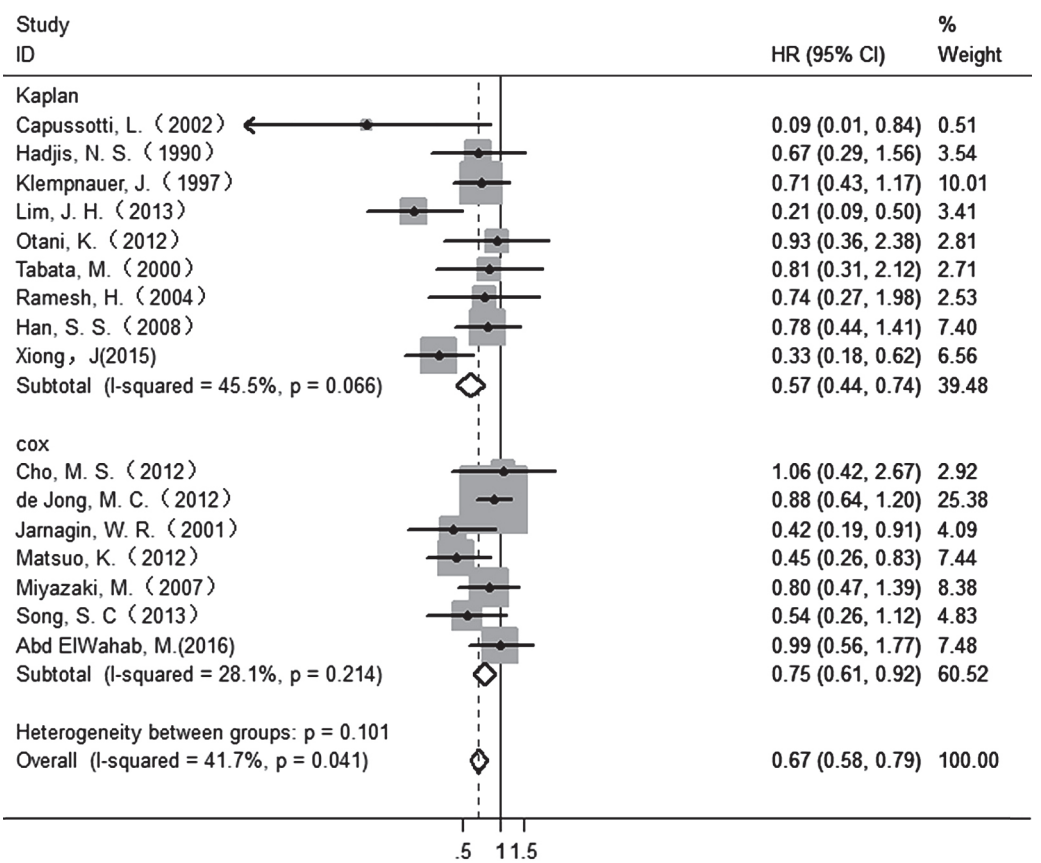

Fig. 3 Forest plot for the hepatectomy survival group Subgroup analysis according to the source of the HR value is showed

that complications occurred in 47.34% (276/583) of patients in the combined hepatectomy group, whereas they occurred in 30.15% (60/199) of patients in the simple bile duct resection group. The collective OR suggested that the risk of postoperative complications in the combined partial hepatectomy group was higher than in the simple bile duct resection group (OR 1.99, 95% CI 1.37–2.90) (Fig. 4).

In regards to the capabilities in the performance of the hepatectomy techniques and preoperative preparation techniques for the past ten years, a subgroup analysis was performed based on the year of publication of the articles, which were subdivided into two groups: publications before or after 2005. The calculated OR was 2.55 (95% CI 1.31–4.97) for the three studies published before 2005, and 1.76 (95% CI 1.12–2.77) for the five studies published after 2005 (including those published in 2005). The subgroup analysis showed that despite the risk of complications following combined partial hepatectomy being significantly higher than following simple bile duct resections after 2005, this risk was reduced when compared to those studies performed before 2005 (Fig. 4).

Meta-analysis for the hepatectomy mortality group

In the 17 articles included in this group, a total of 1792 patients with HCCA were analyzed including 1407 patients who underwent combined partial hepatectomy and 387 patients who underwent simple bile duct resection. Reported causes of death in HCCA patients included infections, liver failure and abdominal bleeding. To determine whether combined partial hepatectomy increased the risk of surgery-related mortality, 17 articles in the hepatectomy mortality group were collectively analyzed. After partial hepatectomy, 6.54% (92 / 1407) of patients with HCCA had died, compared to 2.07% (8 / 387) for patients in the simple bile duct resection group. One article [19] was excluded from this meta-analysis due to the absence of data on short-term postoperative death in both the reported groups. The collective OR suggested that the risk of short-term postoperative mortality in the combined partial hepatectomy group was higher than in the simple bile duct resection group (OR 2.71, 95% CI 1.47–4.98) (Fig. 5).

A subgroup analysis was performed based on the time of publication for each article, before or after 2005. The OR for the 6 papers published before 2005 was 3.43 (95% CI 1.33–8.84), and 2.25 (95% CI 1.01–5.00) for the 11 papers published in or after 2005 (with exception of Lim, *et al* [19]). The subgroup analysis showed that although the risk of short-term postoperative mortality after combined partial hepatectomy was significantly higher than after simple bile duct resection after 2005, this was reduced when compared to studies published prior to 2005 (Fig. 5).

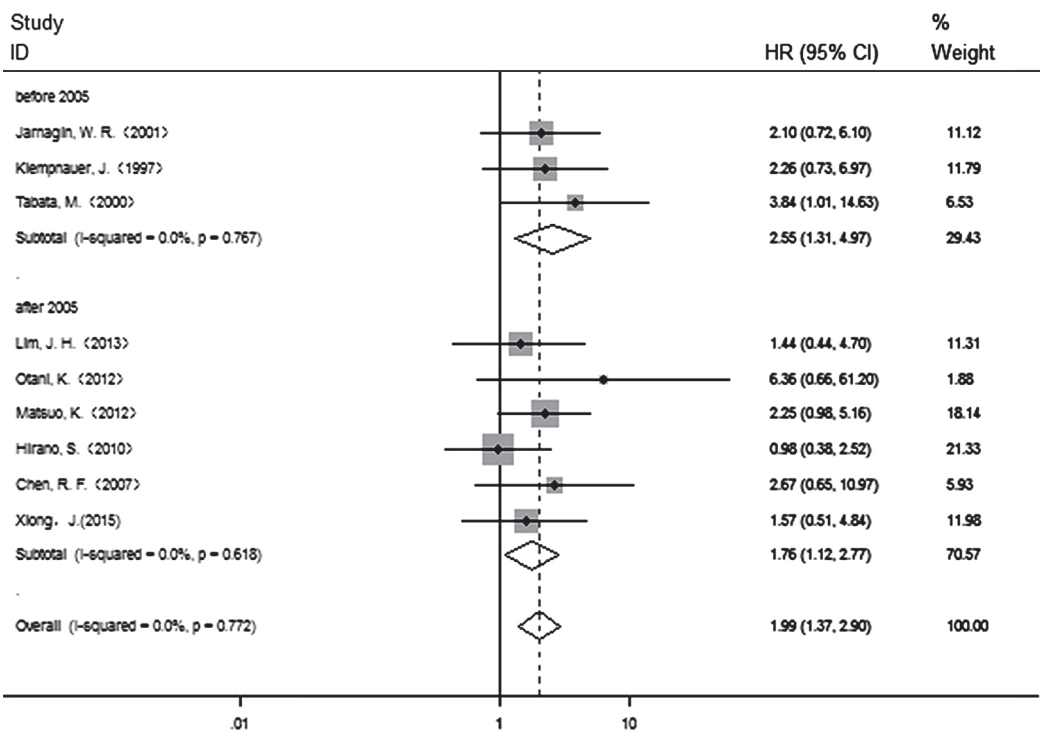

Fig. 4 Forest plot for the hepatectomy morbidity group Subgroup analysis according to the published date of the articles (before and after 2005) is showed

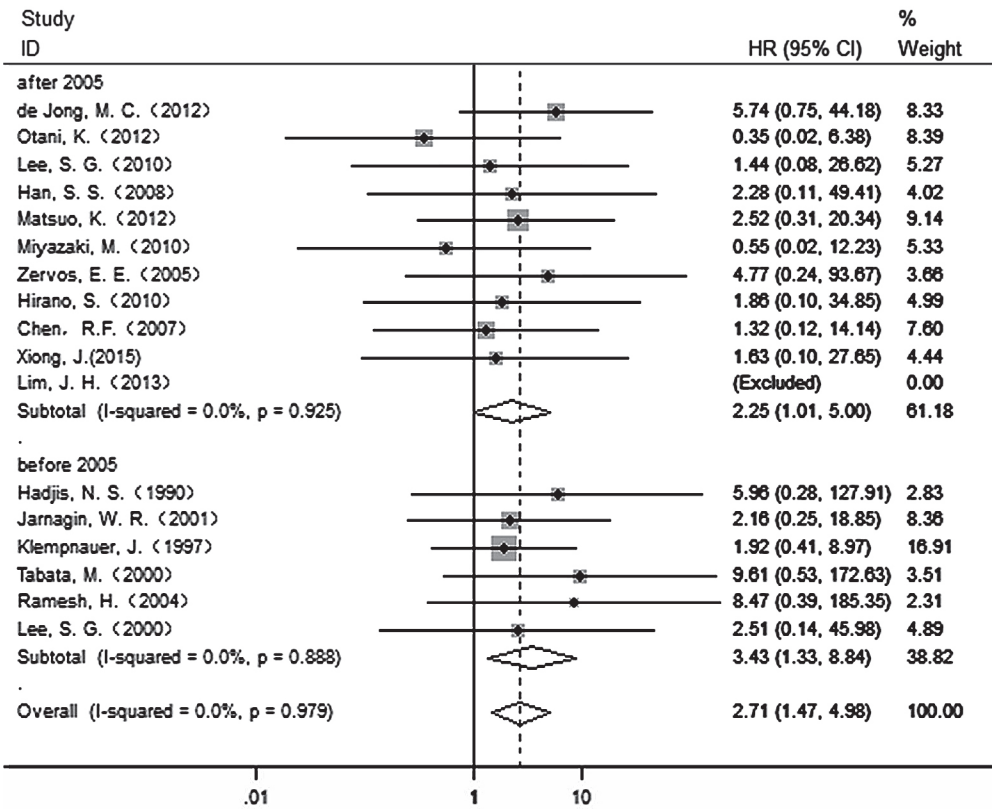

Fig. 5 Forest plot for the hepatectomy mortality group Subgroup analysis according to the published date of the articles (before and after 2005) is showed. Studies by Lim JH were excluded from meta-analysis due to the absence of data on short-term postoperative deaths in both groups

Publication bias

To determine the publication bias in the included articles for each of the above groups, funnel diagrams were drawn (Fig. 6–9). The symmetry state indicated no publication bias in the 4 study groups selected. We also performed the Egger's test using Stata 12.0. No publication bias was found for the hepatectomy radical cure group ($P = 0.686$), the hepatectomy survival group ($P = 0.082$), the hepatectomy morbidity group ($P = 0.109$) or the hepatectomy mortality group ($P = 0.991$).

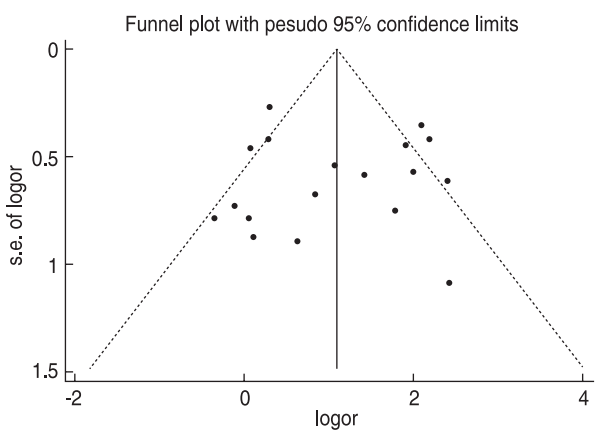

Fig. 6 Funnel plots for detection of publication bias in the hepatectomy radical cure group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

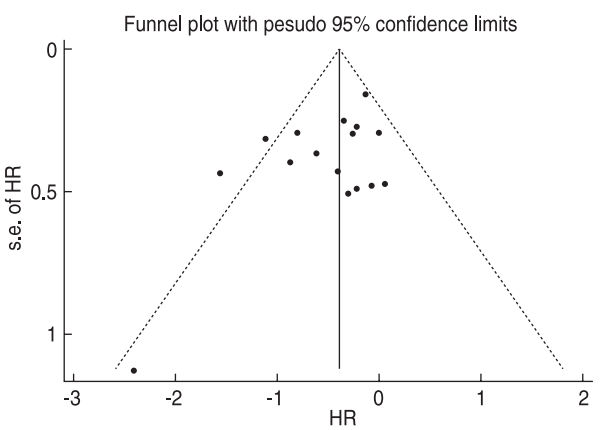

Fig. 7 Funnel plots for detection of publication bias in the hepatectomy survival group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

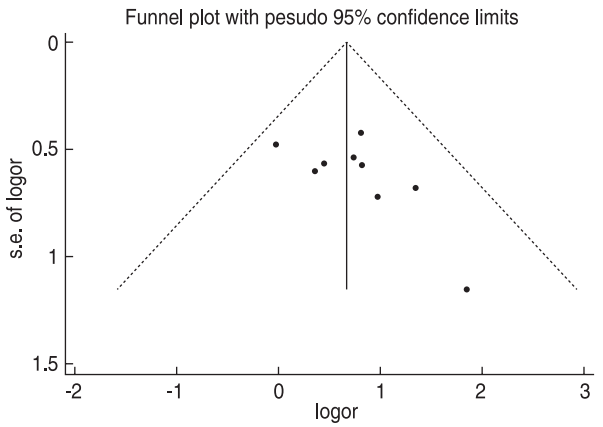

Fig. 8 Funnel plots for detection of publication bias in the hepatectomy morbidity group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

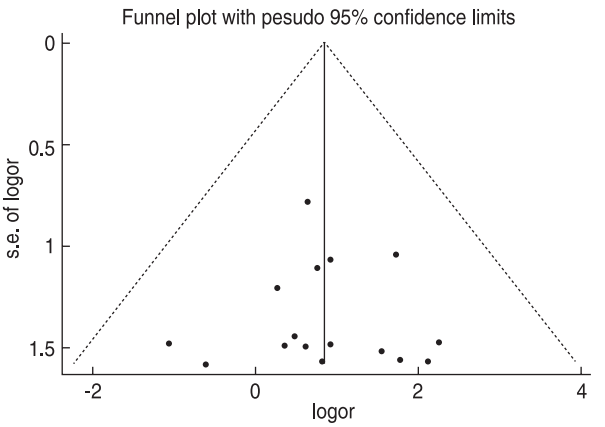

Fig. 9 Funnel plots for detection of publication bias in the hepatectomy mortality group Studies are distributed symmetrically and suggest that publication bias is absent after meta-analysis

Discussion

Altemeier *et al* [29] first reported 3 cases of primary sclerosing hilar cholangiocarcinoma in 1957. In the following decades, HCCA treatment strategies gradually improved. In 1965, Klatskin *et al* [30] first defined HCCA and described its clinical and pathological features in detail and systematically. In the 1970s, the treatment strategy for HCCA patients was to relieve the patient's jaundice using biliary drainage or U-tube drainage. Patients had a short overall survival, and high mortality rates after treatment [31–32]. In the 1980s, bile duct resection replaced bile duct drainage and achieved better outcomes for HCCA patients. However, due to limitations in the surgical resection range, the therapeutic outcomes for type III and IV HCCA patients were still unsatisfactory [33–34]. In the 1990s, Bismuth *et al* [35] proposed the use of simple cholecystectomy or partial hepatectomy for different types of HCCA to improve radical surgery and prolong patients' survival.

Currently, surgical methods used for HCCA patients include either extrahepatic biliary resection or biliary resection combined with hepatectomy. The extent of proximal bile duct resection includes a further 5-mm duct resection from the tumor site. The distal bile duct edge should be located at the upper edge of the pancreas. Extrahepatic biliary resection has a small resection range and may present with lower postoperative complications and low mortality. However, in the case of HCCA, the removal of the bile duct may not provide a R0 resection margin.

In this study, data derived from the hepatectomy radical cure group and the hepatectomy survival group showed that the cure rate for HCCA patients after partial hepatectomy was higher and survival times longer than after simple bile ducts resection. These results confirm that combined partial hepatectomy expands the extent of biliary resection, thereby increasing the chance of radical resection and prolonging postoperative survival.

Due to high heterogeneity in the hepatectomy radical cure group, we performed a subgroup analysis based on the Bismuth-Corlette classification. We found that when HCCA did not invade the second bile duct bifurcation, the choice of simple bile duct resection would achieve a similar outcome as a partial hepatectomy. Our study showed that simple bile duct resection remains a good option for the treatment of Bismuth-Corlette I, II, and well-differentiated HCCA, but this observation will need further confirmation in future clinical studies.

To ensure an R0 resection for HCCA, the location of the proximal bile duct resection is often higher or expands into the liver, resulting in higher incidences of bile leakage after bile duct anastomosis, with reported cases increased by 25.56% [36]. Combined partial hepatectomy may require removal of the left or right portion of the liver, and this can increase the risk of biliary fistula, hemorrhage and liver failure. In addition, some patients often present with endotoxemia, malnutrition, or anemia prior to surgery and subsequently, surgical trauma, and postoperative complications may directly lead to death in those patients. After review of the literature, postoperative complication rates for the combined hepatectomy group were found to be as high as 46.54%, and the postoperative mortality rates were 6.62%. Following a meta-analysis, the resulting OR showed that the complication rates in patients who underwent partial hepatectomy were significantly higher than in patients who underwent simple bile ductectomy. Common postoperative complications reported in the literature included infections, bile leakage, and intra-abdominal hemorrhage. Additionally, liver failure and short-term postoperative deaths in patients with poor liver reserves were common. Combined partial

hepatectomy reduced the difficulty of surgery, but increased the incidence of surgical trauma, postoperative complications and mortality.

In this study, we found that combined hepatectomy increased radical cure and prolonged survival in patients with HCCA. However, in patients with poor general condition and poor liver reserve function, the risk of surgery should be carefully considered. Simple bile duct resection has proven to be a valuable technique for the treatment of hilar cholangiocarcinoma of Bismuth-Corlette type I and II.

HCCA is a relatively rare disease, and therefore it is challenging to conduct large-scale clinical studies. This study used a screening and combinatorial approach where meta-analysis was performed with the extracted data to increase the sample size. The conclusions provided here are evidence based.

This study did have some limitations. The search strategy used in this study yielded a high number of preliminary screening documents (748 articles). Therefore, there is a possibility that relevant literature might have been missed despite it being analyzed by two independent investigators. Due to the nature of HCCA surgery, literature included in this study pertained to retrospective cohort studies only, which could affect the reliability of our conclusions. Lastly, studies included here did not compare the postoperative outcomes for each of the Bismuth-Corlette classifications, and therefore we were unable to draw direct conclusions based on the Bismuth-Corlette's optimal surgical options.

Ethical statement

No ethical approval was obtained because the study did not involve a prospective evaluation, did not involve laboratory animals and the data collected was confidential in nature.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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ORIGINAL ARTICLE

Impact of IL-18 gene promoter polymorphisms on renal cell carcinoma occurrence and prognosis in Chinese Han population*

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Abstract

Objective Genetic polymorphisms in various inflammatory cytokines have been associated with the risk and growth or invasiveness of renal cell carcinoma (RCC). However, the molecular basis of RCC pathogenesis is unclear. The aim of this study was to explore a possible association between two IL-18 gene promoter polymorphisms, –137G/C and –607C/A, and RCC occurrence and prognosis in a Chinese Han population.

Methods Chinese Han patients with RCC (n = 175) and age-matched healthy controls (n = 200) were analyzed by single nucleotide polymorphism genotyping during follow-up.

Results IL-18-137G allele frequency was significantly higher in patients with lymph node metastasis (Odds ratio [OR], 3.52; 95% confidence interval [CI], 0.97–16.17; P = 0.045). The *IL-18-607 CC* genotype was associated with distant metastasis (OR, 2.81; 95% CI, 1.35–6.24; P = 0.025). The IL-18-137 G allele was correlated with more advanced tumor stage (OR, 1.83; 95% CI, 1.05–3.72; P = 0.026) and higher tumor grade (OR, 2.23; 95% CI, 0.78–4.12; P = 0.041). The IL-18-607 CC genotype frequency was significantly higher in patients with more advanced cancer stage (OR, 2.92; 95% CI, 1.80–6.87; P = 0.001) and higher tumor grade (OR, 2.21; 95% CI, 1.25–12.25; P = 0.035). The IL-18-607 allele was associated with more advanced cancer stage (OR, 2.47; 95% CI, 1.38–3.83; P = 0.002).Carriers of the GG genotype with the –137G/ C polymorphism had a 2.165-times higher risk of RCC progression than carriers of the GC genotype (Hazard ratio = 2.15, 95% CI, 1.270–3.687).

Conclusion The IL-18-137 G allele was correlated with more advanced stage, higher tumor grade, and lymph node metastasis. *IL-18* gene promoter polymorphism -137G/C may thus influence the prognosis of RCC patients.

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Key words: *interleukin-18*; renal cell carcinoma; polymorphism; prognosis

Renal cell carcinoma (RCC) is the most common renal tumor and accounts for 2%–3% of all malignancies. RCC is two times more frequent in men than in women, and higher RCC incidence is observed beginning in the sixth decade[1]. Considerable recent evidence has associated increased tumor risk with inflammation, and clinical and experimental studies have associated tumor progression with the upregulation of proinflammatory molecules, especially during late stages of the disease [2].Cytokines are produced by a variety of hemopoietic and nonhemopoietic cell types that mediate and regulate immunity, inflammation, and hemopoiesis. The interaction between a tumor and the immune system and the production of cytokines by the tumor itself can result in differences in local and systemic levels of cytokines in cancer patients [3]. In this context, genetic polymorphisms

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in different inflammatory cytokines have been associated with cancer risk and the growth or invasiveness of RCC [4]. However, the molecular basis of RCC pathogenesis is unclear.

Interleukin-18 (*IL-18*) is an 18-kDa cytokine that belongs to the IL-1 (IL-1) superfamily and is produced by various immune and non-immune cells [5–7]. The expression and secretion of *IL-18* is a crucial event against the oncogenesis of oral carcinoma cells because of its ability to modulate cell cycle progression or trigger an apoptotic pathway [5–7]. We have previously demonstrated a correlation between the levels of serum *IL-18* and disease severity in patients with RCC and prostate cancer [8–9]. In some animal model systems, transfection of the *IL-18* gene into tumor cells enhanced both specific and non-specific antitumor immune responses, which indicates that the transfection of *IL-18* into dendritic cells should induce highly effective antitumor immune responses [10]. These findings provide evidence of an association between susceptibility to cancer and *IL-18* gene expression.

The *IL-18* gene is located on chromosome 11q22. Two functional gene polymorphisms, *-607A/C* and *-137G/C*, are found in its promoter region [11]. Giedraitis *et al* analyzed the *IL-18* gene promoter sequence and found a change from the *C* allele to the *A* allele at position –607 and a change from the G allele to the *C* allele at position –137 of the *IL-18* promoter region [11]. Estimation of the transcription activity of *IL-18* gene promoter fragments showed that C allele of *–607A/C* or *G* allele of *–137G/C* caused higher activity of *IL-18*. Individuals with the CC homozygote of *–607A/C* or the *GG* homozygote of *–137G/C* polymorphism exhibited somewhat higher levels of *IL-18* mRNA compared with individuals with other genotypes [12]. *IL-18* gene polymorphisms have been recently investigated in several cancers, including nasopharyngeal carcinoma [12], prostate cancer [13], cervical cancer [14], and breast cancer [15]. However, these studies yielded different or even controversial results.

We have previously described an effect of *IL-18* polymorphisms at –607 and –137 on clinical characteristics of prostate cancer patients [16]. In this study, we investigated the role of *IL-18* gene promoter polymorphisms in the occurrence of RCC and prognosis to provide data for screening high-risk Han Chinese individuals.

Materials and methods

Study subjects

The study included 175 patients diagnosed with renal clear-cell carcinoma (RCC) at the Department of Urology of The Affiliated Hospital of Nantong University (China) between 2005 and 2015. All patients had undergone radical or partial nephrectomy. Their mean age was 68 years (range, 58–85 years). Clinicopathological characteristics are shown in Table 1. Two consulting pathologists retrospectively and independently reviewed the hematoxylin and eosin stained tissue slides according to the World Health Association classification. The Fuhrman scale was used to assess nuclear grade. Tumor stage was assigned according to the 2002 TNM classification. Patients were actively followed-up from diagnosis to December 2005. Cancer characteristics according to the University of California, Los Angeles integrating staging system included TNM stage, histologic grade (Fuhrman), and performance status as prognostic factors. Only the first two parameters were assessed, because a performance status higher than zero was found in only a very low percentage of patients and was not deemed relevant for the statistical analysis. No other risk factors for an adverse prognosis were evaluated. The control group comprised 200 healthy blood donors with a mean age of 70 years. Control samples were collected between 2005 and 2015. All patients provided signed informed consent to participate in this study, which was approved by the ethics committee of our hospital.

Single nucleotide polymorphism (SNP) genotyping

After DNA extraction, samples were randomly placed in wells of 96-well plates and analyzed using real-time polymerase chain reaction (PCR). The PCR primer designs, reaction mixture composition, and reaction processes of this study were the same as those used in a previous study [16]. Standard samples were sequenced using a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, USA) and ABI 3130 genetic analyzer (Applied Biosystems). Genotyping results of all samples

Table 1 Characteristics of patients

Characteristics	Median	Percentage
Age (years)	68 ± 9.8 (58–85)	
Gender		
Male	95	54.3
Female	80	45.7
Tumor stage		
pT1	55	31.4
pT2	70	40.0
pT3	15	8.6
pT4	35	20.0
Lymph node metastasis		
Negative	124	70.9
Positive	51	29.1
Metastasis		
Negative	118	67.4
Positve	57	32.6
Grade		
G1–2	98	56
G3–4	77	44

were obtained using the Gene Scanning v1.2 software by comparison with standard samples.

Statistical analyses

The observed genotype frequencies in the controls were tested for Hardy-Weinberg equilibrium. Possible significant difference in age was tested by the Student's t-test. The distribution of genotypes and allele frequencies between the two groups was analyzed by the chi-square analysis. Haplotype analysis was carried out using a related software platform. Odds ratio (OR) and 95% confidence interval (95% CI) calculations were conducted with the risk option of Crosstabs. Kaplan-Meier and multivariate Cox proportional hazard models were used to examine the relationship between the genotypes and progression-free survival time. Hazard ratios (HR) and 95% CI were calculated. A two-sided $P < 0.05$ was considered statistically significant.

Results

Subject characteristics

The genotype distribution of the controls was in Hardy-Weinberg equilibrium ($P > 0.05$ for both polymorphisms). The mean ages for cases and controls were 68 ± 9.8 and 70 ± 9.7 years, respectively ($P = 0.12$). Based on the clinical findings, 125 patients were in pT1 or pT2, and 50 patients were in pT3 or pT4 (Table 1).

Association analysis of SNPs and RCC susceptibility

The results of association analyses of alleles and genotypes with RCC cancer susceptibility are shown in Table 2. No differences were observed between the genotype distribution of the two SNPs among the cases and controls ($P = 0.18$ and 0.53 for –137G/C, $P = 0.31$ and 0.54 for –607C/A). No significant associations were detected in the allele frequencies ($P = 0.15$ for –137G/C, $P = 0.55$ for –607C/A). On the basis of the haplotype analysis results shown in Table 3, no promising *P*-values were detected ($P > 0.05$ for all).

Association between cancer progression and genotypes

The associations of the *IL-18* genotypes with tumor grade and stage are shown in Table 4. Genotype GG of *IL-18*-137 was associated with more advanced cancer stage (OR, 2.81; 95% CI, 1.23–5.47; $P = 0.008$) and higher (G3–G4) tumor grade (OR, 3.12; 95% CI, 1.16–8.17; $P = 0.021$). The *IL-18*-137 G allele was correlated with more advanced stage (OR, 1.83; 95% CI, 1.05–3.72; $P = 0.026$) and higher tumor grade (OR, 2.23; 95% CI, 0.78–4.12; $P = 0.041$). The *IL-18*-607 CC genotype was significantly more frequent in patients with more advanced cancer stage (OR, 2.92; 95% CI, 1.80–6.87; $P = 0.001$) and higher tumor grade (OR, 2.21; 95% CI, 1.25–12.25; $P = 0.035$). The *IL-18*-607 C allele was associated with more advanced cancer stage (OR, 2.47; 95% CI, 1.38–3.83; $P = 0.002$).

Association results of the *IL-18* genotypes with lymph node metastasis and distant metastasis are shown in Table 5. The *IL-18*-137G allele was significantly more frequent in patients with lymph node metastasis (OR, 3.52; 95% CI, 0.97–16.17; $P = 0.045$). The *IL-18*-607 CC genotype was associated with distant metastasis (OR, 2.81; 95% CI, 1.35–6.24; $P = 0.025$).

Association between cancer survival and genotypes

In this study, disease progress is represented as progression-free survival. The mean and median progression-free survival values were 20.68 ± 13.77 and 18 months, respectively. The distinction of cancer progress among the different genotypes in the two SNPs is described in Table 6. Carriers of the GG genotype in -137G/C had a 2.165-times higher risk of progress compared with GC carriers (HR = 2.15, 95% CI = 1.270–3.687) (Table 6, Fig. 1).

Table 2 Genotypes and allele frequencies of IL-18 promoters in relation to the occurrence of RCC

Polymorphisms	Cases *n* (%)	Controls *n* (%)	χ^2	*P**	OR	95% CI
–137 C/G						
Genotype						
GG	141 (80.6)	152 (76.0)			1.0	
CG	34 (19.4)	46 (23.0)	1.72	0.18	0.80	0.48–1.12
CC	0 (0.0)	2 (1.0)			0.53	
Allele						
C	40 (11.4)	60 (15.0)			1.00	
G	310 (88.6)	340 (85.0)	2.24	0.15	0.76	0.85–1.27
–607 A/C						
Genotype						
CC	82 (46.7)	47 (23.5)			1.00	
AC	78 (44.6)	99 (49.5)	1.12	0.31	0.85	0.54–1.86
AA	45 (25.7)	54 (27.0)	0.48	0.53	0.81	0.65–1.31
Allele						
C	170 (48.6)	210 (52.5)			1.00	
A	185 (52.4)	190 (47.5)	0.45	0.55	0.95	0.87–1.59

OR = odds ratio; CI, confidence interval; * x^2 test or Fisher's exact test

Table 3 Haplotype frequencies of IL-18 promoters in RCC and controls

Haplotype	Cases *n* (%)	Controls *n* (%)	OR	95% CI	*P**
–607C/–137G	165 (47.1)	184 (46.0)	1.00		
–607C/–137C	7 (2.0)	6 (1.5)	1.12	0.49–2.56	0.78
–607A /–137G	147 (42.0)	168 (42.0)	0.99	0.45–2.05	0.89
–607A /–137C	3 (8.9)	42 (10.5)	0.75	0.53–1.09	0.95

OR = odds ratio; CI: confidence interval; * x^2 test or Fisher's exact test

Table 4 Associations of IL-18 genotypes with tumor stage, and grade

IL-18 Polymorphisms	Tumor pT1 (%)	Stage pT2–4 (%)	OR	95% CI	*P**	Tumor pT1 (%)	Stagep T2–4 (%)	OR	95% CI	*P**
–137 C/G										
CC	7 (5.8)	3 (5.9)	1.33	0.22–7.81	0.625	4 (4.1)	6 (7.8)	1.48	0.25–19.27	0.643
CG	58 (48.4)	15 (29.4)	1.00			54 (55.1)	15 (19.5)	1.00		
GG	55 (45.8)	33 (64.7)	2.81	1.23–5.47	0.008	40 (40.8)	56 (72.7)	3.12	1.16–8.17	0.021
Allele										
C	35 (29.2)	32 (24.8)	1.00			40 (40.8)	21 (27.3)	1.00		
G	85 (70.8)	97 (75.2)	1.83	1.05–3.72	0.026	58 (55.7)	56 (72.7)	2.23	0.78–4.12	0.041
–607 A/C										
Genotype										
AA	14 (11.7)	4 (7.8)	0.75	0.24–2.47	0.627	9 (9.2)	8 (10.4)	1.21	0.28–5.21	0.762
AC	72 (60.0)	22 (43.1)	1.00			69 (70.4)	39 (50.6)	1.00		
CC	34 (28.3)	25 (49.1)	2.92	1.80–6.87	0.001	20 (20.4)	30 (39.0)	2.21	1.25–12.25	0.035
Allele										
A	57 (43.2)	45 (35.4)	1.00			35 (26.9)	23 (17.7)	1.00		
C	75 (56.8)	82 (64.6)	2.47	1.38–3.83	0.002	95 (73.1)	107 (82.3)	1.78	0.77–4.62	0.163

95%CI = 95% confidence interval; * x^2 Test or Fisher's exact test

Table 5 Associations of IL-18 genotypes with lymph node metastasis, metastasis

IL-18 Polymorphisms	Lymph node metastasis		OR	95% CI	*P**	Metastasis		OR	95% CI	*P**
	Negative (%)	Positive (%)				Negative (%)	Positive (%)			
–137 C/G										
CC	7 (6.7)	1 (2.0)	0.95	0.78–1.22	0.662	3 (2.5)	2 (3.5)	2.51	0.42–14.27	0.437
CG	41 (39.4)	24 (47.1)	1.00			42 (25.1)	11 (19.3)	1.00		
GG	56 (53.9)	26 (50.9)	1.89	0.43–8.35	0.416	62 (52.5)	44 (77.2)	1.88	0.93–5.27	0.163
Allele										
C	65 (43.3)	17 (16.7)	1.00			42 (25.1)	19 (16.7)	1.00		
G	85 (56.7)	85 (56.7)	3.52	0.97–16.17	0.045	125 (74.9)	95 (83.3)	1.67	0.82–3.40	0.327
–607 A/C										
Genotype										
AA	10 (9.6)	2 (4.0)	0.97	0.89–1.03	0.343	8 (6.8)	2 (3.5)	2.47	0.57–6.15	0.158
AC	55 (52.9)	17 (33.3)	1.00			69 (58.5)	23 (40.4)	1.00		
CC	39 (37.5)	32 (62.7)	2.62	0.58–9.17	0.82	41 (34.7)	32 (56.1)	2.81	1.35–6.24	0.025
Allele										
A	60 (46.2)	20 (19.6)	1.00			61 (34.7)	33 (28.9)	1.00		
C	70 (53.8)	82 (80.4)	2.58	0.79–8.63	0.066	115 (65.3)	81 (71.1)	1.55	0.93–3.55	0.247

95% CI = 95% confidence interval; * x^2 test or Fisher's exact test

Discussion

The etiology of renal cancer is highly complex and involves both environmental and genetic factors. In addition, genetic polymorphisms in genes encoding cytokines can influence their expression or function, and polymorphisms in genes that regulate the intensity of immune responses may contribute to the pathogenesis of renal cancer and thus influence the clinical outcome of patients [17]. *IL-18*, a proinflammatory cytokine that belongs to the IL-1 family of ligands, induces interferon-gamma (IFN-γ) production in T cells and natural killer cells, which is important in the T helper-cell type 1 response[3–4]. An antitumor effect of *IL-18* has been demonstrated and *IL-18* has been considered for use

Table 6 Survival analysis of the selected SNPs in patients (*n* = 127)

Polymorphisms	Genotypes *n* (%)	Developed *n* (%)	HR	95% CI
IL-18-607C/A				
GG	32 (25.2)	19 (20.0)	1.00	0.67–1.74
TT	89 (70.1)	72 (75.8)	1.05	0.08–1.79
GT	6 (4.7)	4 (4.2)	0.23	
IL-18-137G/C				
GC	26 (20.5)	28 (29.5)	1.00	
GG	101 (79.5)	67 (70.5)	2.36	1.26–3.89

HR = hazard ratio; 95% HCI = 95% confidence interval

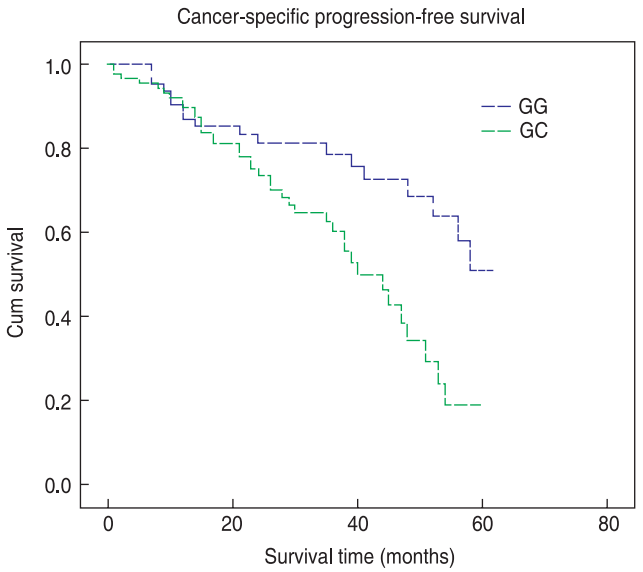

Fig. 1 Progression-free survival time of RCC patients carrying GG or GC genotypes of the SNP-137G/C. Cum = cumulative

in cancer immunotherapy or gene therapy [18]. On the contrary, we have reported that *IL-18* can increase tumor growth via increasing the stimulation of vascular endothelial growth factor and the immune response and can also stimulate solid tumor metastasis [8, 19]. Considering the above findings, the purpose of this study was to investigate whether the *IL-18* promoter (–607) C/A and (–137) G/C gene polymorphisms have any association with the risk for RCC. The *IL-18* promoter region is composed of five single nucleotide positions, among which only –137G/C and –607C/A have confirmed impact on *IL-18* activity and expression in tissues [20]. Different haplotypes of *IL-18* polymorphisms might lead to different expression levels of *IL-18* mRNA[20]. For example, –137G/–607C causes a higher level of *IL-18* mRNA synthesis [20], while the haplotype (–137C/–607A) causes a lower promoter activity.

In the present study, we found no association between *IL-18* polymorphisms and a higher risk of RCC. However, as in other studies [21], *IL-18* polymorphisms were found by us to be correlated with more advanced cancer stages. *IL-18* promoter polymorphisms have been associated with prostate carcinomas [22], although other authors found no association between *IL-18* polymorphisms and cancer risk [23]. In fact, *IL-18* activities are influenced by the tumor microenvironment. So, *IL-18* could exert its antitumor activity by augmenting IFN-γ production, particularly in the presence of IL-12 [24]. However, recent data also suggested a procancerous activity for this multifunctional cytokine under certain conditions depending on the tumor immune response at different tumor sites and probable genetic background [25]. In the present RCC patients, *IL-18* polymorphisms did not appear to be associated with RCC susceptibility. This discrepancy could be attributed to the different genetic backgrounds and environmental factors of patients, such as exposure to different carcinogens that initiate different cancers in different populations. In addition, the inadequate study design, involving nonrandom sampling and a limited sample size, should also be considered. The possible selection bias that might have been present in the hospital-based, case-control study is a relevant issue. Finally, we cannot exclude the fact that the observed association was due to a gene in linkage disequilibrium with the *IL-18* gene or the effect of *IL-18* on another peptide. However, once the tumor appears, high productive *IL-18* polymorphism promotes more advanced tumor grade, stage, and other features. These results may be explained by the fact that *IL-18* induces the production of angiogenic and growth factors [26].

We found that a genotype related to higher production of *IL-18* is associated with higher grade and stage of the tumor. *IL-18* activates vascular endothelial growth factor [26] and can activate angiogenesis in tumor nests [24]. Therefore, *IL-18* polymorphisms that increase its production would increase angiogenesis and provide adequate nutrients to transformed cells, promoting cancer development to a more advanced stage. *IL-18* is also correlated with the progression of the disease. High-production polymorphisms in *IL-18* are associated with differentiation of tumor cells, leading to a more advanced tumor grade and stage grouping. Therefore, *IL-18* can directly promote cancer cell proliferation by regulating proliferation stimulators. *IL-18* was recently implicated in the migration of breast cancer [15] and human melanoma cell lines through the generation of region of interest and the mitogen-activated protein kinase pathway [27]. Proinflammatory cytokines also induce adhesion receptors of endothelial cells for cancer cell attachment [28]. Gunel *et al* [29] showed that breast carcinoma patients with bone metastasis had higher serum *IL-18* levels compared with those with liver metastasis. Our results are similar to these findings. The clinical importance of these parameters is worth investigating in patients with RCC, especially for patients with metastasis. However, such studies should be conducted in a larger cohort of patients.

In the present study, polymorphisms related to *IL-18* production were associated with the development of metastasis and lymph node involvement. As metastasis is a highly complex process that may involve numerous genes, the analysis of the risk of a specific polymorphism leading to metastasis is difficult, as individual genes are likely to contribute only moderately to the risk [30]. This may explain the low correlation found in this study between *IL-18* production and metastasis. The association

between overall survival and *IL-18*-607 polymorphism was also analyzed. Our study showed that carriers of the GG genotype in –137G/C had a 2.165-times higher risk of progression compared with GC carriers. Because the median survival (30% mortality) was not achieved, we cannot confirm or rule out the statistical influence of this variable as a prognostic factor.

Our data demonstrated that the *IL-18*-137 G allele is correlated with a more advanced stage and higher tumor grade and lymph node metastasis. The *IL-18* –137G/C promoter polymorphism might contribute to the prognosis of RCC. However, there was no evidence to support an association between polymorphisms in the *IL-18* gene and RCC susceptibility in Han Chinese individuals, which does not imply exclusion of the contribution of other polymorphisms in *IL-18* to the risk of RCC. Further studies applying a more extensive array of *IL-18* gene SNPs, other independent large-size ethnic group cohorts, detailed clinical data, and long-term follow-up are needed to confirm our results.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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ORIGINAL ARTICLE

Safety and efficacy of acute normovolemic hemodilution during liver surgery: a Meta-analysis

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Abstract

Objective The aim of this study was to evaluate the safety and efficacy of acute normovolemic hemodilution (ANH) during liver surgery.

Methods Structured searches of the PubMed, Chinese Biological Medicine Database, and Cochrane Library electronic databases were performed, followed by a meta-analysis of outcomes, including intraoperative blood transfusion(s), intraoperative bleeding, postoperative hematocrit (Hct) levels, postoperative prothrombin time (PT), and number of patients who underwent transfusions during liver surgery.

Results In total, 14 eligible studies were included in the meta-analysis, which revealed that ANH for liver resection was associated with a reduction in intraoperative blood transfusions [weighted mean difference (WMD) −1.99; 95% confidence interval (CI) −2.82 to −1.16; $P < 0.00001$]. The ANH group experienced less intraoperative bleeding (WMD −72.81; 95% CI −136.12 to −9.50; $P < 0.00001$) and exhibited a lower postoperative Hct level (WMD −3.38; 95% CI −7.14 to −0.67; $P < 0.00001$) than the control group. Moreover, meta-analysis revealed that postoperative prothrombin time was not affected by ANH (WMD −0.02; 95% CI −0.18 to −0.32; $P = 0.65$). Finally, the number of patients requiring allogeneic transfusion was significantly smaller in the ANH group than in the control group (odds ratio 0.13; 95% CI 0.09 to 0.18; $P = 0.24$).

Conclusion Results of the present meta-analysis indicated that ANH can reduce intraoperative bleeding and the need for blood transfusions. In addition, ANH did not negatively affect the coagulation system after surgery; therefore, ANH appears to be safe and effective during liver surgery.

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Key words: safety and efficacy; acute normovolemic hemodilution (ANH); liver surgery; meta-analysis

Liver resection traditionally requires a blood or blood-product transfusion to compensate for excessive bleeding, which is a common intraoperative complication during this type of surgery. The past several years have witnessed exponential advances in surgical and anesthetic techniques applied during hepatic surgery, together with marked reductions in blood transfusions related to liver resection. However, for complicated liver surgeries, especially those for tumors invading the main blood vessels, or when multiple liver resections are needed, bleeding can be fatal, and leave surgeons with poor visualization of the operative field.

With the increasing number of surgeries performed worldwide annually, the transfusion of allogeneic red blood cells (RBCs) and blood products has become even more widespread. The potential risks related to transfusions are well known and include high incidence of tumor recurrence due to inhibited T-lymphocyte immune function and transmission of infectious diseases such as cytomegalovirus [1], and non-A, non-B hepatitis [2]. Reductions in the number of transfusions required have been particularly noteworthy, and several strategies to reduce hemorrhage during surgery have evolved and are now routinely used, such as low central venous pressure, preoperative autologous blood donation [3], and acute normovolemic hemodilution (ANH). It has been reported [4] that ANH is an effective method to reduce intraoperative RBC loss, to save the patient's blood for later use and reduce thrombosis, and to prevent the spread of blood-borne diseases.

In this study, we evaluated the safety and efficacy of acute ANH, an autologous blood transfusion technique that is different from preoperative autologous blood donation. For ANH, a portion of the patient's whole blood

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is pre-surgically removed through the peripheral vein under general anesthesia while maintaining euvolemia; the same amount of colloid is injected to replace the blood removed. The amount of blood collected from the patient is calculated using the equation:

$$V_L = EBV \times H_0 - H_F / H_{AV},$$

in which V_L represents allowable blood loss, EBV is the estimated blood volume, H_0 is the patient's initial hemoglobin (Hb) level, H_F is a patient's minimal allowable Hb level, and H_{AV} is the average of the initial and minimal allowable Hb levels [5]. The collected blood is stored in an acid citrate dextrose blood collection bag in the operating room at room temperature to accurately record blood collection over time. If blood transfusion is indicated post-surgically [Hb < 80 g/L, hematocrit (Hct) < 25%], the patient's autologous blood is returned. During the entire process, the corpuscular portion of the blood is partially diluted, and the circulating blood volume remains equal and stable.

Although ANH has the advantages of lowering surgery costs, avoids the risk for reduced blood coagulation factors for long-term preservation, and reduces the risk for error in matching blood types, evidence supporting the efficacy and safety of ANH during liver surgery remains lacking. Thus, we performed this meta-analysis to determine the safety and efficacy of ANH in decreasing exposure to allogeneic transfusions in adults undergoing major liver resection procedures.

Methods

Literature search

A structured search of the PubMed, Chinese Biological Medicine Database, and Cochrane Library electronic databases was performed. The search was designed to include articles published between data compilation after the creation of electronic resources and August 1, 2019, with publication language restricted to English and Chinese. The search terms were as follows: ((Hemodilution) AND (((((hepalobectomy) OR "liver resection") OR "hepatic resection") OR hepatectomy)). All abstracts of the retrieved articles were independently reviewed for relevance by the two investigators, and the full-text of the included articles was obtained for a second screening.

Inclusion/exclusion criteria

All studies included in the present meta-analysis fulfilled the following criteria: randomized controlled trials (RCTs) and prospective or retrospective cohort studies comparing intraoperative acute ANH and no intervention in liver surgery; population(s) undergoing liver surgery were > 18 years of age; surgical procedure for ANH was consistent, and all patients received ANH; at least one outcome of interest was reported (e.g., amount of intraoperative bleeding, intraoperative allogeneic blood transfusion, number of patients treated with allogeneic blood transfusion, postoperative Hct level, and prothrombin time). For studies in which the same author or research team reported results for the same patient population more than once, the most recent or most comprehensive was used. The publication language was restricted to English and Chinese.

Studies published as letters, reviews, case reports, conference reports, or expert opinions, and those in which the process of hemodilution was not implemented according to the established formula [5–6], were excluded.

Data extraction

Two authors (MY, JL) independently extracted and summarized the following data from the included articles: study characteristics (author name, year of publication, country of origin, study design, and sample size); outcomes of the ANH and control groups; amount of intraoperative bleeding; intraoperative allogeneic blood volume; number of patients receiving an allogeneic blood transfusion; postoperative Hct level; and postoperative prothrombin time. Any disagreements were jointly resolved by the authors.

Methodological quality of the studies

The Jadad scale [7] was used to score the methodological quality of RCTs, with a maximum total score of 5; studies with scores ≥ 3 were defined as high quality. The Newcastle-Ottawa Scale [8] was used to evaluate the quality of non-RCTs. The maximum total score was 9, and studies with scores ≥ 7 were considered to be high quality.

Statistical analysis

Meta-analysis was performed using Review Manager version 5.3 (RevMan, Cochrane Collaboration, Oxford, United Kingdom). The following outcomes were considered to be continuous data and were analyzed using weighted mean difference (WMD): allogeneic RBC transfusion; intraoperative bleeding; postoperative Hct level; and postoperative prothrombin time. Statistical significance was set at $P < 0.05$.

The number of patients undergoing allogenic blood transfusions was considered to be dichotomous data and analyzed using pooled odds ratio (OR). In the process of data pooling, the Q-test was used to estimate heterogeneity and the I^2 statistic to measure the extent of inconsistency among the results. A fixed-effects model was used when there was no heterogeneity ($P > 0.1$), while a random-effects model was used when there was heterogeneity. An I^2 value > 50% was regarded to be an indicator of significant heterogeneity [9].

Table 1 Characteristics of the included studies

Author	Year	Country	Study design	Number of patients	Strategy	Age (year)
Sejourne P [22]	1989	France	RCT	22/22	ANH/non-ANH	48 ± 9/52 ± 15
Chen H [17]	1998	America	RE	100/100	ANH/non-ANH	56 ± 5/58 ± 5
Johnson LB [19]	1998	America	RE	13/13	ANH/non-ANH	59.9 ± 3.3/58.1 ± 3.7
Matot I [23]	2002	Israel	RCT	39/39	ANH + LCVP/LCVP	58 ± 12/55 ± 14
Chen GY [10]	2004	China	RE	20/20	ANH/non-ANH	44.9 ± 9.4/43.9 ± 9.9
Yao XH [11]	2006	China	RCT	10/10	ANH/non-ANH	28–65
Lin JQ [12]	2006	China	RCT	20/20	ANH/non-ANH	52.3 ± 4.6/50.3 ± 3.9
Xia KQ [13]	2007	China	RCT	40/40	ANH/non-ANH	60 ± 12/58 ± 14
Balci ST [21]	2008	Turkey	RE	73/41	ANH/non-ANH	36 ± 9/33 ± 8
Jarnagin WR [18]	2008	America	RCT	63/67	ANH + LCVP/LCVP	54 (31–83)/53 (20–77)
Guo JR [14]	2010	China	RCT	15/15	ANH/non-ANH	65.7 ± 8.1/64.3 ± 10.1
Putchakay K [20]	2013	America	RE	96/63	ANH + LCVP/LCVP	62/62
Zhong TM [15]	2013	China	RCT	45/45	ANH/non-ANH	73.1 ± 8.2/72.9 ± 9.5
Sun H [16]	2014	China	RCT	20/20	ANH/non-ANH	45.0 ± 9.4/43.5 ± 7.8

Author	ASA score	Preoperative Hb (g/L)	Intraoperative transfusion trigger	Quality evaluation
Sejourne P [22]	–	13 ± 1.0/12.8 ± 2.0	Hematocrit < 25%	4
Chen H [17]	–	–	–	6*
Johnson LB [19]	–	–	Hematocrit < 28%	6*
Matot I [23]	1 or 2	–	Hematocrit < 20%	4
Chen GY [10]	1 or 2	125.3 ± 12.5/124.1 ± 10.5	Bleeding > 15% blood volume	6*
Yao XH [11]	1 or 2	135.8 ± 9.7/136.6 ± 9.6	Bleeding > 15% blood volume	3
Lin JQ [12]	–	≥ 110	–	4
Xia KQ [13]	1 or 2	–	Hematocrit < 24%	3
Balci ST [21]	1 or 2	13.9 ± 1.6/13.8 ± 1.5	Hematocrit < 25%	6*
Jarnagin WR [18]	3, 46, 14/5, 54, 8#	13.30 (10.60–16.50)/13.20 (10.20–16.10)	Hemoglobin < 7.0 g/dL	4
Guo JR [14]	1 or 2	–	–	4
Putchakay K [20]	3 or 4	13.0/12.6	–	6*
Zhong TM [15]	1 or 2	130.5 ± 16.1/131.9 ± 15.9	Hematocrit < 25%	3
Sun H [16]	1 or 2	138.4 ± 10.8/134.5 ± 9.6	–	3

RCT: randomized controlled trial; RE: retrospective trial; LCVP: low central venous pressure; non-ANH: control group with no intervention; ASA: American Society of Anesthesiologists; #: Number of people distributed in ASA 1, 2, 3. The study score is marked with an *, using the Newcastle-Ottawa Scale to evaluate the quality of non-RCT studies.

Results

Literature selection and characteristics

A total of 482 potentially eligible studies were retrieved in the initial database search. Two authors (MY, JL) independently read the titles and abstracts of the relevant articles, 451 of which were excluded because the abstract or topic did not fulfill the inclusion criteria. Thus, 31 articles were included in the full-text review, of which 17 were excluded: eight because they did not report eligibility data; eight did not calculate the volume of preoperative blood extracted; and one addressed ANH in pediatric liver resections. Ultimately, 14 studies, comprising 1106 patients, were included in the final qualitative analysis (Fig. 1).

Characteristics of the included studies

The basic characteristics of the 14 included studies are summarized in Table 1. Study sample sizes ranged from 20 to 200, and ANH was applied to all patients in the experimental group. Seven [10–16] studies involved Chinese populations, four [17–20] American, and one each Turkish [21], French [22], and Israeli [23]. All articles provided adequate data for analysis. Eight studies[10–11, 14–15, 18–19, 21–22] reported that ANH reduced allogeneic RBC transfusion and intraoperative bleeding, five [12, 14–16, 24] reported that ANH did not impact the coagulation system, and one [20] reported that ANH was well tolerated by patients with higher American Society of Anesthesiology scores who underwent partial liver resection.

Results of meta-analysis

A total of 14 studies were included based on the defined criteria (Fig. 1). According to the study aim, five items were compared: allogeneic RBC transfusion, patients requiring allogeneic transfusion, intraoperative bleeding, postoperative Hct level, and postoperative prothrombin time.

Allogeneic RBC transfusion

Among the included studies, eight [10–11, 14–15, 18–19, 21–22] reported data pertaining to allogeneic RBC transfusion in both the ANH and control groups, comprising a total of 494 patients. Pooled data from these eight studies indicated that ANH may reduce the volume of allogeneic RBC transfusion [WMD –1.99; 95% confidence interval (CI) –2.82 to –1.16; $P < 0.00001$]. There was, however, significant heterogeneity among these studies ($P < 0.00001$; $I^2 = 92\%$; Fig. 2).

Patients requiring allogeneic transfusion

Eight studies [10–11, 14–17, 19, 22] reported the number of patients who required allogeneic transfusion. The overall number of patients was smaller in the ANH group than in the control group (OR 0.13; 95% CI 0.09–0.18; $P = 0.24$). There was moderate heterogeneity among these studies ($P < 0.00001$; $I^2 = 23\%$; Fig. 3).

Intraoperative bleeding

Eight studies [10–11, 14–17, 19, 22] evaluated the amount of bleeding during liver surgery, which was significantly lower in the ANH group (WMD –72.81; 95% CI –136.12 to –9.50; $P < 0.00001$) than in the control group. There was significant heterogeneity among the studies ($P = 0.02$; $I^2 = 82\%$; Fig. 4).

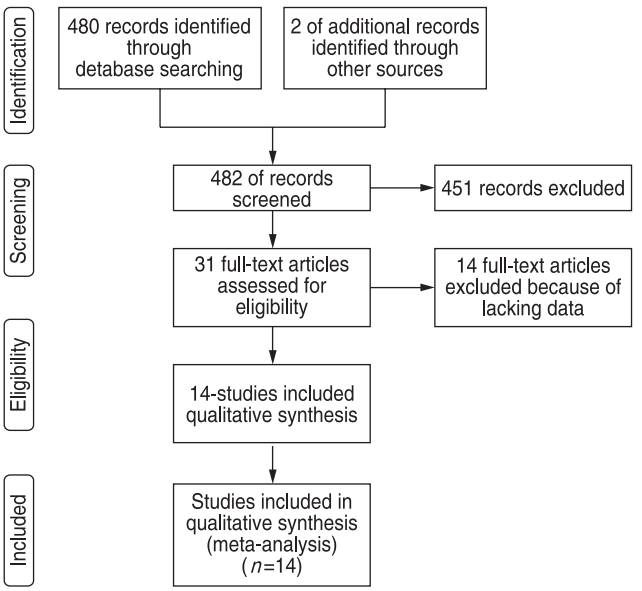

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram depicting the study selection process

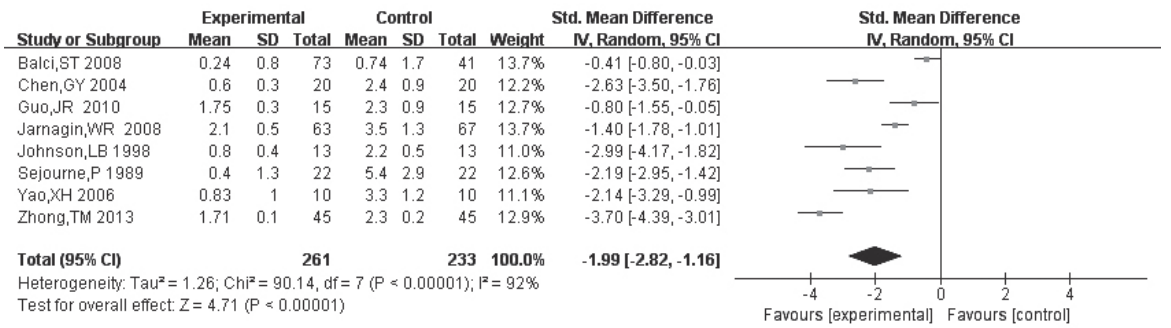

Fig. 2 Meta-analysis of allogeneic red blood cell transfusion

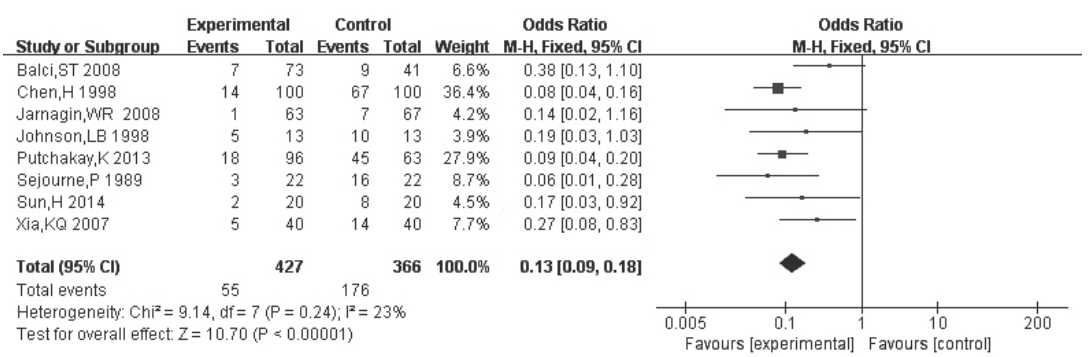

Fig. 3 Meta-analysis of patients requiring allogeneic transfusion

Postoperative Hct level

Eight studies [10–11, 13, 15–17, 19, 23], comprising 574 patients who underwent liver resection, evaluated postoperative Hct level. Meta-analysis revealed that postoperative Hct level was significantly lower in the ANH group than in the control group (WMD –3.38; 95% CI –7.14 to 0.67; P = 0.10); however, there was high heterogeneity among these eight studies (P = 0.00001; I^2 = 99%; Fig. 5). After further analysis, this high heterogeneity may be explained by the lack of a unified indicator for transfusion. In some studies [14, 21, 23], patients in whom Hct level did not reach the level set before surgery did not receive an autologous blood transfusion. The remaining patients received autologous blood transfusion in the ANH group; therefore, the heterogeneity of Hct level significantly increased.

Postoperative prothrombin time

Six studies [12–16, 23], comprising 358 patients who underwent liver resection (ANH, n = 179; control, n = 179), reported postoperative prothrombin time. Meta-analysis indicated no significant difference in postoperative prothrombin time (WMD –0.02; 95% CI –0.68 to 0.32; P = 0.49). There was no significant heterogeneity among these studies (P = 0.65; I^2 = 0%; Fig. 6).

Publication bias

Funnel plots for intraoperative blood transfusion (Fig. 7a), the number of patients who underwent allogenic blood transfusion (Fig. 7b), intraoperative bleeding (Fig. 7c), postoperative Hct level (Fig. 7d), and postoperative prothrombin time (Fig. 7e) demonstrated basic symmetry. As such, no significant publication bias was evident (Fig. 7).

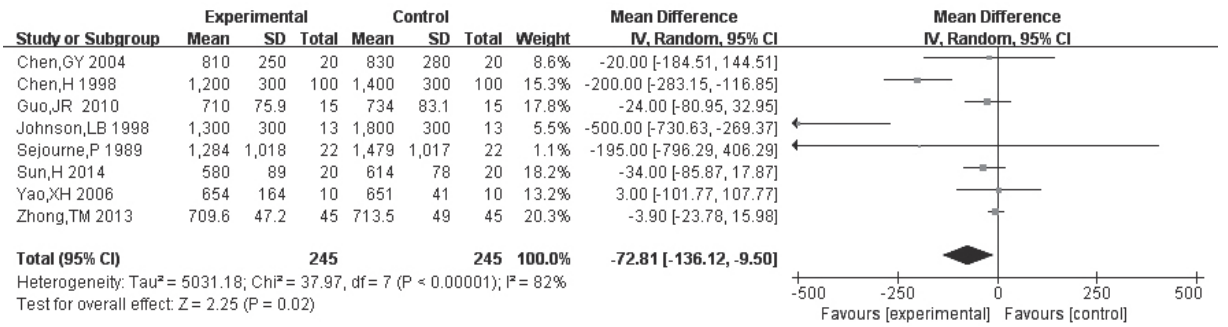

Fig. 4 Meta-analysis of intraoperative bleeding

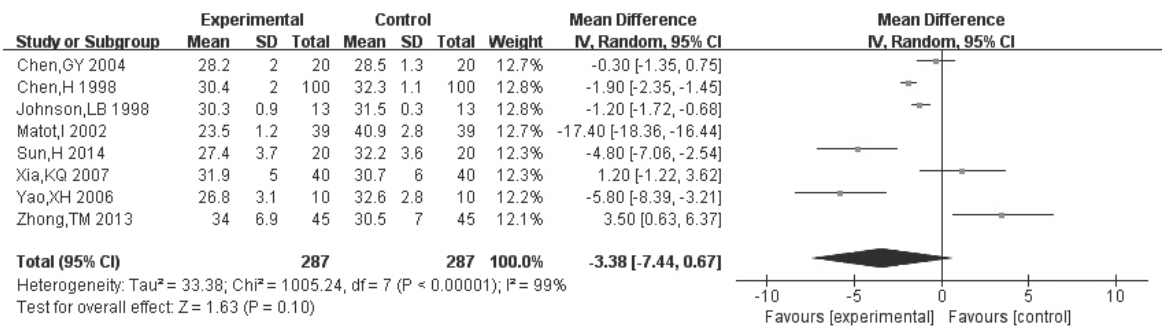

Fig. 5 Meta-analysis of postoperative hematocrit level

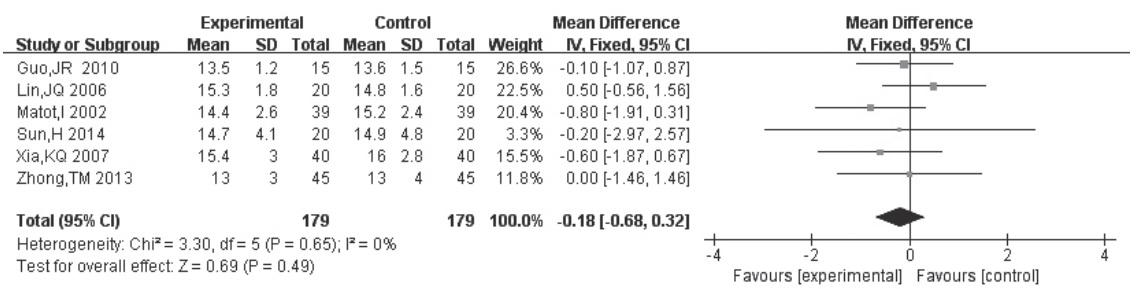

Fig. 6 Meta-analysis of postoperative prothrombin time

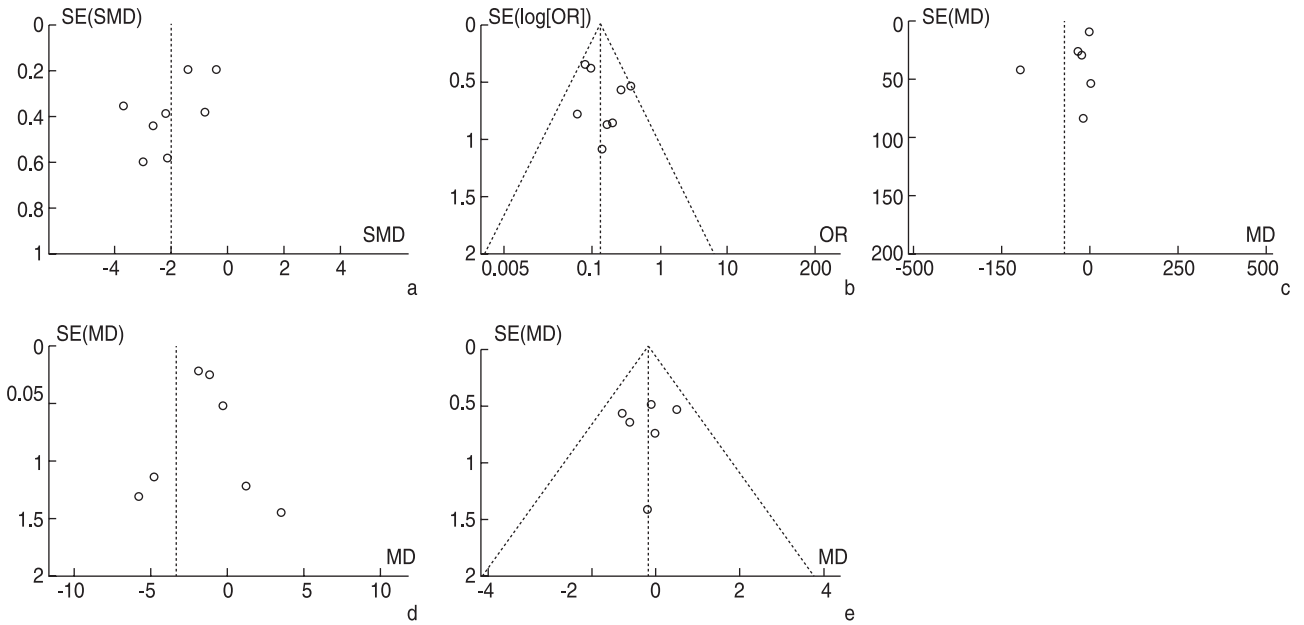

Fig. 7 Funnel plots for meta-analyses. (a) Eight articles in the meta-analysis of blood transfusion; (b) Eight articles in the meta-analysis of number of patients underwent allogenic blood transfusion; (c) Eight articles in the meta-analysis of intraoperative bleeding; (d) Eight articles in the meta-analysis of postoperative hematocrit; (e) Six articles in the meta-analysis of postoperative prothrombin time

Discussion

Although perioperative preparation is usually sufficient for patients with liver cancer, liver resection is still associated with a significant risk for major morbidity, and this is often directly correlated with blood loss and transfusion of allogeneic blood products during surgery [25]. Developing blood conservation techniques has had a positive impact on preventing the risk(s) associated with allogeneic transfusions, including transmission of infectious agents, anaphylaxis, sodium citrate poisoning, and hemolysis. These risks may be a trigger for poor patient prognosis and can aggravate the effects of surgery [26–28]. In addition, for patients undergoing resection for cancer, allogeneic transfusions have the added potential of increasing the risk for cancer recurrence [29–30]. Furthermore, additional important reasons to reduce allogeneic blood transfusions are increased cost and the occasionally tenuous state of the national blood supply, which is sometimes exceeded by demand [31]. A reduction in the need for blood transfusions has been particularly noteworthy, and ANH may be a useful method to resolve the abovementioned risks.

ANH is performed on the day of surgery, which decreases the time the blood is stored *in vitro*. In theory, after surgery, all of the drawn blood is returned to the patient, which reduces the cost of transfusing allogeneic blood. Second, compared with intraoperative cell salvage, ANH does not require additional equipment or specially trained clinicians and is easy to perform. Therefore, among the strategies for reducing intraoperative bleeding and salvaging blood, ANH is preferred in terms of ease of operation and cost. However, ANH has not been widely used in liver resection primarily due to persistent uncertainty regarding its safety and efficacy. Findings from our study may provide the supportive evidence needed to apply ANH during liver surgery.

Evidence-based data regarding ANH from other meta-analyses [32–33] during large-scale surgeries did not demonstrate the safety and efficacy of ANH in liver resection. An investigation by Barile [32] included 23 studies addressing ANH use during cardiac surgery. Although the outcomes demonstrated that ANH can be successfully used during cardiac surgery, its application during liver surgery, and whether it can achieve the same effect, was not determined. Another analysis [33] included only two clinical studies on liver surgery and a subgroup analysis of the two articles [10, 34]. The subgroup outcomes indicated that, although ANH reduced the number of blood transfusions, it did not reduce the amount of bleeding. Furthermore, it has not been proven that ANH is safe and effective during liver surgery, and there was high heterogeneity in the subgroup analysis. In a study by Moggia *et al* [35], the included studies focused on the surgical techniques used to reduce bleeding during liver resection, rather than on blood conservation methods. A meta-analysis by Segal [36] published in 2004 noted that ANH does not play an active role in reducing

intraoperative allogeneic blood input. The type of surgery using ANH was not reported in this article, and our meta-analysis only included studies addressing liver surgery. With advances in imaging and surgical techniques, we have a better understanding of the anatomy of the liver, which leads us to believe that ANH is now safer for patients.

Our meta-analysis comprised 14 studies investigating the effects of ANH during liver surgery. In agreement with our hypothesis, the results demonstrated that ANH can safely and effectively reduce blood transfusions and bleeding during liver surgery. Moreover, our pooled analysis of postoperative prothrombin times revealed that patient coagulation systems were not impaired, which suggests that ANH is safe. Therefore, if patients tend to lose a significant volume of blood during liver surgery, ANH may be an alternative method of preserving blood.

One of the results of our meta-analysis demonstrated a statistically significant decrease in the number of allogeneic RBC transfusions (WMD –1.99; 95% CI –2.82 to –1.16; $P < 0.00001$). This suggests that ANH can reduce the possibility of blood transfusions during liver resection; however, there was high heterogeneity ($P < 0.0001$; $I^2 = 92\%$) among the studies, the main reason for which may be the results of the intraoperative transfusion trigger being different among the eight studies, with some having an Hb level < 7.0 g/dL [18] and Hct levels < 28% [19], 25% [21] and 20% [23], and autogenous blood transfusions that were not counted in the total number of blood transfusions [18]. Our findings suggest that, in future studies, the transfusion threshold should be strictly designated when attempting to optimize outcomes.

Furthermore, in our study, compared with the control group, a slightly lower postoperative Hct level was found in the ANH group after surgery and the difference was statistically significant (WMD –3.38; 95% CI –7.14 to –0.67; $P < 0.00001$); however, the lowest Hct level was > 25% in the seven articles. Habler *et al* [37] reported that if the Hct level is not < 20%, the oxygen supply to the patient's tissues and organs is stable [38–39]. Due to the decrease in viscosity when blood is diluted, cardiac output increases, and tissue perfusion improves and is compensated [40]. These results suggest that the effect of ANH on Hct level is safe.

Although the results of this meta-analysis support the safety and efficacy of ANH and its positive outcomes during liver surgery, the heterogeneity of the allogeneic RBC transfusion group and intraoperative bleeding group remains high. We cannot definitively explain this heterogeneity; however, we propose several possible reasons. First, this meta-analysis lacked recent research on ANH use during liver resection, given that one-half of the included studies were published before 2010. Second, among the included studies, blood transfusion indicators were not uniform, which may have affected the anesthesiologist's tendency to suggest transfusions to the patients. Finally, because there are many ways to evaluate intraoperative bleeding, accurate assessment is difficult [41].

Conclusion

Results of the present review and meta-analysis demonstrated that ANH can reduce bleeding during liver resection and the necessity for blood transfusions without affecting the patient's coagulation system postoperatively. Nevertheless, a well-designed multicenter study of ANH use during liver surgery is needed to further support its safety and efficacy.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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ORIGINAL ARTICLE

Stereotactic radiotherapy for the treatment of nasopharyngeal carcinoma: a Meta-analysis of 1371 cases in China

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Abstract

Objective The aim of this study was to clarify the outcomes of stereotactic radiotherapy for the treatment of local residual and (or) local recurrent nasopharyngeal carcinoma and to promote scientific clinical treatment and research on it in China and other countries by creating a large data resource.

Methods This Meta-analysis conducted a literature search using the China National Knowledge Infrastructure database for all clinical research articles on stereotactic radiotherapy for the treatment of local residual and(or) local recurrent nasopharyngeal carcinoma in China. Data on patient cohort numbers and other research factors were recorded for every relevant clinical research article. Calculated and analyzed these fact sheets to pave the way for the objective of this project.

Results A total of 40 clinical research articles including 1,371 patients in China from 1998 to 2012 were identified. The average cohort size was 34 patients (range 9–98 patients). The average total radiation dose range was 16–33.6 Gy. The average study or treatment duration was 3.51 years. The calculated average follow-up time was 31.59 months.

Conclusion The study provided the largest resource for further research and Meta-analyses to determine the clinical pathway of stereotactic radiotherapy for the treatment of local residual and (or) local recurrent nasopharyngeal carcinoma. The results indicated that variability in the total radiation dose, treatment or research time, and follow-up duration may have contributed to the complications and side effects of stereotactic radiotherapy for local residual and (or) local recurrent nasopharyngeal carcinoma in China. The calculated average total radiation dose, follow-up time, and treatment and research durations may be referenced for future treatment and research. This study also proposed worldwide cooperation for the meta-analysis of research articles on stereotactic radiotherapy for treating local residual and (or) local recurrent nasopharyngeal carcinoma.

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Key words: stereotactic radiotherapy; residual nasopharyngeal carcinoma; recurrent nasopharyngeal carcinoma; Meta-analysis; total radiation dose; radiotherapy

There is a dose-response relationship between tumor control and radiation [1–3]. The local residual and local recurrence rates of nasopharyngeal carcinoma (NPC) are 10% and 30%, respectively [4]. The local recurrence of NPC after radiotherapy (RT) remains a major cause of treatment failure.

The locoregional control rate of NPC has improved significantly in the past decade due to advances in imaging, RT technique, and the use of combined treatment modalities. The reported 5-year local control rates of NPC in modern series ranged from 81% to 85%, with control rates exceeding 90% in patients with T1 disease [5–6]. Despite the improved outcomes in local control, local recurrence still represents a major cause of mortality and morbidity in advanced stages and management of local failure remains an important and challenging issue in NPC treatment.

Aggressive salvage treatment is generally recommended for local recurrence since long-term control can still be achieved in some patients.

Since Konziolka *et al*. reported the use of stereotactic radiosurgery (SRS) to treat one case of recurrent NPC

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in 1991, radiation oncologists have applied stereotactic radiotherapy (SRT) for extracranial tumors, such as those in the head, neck, and body [7]. Multiple medical institutions reported the use of SRS or fractionated stereotactic radiotherapy (FSRT) as a boost for residual NPC after initial RT. Since 1991, retrospective studies have analyzed the efficacy and complications of SRS or FSRT in residual NPC disease.

Retrospective studies have also considered SRT as a boost treatment for residual or recurrent NPC, reporting improved local control and decreased complications [3, 8]. However, the mortality due to nasopharyngeal massive hemorrhage in residual or recurrent NPC after FSRT ranged from 16.0% to 22.2% [9–17].

Other complications of SRS or FSRT can also occur. For example, necrosis of the nasopharyngeal mucous membrane, infection, cranial nerve injuries, cranial neuropathies, temporal lobe necrosis, *et al*. have been reported [15, 17–19].

China, especially the southern region, has higher morbidity due to nasopharyngeal carcinoma. SRT has been widely used clinically since 1991 when its benefits as a boost treatment were reported in residual or recurrent NPC.

Retrospective and cohort studies have assessed the efficacy and complications of SRT in the clinical setting, the results of which may allow radiation oncologists to more effectively treat patients with nasopharyngeal carcinoma. However, Chinese studies and their reporting are inconsistent in radiation dose, dose fraction plans for SRT, and other management of SRT in clinical applications.

The complications of SRT are key factors in determining if the treatment is warranted and remain a significant challenge for radiation oncologists. It is imperative to determine how to reduce SRT complications and create a better clinical pathway for SRT. Therefore, the present study searched for clinical research articles on SRT for the treatment of residual and (or) recurrent nasopharyngeal carcinoma in China between 1998 and 2012 indexed in the China National Knowledge Infrastructure (CNKI) network, with special attention to the patient cohort numbers, radiation dose, and other factors. The research objectives were to enhance the quality of SRT and to pave the way for the creation of a clinical pathway for the application of SRT.

Until now, there has been no report on this kind of analysis; namely, the identification of articles through a search of the titles and keywords of English-language literature from the MEDLINE database instead performed through a CNKI search of the Chinese and English titles of papers and keywords in Chinese-language literature.

Materials and methods

Literature search

The present study searched the CNKI for all relevant clinical research articles on SRT for the treatment of nasopharyngeal carcinoma in China.

The CNKI is the largest digital library in the world in Knowledge Resource. It is operated by Tsinghua University and supported by the Chinese government. It was initiated by World Bank in 1998 [20]. The CNKI contains a China Knowledge Resource Integrated Database for all professions, including medical science and its radiation oncology branch. The CNKI includes a database of qualified medical journals, including all journals on radiation oncology. The CNKI can be reached via the Internet, providing a convenient way to search for clinical research articles on SRT for the treatment of residual and (or) recurrent nasopharyngeal carcinoma in China.

The CNKI was searched for clinical research articles of SRT for residual and (or) recurrent nasopharyngeal carcinoma in China via the Internet on a personal computer. The identified articles were then checked. Information for some articles was obtained by paying the CNKI. The author was only the individual performing the literature search.

The CNKI provides directions for performing searches. However, due to the network limitations, not all information could be obtained and calculated from the 40 identified articles. Moreover, only the latest clinical research article on SRT published in 2012 was available directly from the Chinese Medical Journal at the research time [21].

Inclusion criteria

Data from the identified clinical research articles on SRT for residual and (or) recurrent nasopharyngeal carcinoma in China were recorded in the common reference format for articles included in qualified journals. The patient numbers, total radiation doses, average follow-up times, average research treatment time, and other information were recorded. These data were used to calculate fact sheets describing the clinical studies to achieve the study objective.

Statistical analysis

The statistical method was straightforward: the related facts of the published articles were obtained and the total numbers, averages, etc. were calculated.

Data extraction and quality assessment

Because all data were numbers and article characteristics, their total or average numbers were calculated. Therefore, data extraction and quality assessment were straightforward. Data extraction and quality assessment were performed by re-confirming the findings.

Results

The article first authors, journals, journal grade, patient numbers, publication year, total radiation doses, treatment or study period duration, and follow-up information were listed in Table 1.

A total of 40 clinical research articles on SRT for the

Table 1 Authors, journal, journal grade, patient cohort size, publication year, study period, and follow-up information of the included studies

No.	Author	Published year	Journal	Grade of Journal	Patient numbers	Total radiation dose	Treatment year	Hospital grade	Time of follow-up
1	Deng XQ, *et al*.	1998	J Harbin Med Univ	N	9	1998	1996.12–1998.2		3 months
2	Cao YZ, *et al*.	2000	Chin J Clin Oncol	N&K	10	2000	1997	Province	
3	Xiao JP, *et al*.	2000	Chin J Radiat Oncol	N&K	50	24–30Gy	1995.9.20–1998.12.30	National	
4	Cui SX, *et al*.	2001	Chin J Radiat Oncol	N&K	18	24–40Gy; 24–30Gy; 40–42Gy (divided three groups)		National	
5	Feng J, *et al*.	2001	Guizhou Med J	P	50	(600–800cGy)x3		Province	
6	Xiao H, *et al*.	2001	Cancer Res Prev Treat	P	16	12–25Gy		National	6–12 months
7	Xiao JP, *et al*.	2001	Int J Radiat Oncol Biol Phys	Interna-tional	50	14–35Gy	1995.9.20–1998.12.30	National	year 1, 2, 3
8	Wu SX, *et al*.	2002	Chin J Cancer	N&K	12		1998.9–2000.9	National	
9	Xu WD, *et al*.	2002	Jiangsu Med J	P&K	44	20–49Gy		National	
10	Zhao SX, *et al*.	2002	Chin J Clin Oncol	N&K	16		1996.10–2001.1	National	
11	Chen HJ	2003	Acta Med Sin	P	18	8–24Gy		Province	
12	Zhong J, *et al*.	2003	Pract J Cancer	P	33	12–48Gy	1997.7–2001.7	Province	
13	Zhao SX, *et al*.	2003	Chin J Radiol Med Prot	N&K	16		1996.10–2001.1	National	
14	Guo YX	2003	Shaanxi Med J	P&K	13	(6–8Gy)x3		Province	
15	Jiang W, *et al*.	2003	Tianjing Med J	P&K	27	(5–8Gy)x(5–8)times	1997.6–2002.2	Province	
16	Ning XJ, *et al*.	2003	Cancer Res Clin	N	32		2000.9–2002.5	City	
17	Liu HP, *et al*.	2003	J Third Mil Med Univ	N&K	24		1995–1998	National	
18	WU SX, *et al*.	2004	Chin J Radia Oncol	N&K	30	Residual: 18Gy; Recurrence: 48Gy	1999.9–2002.6.30	National	15 months
19	Cheng GJ, *et al*.	2004	Chin J Cancer Prev Treat	P	22	30–40Gy	Case control study with conventional RT 20 patients	City	3~6 months
20	Shi QF, *et al*.	2004	Shenyang Mil Med	P	38	12–48Gy (Median dose 34 Gy)	1999.4–2001.4	Province	
21	Huang BJ, *et al*.	2004	Cancer Res Clin	N	27		1998.5–2002.12 After Con-ventional RT, SRT	City	

No.	Author	Published Year	Journal	Grade of Journal	Patient numbers	Total radiation dose	Treatment year	Hospital grade	Time of follow-up
22	Song YH, *et al*.	2004	Chin Clin Oncol	N	16		1997.7–2000.12	Province	
23	Pang XL, *et al*.	2004	J Third Mil Med Univ	N&K	32	Median dose 12Gy (8–20Gy)	1998.1–2001.12	National	Year 1, 2, 3
24	Ao F, *et al*.	2004	Pract J Cancer	P	23	24–64Gy, Median dose 52.2Gy		Province	Year 1, 2.
25	Lang JY, *et al*.	2004	Sichuan Med J	P	20 (14 cases FSRT+ other RT; 6 cases FSRT.			Province	3 years
26	Xiao JP, *et al*.	2005	Chin J Radiat Oncol	N&K	98	12–24Gy		National	1–8 years
27	Chen S, *et al*.	2005	J Guangxi Med Univ	P&K	34		2001.11–2003.11	Province	
28	Guo YX, *et al*.	2006	J Zhengzhou Univ (Med Sci)	P&K	13		1999.1–2001.12	Province	
29	Li YM, *et al*.	2006	Cancer Res Clin	N	54 (two groups)	83.23Gy and 99.09Gy (two groups)	1996–2000	City	Year 1, 3, 5
30	Wu SX, *et al*.	2007	Int J Radiat Oncol Biol Phys	Interna-tional	90, with 34 per-sistent; 56 recu-rrence	Median FSRT dose was 18 Gy in three fractions (Group 1) or 48 Gy in six fractions (Group 2).	1999.9–2005.12	National	Median follow-up was 20.3 months
31	Wang RZ, *et al*.	2007	Cancer Res Prev Treat	N&K	31	Median dose 16Gy (12–20Gy)	2004.2–2006.10	Province	Year 1, 2, 3
32	Wu SX, *et al*.	2007	Chin J Radiat Oncol	N&K	90	Median FSRT dose was 18 Gy in three fractions (persistent Group 1) or 48 Gy in six fractions (recurrence Group 2)	1999.9–2005.12	National	Median follow-up was 24.9 months (3.3–86.3)
33	Wu SX, *et al*.	2007	J Oncol	P	90, with34 persis-tent; 56 recurr-ence	Median FSRT dose was 18 Gy in three fractions (persistent Group 1) or 48 Gy in six fractions (recurrence Group 2)	1999.9–2005.12	National	Median follow-up was 24.9 months (3.3–86.3)
34	Zhang SG, *et al*.	2008	J Chin Med Abstr (Oncology)	N	36			City	
35	Lin GJ	2008	J Mod Oncol	N	24	8Gy–24Gy	2001.8–2003.11	Province	
36	WANG RZ, *et al.*	2008	China Oncol	N&K	41	12–28Gy (Median dose: 16Gy)	2004.2–2007.4	Province	Median follow-up was 28 months (3–41 months)
37	Zhou ZJ, *et al*.	2009	J Basic Clin Oncol	P	20	25Gy		Province	Year 1, 2, 3
38	Cao Yi	2010	Mod Med Health	P	32	12Gy (Median dose)		City	Year 1, 2, 3
39	Li L, *et al*.	2010	J Mil Surg in Southwestern China	P	36	12–20Gy		Province	Year 1, 2, 3
40	Liu F, *et al.*	2012	Chin Med J	N&K	36	10.0–24.0 Gy (median, 16.5 Gy)	2006.8–2010.8	National	Median follow-up time was 34 months (range, 12–59 months)

K. National key medical Journal; N. National grade Journal; P. Province grade Journal.

treatment of residual and (or) recurrent nasopharyngeal carcinoma in China were identified. The earliest and most recent published articles were from 1998 and 2012, respectively. The 40 studies included a total of 1,371 patients. The average cohort size was 34 patients, ranging from 9 to 98 patients.

Among the journals in which these research articles were published 19 were national key medical journals. Seventeen were provincial-grade medical journals and 21 were national-grade medical journals.

Among the research hospitals or institutes in which the clinical studies were performed, 16 were national-grade, 17 were provincial-grade, and 6 were city-grade hospitals. Generally, the quality of national-grade hospitals is higher than that of provincial-grade hospitals and the quality of provincial-grade hospitals is higher than that of city-grade hospitals.

Among the 40 research articles, 27 studies indicated or provided data to calculate the total radiation dose. Twenty studies provided data to calculate the average radiation dose (16–33.6 Gy). The average radiation dose could not be calculated in seven articles because their units of measurement were not consistent. The highest total radiation dose was 99.09 Gy.

The average SRT treatment or study duration among 26 studies was 3.51 years, ranging from 1.25 to 6.33 years. The earliest reported start time for SRT and study was September 20, 1995.

The follow-up durations of the 19 studies for which this information was available ranged from 3 months to 8 years. The average follow-up time for 19 studies was 31.59 months.

The first author, article title, journal, publication year, volume, and page are listed in Table 2.

Table 2 The author of article, article title, published Journal, published year, volume and page

No.	Author	Article title	Journal published, and published year	Volume and number and page
1	Deng XQ, *et al*.	Treatment of residual or recurrent nasopharyngeal carcinoma by X-knife with 9 patients	J Harbin Med Univ (Chinese), 1998	48 (3): 63–64
2	Cao YZ, *et al*.	Stereotatic radiotherapy on 10 patients with nasopharyngeal carcinoma	Chin J Clin Oncol (Chinese), 2000	38 (3): 72–73
3	Xiao JP, *et al*.	Fractionated stereotatic radiotherapy for 50 patients with recurrent and residual nasopharyngeal carcinoma	Chin J Radia Oncol (Chinese), 2000	14 (4): 40–44
4	CUI SX, *et al*.	Nasopharyngeal hemorrhage after radiotherapy of nasopharyngeal carcinoma	Chin J Radiat Oncol (Chinese), 2001	15 (3): 39–41
5	Jin Fe, *et al*.	Fractionated stereotatic radiotherapy on 50 patients with residual or recurrent nasopharyngeal carcinoma	Guizhou Med J (Chinese), 2001	26 (2): 119–120
6	Xiao H, *et al*.	Preliminary clinical study of the effect of stereotactic radiotherapy boost following conventional radiotherapy on local control rate of primary nasopharyngeal carcinoma	Cancer Res Prev Treat (Chinese), 2001	29 (5): 405–406
7	Xiao JP, *et al*.	Fractionated stereotatic radiotherapy for 50 patients with recurrent and residual nasopharyngeal carcinoma	Int J Radiat Oncol Biol Phys, 2001	51: 164–170
8	Wu SX, *et al*.	Fractionated stereotactic radiotherapy for locally recurrent nasopharyngeal carcinoma, the primary result	Chin J Cancer (Chinese), 2002	21 (7): 804–805
9	Xu WD, *et al*.	Stereotactic radiotherapy for locally residual and recurrent nasopharyngeal carcinoma	Jiangsu Med J (Chinese), 2002	28 (6): 441-441+397
10	Zhao SX, *et al*.	Stereotactic radiotherapy for locally residual and recurrent nasopharyngeal carcinoma	Chin J Clin Oncol (Chinese), 2002	40: 64–65
11	Chen HJ	Fractionated stereotatic radiotherapy on 24 patients with nasopharyngeal carcinoma	Acta Med Sin (Chinese), 2003	16: 823–824
12	Zhong J, *et al*.	Stereotactic radiotherapy for residual or recurrent nasopharyngeal carcinoma	Pract J Cancer (Chinese), 2003	18: 74–76
13	Zhao SX, *et al*.	Nasopharyngeal hemorrhage after stereotactic radiotherapy for locally residual and recurrent nasopharyngeal carcinoma	Chin J Radiol Med Prot (Chinese), 2003	23 (4): 52–53
14	Guo YX	Fractionated stereotactic radiotherapy for patients with residual or recurrent nasopharyngeal carcinoma	Shaanxi Med J (Chinese), 2003	41: 993–994
15	Jiang W, *et al*.	Stereotactic radiotherapy with 27 patients following conventional radiotherapy in nasopharyngeal carcinoma	Tianjing Med J (Chinese), 2003	45 (11): 710–712
16	Ning XJ, *et al*.	Fractionated stereotatic radiotherapy with 32 patients of nasopharyngeal carcinoma after primary conventional radiotherapy	Cancer Res Clin (Chinese), 2003	18: 262–263

No.	Author	Article title	Journal published, and published year	Volume and number and page
17	Liu HP, *et al*.	Treatment of nasopharyngeal carcinoma by X-knife	J Third Mil Med Univ (Chinese), 2003	25 (20): 1871–1872
18	WU SX, *et al*.	Fractionated stereotactic radiotherapy for locally residual or recurrent nasopharyngeal carcinoma	Chin J Radiat Oncol (Chinese), 2004	23 (1): 10–13
19	Cheng GJ, *et al*.	Late course stereotactic radiotherapy locally recurred nasopharyngeal carcinoma after radiotherapy: Including clinical analysis of 42 cases	Chin J Cancer Prev Treat (Chinese), 2004	11 (5): 527–528
20	Shi QF, *et al*.	Stereotactic radiotherapy for residual or recurrent nasopharyngeal carcinoma after radiotherapy	Shenyang Mil Med, 2004	17 (2): 103–105
21	Huang BJ, *et al*.	Fractionated stereotatic radiotherapy on 27 patients with residual nasopharyngeal carcinoma	Cancer Res Clin (Chinese), 2004	19 (1): 38–39
22	Song YH, *et al*.	Stereotatic radiotherapy on 16 patients with residual or recurrent nasopharyngeal carcinoma	Chin Clinl Oncol (Chinese), 2004	10 (2): 180–181
23	PANG XL, *et al*.	Clinical study of stereotactic radiotherapy boost on improvement of local control and survival of nasopharyngeal carcinoma	J Third Mil Med Univ (Chinese), 2004	26 (24): 2203–2205
24	Ao F, *et al*.	Fractionated 3-Dimensional Stereotactic Radiotherapy for Locally Recurrent Nasopharyngeal Carcinoma	Pract J Cancer (Chinese), 2004	20 (5): 530–532
25	Lang JY, *et al*.	Prospective research on the efficacy of residual or recurrent nasopharyngeal carcinoma treated with fractionated stereotactic radiotherapy (SRT)	Sichuan Med J (Chinese), 2004	25: 951–955
26	Xiao JP, *et al*.	Fractionated radiosurgery for residual lesion after the first course of radiotherapy for nasopharyngeal carcinoma	Chin J Radiat Oncol (Chinese), 2005	19 (2): 8–11
27	Chen S, *et al*.	Clinical study on fractionated stereotatic radiotherapy for 34 patients with nasopharyngeal carcinoma	J Guangxi Med Univ (Chinese), 2005	35 (2): 308
28	Guo YX, *et al*.	Stereotactic radiotherapy with 13 patients for locally residual or recurrent nasopharyngeal carcinoma	J Zhengzhou Univ (Med Sci) (Chinese), 2006	50: 1196–1197
29	Li YM, *et al*.	Evaluation of late course fractionated stereotactic radiotherapy for nasopharyngeal carcinoma	Cancer Res Clin (Chinese), 2006	21 (10): 672–673
30	Wu SX, *et al*.	Outcome of fractionated stereotactic radiotherapy for 90 patients with locally persistent and recurrent nasopharyngeal carcinoma	Int J Radiat Oncol Biol Phys, 2007	69: 761–769
31	Wang RZ, *et al*.	Fractionated stereotatic radiotherapy boost on 31 patients with residual nasopharyngeal carcinoma	Cancer Res Prev Treat (Chinese), 2007	35 (10): 773-776
32	Wu SX, *et al*.	Prognostic factors of locally persistent and recurrent nasopharyngeal carcinoma treated with stereotactic radiotherapy	Chin J Radiat Oncol (Chinese), 2007	21 (6): 407–410
33	Wu SX, *et al*.	Preliminary study of target volume delineation for locally persistent and recurrent nasopharyngeal carcinoma treated with fractionated stereotactic radiotherapy	J Oncol (Chinese), 2007	31 (5): 355–358
34	Zhang SG, *et al*.	Fractionated stereotactic radiotherapy for locally residual or recurrent nasopharyngeal carcinoma	J Chin Med Abstr (Oncology) (Chinese), 2008	27 (4): 351
35	Lin GJ	Fractionated stereotactic radiotherapy for locally residual or recurrent nasopharyngeal carcinoma	J Mod Oncol (Chinese), 2008	16 (6): 940–941
36	Wang RZ, *et al.*	Fractionated stereotactic radiotherapy for locally residual or recurrent nasopharyngeal carcinoma	China Oncol (Chinese), 2008	18 (2): 128–134
37	Zhou Zj, *et al*.	Treatment of 20 patients with locally Residual nasopharyngeal carcinoma by X-knife	J Basic Clin Oncol (Chinese), 2009	19 (2): 170–171
38	Cao Y	Stereotactic radiotherapy for nasopharyngeal carcinoma after first primary radiotherapy	Mod Med Health (Chinese), 2010	26 (1): 98–99
39	Li L, *et al*.	Stereotactic radiotherapy for nasopharyngeal carcinoma after first primary radiotherapy	J Mil Surg Southwestern China (Chinese), 2010	20 (4): 678–679
40	Liu F, *et al.*	Fractionated stereotactic radiotherapy with vagina carotica protection technique for local residual nasopharyngeal carcinoma after primary radiotherapy	Chin Med J, 2012	125 (14): 2525–2529

Discussion and conclusion

SRT is effective for local residual and (or) local recurrent NPC. However, its complications and side effects are obstacles for the treatment of local residual and (or) local recurrent NPC. It will take considerable time to overcome these challenges. There is currently no standard clinical pathway for SRT for treating local residual and (or) local recurrent NPC. Thus, deadly complications still occur.

To our knowledge, this is the first and largest study that clarified the best management strategies regarding SRT for the treatment of local residual and (or) local recurrent NPC, considering the number of patients and clinical pathway initiatives.

To explore the reasons for the complications and side effects of SRT for the treatment of local residual and (or) local recurrent NPC, this study searched and summarized the full texts of relevant published articles in China from 1998 to 2012, including 1371 patients. The journals and their grades, the research hospital grades, the total radiation dose, the time of treatment or research on SRT, and follow-up duration were summarized and analyzed.

Variability in journal grade was also observed. Only two studies were published in an international journal, the International Journal Radiation Oncology, Biology, Physics. Among the 40 articles, research patient cohorts were used repeatedly in different articles. Thus, the quality of these 40 studies did not meet internationally accepted standards'for a more formal tone.

In the context of hospital grade, research hospitals in China are of better quality, as assessed by Chinese standards.

This study observed variability in the total radiation dose, research or treatment time, and follow-up duration. The highest total radiation dose was 99.09 Gy. The longest and shortest research or treatment times were 6.33 and 1.25 years, respectively, and the longest and shortest follow-up durations were 8 years and 3 months, respectively.

To promote the quality of the studies and SRT, the total radiation dose, treatment time, and follow-up duration should be standardized.

The present analysis included 40 studies and 1,371 patients to explore the clinical pathway of SRT for local residual and (or) local recurrent NPC and provides information on these published articles, which can be accessed by medical professionals from the internet and libraries.

This meta-analysis has some limitations. First, the CNKI did not provide access for downloading the full text of all 40 of the published articles. Only the abstracts for some articles were included in the CNKI. Due to research limitations, the printed articles could not be obtained. Third, some studies did not report radiation doses in Gy. Therefore, the statistical analysis did not include all 40 articles. Because some target information cannot be found on the CNKI. However, we have provided information on these articles and their publication journals for reference and further research.

In conclusion, this meta-analysis provided a large resource for further research and meta-analyses to identify the clinical pathway for SRT for the treatment of local residual and (or) local recurrent NPC.

The results of this study indicated that a lack of consistency in the total radiation dose, the research or treatment time, and the follow-up duration may contribute to complications and side-effects in SRT for the treatment of local residual and (or) local recurrent NPC.

The calculated average total radiation dose in this study, 16–33.6 Gy, may be referenced for future SRT for the treatment of local residual and (or) local recurrent NPC.

The calculated average follow-up time, 31.59 months, may be referenced in future research and clinical quality control.

The calculated average SRT research or treatment time, 3.51 years, may be referenced in future clinical practice.

Cooperation among multiple centers worldwide is required for meta-analyses of more studies on SRT for the treatment of local residual and (or) local recurrent NPC. Therefore, we propose this global effort.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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REVIEW ARTICLE

Mental distress evaluation and intervention for cancer patients*

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Abstract

Mental distress is prevalent among cancer patients. Many measurements have been developed to screen and evaluate such distress. About one-third of the persons with cancer will experience significant levels of distress, requiring targeted psychosocial intervention. Mental distress has been endorsed as the sixth vital sign by the International Psycho-Oncology Society (IPOS) in 2009. The need for effective screening and psychological interventions is well recognized as a necessary, integral part of oncology care. This systematic review examines the psychometric properties of the existing tools used to screen patients for emotional distress and the applicable intervention methods.

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Cancer is one of the leading causes of global morbidity and mortality [1–2], causing 8.8 million deaths in 2015. Globally, nearly one-sixth of deaths are caused by cancer [3]. The economic impact of cancer is large and growing; the estimated total annual economic cost of cancer in 2010 was about 1.16 trillion US dollars [4].

Cancer patients not only suffer from physical pain, but their quality of life is also largely affected by psychological distress. According to Vachon [5], one-third of cancer patients experience mental distress. The National Comprehensive Cancer Network (NCCN) defines distress as "a multifactorial unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fear. Such can transform into disabling conditions, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis [6]. At present, mental distress has become the sixth vital sign [7]. Therefore, effective identification of the psychological distress level of cancer patients and effective intervention are very important for the treatment and quality of life for cancer patients. This systematic review below examines the psychometric properties of the existing tools used to screen patients for emotional distress and the applicable methods of intervention.

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Evaluation measurements

Shneidman proposed a paper-and-pencil test (with pictures), called the Psychological Pain Assessment Scale (PPAS), for assessing the level of "psychache" experienced by individuals, a term he defines as follows: "Psychache is the hurt, anguish, or ache that takes hold in the mind…the pain of excessively felt shame, guilt, fear, anxiety, loneliness, angst, dread of growing old or of dying badly." (p. 13). The PPAS is an attempt to bridge the interpersonal phenomenological gulf (or problem) regarding psychological pain by means of using visual stimuli (pictures); it is an obvious application of Murray's TAT principle [8].

Orbach *et al* [9] developed the Orbach & Mikulincer Mental Pain Scale (OMMP) based on the theory of Shneidman [8] and Bolger [10]. This self-rating 5-point Likert scale with 44 items consists of nine factors: (1) irreversibility, (2) loss of control, (3) narcissist wounds, (4) emotional flooding, (5) freezing, (6) self-estrangement, (7) confusion, (8) social distancing, and (9) emptiness (4 aspects). The higher the value on each factor, the higher the mental pain. Some studies [11] performed a confirmatory factor analysis on OMMP and confirmed the five-factor model after excluding some items and showed acceptable internal consistency levels and test-retest reliability.

Holden *et al* [12] developed the Psychache Scale (PAS), a more concise tool for assessing psychological distress, with 13 items rated on a 5-point scale. PAS assesses the frequency of psychological distress rather than its intensity. Similar to OMMP, PAS aims to explore the relationship between psychological distress and suicidal tendencies. The reliability and validity test of the Chinese version of the scale [13] shows that the fitting index of the factor form structure is good (χ^2/df = 2.66, RMSEA = 0.06, CFI = 0.97, NFI = 0.95, IFI = 0.97). The internal consistency coefficient of the scale is 0.90, the split-half reliability is 0.80, and the test-retest reliability after 2 weeks is 0.60.

Steven Mee *et al* [14] developed the Mee-Bunney Psychological Pain Assessment Scale (MBPPAS) to assess the frequency and intensity of psychological distress in patients with major depressive episodes. This 5-point Likert scale includes 10 items, to provide clinicians with a quick assessment of psychological pain. The Cronbach's alpha coefficient of the scale in the depression test was 0.827, with the control group at 0.941 [14]. The revision of MBPPAS in other countries also shows good reliability and validity (Cronbach's alpha coefficient is 0.95, and the total score of the project is 0.51–0.89) [15].

The Three-Dimensional Psychological Pain Scale (TDPPS) is a self-evaluation scale with a total of 17 items of the Likert 5-point scale. It is divided into three dimensions of pain arousal (with eight items), painful feelings (with six items), and active pain avoidance (with three items). The original intention of the scale was to explore the role of psychological distress in suicide risk. The Cronbach's alpha coefficient of the scale was 0.88, and the Cronbach's alpha coefficients of the three subscales were 0.68, 0.84, and 0.89, respectively [16].

The Distress Management Screening Measure (DMSM) [17] is a tool for assessing the psychological pain of cancer patients. This tool includes a Distress Thermometer (DT) and a Problem List (PL). The DT is a single-item psychological pain self-assessment tool which assesses the average pain level experienced by patients in the past week; scores range from 0 to 10 (0 = painless and 10 = extremely painful). The DT also includes a list of questions with a total of 40 questions, covering five areas of the cancer patient's illness, including practical, communication, emotional, physical, and belief/religious issues. The NCCN recommends the use of distress thermometers as a screening tool to quickly identify the psychological distress of cancer patients and is widely used in clinical practice globally.

The following scales are also often used in clinical practice to assess the psychological status of cancer patients:

Brief Pain Inventory (BPI) [18]. It measures the patient's pain history, pain intensity, and the effects various activities have on pain. BPI is well validated in patients with cancer and chronic pain.

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [19] is used to measure the quality of life associated with cancer. The questionnaire is composed of 5 multi-item scales (physical, role, social, emotional and cognitive functioning) and 9 single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance and quality of life). The EORTC QLQ-C30 consists of 30 items, each rated from 1 ("not at all") to 4 ("very"), according to the 4-point Likert scale. Two items in the Global Health and Quality of Life subscale use 7 points. All functional scales and individual scores are converted to a score between 0–100 points. The higher the scores of the five functional scales and the Global Health Status Scale, the better the function. The higher the symptom scale score, the more severe the symptoms.

In addition, some scales that measure general psychological conditions such as depression and anxiety can also reflect the level of psychological distress in cancer patients to some extent. There are several categories according to the number of entries in the scale:

Ultra-short scale (1–4 entries)

Anxiety questions, Brief Case Find for Depression (BCD), Depression question, Interest questions, Complex Depression and Combination Depression Questions, One-question Interview, Edmonton Symptom Assessment

System (ESAS), and the Visual Analog Scale (VAS).

Short scale (5–20 entries)

Beck Depression Inventory-Short Form (BDI-SF), Brief Edinburgh Depression Scale (BEDS-6), Brief Symptom Inventory-18, (BSI-18), the Center for Epidemiological Studies' Depression Scale (CES-D), Edinburgh Postnatal Depression Scale (EPDS), General Health Questionnaire-12 (GHQ-12), Hospital Anxiety and Depression Scale (HADS), Hornheide Questionnaire (9-9), Impact of Event Scale (IES), Memorial Anxiety Scale for Prostate Cancer (MAX-PC), Psychological Distress Inventory (PDI), Patient Health Questionnaire–9 (PHQ-9), Post-Traumatic Stress Disorder Checklist (PTSD checklist and PCL-C), Life Comprehensive Quality Visual Analog Scale (overall quality of life visual analog scale, POMS-LASA), and the Zung Self-Rating Depression Scale (ZSDS).

Long scale (greater than or equal to 21 items)

Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Distress Inventory for Cancer (DI-C), General Health Questionnaire-28 (GHQ-28), Mood Evaluation Questionnaire (MEQ), Profile of Moods State-short form (POMS-SF), Cancer Psychosocial Screening Questionnaire (Psychosocial Screening for Cancer, PSSCAN), Questionnaire on Stress in Cancer Patients (QCS-R23), and the Rotterdam Symptom Checklist (RSCL).

However, there are certain problems in using the above tools:

(1) There are differences in the definition of the concept of psychological distress. In some studies, simple anxiety and depression are used instead of psychological distress;

(2) Assessment scales are mostly universal scales, lacking specific scales for cancer patients, such as the commonly used Hospital Anxiety and Depression Scale (HADS), Brief Symptom Inventory (BSI), Symptom Checklist (SCL-90), Profile of Mood Scale (POMS), Patient Health Questionnaire (PHQ-2), etc.;

(3) Some assessment scales do not report their psychometric properties well, thus limiting their clinical use value;

(4) Some scales are just translated into Chinese without modification, and there is a lack of consideration of cultural differences between Chinese and foreign cultures, such as the Chinese version of the Concise Pain Scale (BIP-C);

(5) Tools like the PPAS, PAS, TDPPS only emphasize the relationship between distress and suicide;

(6) Some tools are not specifically used in cancer patients, for example, the MBPPAS is used to assess patients with major depressive episodes;

(7) Some tools like the PAS only evaluates the frequency of psychological pain and not the intensity;

(8) Distress management screening tools like the DT and PL are currently widely used in cancer patients, however, one simple item on the DT thermometer might produce great error, and the PL uses closed questions (only yes or no) without taking intensity into account.

Mental intervention methods

With the development of medical technology in recent years, the survival rate of cancer patients has increased significantly and the quality of life with the disease and survival have become more prominent. The impact of various medical treatments on the patient's psychology and life are the cause of the decline in quality of family life. Studies inside China and abroad have confirmed that cancer patients have different levels of emotional disorders and affect the rehabilitation and prognosis of patients [20–22]. Psychological research shows that when people are emotionally anxious, nervous, or depressed for extended periods due to certain factors, the concentration of corticosteroids in the blood will continue to be high, which will inhibit the phagocytosis of macrophages, the proliferation of T-cells, and the ability of cells in general to secrete antibodies. In Zebrack *et al* [23], a study of adolescent cancer patients showed that without counseling services, especially professional mental health services, long-term psychological distress was significantly associated. Therefore, the psychological status of cancer patients should be given full attention in nursing and treatment work.

Present methods of intervention for cancer patients include psychological education training, skills training, and psychotherapy consultation. Common psychological interventions are described below.

Cognitive-Behavior Therapy (CBT)

CBT is a short-term, goal-oriented psychotherapy treatment that takes a hands-on, practical approach to problem-solving (and was developed by A. T. Beck). It is an effective skill to improve the quality of life of both patients and caregivers and also reduces the degree of psychological distress by correcting irrational thoughts, thereby reducing negative emotions and behaviors. Studies have confirmed the improvement of CBT effectiveness in the treatment of depressive symptoms in diabetic patients [24], chronic pain management [25] and the use of psychological education interventions in the framework of self-care, combined with nurse guidance, can decrease the mental distress of patients [26]. In addition, a large number of studies have shown that CBT has a significant effect on decreasing the psychological pain of cancer patients, such as decreasing insomnia [27], relieving stress and emotional distress [28–29].

Mindfulness-Based Stress Reduction (MBSR)

Mindfulness is the psychological process of purposely bringing one's attention to experiences occurring in the

present moment without judgment, which one can develop through the practice of meditation and other training [30]. MBSR advocates eight attitudes: The beginner's state of mind; Non-judgment; Acknowledgment; Non-striving; Equanimity; Letting-be; Self-reliance; Self-compassion [31].

MBSR is an 8-week evidence based, scientifically researched program, developed in 1979 by Dr. Jon Kabat-Zinn at The University of Massachusetts Medical School. Its purpose is to teach patients to use their inner physical and mental strength to actively do something irreplaceable for others. MBSR emphasizes focusing on patients being present and accepting the current experiences in their entirety; encouraging patients to behave in active and flexible ways to change areas of their lives where change is possible [32].

MBSR is often used clinically in affective disorders and chronic pain to assist in alleviating certain symptoms suffered by patients. Domestic and international studies have shown that MBSR treatment of patients suffering cancer [33], cardiovascular disease [34], arthritis [35], infertility [36], diabetes [37], undergoing elective surgery [38] and community chronic pain patients [39], has good intervention effects and a variety of outcomes for patients, such as improving anxiety and depression levels, reducing perceived stress levels [40–41], reducing pain perception and degree [39], reducing the degree of cancer-induced fatigue [42], improving quality of life [36] and sleep quality [43], improving immunity [44], and self-efficacy [45].

At present, MBSR is an effective treatment in alleviating the psychological pain of cancer patients. A number of international studies have shown that MBSR can significantly reduce the psychological pain of patients with lung cancer [46–47], breast cancer [48–49], and prostate cancer [50].

Music Therapy

This treatment approach utilizes evidence-based musical interventions in the clinical context to improve patients' quality of life. Music therapists use music and its many facets—physical, emotional, mental, social, aesthetic, spiritual—to help patients improve their health in cognitive, motor, emotional, communicative, social, sensory, and educational domains by using both active and receptive music experiences. Such includes improvisation, re-creation, composition, receptive methods, and discussions of music.

Guo JY *et al* [51] showed that individualized music intervention can alleviate preoperative anxiety in patients undergoing laparoscopic surgery. Zheng ML *et al* [52] conducted both music interventions and health education for an experimental group, whilst the control group only received health education. Their results show that the anxiety levels of the experimental group decreased significantly after the intervention and, additionally, physiological indexes such as blood pressure and heart rate became more stable. The results of Li Ronghuan *et al*. [53] show that factor scores of compulsivity, interpersonal, anxiety, depression, paranoid and hostility of the music intervention group were significantly lower than in the conventional care group. Additionally, studies have shown that yoga combined with music relaxation training can alleviate cancer-related fatigue in breast cancer chemotherapy patients [54], increase the compliance [55] and also relieve pain.

Supportive-Expressive Therapy (SET)

SET is a psychological treatment method that intervenes in patients with severely impaired mental health through advice, encouragement, and related measures. The goal of SET is to maximize or improve the patient's psychological state by maintaining or improving their self-esteem level and minimizing or even preventing the symptoms from being repeated. Goodwin's study [56] showed that group-supported expression therapy does not prolong the survival of patients with metastatic breast cancer, but it can improve the patient's mood and perception of pain. Reuter *et al* [57] show that breast cancer patients have a good acceptance of group support expression therapy, postoperative quality of life, decreasing tumor-related fatigue and coping strategies have improved. Additionally, 1 year after intervention, patients report continued positive results.

Meaning-Centered Group Psychotherapy (MCGP)

The Center of Mind Psychotherapy (MCP) is a form of psychological intervention specifically developed for when patients exhibit a loss of mental health or a loss of the meaning of life, as well as the potential pain that often occurs in patients with advanced cancer. The MCGP intervention conducts meaning-centered psychotherapy in the form of a group. Studies [58] have shown that patients treated with MCGP have significantly improved mental health and quality of life, and depression, despair, accelerated death desires, and physical symptoms are decreased, compared with those receiving supportive group therapy.

Conclusion

Mental distress is an important factor affecting cancer patients' psychological and physical well-being. Though much research in Western countries has been conducted on distress evaluation and intervention with cancer patients, there is not enough evidence for China. Reliable and effective intervention methods and tools need to be developed and tested.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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