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RAPID COMMUNICATION

Analysis of risk factors for the interval time, number and pattern of hepatic metastases from gastric cancer after radical gastrectomy

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Abstract

AIM: To analyze the risk factors for interval time, number and pattern of hepatic metastases from gastric cancer after radical gastrectomy, and provide evidence for predicting and preventing hepatic metastasis from gastric cancer after radical gastrectomy.

METHODS: A retrospective study of 87 patients with hepatic metastasis who underwent radical gastrectomy for gastric cancer from 1996 to 2001. The data was analyzed to evaluate significant risk factors for interval time, number and pattern of hepatic metastases originating from gastric cancer after radical gastrectomy.

RESULTS: The size of gastric cancer and lymph node metastases were independently correlated with the interval time of hepatic metastases; the depth of invasion was independently correlated with the number of hepatic metastases; while the depth of invasion and Lauren classification were independently correlated with the pattern of hepatic metastases.

CONCLUSION: We evaluated the interval time of hepatic metastases with the size of gastric cancer and lymph node metastases. The depth of invasion could be used to evaluate the number of hepatic metastases, while the depth of invasion and the Lauren classification could be used to evaluate the pattern of hepatic metastases in patients who underwent radical gastrectomy.

INTRODUCTION

Over 60% patients with gastric cancer are diagnosed at an advanced stage in China, and the overall 5-year survival remains less than 50%. Advances in the operative techniques and perioperative care have reduced the operative mortality and morbidity, but have not improved the stage-specific cancer survival rate. Long-term survival after radical gastrectomy for gastric cancer in China is very poor[1,2]. A number of prospective trials have failed to show a survival advantage with more extensive gastric resection[3-5] and extensive lymphadenectomy[6,7]. Moreover, patients with advanced stage disease continue to have disease recurrence at a high rate, and the recurrence is mainly focused in specific areas (locoregional, peritoneal, or liver). Hepatic metastasis from gastrointestinal carcinoma is a frequent and critical problem. Several studies have shown that hepatic resection for metastatic tumors from colorectal cancer is associated with improved outcome[8-10], and as this procedure has become safer, the indications for its use in such situations have expanded. However, in the case of liver metastases from gastric carcinoma, which is equally common, very few patients are candidates for hepatic resection because of the presence of multiple, widespread, bilobar metastases. As a result, spread of disease to different sites such as peritoneal dissemination, lymph node metastases, and distant metastasis is very common. There are very few reports on surgical resection of hepatic metastases from gastric cancer, and the results are disappointing[11,12]. It is important to determine the

risk factors for hepatic metastasis in order to improve the survival rate of gastric cancer after radical gastrectomy. The aims of this study were to identify independent risk factors for interval time, number and pattern of hepatic metastases originating from gastric cancer after radical gastrectomy, and to propose steps for the prevention of hepatic metastases after radical gastrectomy.

MATERIALS AND METHODS

Patients

Between 1996 and 2001, 87 patients with gastric carcinoma who underwent radical gastrectomy in the Gastrointestinal Cancer Department, Tianjin Cancer Hospital, Tianjin Medical University, Tianjin were selected. These patients consisted of 32 with the primary tumor located in the proximal stomach, 8 with tumor in middle stomach and 45 with distal stomach tumor. There were 77 men and 10 women, with a mean age of 62 years (range 38-78). All patients had complete resection of the primary gastric cancer. No patient died during the initial hospital stay or for 1 mo after surgery. Follow-up ranged from 3 mo to 60 mo (median 32 mo).

Methods

The demographic and clinical information comprised of the following parameters: age, gender, interval time between radical gastrectomy and hepatic metastases, surgical procedure and postoperative chemotherapy.

Macroscopically, the size of the primary tumor, primary tumor location, number and pattern of metastasis, and metastatic interval time were recorded. Microscopic features evaluated were histologic differentiation, depth of invasion of the primary tumor, lymph node metastasis, Lauren classification, presence of vascular invasion, presence of neural invasion, and peritoneal metastasis. In patients with multiple hepatic metastases, the pathologic findings of the largest tumor were taken as representative of the other tumors, because all the tumors showed similar pathologic features. The histologic types of the primary gastric cancer and the hepatic metastasis were determined according to the World Health Organization Classification[6]. The depth of invasion, extent of lymph node metastasis, Lauren classification, and presence of vascular and neural invasion of the primary gastric cancer were also evaluated. The pathologic diagnosis and classification of the primary cancer were performed by at least two pathologists using the TNM classification of the UICC[7], and results of gastric cancer study in surgery and pathology in Japan[8].

Statistical analysis

The various clinicopathologic factors were analyzed by the method of Kaplan and Meier, and Log-rank test was used to determine univariate significance. Factors that were deemed of potential importance on univariate analysis ($P < 0.05$) were included in the multivariate analysis. Logistic regression or Cox proportional hazards model were used for multivariate analysis. Significance was defined as $P < 0.05$. Surgical procedures were classified as proximal radical gastrectomy, esophago-gastric resection, distal radical gastrectomy or total gastrectomy. Statistical analysis was performed using the statistical analysis program package (SPSS 13.0, Chicago, IL).

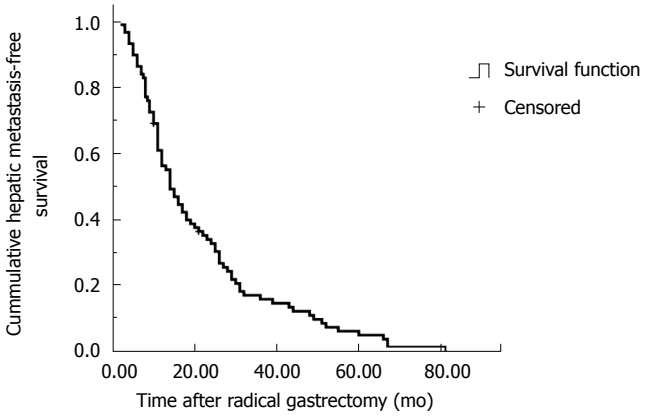

Figure 1 Kaplan-Meier cumulative hepatic metastasis-free survival plot for the entire cohort of 87 patients who underwent gastrectomy of gastric adenocarcinoma.

RESULTS

Clinicopathologic data

Histological analysis revealed that all the primary gastric tumors were adenocarcinomas. There was no evidence of metastases to other organs or peritoneal dissemination determined by imaging studies (such as B ultrasonography, CT or MRI), before curative gastrectomy was performed. Esophago-gastric resection was performed on 23 patients, proximal radical gastrectomy 8 patients, distal radical gastrectomy 45 patients and total gastrectomy 11 patients. The median interval time between gastrectomy and hepatic metastasis in all patients was 14 mo (range 3-31).

Patient outcome

The time interval for hepatic metastasis free survival for the 87 patients who underwent radical gastrectomy is shown in Figure 1. Factors associated with interval time of hepatic metastases after radical gastrectomy are shown in Table 1. The actuarial interval time for < 6 mo, 6-12 mo, 12-36 mo, and more than 36 mo for hepatic metastases after primary radical gastrectomy were 9 (10.3%), 26 (29.9%), 38 (43.7%) and 14 (16.1%) respectively. The median hepatic metastasis-free survival time was 14.0 mo. With univariate analysis, five factors were found to have statistically significant association with the interval time of hepatic metastases after radical gastrectomy: size of gastric cancer, lymph node metastasis, No. 12 lymph node group metastases, No. 8 lymph node group metastases, and Lauren classification. Only the size of gastric cancer and lymph node metastasis showed significant correlation with the interval time of hepatic metastases using the Cox proportional hazards model analysis.

Factors associated with the number of hepatic metastases after radical gastrectomy are shown in Table 2. The number of patients with solitary metastasis and multiple metastases after primary radical gastrectomy were 11 (12.6%), and 76 (87.4%) respectively. With univariate analysis, three factors were found to have statistically significant association

Table 1 Univariate and multivariate analysis of clinicopathologic factors potentially associated with the interval time of hepatic metastases after radical gastrectomy

Factor	*n*	Cases of hepatic metastases after surgery				Univariate *P* value	Multivariate *P* value	Odds ratio
		< 6 mo	6-12 mo	12-36 mo	> 36 mo			
Age								
≤ 50 yr	13	0	5	7	1	0.634	0.334	0.800
51- 69 yr	55	6	16	22	11	-	-	-
≥ 70 yr	19	3	5	9	2	-	-	-
Gender								
Male	77	9	24	31	13	0.309	0.149	1.949
Female	10	0	2	7	1	-	-	-
Gastric carcinoma								
Size								
≤ 5 cm	39	2	5	21	11	0.001	0.019	1.989
> 5 cm	48	7	21	17	3	-	-	-
Location								
Proximal	25	2	10	9	4	0.512	0.966	1.007
Middle	17	1	6	8	2	-	-	-
Distal	43	5	9	21	8	-	-	-
Diffuse	2	1	1	0	0	-	-	-
Histologic differentiation								
Poorly undifferentiated	42	6	14	17	5	0.454	0.091	0.629
Well, moderately	45	3	12	21	9	-	-	-
Vascular invasion								
Absent	70	6	19	32	13	0.296	0.134	1.928
Present	17	3	7	6	1	-	-	-
Neural invasion								
Absent	74	7	20	33	14	0.232	0.383	1.502
Present	13	2	6	5	0	-	-	-
Depth of invasion[1]								
T1	4	0	1	2	1	0.085	0.400	0.845
T2	26	1	5	14	6	-	-	-
T3	48	5	20	18	5	-	-	-
T4	9	3	0	4	2	-	-	-
Lymph node metastases[1]								
N1	31	0	3	19	9	< 0.001	0.001	1.892
N2	37	3	17	13	4	-	-	-
N3	19	6	6	6	1	-	-	-
No. 12 lymph node group metastases								
Absent	75	5	21	35	14	0.011	0.880	0.915
Present	12	4	5	3	0	-	-	-
No. 8 lymph node group metastases								
Absent	72	5	20	33	14	0.034	0.647	0.792
Present	15	4	6	5	0	-	-	-
Lauren classification								
Intestinal	36	4	8	15	9	0.037	0.331	1.171
Diffuse	29	5	13	10	1	-	-	-
Mixed	22	0	5	13	4	-	-	-
Surgical procedure								
Esophago-proximal	23	2	1	17	3	0.056	0.481	1.098
Proximal subtotal	8	1	4	2	1	-	-	-
Distal subtotal	45	4	18	14	9	-	-	-
Total	11	2	3	5	1	-	-	-
Ascites								
Absent	57	8	17	22	10	0.338	0.608	0.866
Present	30	1	9	16	4	-	-	-
Soft tissue invasion								
Absent	47	6	18	17	6	0.170	0.136	0.559
Present	40	3	8	21	8	-	-	-

[1]According to pTNM classification of UICC; Esophago-proximal, resection of the distal esophagus and proximal stomach; total, resection of the whole stomach.

with the number of hepatic metastases after radical gastrectomy: size of gastric cancer, depth of invasion, and Lauren classification. Only the depth of invasion of primary gastric tumor showed significant correlation with the number of hepatic metastasis, using the Logistic regression multivariate analysis.

Factors associated with the pattern of hepatic metastases after radical gastrectomy are depicted in Table 3. The pattern of hepatic metastases comprised of three subtypes (H1-3, according to the general rules for gastric cancer study in surgery and pathology in Japan). H1 subtype indicates that all the hepatic metastatic lesions are unilobar in

Table 2 Univariate and multivariate analysis of clinicopathologic factors potentially associated with the number of hepatic metastases after radical gastrectomy

Factor	*n*	Cases of hepatic metastases after surgery		Univariate *P* value	Multivariate *P* value	Odds ratio
		Solitary	Multiple			
Age						
≤ 50 yr	13	2	11	0.171	0.398	2.480
51-69 yr	55	9	46	-	-	-
≥ 70 yr	19	0	19	-	-	-
Gender						
Male	77	10	67	0.798	0.732	0.392
Female	10	1	9	-	-	-
Gastric carcinoma						
Size						
≤ 5 cm	39	10	29	0.001	0.133	12.271
> 5 cm	48	1	47	-	-	-
Location						
Proximal	25	3	22	0.678	0.539	1.487
Middle	17	1	16	-	-	-
Distal	43	7	36	-	-	-
Diffuse	2	0	2	-	-	-
Histologic differentiation						
Poorly undifferentiated	42	4	38	0.398	0.797	1.359
Well, moderately	45	7	38	-	-	-
Vascular invasion						
Absent	70	11	59	0.08	0.998	-
Present	17	0	17	-	-	-
Neural invasion						
Absent	74	11	63	0.137	0.998	-
Present	13	0	13	-	-	-
Depth of invasion[1]						
T1	4	3	1	< 0.001	0.046	8.799
T2	26	6	20	-	-	-
T3	48	2	46	-	-	-
T4	9	0	9	-	-	-
Lymph node metastases[1]						
N1	31	7	24	0.060	0.991	0.989
N2	37	4	33	-	-	-
N3	19	0	19	-	-	-
No. 12 lymph node group metastases						
Absent	75	11	64	0.156	0.998	-
Present	12	0	12	-	-	-
No. 8 lymph node group metastases						
Absent	72	10	62	0.444	0.428	0.125
Present	15	1	14	-	-	-
Lauren classification						
Intestinal	36	9	27	0.009	0.288	3.261
Diffuse	29	0	29	-	-	-
Mixed	22	2	20	-	-	-
Surgical procedure						
Esophago-proximal	23	3	20	0.056	0.395	1.953
Proximal subtotal	8	1	7	-	-	-
Distal subtotal	45	7	38	-	-	-
Total	11	0	11	-	-	-
Ascites						
Absent	57	8	49	0.338	0.718	0.544
Present	30	3	27	-	-	-
Soft tissue invasion						
Absent	47	5	42	0.170	0.950	1.102
Present	40	6	34	-	-	-

[1]According to pTNM classification of UICC; Esophago-proximal, resection of the distal esophagus and proximal stomach; total, resection of the whole stomach.

distribution. H2 subtype suggests metastases in both lobes. H3 subtype refers to scattered metastases in both lobes. The number of patients with H1, H2 and H3 metastases after primary radical gastrectomy were 12 (13.8%), 31 (35.6%) and 44 (50.6%) respectively. With univariate analysis, four factors were found to have statistically significant association with the number of hepatic metastasis after radical gastrectomy: size of gastric cancer, depth of invasion, Lauren classification, and vascular invasion. Only the depth of invasion and Lauren classification showed significant correlation with the pattern of hepatic metastasis, based on Logistic regression multivariate analysis.

Table 3 Univariate and multivariate analysis of clinicopathologic factors potentially associated with the pattern of hepatic metastases after radical gastrectomy

Factor	*n*	Cases of hepatic metastases after surgery			Univariate *P* value	Multivariate *P* value	Odds ratio
		H1	H2	H3			
Age							
≤ 50 yr	13	2	7	4	0.221	0.098	2.034
51-69 yr	55	9	15	31	-	-	-
≥ 70 yr	19	1	9	9	-	-	-
Gender							
Male	77	11	30	36	0.126	0.168	0.202
Female	10	1	1	8	-	-	-
Gastric carcinoma							
Size							
≤ 5 cm	39	10	13	16	0.014	0.618	0.758
> 5 cm	48	2	18	28	-	-	-
Location							
Proximal	25	3	5	17	0.180	0.985	1.006
Middle	17	1	8	8	-	-	-
Distal	43	8	18	17	-	-	-
Diffuse	2	0	0	2	-	-	-
Histologic differentiation							
Poorly undifferentiated	42	4	12	26	0.118	0.621	0.763
Well, moderately	45	8	19	18	-	-	-
Vascular invasion							
Absent	70	12	28	30	0.011	0.190	4.267
Present	17	0	3	14	-	-	-
Neural invasion							
Absent	74	12	28	34	0.087	0.844	1.235
Present	13	0	3	10	-	-	-
Depth of invasion[1]							
T1	4	3	1	0	< 0.001	0.037	2.078
T2	26	6	13	7	-	-	-
T3	48	3	13	32	-	-	-
T4	9	0	4	5	-	-	-
Lymph node metastases[1]							
N1	31	7	13	11	0.073	0.194	1.634
N2	37	5	13	19	-	-	-
N3	19	0	5	14	-	-	-
No. 12 lymph node group metastases							
Absent	75	12	25	38	0.256	0.224	0.277
Present	12	0	6	6	-	-	-
No. 8 lymph node group metastases							
Absent	72	11	26	35	0.603	0.677	1.483
Present	15	1	5	9	-	-	-
Lauren classification							
Intestinal	36	10	17	9	0.001	0.005	2.552
Diffuse	29	0	8	21	-	-	-
Mixed	22	2	6	14	-	-	-
Surgical procedure							
Esophago-proximal	23	3	8	12	0.807	0.698	1.122
Proximal subtotal	8	1	2	5	-	-	-
Distal subtotal	45	8	16	21	-	-	-
Total	11	0	5	6	-	-	-
Ascites							
Absent	57	9	21	27	0.644	0.984	1.012
Present	30	3	10	17	-	-	-
Soft Tissue Invasion							
Absent	47	6	22	19	0.057	0.765	1.179
Present	40	6	9	25	-	-	-

[1]According to pTNM classification of UICC; Esophago-proximal, resection of the distal esophagus and proximal stomach; total, resection of the whole stomach.

DISCUSSION

The outcome of gastric cancer has not shown a significant improvement with the current treatment approaches. Although early detection improves the prognosis, most patients with gastric cancer are identified at an advanced stage and have a poor prognoses despite developments in surgical techniques and the use of anticancer chemotherapy. In addition, patients with advanced cancer have very high rate of tumor recurrence, which is nearly always lethal[1,13]. Hepatic metastasis is the most frequent presentation of recurrent gastric cancer after radical

gastrectomy. The prognosis of gastric cancer in patients with hepatic metastasis is poor, and the best method of treatment remains unclear. The benefit of resection of hepatic metastases from gastric carcinoma is not widely accepted, and nonsurgical treatments, including the use of systemic or hepatic artery infusion chemotherapy has not produced satisfactory results. Hepatic resection of metastatic tumors from colorectal cancer is considered the standard of care, however, patients with metastatic liver tumors from gastric cancer are rarely considered good candidates for surgical treatment because most cases have multiple metastases and peritoneal dissemination[12,14]. Only 10% to 20% of patients with hepatic metastases from gastric cancer after gastrectomy are suitable for surgical treatment; the procedure has a median survival of 5-8 mo, with 15%-50% survival at 1 year and the 5-year survival rate is close to zero[15-19].

The prolonged disease-free interval after gastrectomy in long-term survivors suggests that these tumors have a more indolent biologic character. Imamura *et al* reported that the prognosis of patients with an interval time > 1 year was better than that of patients whose interval time from gastrectomy to hepatic metastasis was < 1 year[19]. This feature may be useful in designing an adjuvant treatment program for such patients after surgical resection. Ambiru *et al* observed that the interval time from gastrectomy to hepatic metastases was an independent factor in determining the prognoses of patients who underwent hepatic resection[20]. Our findings show that the size of gastric cancer (OR = 1.989, $P = 0.019$) and lymph node metastases (OR = 1.892, $P = 0.001$) has significant correlation with the interval time of hepatic metastases, based on the results of the Cox proportional hazards model analysis. Lee *et al* proposed that both size and pattern of lymph node metastases provide prognostic information on the survival rate of gastric cancer patients[21]. Dong *et al* observed that the regional lymph node metastatic rate of patients with a mean gastric tumor size > 3 cm was greater than that of patients with a mean gastric tumor size less than 2 cm ($P < 0.01$)[22]. Baba *et al* reported absence of metastasis in lesions less than 1 cm in diameter, and the incidence of positive nodes increased with increasing size of the primary gastric tumor[23]. These observations and our own findings indicate that the size of the primary gastric tumor is associated with lymph node metastases, which is the most important factor in determining the recurrence of gastric cancer after radical gastrectomy, and has critical impact on the interval time from gastrectomy to hepatic metastases.

The presence of solitary or metachronous hepatic metastases are significant determinants for a favorable prognosis after radical gastrectomy. In liver metastases from colorectal carcinoma, the number of metastases is no longer considered an important predictor of long-term survival, if complete excision is achieved, survival after resection of up to eight metastases is similar to that after resection of a solitary metastasis[24]. The difference in the results between colorectal and gastric metastases is believed to reflect the aggressive biologic behavior of gastric cancer. Indications for resection of hepatic metastases should be based on the biologic character of the primary tumor. In our study, all patients who underwent radical gastrectomy and resection of the hepatic metastases had metachronous metastases. Solitary hepatic metastasis was seen in only 11 cases, the remaining 76 patients had multiple hepatic metastases. In the present study, we attempted to correlate several clinical and histological factors with the number of hepatic metastases from gastric cancer after radical gastrectomy. By univariate analysis, a number of variables that affected the outcome were identified. However, by multivariate logistic regression analysis, only the depth of invasion of the primary gastric tumor was an independent risk factor for hepatic metastasis (OR = 8.799; $P = 0.046$; 95% CI, 0.789-79.280). The depth of invasion of the primary gastric tumor and the number of metastatic lymph nodes were considered the most reliable prognostic indicators, with the strongest influence on the risk of recurrence after radical gastrectomy[25-30]. Michael *et al* reported that the depth of primary gastric tumor was associated with higher rates of metastasis to the peritoneum (locoregional, peritoneal, or distant), and was associated with a significantly shorter median time from recurrence to death[31]. Patients who had surgery for early gastric cancer had an excellent chance of long-term survival, whereas patients with serosal involvement had a very poor prognosis[32-34]. These studies suggested that greater depth of primary gastric cancer was associated with higher propensity to develop hematogenous metastases.

Usually, patients with hepatic metastasis were initially found to have multiple lesions in the liver. According to the general rules for the study of gastric cancer in surgery and pathology in Japan, hepatic metastases from gastric cancer should be divided into three subtypes (H1-3). H1 subtype refers to unilobar distribution metastasis. H2 subtype indicates metastatic lesions in both lobes. H3 subtype of hepatic metastases indicates the presence of numerous metastatic lesions in both lobes. Irrespective of whether the number of hepatic lesions is single or multiple, H1 subtype of hepatic metastases is an absolute indication for hepatic resection. However, most experts consider H2 and H3 subtypes as contraindications for hepatic resection[12,17,19,20,35]. Chen *et al* reported that the median survival time of H1 subtype treated with hepatic resection was longer than that of H2 or H3 subtypes treated without surgery ($P = 0.0072$)[36]. In the present study, the number of patients with H1, H2, and H3 metastases were 12, 31 and 44 respectively. Only the depth of invasion of the primary gastric cancer and Lauren classification showed significant correlation with the number of hepatic metastases, based on Logistic regression multivariate analysis. The Lauren classification divides tumors into intestinal type, diffuse type, and mixed (unclassifiable) type[37]. The Lauren diffuse type is associated with significantly worse prognosis for gastric cancer compared to the other types[38-40]. The depth of primary gastric tumor was associated with higher rate of recurrence of gastric cancer after gastrectomy[31]. These observations suggest that both the Lauren diffuse type and advanced depth of primary tumor are important

risk factors for hepatic metastasis from gastric cancer after radical gastrectomy.

The following conclusions can be drawn based on the present study. The size of the primary tumor (> 5 cm) and advanced lymph node metastases are important predictors of the interval time for hepatic metastases from gastric cancer after radical surgery. The prognostic value of the depth of the primary gastric cancer is independent of the number of hepatic metastases from gastric cancer after radical surgery. Both advanced depth of the primary gastric cancer and diffuse Lauren type are associated with H2 and H3 subtypes of hepatic metastases from gastric cancer after radical surgery.

COMMENTS

Background

Several studies have shown that resection is the ideal treatment for hepatic metastases from gastric cancer after radical gastrectomy. Assessment of the number and the pattern of hepatic metastases are very important for the surgeon to ascertain suitable candidates for surgical treatment. In addition, the interval time of hepatic metastases can determine in part the biologic character of the tumor. However, factors which affect the interval time, and the number and pattern of hepatic metastases from gastric cancer after radical surgery remain unclear.

Research frontiers

We observed that the size of the gastric cancer and lymph node metastases are independent risk factors in predicting the interval time of hepatic metastases after radical gastrectomy. In the present study, only the depth of invasion was an independent risk factor for the number of hepatic metastases after radical gastrectomy. In addition, both the depth of invasion and the Lauren classification were found to be independently correlated with the pattern of hepatic metastases.

Innovations and breakthroughs

From the results of this study, we can draw the following conclusions about hepatic metastases from gastric cancer after radical gastrectomy: the size of primary tumor and lymph node metastases are important predictors of the interval time; the depth of the primary gastric cancer is independent of the number of hepatic metastases; both the depth of primary gastric cancer and the Lauren type are associated with the pattern of hepatic metastases.

Applications

The clinicopathological risk factors for hepatic metastases from gastric cancer after radical gastrectomy have been elucidated in the present study. Based on our findings, we can predict hepatic metastases in patients with gastric cancer after radical gastrectomy.

Peer review

The author retrospectively analyzed 87 patients with hepatic metastasis who underwent radical gastrectomy for gastric cancer, and elucidated the risk factors for interval time, number, and pattern of hepatic metastases after curative gastrectomy. The results of this study provide important clues to predicting hepatic metastases in gastric cancer patients after radical gastrectomy.

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