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Hepatic resection for colorectal liver metastases: prospective study

結腸腫瘤肝轉移的肝切除：預期研究

Objective. To assess the operative and long-term survival outcomes of hepatic resection for colorectal liver metastases during an 11-year period in a tertiary referral centre in Hong Kong.
Design. Prospective study.
Setting. University teaching hospital, Hong Kong.
Subjects and methods. Between January 1989 and December 1999, 72 patients underwent hepatic resection for colorectal liver metastases. Clinical, pathological, and outcome data were prospectively collected and analysed. Factors affecting long-term survival were also evaluated.
Results. Twenty-five (34.7%) patients were found to have synchronous hepatic metastasis at the time of colorectal resection. Fifty-two (72.2%) patients underwent major hepatic resection. The operative morbidity and hospital mortality rates were 19% and 4%, respectively. The 5-year survival rate after hepatectomy was 31.9%. The median disease-free survival and median overall cumulative survival were 18.5 months and 30.8 months, respectively. On multivariate analysis, a high preoperative serum carcinoembryonic antigen level (>200 ng/mL) and tumour involvement of the resection margin at histology were the two independent risk factors that adversely affected survival outcome.
Conclusion. Hepatic resection for colorectal liver metastases can be performed safely, with minimal operative mortality and acceptable morbidity, and results in satisfactory survival. High preoperative serum carcinoembryonic antigen level and histological involvement of resection margin by cancer adversely affect the survival outcome.

目的：評估香港一所三級轉介中心在過去11年期間，以肝切除手術治療結腸腫瘤肝轉移的病例及長期存活率結果。
設計：預期研究。
安排：大學教學醫院，香港。
患者及方法：在1989年1月至1999年12月期間，72名患有結腸腫瘤肝轉移的病人接受了肝切除手術。我們前瞻性收集並分析了病人臨床、病理及術後結果資料，並評估了影響他們長期存活率的因素。
結果：25人(34.7%)在切除結腸的同時發現有肝腫瘤轉移，52人(72.2%)接受了大部份肝切除手術。手術併發症發生率和醫院死亡率分別為19%和4%。肝切除後的5年存活率是31.9%。而無腫瘤存活中位數和整體累積存活中位數分別為18.5個月和30.8個月。多元分析顯示，術前高血清癌胚抗原(高於200 ng/mL)水平及從組織學上觀察到的切緣腫瘤侵犯是影響存活結果的獨立危險因素。
結論：以肝切除手術治療結腸腫瘤肝轉移是一項安全的手術，其手術死亡率可減至最低，併發症發生率亦能維持到可接受水平，且有令人滿意的存活結果。術前的高血清癌胚抗原水平及從組織學上觀察到的切緣腫瘤侵犯都會嚴重影響存活結果。

Key words:
Colorectal neoplasms;
Hepatectomy;
Survival analysis

關鍵詞：
結腸瘤；
肝切除；
存活分析

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Introduction

Colorectal cancer is the second most common cancer in Hong Kong, with an incidence of 45.5 per 100 000 population in 1996.[1] Liver metastasis frequently occurs and is the major cause of treatment failure and death. Simultaneous hepatic metastases have been observed in 11.5% of the patients undergoing resection for primary colorectal cancer. Approximately 30% of the patients who underwent apparently curative resection for the primary cancer subsequently

developed liver metastases.[2-4] Studies of the natural course of the disease in patients with colorectal liver metastasis have shown that untreated patients have a median survival of 6 to 12 months, which would increase to 12 to 18 months with chemotherapy.[5-8] Hepatic resection is the most effective therapy for metastatic colorectal cancer, and is the only curative therapy. Recent studies showed that liver resection for metastatic colorectal cancer resulted in a 10-year survival of more than 20% and a 5-year survival for one third of the patients.[9,10]

This study assessed the operative and long-term survival outcomes of hepatic resection for colorectal liver metastases during an 11-year period in a tertiary referral centre in Hong Kong. Factors affecting long-term survival were also evaluated.

Subjects and methods

Between January 1989 and December 1999, 72 patients with liver metastases from colorectal carcinoma underwent hepatic resection in the Department of Surgery of Queen Mary Hospital in Hong Kong.

Patients with synchronous hepatic metastasis were considered for simultaneous hepatic resection if curative resection was possible for all extrahepatic disease and a limited hepatic resection was considered adequate. Patients with metachronous liver metastasis and those who underwent interval hepatic resection for synchronous metastasis received preoperative evaluation for delineation of intrahepatic pathology and detection of extrahepatic disease. Preoperative investigations included blood biochemistry, carcinoembryonic antigen (CEA) assay, chest X-ray, percutaneous ultrasonography, computed tomography (CT) scan of the thorax and abdomen, and indocyanine green (ICG) clearance test.

Hepatic resection followed the standard technique that has been described previously[11] and ultrasonic dissection was used for parenchymal transection.[12] For patients with a large tumour situated at the right lobe of the liver, the technique of anterior approach hepatic resection was employed.[13,14] All patients received the same perioperative care by the same team of surgeons, and were nursed in the intensive care unit during the early postoperative course. All intra-operative complications and postoperative morbidities were prospectively recorded. Hospital mortality was defined as death during the same period of hospitalisation for the hepatic resection. After hepatic resection, CEA assay, ultrasonography, and chest X-ray were performed every 3 months for the first 2 years and then once a year. A CT scan of the abdomen was also performed annually. Disease-free survival time was calculated from the date of hepatic resection to the date when recurrence was diagnosed.

For all patients, clinical data were prospectively recorded in a computerised database by a research assistant. Statistical analysis included using the Chi squared test or Fisher's exact test to compare discrete variables and the Mann-Whitney *U* test to compare continuous variables. Multivariate analysis utilised the logistic regression model and survival analysis was estimated by the Kaplan-Meier survival method. Statistical analysis was performed with the help of the Statistical Package for Social Science (Windows version 10.0, SPSS Inc., Chicago, US). P values of less than 0.05 were considered statistically significant.

Results

During the study period, 72 patients underwent hepatic resection for colorectal liver metastasis. There were 51 men and 21 women, with a median age of 61.5 years (range, 24-78 years). The clinical data of the patients are summarised in Table 1. Fifty-three (73.6%) patients had primary colonic cancer and 19 (26.4%) had rectal cancer. The characteristics of the primary carcinoma are summarised in Table 2. Twenty-five patients were found to have synchronous hepatic metastasis at the time of colorectal resection, six of whom underwent synchronous minor hepatic resection for small hepatic metastases. The other 19 patients plus the remaining 47 patients who had metachronous liver metastasis underwent interval hepatic resection, with a median interval of 7.5 months.

Fifty-two (72.2%) patients underwent major hepatic resections (ie resection of three or more liver segments by

Table 1. Clinical and biochemical characteristics of the study population

Clinical/biochemical characteristic	Data
No. of patients	72
Sex ratio (M:F)	51:21 (2.4:1)
Age*	61.5 (24-78)
Serum carcinoembryonic antigen* (ng/mL)	39.0 (1-3974)
Serum albumin* (g/L)	43.0 (33-55)
Serum total bilirubin* (μmol/L)	9.0 (3-39)
Aspartate aminotransferase* (U/L)	23.0 (10-180)
Haemoglobin* (g/dL)	13.4 (8.5-17.0)
Prothrombin time* (s)	11.0 (9.5-13.3)
Indocyanine green retention at 15 min* (%)	8.8 (1.1-21.2)

* Data expressed as the median (range)

Table 2. Characteristics of the primary carcinoma in the study population

Characteristic	Patients No. (%)
Location	
Caecum	5 (6.9)
Ascending colon	9 (12.5)
Hepatic flexure	3 (4.2)
Transverse colon	3 (4.2)
Splenic flexure	1 (1.4)
Descending colon	2 (2.8)
Sigmoid colon	29 (40.3)
Rectum	19 (26.4)
Hepatic flexure and splenic flexure	1 (1.4)
Dukes' staging	
A	3 (4.2)
B	18 (25.0)
C	24 (33.3)
Metastatic	25 (34.7)
Not defined	2 (2.8)

Table 3. Pathological data of the study population

Pathological data	Value
Size of liver metastasis* (cm)	4.0 (1-16)
No. of liver metastasis*	1.0 (1 to >9)
Time of diagnosis	
Synchronous	25.0 (35%)
Metachronous	47.0 (65%)
Interval between resection of primary tumour and detection of liver metastasis* (months)	7.5 (0-61)
Tumour-free resection margin* (cm)	1.0 (0-5)
Resection margin involved by tumour at histology	11.0 (15%)

* Data expressed as the median (range)

Couinaud's nomenclature[15]). Anterior approach hepatic resection was performed for large right-lobe liver metastasis in 12 (16.7%) patients and the intermittent Pringle manoeuvre was employed in 28 (38.9%) patients. The pathological data are outlined in Table 3. The median tumour-free resection margin was 1 cm (range, 0-5 cm) and the resection margin was involved at histology in 11 patients. The operative morbidity and hospital mortality rates were 19% and 4%, respectively (Table 4). The three operative deaths occurred early in the series (from 1989 to 1995), and were related to liver failure and multi-organ failure (two patients) and intra-abdominal sepsis secondary to bile leakage (one patient).

All patients were followed up from the time of hepatic resection to the time of preparation of the manuscript or death. The 5-year survival rate was 31.9%. The median disease-free survival and median overall cumulative survival were 18.5 months and 30.8 months, respectively (Fig 1). Twenty patients were still alive and disease-free with a median follow-up of 42 months (range, 17-117 months). The survival results of these 72 patients were not significantly different from those of 473 patients who underwent hepatic resection in Queen Mary Hospital for hepatocellular carcinoma during the same study period. The latter had a median disease-free survival of 14.1 months (P=0.18 for the comparison with the study population) and a median overall cumulative survival of 43.2 months (P=0.58).

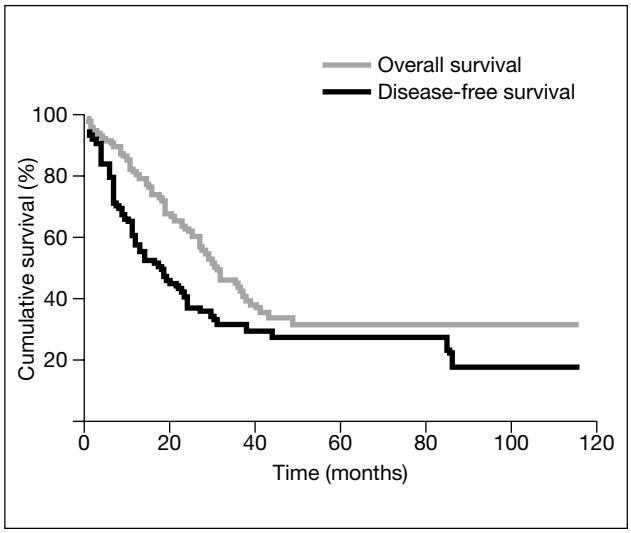

Fig 1. Cumulative overall and disease-free survival in the study population

Table 4. Intra-operative and postoperative data of the study population

Intra-operative/postoperative data	Value
Intra-operative blood loss* (L)	1.3 (0.1-9.7)
Intra-operative blood transfusion* (L)	0.3 (0-8.6)
No. of patients without transfusion	31.0 (43.0%)
No. of patients with anterior approach hepatectomy	12.0 (17.0%)
Operating time* (min)	335.0 (120-750)
No. of patients with operative morbidity	14.0 (19.0%)
No. of patients with hospital mortality	3.0 (4.0%)
Median disease-free survival (months)	18.5
Median survival (months)	30.8
No. of patients with 5-year survival	23.0 (32.0%)

* Data expressed as the median (range)

Statistical analysis was performed to identify the factors affecting survival after hepatic resection in the study population. Seventeen potential prognostic discriminants were studied, including: patient factors (age, sex, preoperative ICG clearance test, and serum total bilirubin); tumour factors (preoperative serum CEA level, site of primary lesion, Dukes' classification, location, size, number, and time of hepatic metastases); and operative factors (time and extent of hepatic resection, anterior approach hepatic resection, intra-operative blood loss and transfusion requirement, and width of tumour-free resection margin). On multivariate analysis, a high preoperative serum CEA level (>200 ng/mL) and an involvement of tumour in the resection margin at histology were the two independent risk factors that adversely affected the survival outcome after hepatic resection for colorectal liver metastases.

Discussion

Hepatic resection has become an accepted form of surgical therapy for patients with hepatic malignant tumours, with low operative morbidity and mortality.[16] Hepatic resection for colorectal liver metastases has become a safe procedure, with a reported mortality rate of less than 5% and acceptable morbidity.[9] The mortalities reported in this series occurred early on in the study, and there has been no operative mortality after hepatic resection for colorectal liver metastasis during the past 6 years. Selection criteria for patients with colorectal liver metastases to undergo hepatic resection included the absence of extrahepatic metastasis, satisfactory liver function, minimal co-morbid disease, and technical feasibility for curative hepatic resection.

The 5-year survival rate of 31.9% for these patients is far better than the expected survival for patients who do not undergo hepatic resection,[17,18] and is in accordance with the 5-year survival rate of approximately 30% reported in large western series.[9,19,20] The survival results were comparable to those of patients with primary hepatocellular carcinoma after hepatic resection in Queen Mary Hospital. With improved understanding of the disease and its prognosis after surgical resection, major centres in western countries experienced an increased number of referrals of patients with colorectal carcinoma for hepatic resection.[10] The same increase in referrals has not been experienced at Queen Mary

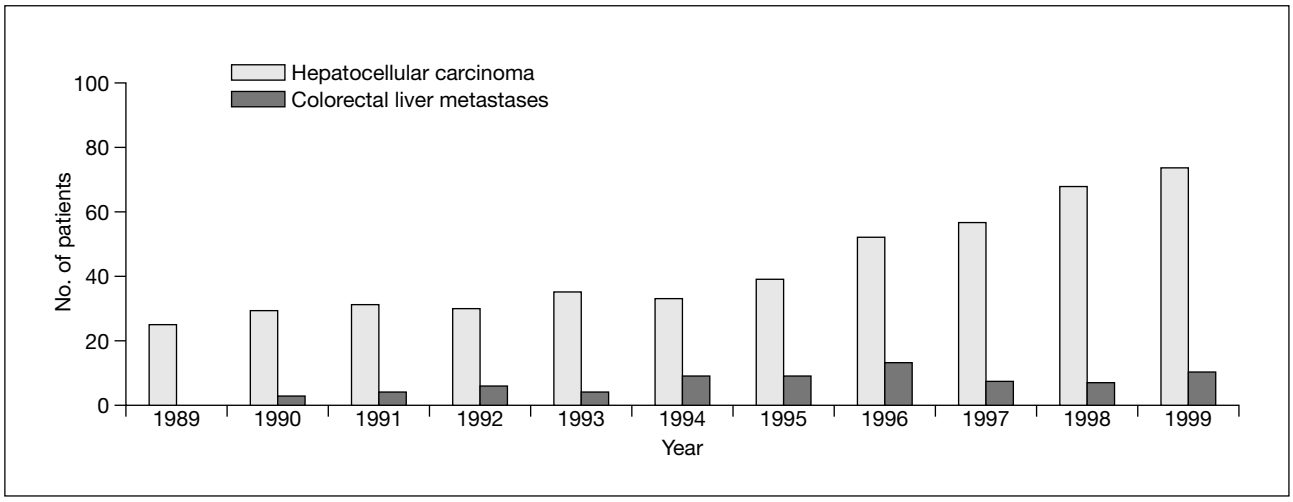

Fig 2. Number of patients undergoing hepatic resection for colorectal liver metastases or hepatocellular carcinoma from 1989 to 1999 at Queen Mary Hospital, Hong Kong

Hospital, however, despite there having been a significant increase in the number of referrals of patients with hepatocellular carcinoma for hepatic resection (Fig 2). This lack of uptake probably reflects a pessimistic attitude on the part of clinicians and a poor understanding of the surgical outcome of the disease. Certainly, surgical resection has been regarded with great scepticism. Despite the satisfactory survival outcome, it has been estimated that only about one fifth of patients who might be potential candidates have been referred for evaluation.[21] Some of our patients, who were not referred for any surgical opinion and were given a guarded prognosis, came for medical advice after a long post-diagnostic delay and subsequently underwent curative hepatic resection. There were also patients who were referred to oncologists for 'palliative care' and were indirectly referred to us for surgical resection.

Currently, there is no consensus as to the important prognostic factors after hepatic resection for colorectal liver metastases. Prognostic factors that have been identified include patient factors, tumour factors, and operative factors. With regard to tumour factors, for example, Hananel et al[22] observed a better survival rate for patients with metachronous metastases compared with those with synchronous metastases. Fong et al[10] identified seven factors that were significant and independent predictors of poor long-term outcome, including positive resection margin at histology; extrahepatic disease; node-positive primary tumour; short (<12 months) disease-free interval from primary tumour to metastases; more than one liver metastasis; largest hepatic tumour greater than 5 cm in size; and a CEA level above 200 ng/mL. In this study population, a high preoperative serum CEA level (>200 ng/mL) and a resection margin involved by tumour at histology were the two independent risk factors that adversely affected survival after hepatic resection for colorectal liver metastases. Early referral and surgical resection are therefore important for satisfactory survival outcome. Surgical resection for liver metastases should also be planned and performed carefully to obtain a clear resection margin.

Local ablative therapies, including cryotherapy[23,24] and radiofrequency ablation,[25,26] have been advocated for the treatment of colorectal liver metastases. It is likely that these techniques can produce complete destruction of small lesions (<3 cm), although they may be less successful in terms of curing larger tumours. Further studies are required to document the role of ablative therapies in the care of patients with colorectal liver metastases. This notwithstanding, since hepatic resection is the only documented treatment to achieve a complete cure of the disease and is currently the treatment of choice, it should be regarded as the standard for the comparison of treatment of metastatic disease isolated to the liver.

With the advent of new chemotherapeutic agents for colorectal liver metastases, adjuvant chemotherapy after hepatic resection may have a significant impact on improving patients' survival, especially for patients who are predicted to have a poor outcome, for example, those with a positive resection margin.[7] Further studies are also required on the role of regional adjuvant chemotherapy for this group of patients.[27,28]

Conclusion

Hepatic resection for colorectal liver metastases can be safely performed with minimal operative mortality and acceptable morbidity, and results in satisfactory survival. A high preoperative serum CEA level and tumour involvement of resection margin at histology adversely affect the survival outcome. Early referral and surgical treatment with a clear resection margin are recommended.

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