

Surveillance and outcome of liver metastasis in patients with colorectal cancer who had undergone curative-intent operation

CME

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Objective To assess the outcome of patients diagnosed to have liver metastasis by ultrasonography, following curative-intent resection of colorectal adenocarcinoma.

Design Prospective study.

Setting Regional hospital, Hong Kong.

Patients A total of 650 patients who underwent curative-intent resection of colorectal adenocarcinoma between January 2000 and December 2006.

Main outcome measures Pattern of liver recurrence, treatment and outcome after recurrence, and overall patient survival.

Results Of the 650 patients, 553 (85%) were followed up per protocol. Of 104 patients who developed systemic recurrence, 45 (43%) had liver-only metastases. The resection rate for liver metastases was 38% (17/45). The median survival of such patients was significantly longer than those who did not undergo liver metastasectomy (50 vs 26 months, $P=0.017$).

Conclusion Our ultrasonography-based surveillance protocol was low-cost, simple, and effective in detecting asymptomatic liver metastases, so that curative-intent metastasectomy could be performed. Further prospective studies are required to determine the optimal frequency and imaging mode for surveillance, so as to improve the resectability of liver-only colorectal metastases as well as overall patient survival.

Introduction

Colorectal adenocarcinoma is the second commonest cancer and the second leading cause of cancer deaths in Hong Kong, and accounts for more than 1500 deaths annually.¹ Approximately 75% of such patients have localised disease on diagnosis,^{2,3} for which radical surgery is the main curative treatment. Adjuvant radiation therapy, chemotherapy, or both are useful in selected patients.⁴

After curative resection, hepatic metastases occur in approximately one third of colorectal cancer patients⁵ and are responsible for the majority of deaths attributable to recurrent disease.⁶ Hepatic resection represents the most cost-effective and only curative option for treating established metastatic disease confined to the liver; metastasectomy can achieve an overall postoperative survival of 30 to 40% at 5 years.^{3,5,7} Therefore, one of the central goals of surveillance after curative resection of colorectal adenocarcinoma is to identify liver metastases at an early stage, when they are more amenable to surgical resection. At this early stage however, liver metastases are usually asymptomatic, and imaging is an important means of detection. Hence, an intensive liver surveillance programme has been widely practised, and includes regular assays of serum carcinoembryonic antigen (CEA) level, liver ultrasonography (USG), or computed tomography (CT). Among the eight randomised trials on survival benefits of such surveillance programmes, only two showed significant overall survival benefit in favour of intensive surveillance.⁸ However, pooled data show that the curative re-operation rate for liver metastasis ($P=0.002$) and overall mortality ($P=0.008$) improved following regular liver USG.⁸ Based on this meta-analysis, it was concluded that the optimal strategies for surveillance after initial treatment with curative intent for colorectal cancer remained uncertain, and that further trials might clarify the issue.⁸

Key words

Colorectal neoplasms; Neoplasm metastasis; Survival analysis

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The aim of this study was to assess the outcome of patients with colorectal adenocarcinoma in our hospital, where a defined ultrasonographic surveillance policy on liver metastases had been followed.

Methods

From January 2000 to December 2006, data from every patient with colorectal adenocarcinoma who had undergone an intended curative operation were prospectively entered into a computer database, which was retrospectively analysed. The definition of curative colonic resection was determined by the operating surgeon during the surgery. If the resection could not achieve macroscopic clearance, it was considered palliative (not curative) and not included in this study. In our centre, the regimen of adjuvant chemotherapy after curative resection was determined by oncologists, and given according to their protocols. Moreover, there was no single protocol for our patients, because patients were referred out to different oncology centres according to geographic location since we did not have an oncology service at our institution.

Surveillance for liver metastases was performed according to the protocol of our institution (Table 1). After the 5-year surveillance, patients would be followed up only if they had symptoms. If there was any suspicious lesion on liver ultrasound, further investigations such as CT and magnetic resonance imaging (MRI) were performed for further evaluation.

During the study period, liver metastases were considered unresectable if the predicted residual functional liver remnant was less than 35% after a planned 1-cm margin of resection, if the patient was physically unfit for operation, or if there was evidence of extrahepatic disease not amenable to resection. All patients with more than liver-only metastasis (metastases to liver and other organs) were considered not resectable and not included in the final survival analysis. Patients with synchronous liver metastasis were also excluded from this study.

Descriptive data were presented as medians

曾接受治癒性手術的結直腸癌肝轉移患者的 監察與結果

目的 用超聲描記術評估病人接受治癒性大腸直腸癌切除術後，肝癌轉移的情況。

設計 前瞻性研究。

安排 香港一所地區醫院。

患者 2000年1月至2006年12月期間，共650名接受治癒性大腸直腸癌切除術的病人。

主要結果測量 肝癌轉移復發的模式、復發後的治理及結果，以及病人的總存活率。

結果 650名病人中，方案分析隨訪了553（85%）位。104名有系統性復發的病人中，45位（43%）的癌轉移只限於肝臟。肝癌轉移的切除率為38%（17/45）。接受切除術的病人的中期存活率（50個月），比沒有接受切除術的病人（26個月）明顯長（ $P=0.017$ ）。

結論 本研究使用超聲描記術監察無症狀的肝轉移，由於成本低、簡單、有效，可進行治癒性的腫瘤切除。進行更多的前瞻性研究以決定監察的模式及最佳頻率，可以改善結直腸癌肝轉移的切除可行性及病人的總存活率。

and interquartile ranges (IQRs) [for skewed distributions], or means and standard deviations (for normal distributions). Censored survival times were calculated using the Kaplan-Meier method⁹ and survival curves compared by the log-rank test. The standard end-points of death or date of last clinic visit were used for final analysis. Statistical analysis was performed using the Statistical Package for Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], US). P values of less than 0.05 were considered statistically significant.

Results

Of the 650 patients who underwent intended curative operations for colorectal adenocarcinoma, 553 (85%) were followed up per protocol; their characteristics are listed in Table 2.

TABLE 1. Surveillance protocol for patients undergoing curative-intent resection of colorectal adenocarcinoma

Protocol	Months after curative resection of colorectal adenocarcinoma													
	3	6	9	12	15	18	21	24	30	36	42	48	54	60
History	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum carcinoembryonic antigen level	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ultrasonography of abdomen		✓		✓		✓		✓		✓		✓		✓
Flexible colonoscopy				✓						✓				

TABLE 2. Demographic patient data (n=650)

Demographics	Data
Median age (interquartile range) [years]	70 (61-77)
Gender	
Male	378 (58%)
Female	272 (42%)
Site of primary	
Caecum	41 (6%)
Ascending colon	68 (10%)
Hepatic flexure	35 (5%)
Transverse colon	37 (6%)
Splenic flexure	8 (1%)
Descending colon	41 (6%)
Sigmoid	168 (26%)
Rectosigmoid	20 (3%)
Rectum	232 (36%)
Dukes' staging of primary tumour	
A	100 (15%)
B	225 (35%)
C	325 (50%)
Median (IQR) tumour length (cm)	4 (3-5)
Median (IQR) proximal margin length (cm)	8.5 (6-12.5)
Median (IQR) distal margin length (cm)	4 (2.5-7)

The median follow-up was 26 months (IQR, 12-46 months). Of the 553 patients, 171 (31%) developed

recurrence. Of these 171 with recurrences, 37 (22%) developed local colorectal recurrence only, 104 (61%) developed systemic recurrences, while 30 (18%) developed both local and systemic recurrences.

Among the 104 patients who developed systemic-only recurrences, 45 (43%) were liver-only metastasis, which equated to 26% (45/171) of all recurrences and the isolated hepatic recurrence (metastasis) pick-up rate was 8% (45/553). On the other hand, the overall hepatic recurrence pick-up rate was 14% (79/553). However, only 44% (20/45) of the liver-only colorectal metastases were operable (Fig 1). Three patients in the operable group refused surgery and therefore 17 patients underwent resections. Patients who had inoperable liver metastasis received no treatment, palliative chemotherapy, or traditional Chinese medicine.

For patients with liver-only metastasis, the median survival of operable patients was significantly longer than that of non-operable patients (50 vs 26 months, P=0.017) [Fig 2]. The 1-, 2-, 3-, and 4-year survivals of the operable patients were 90%, 90%, 77%, and 54% respectively, whereas the corresponding survival rates for those with inoperable recurrences were 90%, 65%, 29%, and 18%, respectively.

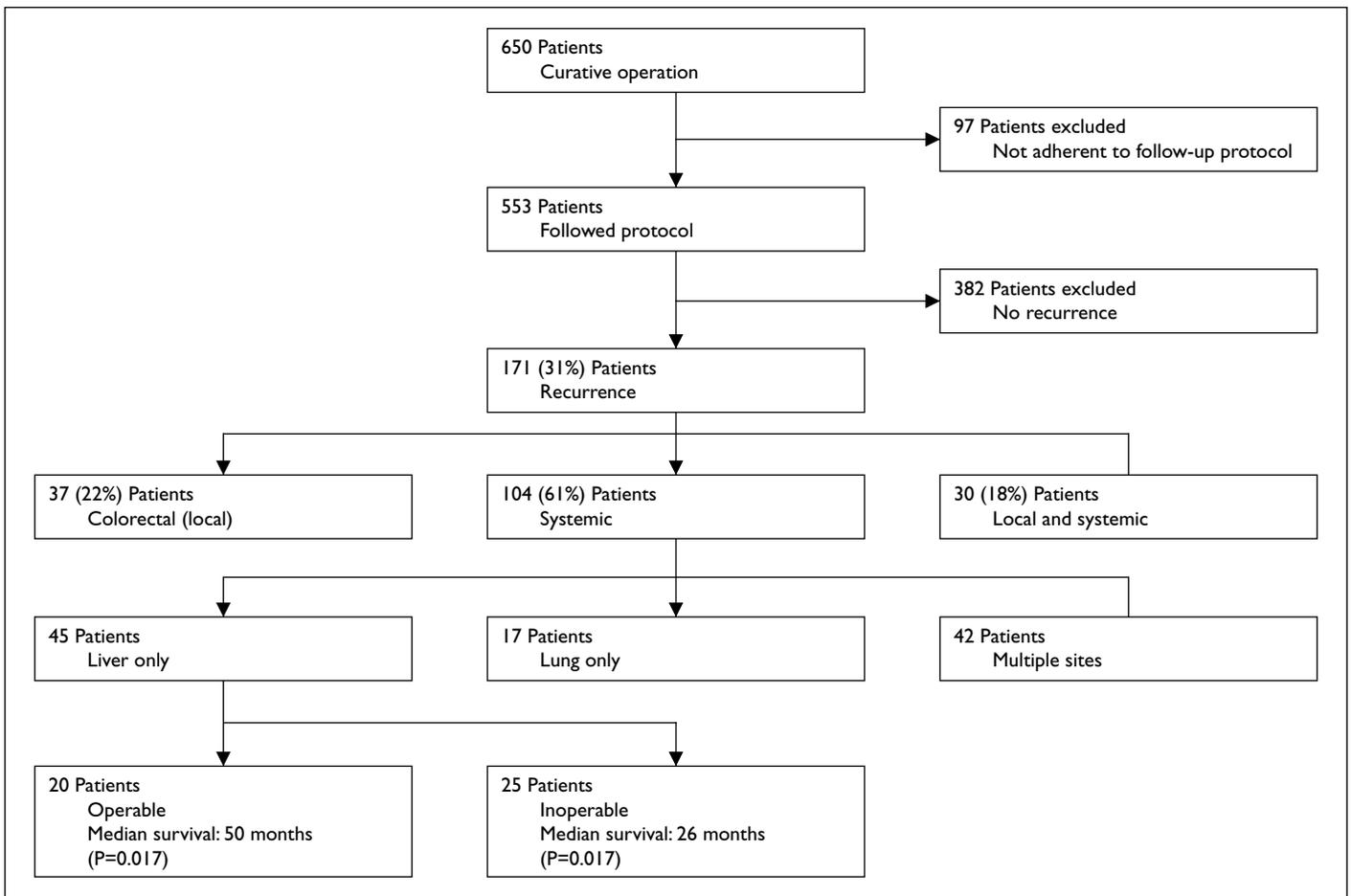


FIG 1. Results

Discussion

Surveillance programmes after curative resection of colorectal adenocarcinoma are based on the assumption that early detection of asymptomatic relapse results in longer survival. However, the optimal modality and frequency of surveillance for liver metastasis remain unclear.

Collective data from eight randomised trials⁸ showed that for all hepatic recurrences pick-up rate was 11% and for isolated hepatic recurrences it was 5%, whereas in our series the respective pick-up rates were 14% (79/553) and 8% (45/553).

Several trials have investigated different imaging modalities including USG, CT, or even MRI, using different schedules for the surveillance of recurrent disease. In one study describing a risk-adjusted ultrasound-based surveillance programme, 26% of 192 patients had resectable liver metastasis.¹⁰ Another study of 583 patients with yearly CT-based surveillance reported a liver metastasis resectability rate of 30%.³ In another trial of 293 patients,⁷ MRI was also investigated as an imaging technique and reported that 24% of liver metastases were resectable. The overall resectability rate of liver metastases was 24 to 30%,^{3,7,10} which was comparable to our rate of 26%. The median survival (50 months) of our patients with operable liver-only metastasis was also similar to that reported in the recent literature (32-62 months).^{3,7} The current argument for intensive surveillance strikes a balance between the risks and benefits. The risk of treatable recurrence, outcome of treatment, and cancer-specific survival benefit should be weighed against the cost of follow-up tests, patient compliance issues, and the psychological impact on patients. However, there are no agreed/accepted specific recommendations in the current literature. In most of the randomised trials, the interval for intensive surveillance for liver metastasis by USG was 6 months.¹⁰⁻¹³ Hence, in our protocol too, 6-monthly liver USG was performed. Compared to other imaging-based surveillance for patients with colorectal liver metastases, it appeared that our USG-based programme performed satisfactorily in terms of pick-up rate, resectability, and survival (Table 3^{3,7,10}).

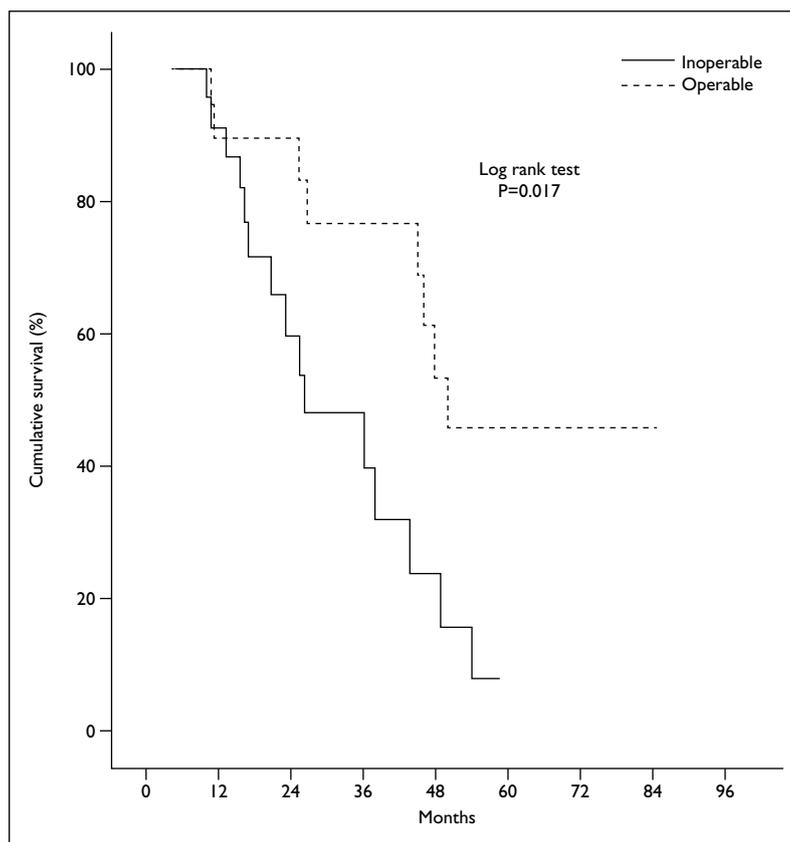


FIG 2. Survival data

One shortcoming of our study was the high default rate of 15% (97/650) in patients assigned to our follow-up regimen, possibly because we did not actively contact individuals when they did not attend our follow-up. To overcome this problem, it is necessary to initiate an active call-back system for patients who have defaulted their planned follow-up.

Another approach to improve the survival of patients is to undertake more intensive follow-up for those who have a higher chance of resectable liver metastasis. We, however, found no demographic data or primary colorectal adenocarcinoma features that differed significantly between patients with

TABLE 3. Comparison of imaging studies^{3,7,10}

Imaging modality	Current ultrasonography study	Ultrasonography ¹⁰	Computed tomography ³	Magnetic resonance imaging ⁷
No. of patients	553	192	583	293
Median follow-up (months)	26	62	67	41
Recurrence rate: all sites	171 (31%)	101 (53%)	208 (36%)	87 (30%)
No. with resectable liver metastases	20 (44%)	10 (26%)	34 (30%)	9 (24%)
Median survival (resectable vs non-resectable liver metastases) [months]	49.9 vs 26.0 (P=0.017)	Not available	62 vs 12.4 (P<0.001)	32 vs 13 (P=0.001)

resectable and non-resectable liver metastasis (data not shown).

Conclusion

The current study showed that our simple and low-cost regular surveillance programme after curative

resection of colorectal adenocarcinoma results in acceptable resectability rates for liver metastasis and acceptable cancer-related survival. Further prospective studies are required to determine the optimal frequency and mode of surveillance, with a view to improving the resectability rate of liver-only metastases and overall patient survival.

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Corrigendum

We have been alerted to errors in the article titled 'Using the National Institutes of Health Stroke Scale (NIHSS) to predict the mortality and outcome of patients with intracerebral haemorrhage' (October 2008;14:367–70). In the Abstract, the results should have referred to: "The NIHSS can predict 30-day mortality with a sensitivity of 81% and a specificity of 90%. The NIHSS can predict 5-year mortality with a sensitivity of 57% and a specificity of 92%. In predicting favourable functional outcomes at 5 years, the NIHSS had a sensitivity of 98% and a specificity of 16%." In the Discussion (second paragraph) section should have read: "When the NIHSS is used to predict 30-day mortality, it has good sensitivity (81%) and specificity (90%) using a cut-off point of 20 (0-20 vs >20). Using the same cut-off point to predict 5-year mortality, the NIHSS has a lower sensitivity (57%) but good specificity (92%). When using an NIHSS cut-off point of ≤20 to predict a good outcome among survivors at 5 years, its sensitivity was 98% but specificity was 16%. If the cut-off point is changed from 20 to 5 (0-5 vs >5), sensitivity was reduced to 72% but specificity increased to 68%."