

'Close Shave' in liver resection for colorectal liver metastases

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Abstract

Introduction

The optimal size of clear liver resection margin width in patients with colorectal liver metastases (CRLM) remains controversial. The aim of this study was to investigate the effects of margin width on long-term survival after liver resection for CRLM with a policy of standard neo-adjuvant chemotherapy.

Methods

Consecutive patients (n=238) who underwent liver resection for CRLM were included over a ten year period. All patients with synchronous or early (< 2 years) metachronous tumours were treated with neo-adjuvant chemotherapy. Data were recorded prospectively.

Results

Overall survival of the cohort at 1, 3 and 5 years were 90.3%, 68.1% and 56.1% respectively. The incidence of cancer involved resection margins (CIRM) was 5.8%. Patients with macroscopically involved resection margins had a poorer overall survival than those with microscopically involved margins (p=0.04). Involved resection margins had a poorer overall survival (p=0.002) than patients with clear margins. Width of clear resection margin did not affect long-term survival.

Conclusion

CIRM independently predicts poor outcome in patients with CRLM. Clear margin width does not affect survival. A standard policy of neo-adjuvant chemotherapy may be associated with a low incidence of CIRM and improved long-term outcome of subcentimetre margin widths, resembling those with >1cm resection margins.

Introduction

Hepatic resection provides the best prospect of cure for patients with colorectal liver metastases (CRLM). Reports have documented the potential benefit associated with a resection margin of 1cm or greater¹⁻⁴. There is little doubt that patients with macroscopic (R2) or microscopic (R1) cancer involved resection margins (CIRM) have significantly poorer outcomes than those with clear resection margins⁵⁻⁷ and studies have reported incidences of CIRM ranging from 8.8% to 33%⁵⁻⁹. However, the impact of the width of clear resection margins remains controversial. Some studies report that width has no influence on overall survival^{5,6}, while others state that widths greater than 1cm are desirable and significantly affect outcome^{7,10-12}.

Research has been dedicated to identifying clinico-pahologic features that might predict outcome in this heterogenous disease^{13,14}. Many units are now offering neo-adjuvant chemotherapy followed by liver resection. In recent years, available chemotherapy regimens have altered and improved. Different approaches to treating CRLM may influence established predictors of outcome.

The British Society of Gastroenterology national guidelines, published in 2006, for the treatment of patients with resectable colorectal metastases within the liver state that preoperative chemotherapy is only required if the tumours are thought to be borderline for resection¹⁵. However, studies have shown the benefit of neo-adjuvant chemotherapy in rendering unresectable tumours into operable candidates^{11,16,17}, and more recently, early data from randomised trials have suggested that a standard policy of neo-adjuvant chemotherapy followed by liver resection may positively affect progression free survival^{18,19}.

We adopted a policy in 1996 of standard neo-adjuvant chemotherapy followed by liver surgery for synchronous and early (<2years) metachronous CRLM, and for late metachronous (>2years) CRLM who were considered to have potentially threatened resection margins on pre-operative imaging²⁰⁻²³. The aim of this study was to analyse the effects of width of resection margin as a predictor of outcome in this setting.

Patients and Methods

The data from all patients with CRLM who underwent hepatic resection from September 1996 to November 2006 in a single centre were collected prospectively on a database (Patient Management & Analysis System 2004: Statistics Software) and were included in the study. The data were analysed retrospectively.

All patients referred with CRLM were treated pre-operatively with 6-8 cycles (depending on response) of chemotherapy if they had synchronous or early (< 2 years) metachronous liver metastases¹¹. Patients with metachronous tumours diagnosed greater than two years after their primary colorectal cancer were only offered neo-adjuvant chemotherapy if they had large tumours with potentially threatened resection margins. Otherwise, if they were considered to be resectable, they proceeded directly to surgery. Decisions regarding neo-

adjuvant chemotherapy were made in an hepatopancreatobiliary (HPB) multi-disciplinary team (MDT) setting²².

Pre-operative assessment was standardised using contrast enhanced computerised tomography (CT) of the thorax, abdomen and pelvis and magnetic resonance imaging (MRI) of the liver using intravenous Teslascan. Operative assessment always included intra-operative ultrasound scanning (Terason, California). Resections were undertaken or directly supervised by the senior surgeon (NDK).

The selection criteria for liver surgery included resected primary colorectal tumour, resectable extra-hepatic metastases, achievable tumour free margins within the liver taking into account anatomical distribution, number and size of lesions, and the preservation of at least 30% of functioning liver parenchyma^{4,24,25}.

All pre-, peri- and post-operative factors were recorded including age, patients' demographics, diagnosis, intra-operative blood loss, blood chemistry, intra- and post-operative complications, hospital stay, histology (including resection margins), tumour size, number of metastases, repeat procedures, local recurrence, disease free and overall survival. Post-operative mortality was defined as death within hospital or within 30 days following surgery. Overall survival was defined from the date of hepatic resection to the date of death or latest follow up appointment.

Histological analyses were carried out by dedicated histopathologists. CIRM was divided into macroscopic (R2) and microscopic (R1). Resection margins clear by less than 1mm were also considered to be R1 CIRM resections.

Statistical analyses, including the χ^2 test, *t* test, log ranking and Cox regression, were performed using the Patient Management & Analysis System 2004: Statistics Software and SPSS (Statistical Package for Social Sciences) version 15. P values of less than 0.05 were considered to be statistically significant.

Results

Patients' Demographics and Inclusion Criteria

Consecutive patients (n=319) with CRLM underwent surgical exploration from 1996 to 2006. Of these, 268 (84%) had completed liver resections, 16 (5%) had 'open and close' procedures and 35 (10.9%) were found to have extensive peritoneal disease at laparoscopy and so did not undergo liver resection. Only completed resections were included in the survival analysis. Of the 268 patients, those with no clear numerical description of margin width (n=4) were excluded, although the histopathologist had recorded complete excision for all four of these patients. Patients with no residual disease at histology (n=12) following liver resection were also excluded from the survival analysis. 13 patients had a single repeat liver resection and 1 patient had 2 repeat resections. These patients were also excluded from the survival analysis. The remaining 238 patients underwent survival analysis.

Patients' demographics and operative outcomes are summarised in table 1. The median age was 68 years, the median intra-operative blood loss was 200ml and the median hospital stay was 10 days.

Of the 238 patients included in the study, 174 (73.1%) had synchronous or early metachronous CRLM, and 144 (60.5%) had tumour-positive lymph nodes following their primary colorectal resection.

Pre-operative Chemotherapy and Operative Details

Of those included in the study, 208 (87.4%) received neo-adjuvant chemotherapy followed by surgery. Regimens altered during the 10 year study. Chemotherapy regimens included oxaliplatin alone or in combination with 5-fluorouracil (5-FU), leucovorin, tomudex or capecitabine (n=123), irinotecan alone or in combination (n=9), de Gramont and 5-FU (n=11), capecitabine and mitomycin (n=13), 5-FU alone or in combination with mitomycin C, folinic acid, levamisole or leucovorin (n=52).

Approximately 2% of all patients discussed at the HPB MDT had rapidly progressive disease despite neo-adjuvant chemotherapy and thus liver resection was not attempted (data not included here).

77 patients had segmentectomies, 90 had hemi-hepatectomies, 63 had extended hemihepatectomies and 8 had non-anatomical wedge resections. Liver transection was carried out by Cavitron Ultrasonic Surgical Aspirator (CUSA, Valley Lab.) and argon beam. The transection technique remained the same throughout the 10 year study.

Operative and Histological Outcomes

Histopathological analyses and measurement of margin excision were carried out prospectively by dedicated hepatobiliary histopathologists. The number and distribution of metastases are listed in table 1. 121 patients had ≥ 2 liver metastases and 23 (9.7%) patients had bilobar metastases within the liver. Eight (3.4%) patients had macroscopically involved resection margins (R2) and 6 (2.5%) patients had microscopically involved margins (R1, table 2).

Six (2.5%) patients who underwent hepatic resection died in hospital, 4 within 30 days of surgery. There were sixty seven complications in sixty three patients (28.1%).

Of the fourteen patients who underwent repeat resections, 1 patient had R2 resection margins following the first and second liver resections, 1 patient had an R2 resection initially, and a >10mm R0 resection margin at the repeat resection and 1 patient had an R2 resection initially followed by an R1 margin at the repeat resection. The remaining patients had R0 resection margins following their first and repeat liver resections.

Survival and Margin Analyses

The overall survival of the entire cohort at 1, 3 and 5 years was 90.3%, 68.1% and 56.1% respectively. The median follow up period was 34 months. Survival analysis using the Kaplin-Meier technique compared those with cancer involved resection margins (CIRM, R1 or R2) with those with clear margins of any width (R0). As expected it shows a significantly improved survival in those with R0 resections. R1 resections had a significantly improved overall survival compared with R2 resections. Based on previous published data, analyses were carried out according to varying resection margin widths of 1-3mm, 3-5mm, 5-10mm and >10mm (table 2). Only CIRM (R1 or R2) affected overall survival. The width of R0 resection margins did not influence survival.

Figure 1 is a survival curve using the Kaplin-Meier technique comparing CIRM, R0 resections of 1-3 mm and R0 resections greater than 3 mm. It shows that there is no significant difference in survival with close R0 resection margins (1-3 mm) versus those with R0 resection margins > 3 mm.

Further analysis was undertaken to compare those who received neo-adjuvant chemotherapy versus those who proceeded directly to liver resection (figure 2). The overall survival of patients who received neo-adjuvant chemotherapy prior to liver resection at 1, 3 and 5 years was 92.7%, 72.1% and 55.3% respectively. Of the patients who proceeded directly to liver resection, the overall survival at 1, 3 and 5 years, was 93.2%, 60.7% and 58.0% respectively. There was no difference between these two groups (p=0.91).

CIRM was shown by univariate analysis (p=0.002, table 2) and multivariate analysis (p=0.02) to be an independent factor significantly affecting overall survival. No other factors within the multivariate analysis achieved statistical significance.

Discussion

Several studies have identified factors that predict overall and disease free survival following liver resection for CRLM. Our data concur with more recent studies that survival is significantly improved with clear resection margins compared with CIRM but that the size of the clear margin does not influence survival⁵⁻⁷. Patients with macroscopically involved (R2) resection margins had a significantly worse overall survival than those with microscopically involved margins (R1), which was not demonstrated in more recent studies although had been noticed in earlier publications^{5,6,10-12}.

The controversy of clear margin widths following liver resection for CRLM continues. More recent studies have contradicted older data stating that sub-centimeter resections result in similar outcomes to resection margins greater than 1cm. However, many of these reports have small numbers of patients resulting in limited statistical power^{4,12,26}. Are et al recently published a multicentre study which included 1019 patients⁷. They concluded that sub-centimeter resections had a significantly worse outcome compared with widths

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greater than 1cm. However, their analysis was retrospective and included different surgeons with different transection techniques and different centres carrying out histological analysis. Although our study contained fewer numbers, the surgeon and transection technique remained the same for all patients involved, as did the histological analysis. Also, in the study published by Are et al, 29.6% of patients received neo-adjuvant chemotherapy compared with 87.4% in our series.

In this study the patients with R0 liver resections were arbitrarily divided into 4 groups to better analyse sub-centimeter resection margin widths. Our data demonstrated that resection margin width made no difference to survival. If this is a true finding then it may be explained by the policy of neo-adjuvant chemotherapy. Although the types of chemotherapy altered over the 10 year study period, the policy did not. It is possible that neo-adjuvant chemotherapy improves the outcome of patients with sub-centimeter margin widths to resemble those with widths greater than 1cm. There is some evidence to support this hypothesis from the current study as there was no difference in long term survival between patients who received neo-adjuvant chemotherapy versus those who proceeded directly to liver resection.

Although approximately two thirds of the patients had 1 or 2 CRLM, the high proportion of patients with synchronous or early metachronous tumours and node-positive colorectal resections suggests the majority of the patients in the current study had unfavourable biological disease. Further evidence to support that neo-adjuvant chemotherapy improves the overall outcome can be found when one considers, in the study published by Are et al⁷, the CIRM rate of 11% and 5-year survival rate of 37% compared with 5.8% and 56.1% respectively from the present study.

The standard policy of neo-adjuvant chemotherapy may also have influenced the incidence of CIRM. Studies have shown that the incidence of CIRM following liver resection is 8.8 to $33\%^{5.9}$ compared with only 5.8% in this study. The aggressive use of chemotherapy may cause sterilisation of micro-metastatic disease, which could also explain the 12 (5%) patients in our study who had no residual malignant disease seen histologically in the resected liver.

A policy of neo-adjuvant therapy may act as an additional level of patient selection. In our series, 2% of all patients discussed at the HPB MDT had rapidly progressive disease despite neo-adjuvant chemotherapy and so did not proceed to liver resection. This may be an appropriate addition to patient selection criteria, as rapid progression despite neoadjuvant chemotherapy suggests aggressive disease and these patients may not benefit from a liver resection.

In conclusion, this study provides evidence that CIRM for CRLM is an independent predictor of poor overall survival while the width of clear resection margin does not influence long term survival.

Legends

Figure 1. Kaplin-Meier survival curve comparing CIRM with clear resection margins of 1-3mm and clear resection margins >3mm.

Figure 2. Kaplin-Meier survival curve comparing overall survival of patients who received neo-adjuvant chemotherapy versus those who proceeded directly to liver resection.

Table 1. Patients' demographics and operative outcomes. Median values.

Table 2. Analysis of impact of resection margin width on survival.

Conflict of interest

The authors state that they have no conflict of interest.

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10

Table 1.

Age / years (range)	68 (37 to 87)
Male : Female (ratio)	2.1:1
Operative blood loss / ml (range)	200 (0 to 2,500)
Number of patients who received intra-	7
operative blood transfusions	
Number of patients who received post-	7
operative blood transfusions	
Hospital stay / days (range)	10 (3 to 53)
Resection margin / mm (range)	7 (involved to 150)
Number of patients with involved margins	14
Tumour size / mm (range)	32 (3 to 165)
Number and distribution of colorectal liver	
metastases / n (%)	
Single metastasis	117 (49.2%)
2 metastases	55 (23.1%)
3 metastases	32 (13.4%)
4 metastases	14 (5.9%)
>4 metastases	20 (8.4%)

ASA = American Society of Anaesthesiologists.

Table	2.
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Closest	No of	1-Year	95%	3-Year	95%	5-Year	95%	P Value
Resection	Patients	Survival	CI	Survival	CI	Survival	CI	(HR)
Margin	(%)	/ %		/ %		/ %		
Macroscopically	8 (3.4)	75	56.4-	-		-		Reference
Involved (R2)			96.3					
Microscopically	6 (2.5)	79.2	58.6-	50.3	37.8-	-		0.04
Involved (R1)			98.7		87.9			(1.24)
1 – 3mm	48	85.4	76-	62.8	49.7-	49.7	43.7-	0.002
	(20.2)		96		79.5		77	(1.27)
>3mm, 5mm<	17 (7.1)	88.2	74.2-	61.7	58.7-	51.3	44.3-	0.76 (1)
			95.5		84.2		78.1	
>5mm, 10mm<	55	91	83.6-	60.4	46.2-	52.9	44.3-	0.48 (1)
	(23.1)		98.8		78.8		75.3	
10 mm ≤	104	90.4	85.9-	70.1	60.5-	58.4	54.8-	0.07(1)
	(43.7)		96.2		81.2		78	
Margin width	4							
not recorded								
No residual	12							
malignant								
disease					Y			

95% CI = 95% confidence interval HR=Hazard ratio.





Kaplan-Meier Survival Curve

Figure 2.



Kaplan-Meier Survival Curve