Original article

Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases

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Background: **The management of patients with colorectal cancer and simultaneously diagnosed liver and lung metastases (SLLM) remains controversial.**

Methods: **The LiverMetSurvey registry was interrogated for patients treated between 2000 and 2012 to assess outcomes after resection of SLLM, and the factors associated with survival. SLLM was defined as liver and lung metastases diagnosed 3 months or less apart. Survival was compared between patients with resected isolated liver metastases (group 1, control), those with resected liver and lung metastases (group 2), and patients with resected liver metastases and unresected (or unresectable) lung metastases (group 3). An Akaike test was used to select variables for assessment of survival adjusted for confounding variables.**

Results: **Group 1 (isolated liver metastases, hepatic resection alone) included 9185 patients, group 2 (resection of liver and lung metastases) 149 patients, and group 3 (resection of liver metastases, no resection of lung metastases) 285 patients. Ten variables differed significantly between groups and seven were included in the model for adjusted survival (age, number of liver metastases, synchronicity of liver metastases with primary tumour, carcinoembryonic antigen level, node status of the primary tumour, initial resectability of liver metastases and inclusion in group 3). Adjusted overall 5-year survival was similar for groups 1 and 2 (51·5 and 44·5 per cent respectively), but worse for group 3 (14·3 per cent) ($P = 0{\cdot}001$).**

Conclusion: **Patients who had resection of liver and lung metastases had similar overall survival to those who had undergone removal of isolated liver metastases.**

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Introduction

Half of all patients with resected colorectal cancer develop liver and/or lung metastases. Complete resection is the goal of managing liver[1,2] and isolated lung metastases, with an expected 5-year survival rate in excess of 40 per cent[3–5]. The management of simultaneously diagnosed liver and lung metastases (SLLM) from colorectal cancer is a matter of debate[6–14]. A number of studies have suggested potential benefit from resecting both liver and lung metastases, supported by better outcomes for patients with lung metastases compared with metastases at other extrahepatic sites[15,16], but contradictory outcomes have been reported[12,13,16]. These inconsistencies relate to the inability to adjust for confounding factors owing to the limited sample sizes[9–13,16–22]; the largest published study so far included 32 patients with SLLM[8]. The aim of this registry-based study was to assess the benefit of curative surgery in patients with SLLM, and to define potential factors predicting outcome.

Methods

The study was based on analysis of the LiverMetSurvey, a prospective international registry of patients undergoing surgery for colorectal liver metastases involving 253 centres

in 66 countries. Patients were checked every 6 months, allowing assessment of adjuvant treatment, recurrence and survival.

Definitions

The interval between diagnosis of colorectal cancer and diagnosis of liver metastases was chosen according to Fong's Clinical Risk Score (CRS)[23], which showed better survival when the interval was over 12 months, and has been validated by other investigators[24,25]. No international definition was available for the interval between diagnosis of liver and lung metastases. In the literature, the interval between diagnoses in the definition of SLLM varies from 0 days, 1 month[13,26], 3 months[10,11] to 1 year[8]. Liver and lung metastases were considered as simultaneous when diagnosed less than 3 months apart. Disease-free survival was considered to be from the time of liver resection. Death and recurrence were considered events, and patients with no recurrence were censored at the last follow-up.

Inclusion and exclusion criteria

Inclusion criteria were: patients receiving surgery for colorectal cancer liver metastases after 1 January 2000, who had isolated liver metastases resected with curative intent, SLLM with resection of both liver and lung metastases with curative intent, or SLLM with resection of the liver metastases with curative intent, but no resection of the lung metastases.

Exclusion criteria were: non-curative liver or lung resections; a diagnosis of liver or lung metastases preceding diagnosis of the primary tumour by more than 30 days; the presence of non-pulmonary extrahepatic metastases diagnosed within 3 months after the resection of lung and/or liver metastases; and missing dates needed to measure time interval.

For analysis, data were categorized by age and sex, location of the primary tumour (colon or rectum), tumour (T) and node (N) categories of the primary tumour, synchronicity of liver metastases to the primary tumour, number and location of liver metastases, size of the largest liver metastasis, bilaterality of liver metastases, carcinoembryonic antigen (CEA) level before liver resection, initial resectability of all metastases (as defined by the surgical team), extent of liver resection (major resection defined as removal of at least 3 segments), use of portal vein embolization before liver surgery, whether single- or two-stage liver resection was used, and the presence and bilaterality of lung metastases. The use and type of chemotherapy were recorded before (neoadjuvant) and after (adjuvant) liver resection. The result after the last cycle of neoadjuvant chemotherapy was classified according to the World Health Organization criteria[27].

Three groups were defined: patients presenting with isolated liver metastases who underwent resection (group 1); patients presenting with SLLM who underwent resection of both liver and lung metastases (group 2); and patients presenting with SLLM who underwent resection of the liver metastases only (group 3).

Statistical analysis

Patient demographics, characteristics of the primary tumour, liver metastases and lung metastases, and chemotherapies used were compared between the three groups. The following scale variables were converted into dichotomous variables according to Fong's CRS: number of liver metastases (single *versus* multiple), interval between diagnosis of the primary and liver metastases (12 months or less – synchronous *versus* more than 12 months – metachronous), size of the largest liver metastasis (less than 5 *versus* 5 cm or more), CEA level (200 or less *versus* more than 200 ng/ml) and N status of the primary tumour (N0 *versus* N+). T category of the primary tumour was split into T1–2 *versus* T3–4.

Continuous variables are expressed mean(s.d.). Differences between the three groups were assessed by bilateral Student's t test for continuous variables and by χ^2 tests for dichotomous variables. Survival rates were estimated by the Kaplan–Meier method and compared by means of the log rank test. Cox models were used for univariable and multivariable survival analyses. To select variables for the multivariable Cox regression model, a stepwise Akaike test[28] was used on the total population, which included any variable with $P < 0{\cdot}150$ in the univariable analysis. The Akaike test allowed identification of variables that could be determined at the time of the liver resection (thus excluding adjuvant chemotherapy) and for which an increase in the likelihood of death was significant. The assumption of proportionality of hazards was assessed using Schoenfeld residuals. Overall, survival of patients in the three groups was adjusted for variables identified by the Akaike test. To compare groups 2 and 3 with group 1, variables related to lung metastases were not included in the adjusted model. Adjusted survival curves were obtained using co-variables set to their mean values.

Univariable and multivariable Cox regression analyses were performed with SPSS® version 17.0 (IBM, Armonk, New York, USA) and Stata® version 10.1 (StataCorp LP, College Station, Texas, USA). The Akaike test, and raw and adjusted survival analyses were carried out in Stata® version 10.1. $P < 0{\cdot}050$ was considered significant.

Table 1 Demographics and tumour characteristics

	Resected isolated liver metastases (group 1; $n = 9185$)	Resected simultaneous liver and lung metastases (group 2; $n = 149$)	Simultaneous resected liver and unresected lung metastases (group 3; $n = 285$)	P*
Mean(s.d.) age (years)	62·6(10·7)	60·3(10·8)	61·2(11·1)	0·010 (group 1 *versus* 2)† 0·039 (group 1 *versus* 3)† 0·416 (group 2 *versus* 3)†
Sex ratio (M : F)	5689 : 3493	93 : 56	161 : 124	0·003
Primary tumour category				< 0·001
T1–2	6804	120	235	
T3–4	2158	27	41	
Primary tumour node status				0·059
N+	5021	92	167	
N0	2899	37	78	
Primary tumour location				0·028
Rectum	2896	59	109	
Colon	5816	86	172	
No. of liver metastases				0·060
Multiple	4709	78	168	
Single	3825	65	101	
Extent of liver metastases				< 0·001
Bilobar	3279	38	137	
Unilobar	5617	110	143	
Timing of liver metastases				< 0·001
Synchronous	6316	74	211	
Metachronous	2869	75	74	
Size of liver metastases (cm)				0·129
≥ 5	2062	34	79	
< 5	5874	89	171	
CEA (ng/ml)				0·028
> 200	518	5	32	
≤ 200	4947	92	165	
Two-stage liver resection				< 0·001
Yes	581	9	38	
No	7921	135	245	
Embolization before liver resection				0·099
Yes	868	15	39	
No	7898	126	244	
Extent of liver resection				0·666
Major	4775	77	157	
Minor	3382	63	107	
Initial resectability of liver metastases				< 0·001
Unresectable	1442	35	91	
Resectable	6460	102	175	
Site of lung metastases				< 0·001
Bilateral		27	101	
Unilateral	–	115	165	

Some data were missing for all variables. CEA, carcinoembryonic antigen. *χ^2 test, except †Student's t test.

Results

From 1 January 2000 to 1 January 2012, initial liver metastatic disease was recorded in 9619 patients meeting the inclusion criteria. Ten of 15 variables analysed demonstrated a statistically significant difference between the three groups (*Table 1*). Groups 2 and 3 received significantly more neoadjuvant chemotherapy than group 1 before liver resection (*Table 2*). There was no difference in terms of number of cycles or type of chemotherapy between groups 2 and 3. The response rate to neoadjuvant chemotherapy was similar in the three groups.

Mean(s.d.) survival was 757(900) days. Crude survival probabilities after hepatectomy are shown in *Fig. 1*. Patients who had resection of both liver and lung metastases had similar survival to those with resected

Table 2 Chemotherapy before and and after hepatectomy by treatment group

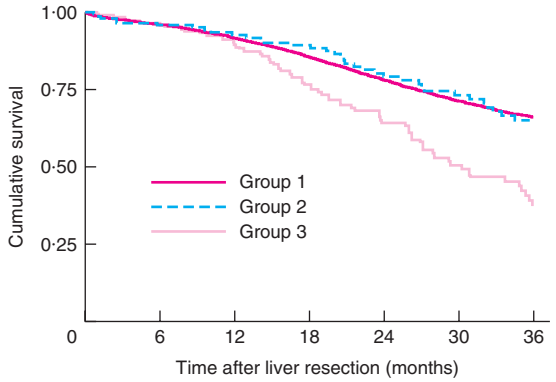
	Resected isolated liver metastases (group 1; $n = 9185$)	Resected simultaneous liver and lung metastases (group 2; $n = 149$)	Simultaneous resected liver and unresected lung metastases (group 3; $n = 285$)	P* (group 1 *versus* 2)	P* (group 1 *versus* 3)	P* (group 2 *versus* 3)
Prehepatectomy (neoadjuvant) chemotherapy				0·002	< 0·001	0·176
No	4736	64	105			
Yes	3618	82	178			
No. of cycles				0·898	0·008	0·176
Mean	6·6	7·1	7·8			
≤ 6	1919	43	84			
> 6	1080	25	73			
5-Fluorouracil				0·489	0·040	0·490
No	647	13	22			
Yes	2617	65	143			
Oxaliplatin				0·736	0·804	0·891
No	1166	29	61			
Yes	2091	48	105			
Irinotecan				0·630	0·423	0·388
No	2219	57	107			
Yes	1052	24	58			
Result after last cycle				0·704†	0·992†	0·793†
Progression	267	4	14			
No change	636	14	34			
Partial response	2114	49	114			
Complete response	135	3	8			
Toxicity	66	2	2			
Posthepatectomy (adjuvant) chemotherapy				0·193	0·155	0·858
No	3148	48	86			
Yes	3645	71	122			
No. of cycles				0·305	0·725	0·303
Mean	6·8	6·9	6·7			
≤ 6	1524	28	53			
> 6	936	23	30			
5-Fluorouracil				0·548	0·551	0·915
No	657	12	20			
Yes	2345	52	83			
Oxaliplatin				0·452	0·195	0·826
No	1214	29	48			
Yes	1773	35	54			
Irinotecan				0·879	0·074	0·337
No	2147	46	66			
Yes	805	18	36			

*χ^2 test; †comparison of progression *versus* no change *versus* downsizing (partial + complete response).

isolated liver metastases (5-year survival rates 50·0 and 40·7 per cent for groups 1 and 2 respectively). In contrast, patients who underwent resection of liver metastases but not lung metastases had significantly worse outcomes (5-year survival rate 9·4 per cent; $P < 0·001$). Of note, 5-year survival rates for patients who had surgery before *versus* after 2007 were 49·6 *versus* 48·4 per cent for group 1 ($P = 0·278$), 44 *versus* 41 per cent for group 2 ($P = 0·305$), and 10 *versus* 31.9 per cent for group 3 ($P = 0·596$). Compared with groups 1 and 2, group 3 had significantly worse survival in both intervals ($P < 0·001$).

Disease-free survival was assessed for groups 1 and 2 (group 3 had no global R0 resection by definition). The 5-year disease-free survival rate was 31·0 per cent for group 1 and 12·9 per cent for group 2 ($P < 0·001$) (*Fig. 2*). Recurrence sites were reported in 2777 of 3635 patients in group 1, and all 85 patients in group 2. There was liver recurrence in 64·0 and 37·6 per cent, lung recurrence in 26·8 and 41·2 per cent, both liver and lung recurrence in 7·1 and 0 per cent, and recurrence at other sites in 2·1 and 21·2 per cent, in groups 1 and 2 respectively.

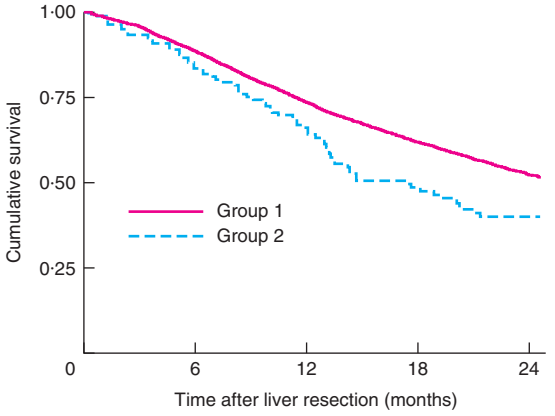
In the univariable analysis, 16 of 18 variables correlated with overall survival among the total of 9619 patients,



No. at risk

Group 1	8951	6814	5724	4597	3598	2787	2213
Group 2	146	134	114	95	72	57	45
Group 3	279	209	160	97	65	41	24

Fig. 1 Overall survival after resection of liver metastases in patients with liver metastases only (group 1), patients with resected liver and pulmonary metastases (group 2) and patients with resected liver metastases but unresected pulmonary metastases (group 3). $P < 0{\cdot}001$ (group 3 *versus* groups 1 and 2) (log rank test)



No. at risk

Group 1	8361	5844	4308	3156	2296
Group 2	130	103	71	46	35

Fig. 2 Disease-free survival after resection of the liver metastases in patients with liver metastases only (group 1) and patients with resected liver and pulmonary metastases (group 2). $P < 0{\cdot}001$ (log rank test). Patients with resected liver metastases but unresected pulmonary metastases (group 3) are not shown as their global status was R2 owing to unresected pulmonary metastases

Table 3 Significant factors affecting overall survival after liver resection in Cox univariable analysis

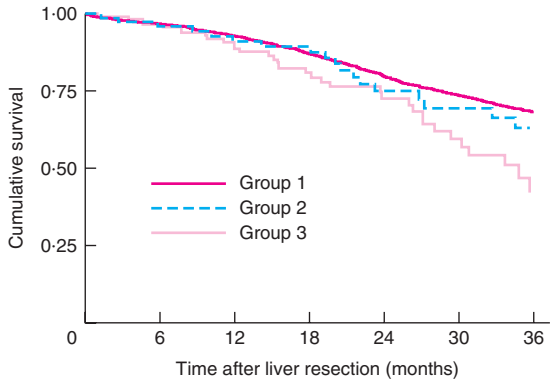
	Hazard ratio	*P*
Age (per year)	1·01 (1·00, 1·01)	0·016
Primary tumour (T3–4 *versus* T1–2)	1·05 (1·00, 1·11)	0·040
Primary tumour node status (N+ *versus* N0)	1·35 (1·28, 1·43)	< 0·001
Primary location (rectum *versus* colon)	1·15 (1·05, 1·25)	0·002
No. of liver metastases (multiple *versus* single)	1·47 (1·35, 1·60)	< 0·001
Extent of liver metastases (bilobar *versus* unilobar)	1·51 (1·38, 1·64)	< 0·001
Timing of liver metastases (synchronous *versus* metachronous)	0·72 (0·65, 0·78)	< 0·001
Size of liver metastases (≥ 5 *versus* < 5 cm)	1·42 (1·29, 1·56)	< 0·001
CEA level (> 200 *versus* ≤ 200 ng/ml	1·66 (1·42, 1·90)	< 0·001
Two-stage liver resection (yes *versus* no)	1·75 (1·51, 2·02)	< 0·001
Embolization before liver resection (yes *versus* no)	1·55 (1·36, 1·76)	< 0·001
Extent of liver resection (major *versus* minor)	1·31 (1·19, 1·43)	< 0·001
Initial resectability of liver metastases (unresectable *versus* resectable)	0·63 (0·57, 0·70)	< 0·001
Chemotherapy before liver resection (yes *versus* no)	1·16 (1·07, 1·27)	< 0·001
Chemotherapy after liver resection (yes *versus* no)	0·68 (0·62, 0·75)	< 0·001
Site of lung metastases (bilateral *versus* unilateral)	1·43 (1·26, 1·61)	< 0·001

Values in parentheses are 95 per cent c.i. CEA, carcinoembryonic antigen.

Table 4 Cox multivariable regression analysis of factors affecting overall survival after liver resection

	Hazard ratio	*P*
Age (per year)	1·01 (1·01, 1·02)	< 0·001
Primary tumour category (T3–4 *versus* T1–2)	1·08 (0·97, 1·21)	0·154
Primary tumour node status (N+ *versus* N0)	1·34 (1·23, 1·46)	< 0·001
No. of liver metastases (multiple *versus* single)	1·41 (1·21, 1·65)	< 0·001
Timing of liver metastases (synchronous *versus* metachronous))	0·84 (0·72, 0·98)	0·029
Size of liver metastases (≥ 5 *versus* < 5 cm)	1·12 (0·96, 1·32)	0·152
CEA level (> 200 *versus* ≤ 200 ng/ml)	1·30 (1·05, 1·06)	0·017
Embolization before liver resection (yes *versus* no)	1·23 (1·00, 1·51)	0·053
Extent of liver resection (major *versus* minor)	1·13 (0·97, 1·31)	0·109
Initial resectability of liver metastases (unresectable *versus* resectable)	0·79 (0·66, 0·94)	0·007
Resection of liver and lung metastases *versus* liver resection alone	1·10 (0·70, 1·72)	0·675
Liver resection but no lung resection *versus* liver resection alone	1·77 (1·27, 2·46)	0·001

Values in parentheses are 95 per cent c.i. CEA, carcinoembryonic antigen.



No. at risk

Group 1	8951	6814	5724	4597	3598	2787	2213
Group 2	146	134	114	95	72	57	45
Group 3	279	209	160	97	65	41	24

Fig. 3 Overall survival after resection of liver metastases, adjusted for significant variables defined by the Akaike test, in patients with liver metastases only (group 1), patients with resected liver and pulmonary metastases (group 2) and patients with resected liver metastases but unresected pulmonary metastases (group 3). $P = 0{\cdot}001$ (group 3 *versus* groups 1 and 2) (log rank test)

and nine of these differed significantly between the three groups (*Table 3*). The multivariable analysis included 12 variables selected by an Akaike test, of which seven were linked to survival (*Table 4*). Of note, inclusion in group 3 compared with group 1 was associated with the worst survival (hazard ratio 1·77, 95 per cent c.i. 1·27 to 2·46). Survival for the three groups was adjusted for variables selected by the Akaike test. After adjusting for co-variables, 5-year survival was similar in groups 1 and 2 (51·5 and 44·5 per cent respectively; $P = 0{\cdot}675$) but worse in group 3 (14·3 per cent; $P = 0{\cdot}001$) (*Fig. 3*).

Discussion

This study has demonstrated that patients with SLLM suitable for resection of all metastases have similar survival to patients who undergo removal of isolated liver secondaries. Of note, almost 20 per cent of patients who underwent resection of lung metastases had bilateral disease. This suggests that resectable SLLM should not be considered a contraindication to surgery.

The factors independently associated with survival (age, number and synchronicity of liver metastases, CEA level, primary lymph nodes, initial resectability of liver metastases and unresected lung metastases) are established prognostic indices[8,9,17,23,29,30]. Presence of unresectable or unresected lung metastases was a strong variable. This is interpreted as suggesting that lung metastases should be removed wherever feasible. Treatment alternatives include radiofrequency ablation[31–34] and stereotactic radiotherapy[35–37], but the results are heterogeneous.

The reasons for absence of lung resection were not available in the database, but may have been related to disease progression. The results of this study do not provide information that could be used to select patients who should not undergo resection of the lung metastases. In general, patients with isolated disease do best and multilobar involvement has a poor prognosis.

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