Original article

Long-term outcome in patients with adrenal metastases following resection of colorectal liver metastases

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Background: The prognostic significance of adrenal metastases (AMs) in patients with colorectal liver metastases (CLMs) remains unknown. The aim of this study was to determine the influence of AMs on long-term outcome and the role of adrenalectomy in patients with CLMs.

Methods: All patients resected for CLMs who developed AMs at a single institution between 1992 and 2006 were included in the study. Their long-term outcome was compared with that of all other patients resected for CLMs but without AMs.

Results: Hepatectomy was performed in 796 patients, of whom 14 (1·8 per cent) developed AMs, a median of 28 months after initial diagnosis of CLMs; the remaining 782 patients (98·2 per cent) had no AMs. All 14 patients had chemotherapy, and ten went on to adrenalectomy. Median survival after diagnosis of CLMs was 50 months in patients with AMs *versus* 68 months in those without ($P = 0{\cdot}020$). After diagnosis of AMs, median survival was 23 months, whether or not adrenalectomy was performed.

Conclusion: The development of AMs after liver resection for colorectal cancer deposits carries a poor prognosis, and adrenalectomy is probably not warranted.

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Introduction

Adrenal metastases (AMs) are often found at autopsy[1] but it is uncommon for them to be identified in patients living with or recovering from colorectal cancer (*Table 1*)[2–15]. Interestingly, only two cases have been described in which extra-adrenal metastasis was present at identification of AMs[10,15]. Adrenalectomy is well described for metastatic disease, but any additional benefit over chemotherapy alone is questionable in patients with colorectal cancer[6,7,11,12,14,16–18].

Increased detection of extrahepatic colorectal metastases by modern imaging, including positron emission tomography (PET)[19], results in a probable increase in the numbers of patients identified with AMs. As the optimal treatment strategy for colorectal AMs is still unclear, this study was undertaken to evaluate whether it is justifiable to resect AMs following liver resection.

Methods

Study design

All patients who underwent hepatectomy for colorectal liver metastases (CLMs) at the Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, between January 1992 and December 2006, and who developed AMs were included in the study. To evaluate the impact of AMs on long-term outcome, comparison was made with all other patients who had surgery for CLMs during the same period. Patients were identified from the authors' prospective database. Data were collected on patient demographics, primary colorectal tumour, liver metastases

Table 1 Overview of publications of patients with adrenal metastases from colorectal carcinoma

		Primary tumour		Side of adrenal metastasis			Treatment				
Reference	No. of patients	Colon	Rectum	Left	Right	Both	Surgery	Chemo.	RTx	Mean follow-up (months)	Outcome
3	1 (SC)	0	1	1	0	0	1	0	0	23*	ANED
15	3 (SC)	2	1	1	1	1	3	0	0	18*	ANED 1, DOD 2
13	1 (SC)	1	0	0	1	0	0	0	1	12	AWD
7	7 (SC)	7	0	NA	NA	NA	7	0	0	NA	NA
6	5 (SC)	NA	NA	NA	NA	NA	5	0	0	21*	NA
14	8 (MC)	NA	NA	NA	NA	NA	8	0	0	22*	NA
5	1 (SC)	0	1	1	0	0	1	0	0	41*	AWD
2	1 (SC)	1	0	0	0	1	1	0	0	12	ANED
10	1 (SC)	1	0	0	1	0	1	0	0	84*	ANED
11	3 (SC)	NA	NA	NA	NA	NA	3	0	0	NA	NA
9	1 (SC)	0	1	1	0	0	1	0	0	6*	DOD
8	3 (SC)	3	0	NA	NA	NA	3	0	0	8*	Died
4	1 (SC)	1	0	1	0	0	1	0	0	84*	ANED
12	1 (SC)	1	0	NA	NA	NA	1	0	0	18	DOD

*After adrenal resection. RTx, radiotherapy; SC, single centre; ANED, alive with no evidence of disease; DOD, died from disease; AWD, alive with disease; NA, not available; MC, multicentre.

at initial diagnosis, first hepatectomy, AMs and long-term outcome.

Hepatic metastases

Preoperative evaluation consisted of abdominal ultrasonography and computed tomography (CT), thoracic CT and colonoscopy. Preoperative chemotherapy was given when lesions were initially unresectable, when the estimated remnant liver was too small and/or when synchronous extrahepatic disease sites were present. More recently, chemotherapy has increasingly been given in a neoadjuvant setting, in patients with initially resectable liver metastases.

All hepatectomies were performed with curative intent. Intraoperative ultrasonography was performed in all patients to determine the extent of liver disease. The extent of hepatectomy was classified as major (three or more liver segments) or minor (fewer than three segments), according to Couinaud's classification[20,21]. Resectable, concomitant extrahepatic disease was not considered a contraindication to surgery. If located within the abdominal cavity, extrahepatic metastases were resected at the hepatectomy. If outside the abdomen, resection of extrahepatic disease was postponed for 2–3 months, with chemotherapy in the interim, to prevent disease progression.

At 1 month after surgery, and then every 4 months, follow-up included the history, physical examination, serum tumour markers, liver function parameters and abdominal ultrasonography. Abdominal and thoracic CT was performed every 8 months. Most patients received adjuvant chemotherapy to reduce the risk of recurrence.

Adrenal metastases

AMs were diagnosed by CT during preoperative investigation for hepatectomy, at operation, or during postoperative surveillance. If suspected, resection of AMs was combined with hepatectomy, following histological confirmation of their malignant nature, provided that complete resection of both CLMs and AMs could be performed. If diagnosed during follow-up after hepatectomy, AMs were resected in a separate operation, again after histological confirmation of the diagnosis. When surgical resection could not be performed with curative intent, AMs were not removed and systemic chemotherapy alone was given.

Statistical analysis

Categorical variables were compared using the χ^2 test, and continuous data with the independent-samples t test. The Kaplan–Meier method was used to estimate survival probabilities, which were compared with the log rank test. $P \leq 0{\cdot}050$ was considered statistically significant. All statistical calculations were performed with SPSS® version 13.0 (SPSS, Chicago, Illinois, USA).

Results

A total of 796 patients underwent hepatic resection for CLMs between January 1992 and December 2006. Of these, 14 patients (1·8 per cent) developed AMs a median of 30 months after resection of the primary colorectal tumour and 28 months after the first diagnosis of liver metastasis.

Table 2 Characteristics of 796 patients with liver metastases from colorectal carcinoma

	Adrenal metastases ($n = 14$)	No adrenal metastases ($n = 782$)	P†
Mean(s.d.) age (years)	59(9)	59(11)	0·942‡
Sex			0·846
M	8 (57)	467 (59·7)	
F	6 (43)	315 (40·3)	
Primary tumour			
Site			0·344
Colon	12 (86)	553 (74·6)	
Rectum	2 (14)	188 (25·4)	
Tumour stage			0·268
T1–2	3 (30)	50 (16·6)	
T3–4	7 (70)	251 (83·4)	
Node stage			0·142
N0	1 (11)	97 (34·6)	
N1–2	8 (89)	183 (65·4)	
Liver metastasis at initial diagnosis			
Timing of occurrence			0·147
Synchronous*	11 (79)	464 (59·4)	
Metachronous	3 (21)	317 (40·6)	
No. of CLMs			0·805
1	4 (33)	232 (32·7)	
2–3	3 (25)	235 (33·1)	
> 3	5 (42)	242 (34·1)	
Mean(s.d.) maximum size (mm)	43(27)	44(32)	0·982‡
Location			0·603
Unilateral	6 (43)	377 (49·9)	
Bilateral	8 (57)	379 (50·1)	
Initially unresectable	7 (50)	247 (31·6)	0·215
Hepatic resection			
Preoperative chemotherapy	13 (93)	645 (82·5)	0·313
Extent of resection			0·830
Minor (< 3 segments)	9 (64)	305 (67·0)	
Major	5 (36)	150 (33·0)	
Concomitant extrahepatic disease	10 (71)	143 (18·3)	<0·001
Postoperative chemotherapy	13 (93)	536 (68·5)	0·049

Values in parentheses are percentages unless indicated otherwise. *Diagnosed before, during or within 3 months of colorectal resection. CLM, colorectal liver metastasis. †χ^2 test unless indicated otherwise; ‡independent-samples t test.

The mean age was 59 years in both groups, with similar male : female ratios (*Table 2*). In most patients the primary tumour was located in the colon. In patients with AMs, initial diagnosis of liver metastasis was more often synchronous with that of the primary tumour (diagnosed before, during or within 3 months of colorectal resection) (79 per cent *versus* 59·4 per cent in those without AMs; $P = 0·147$), and liver metastases tended more often to be initially unresectable (50 *versus* 31·6 per cent respectively; $P = 0·215$) (*Table 2*). In addition, significantly more patients with AMs presented with extrahepatic disease concomitant with hepatectomy (71 *versus* 18·3 per cent; $P < 0·001$). Hepatic resection was more often followed by systemic chemotherapy in patients who developed AMs (93 *versus* 68·5 per cent; $P = 0·049$).

Adrenal metastases

Involvement of the adrenal gland was diagnosed before hepatectomy in four patients, during hepatectomy in four, and after hepatectomy in six patients. All patients with adrenal involvement had true AMs (no direct extension of hepatic lesions to the adrenal gland). Diagnosis of AMs was related to the first hepatectomy in six patients, to the second hepatectomy in six, and to the third and fourth hepatectomy in one patient each.

Four patients had isolated AMs, whereas other organs were also involved in the other ten patients (liver metastases, eight; lung metastases, one; both liver and lung metastases, one). Before diagnosis of AMs, six patients had already undergone a first liver resection, three had undergone hepatectomy and pulmonary resection, one patient had had a liver, pulmonary and bone resection, and

Table 3 Long-term outcome of 796 patients with and without adrenal metastases

	Adrenal metastases ($n = 14$)	No adrenal metastases ($n = 782$)	P¶
Recurrence	14 (100)	527 (67·4)	0·010
Hepatic	1 (7)	136 (25·8)	0·036
Extrahepatic	2 (14)	159 (30·2)	
Both	11 (79)	232 (44·0)	
Total no. of hepatectomies			0·021
1	5 (36)	537 (68·7)	
2	6 (43)	187 (23·9)	
≥ 3	3 (21)	58 (7·4)	
Total no. of EHD resections			< 0·001
0	2 (14)	600 (76·7)	
1	6 (43)	119 (15·2)	
2	4 (29)	42 (5·4)	
≥ 3	2 (14)	21 (2·7)	
Status at last follow-up			< 0·001
Alive without disease	0 (0)	285 (36·4)	
Alive with disease	1 (7)	245 (31·3)	
Dead	13 (93)	252 (32·2)	
Survival (months)*			
After diagnosis of CLM	50 (41, 60)	68 (58, 78)	0·020#
After diagnosis of AM	23 (18, 29)	–	
Treated by adrenalectomy ($n = 10$)†	23 (14, 31)#	–	
Adrenalectomy + hepatic resection ($n = 4$)	23 (7, 38)	–	
Metachronous adrenalectomy ($n = 6$)	19 (10, 28)‡	–	
Treated by chemotherapy ($n = 4$)†	23 (7, 40)§	–	

Values in parentheses are percentages unless indicated otherwise; *values are median (95 per cent confidence interval). †Calculated from the date of diagnosis of adrenal metastasis (AM). EHD, extrahepatic disease; CLM, colorectal liver metastasis. ‡$P = 0·675$ *versus* combined adrenalectomy and hepatic resection; §$P = 0·822$ *versus* adrenalectomy (log rank test). ¶χ^2 test unless indicated otherwise; #log rank test.

one a liver and lung resection as well as partial resection of the diaphragm.

The left adrenal gland was involved in four patients, the right adrenal gland in nine, and one patient had metastases in both adrenal glands. The mean(s.d.) diameter of the AMs was 36(16) mm. No patient had symptoms of adrenal insufficiency.

In ten of the 14 patients the AMs were surgically resected; nine had a conventional adrenalectomy via an anterior subcostal approach (in four patients combined with hepatectomy) and one patient had a laparoscopic resection. No patient died within 60 days of adrenalectomy. Postoperative complications were observed in three patients. One patient developed pneumonia, which was treated successfully with antibiotics, another developed thrombosis of the inferior caval vein, treated successfully with heparin, and the third had an infected perihepatic fluid collection, which resolved completely after antibiotic treatment (all Clavien grade II[22]). In all patients adrenalectomy was combined with systemic chemotherapy. In four patients the overall treatment strategy was not curative because disease other than the AMs was irresectable, so adrenalectomy was not performed and systemic chemotherapy was administered.

Long-term outcome

The mean length of follow-up for the whole study population was 41 months. At last follow-up of patients with AMs, 13 had died from disease progression and one patient was alive with recurrence (*Table 3*). Significantly more patients with AMs underwent repeat hepatectomy (64 (9 of 14) *versus* 31·3 per cent; $P = 0·009$) and resection of extrahepatic disease (86 (12 of 14) *versus* 23·3 per cent; $P < 0·001$), compared with patients without AMs.

Three- and 5-year overall survival rates after the initial diagnosis of CLMs were 79 and 32 per cent respectively in the AM group, compared with 76 and 53 per cent for patients who did not develop AMs ($P = 0·020$). Median survival from this first diagnosis was 50 (95 per cent confidence interval (c.i.) 41 to 60) months for patients with AMs *versus* 68 (95 per cent c.i. 58 to 78) months for those without AMs.

For the 14 patients with AMs, median survival after diagnosis of AMs was 23 (95 per cent c.i. 18 to 29) months (*Table 3*), and was similar whether treated by adrenalectomy plus chemotherapy (ten patients) or chemotherapy alone (four) (23 months in both groups; $P = 0·822$). In the four patients who had concomitant adrenalectomy and

hepatectomy, median survival after diagnosis of AMs was 23 (95 per cent c.i. 7 to 38) months, compared with 19 (10 to 28) months in the six patients having metachronous adrenalectomy ($P = 0{\cdot}675$).

Discussion

As the prognostic significance of AMs in patients with CLMs remains unknown, the principal aims of the present study were to determine their influence on long-term outcome after liver resection and the value of adrenal resection. Patients with AMs had a significantly lower 5-year survival rate than those without AMs. After diagnosis of AMs, median survival was 23 months, and was not influenced by the type of treatment (chemotherapy plus adrenalectomy, or chemotherapy alone).

Within the English literature, only 14 case reports and small series of patients with AMs from colorectal cancer have been published, some of them reporting prolonged survival (*Table 1*)[2–15]. Notably, all but two case reports concerned isolated AMs[10,15], in contrast to the present study where other organs were also involved in ten of the 14 patients.

As a result of the improving diagnostic accuracy of CT in evaluating adrenal masses, as well as the introduction of PET, surgeons and medical oncologists will be faced more often with patients with AMs of colorectal origin[23–27]. In addition, the significant increase in survival and follow-up observed in recent years favours the emergence of late metastatic sites, such as the adrenals. Therefore, it is important to know whether or not these patients correspond to a specific patient profile. In the authors' experience, patients treated for CLMs who also developed AMs tended more often to have initially unresectable liver metastasis synchronous with the primary colorectal tumour, compared with patients without AMs. Furthermore, patients with AMs presented more often with extrahepatic disease concomitant with hepatectomy. They also had a significantly lower 5-year survival rate, although 3-year survival rates in patients with and without AMs were comparable. This finding emphasizes the adverse prognostic influence of the development of AMs.

To determine whether the present results might be considered representative of daily practice, the international registry LiverMetSurvey (http://www.livermetsurvey.org), a multicentre online registry of patients undergoing surgery for CLMs, was consulted. Of a total of 7302 patients in the database, AMs had been found in only 32 patients (0·4 per cent). Of these, 21 patients underwent adrenalectomy. Median survival after the initial diagnosis of liver metastasis was 53 (95 per cent c.i. 41 to 64) months, that after diagnosis of AMs was 23 (95 per cent c.i. 14 to 33) months, and the subgroup treated by adrenalectomy had a median survival of 25 (95 per cent c.i. 14 to 33) months. Taken together, these multicentre results are in accord with the present findings.

At the authors' hospital, the treatment policy for patients presenting with intrahepatic and/or extrahepatic metastases of colorectal origin has always been surgical, provided that resection of all disease sites is possible. Using this approach, in patients treated for CLMs who presented with AMs, a median survival of 23 months after diagnosis of AMs was achieved whether treatment was with combined chemotherapy and adrenalectomy, or chemotherapy alone. However, one patient survived for more than 7 years following the combined treatment, indicating that long-term remission may be possible in highly selected patients. Therefore, the authors perform adrenalectomy only when patients are also scheduled for hepatectomy, as a combined procedure can be performed safely. When diagnosed during follow-up after hepatic resection for CLMs, patients with AMs could be treated by chemotherapy alone, reserving adrenalectomy for highly selected patients, as surgery does not appear to offer any benefit over chemotherapy alone.

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