International Journal of Surgery 8 (2010) 453–457

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com

Larger hepatic metastases are more frequent with N0 colorectal tumours and are associated with poor prognosis: Implications for surveillance

S. Partelli [a,b,1], S. Mukherjee [a,1], K. Mawire [a], R.R. Hutchins [a], A.T. Abraham [a], S. Bhattacharya [a], H.M. Kocher [a,b,*]

[a] Barts and the London HPB Centre, The Royal London Hospital, Whitechapel, London E1 1BB, UK
[b] Instiute of Cancer, Barts and the London School of Medicine and Dentistry, Charterhouse Square, London, UK

ARTICLE INFO

Article history:
Received 1 February 2010
Received in revised form
16 May 2010
Accepted 27 May 2010
Available online 19 June 2010

Keywords:
Liver
Metastases
Nodal status
Survival
Size
Risk

ABSTRACT

Background: Surgery is the treatment of choice for colorectal cancer liver metastases (CLM). The aim of our study was to analyze which clinical and pathological risk factors can predict recurrence after liver resection.
Methods: Consecutive patients who underwent hepatic resection for CLM were studied retrospectively to identify risk factors influencing cancer recurrence, by univariate and multivariable analyses.
Results: 97 patients (2004–2008) with a median age of 64.6 years (inter-quartile range 57.6–72.6) had a median disease free survival of 16.4 months. On univariate analysis the largest metastasis >5 cm (hazard ratio, HR 2.04, 95% CI 1.10–3.80, $p = 0.03$), presence of extra-hepatic disease (HR 2.39, 95% CI 1.14–5.02, $p = 0.02$) and a resection margin ≤5 mm (HR 1.91, 95% CI 1.06–3.47, $p = 0.03$) were significantly associated with a higher risk of recurrence after curative resection for CLM. These were confirmed as independent predictors for recurrence on multivariable analysis. There were significantly more patients with lymph node negative (N0) primary in the group with liver secondary > 5 cm ($n = 18$, 39%), than in the group with liver secondary £5 cm ($n = 7$, 14.6%) ($p = 0.01$).
Conclusion: We demonstrated a positive correlation between N0 primary tumour and large liver metastases, which have a higher risk of disease recurrence. If validated in larger, independent studies, this study would suggest routine imaging surveillance follow up of even N0 colorectal tumours, until the biology of these tumours is fully understood.

1. Introduction

Five-year survival after hepatic resection of colorectal metastases ranges from 32% to 65% in the largest series.[1–4] However, which patients benefit maximally is unclear. Fong et al.,[1] proposed a Clinical Risk Score (CRS) based on five criteria which were highly predictive of poor outcome after resection of colorectal liver metastases: node-positive primary tumour, disease free interval from primary to discovery of metastases of <12 months, >1 liver metastases, pre-operative CEA > 200 ng/ml and size of the largest tumour > 5 cm. The predictive value of the CRS has been corroborated by only two retrospective studies.[5,6] The presence of 3 or more of these criteria is strongly associated with a poor prognosis. Others have suggested that pre-operative prognostic factors such as the Duke's stage status, lymph node involvement and the grade of differentiation, the presence of extra-hepatic disease[6–10] and operative indicators such as resection margins, as well as extra-hepatic invasion are associated with a higher risk of recurrence.[4,11–23] Independent validation of these criteria is lacking. The aim of our study was to analyze these clinical and histological factors, including the CRS, and to evaluate possible correlations with pre-operative and other independent predictors, if any, with the outcome.

2. Methods

All hepatic resections for CLM performed at the Barts & The London HPB Centre during a 5-year period (January 2004 to December 2008) were prospectively recorded in our database and retrospectively analyzed. Data examined included demographics, features of primary colorectal lesion, disease-free interval from the primary to discovery of the liver metastases, histopathology of the liver lesions and the surgical outcome.

* Corresponding author at: Barts and the London HPB Centre, The Royal London Hospital, Whitechapel, London E1 1BB, UK. Tel./fax: +44 20 7377 7491.
E-mail address: hemant.kocher@bartsandthelondon.nhs.uk (H.M. Kocher).
[1] Contributed equally to this work.

1743-9191/$ – see front matter
doi:10.1016/j.ijsu.2010.05.013

A pre-operative CRS was calculated for each patient as proposed by Fong et al.[1] and the composite score as well as individual factors were assessed for their effect on disease-free survival. All patients underwent thoracic, abdominal and pelvic computed tomography (CT) and Positron Emission Tomography (PET) scan prior to liver resection and were discussed at a weekly hepatobiliary multi-disciplinary meeting to determine the size, location and number of deposits. Portal vein embolization (PVE) was performed in selected cases when functional remnant liver after planned resection was deemed to be too small (<0.5 ml/kg body weight). All the operations were performed by four experienced hepatobiliary surgeons (ATA, RRH, SB and HMK) and in the majority of patients, intraoperative ultrasound (IOUS) was used for localization of the tumour and confirmation of vasculature and biliary anatomy.

Morbidity was defined as any peri-operative complication that prolonged the hospital stay or needed active management. Peri-operative mortality was defined as any in-hospital death or death within 30 days when patients were discharged from the hospital earlier. Patients were followed up at regular intervals after discharge. Follow up data was obtained by review in the out-patient clinic or by telephone clinic run by clinical nurse specialist (KM). Recurrence was defined as presence of radiologically confirmed metastases with histological confirmation, whenever possible. To ascertain complete histological evaluation of tumours specimen, we obtained full histology report of primary tumours (mostly carried out in other hospitals). Histology reports were available for 90 of 97 patients and demonstrated complete lymph node staging as per international guidelines.

2.1. Statistical analysis

Distribution of continuous variables were reported as median and inter-quartile range (IQR) (25th; 75th percentiles), and categorical variables are presented as numbers and percentages. The comparison between subgroups, identified by status at end of follow-up (disease recurrence), was carried out using Student's *t* test, or Mann–Whitney *U* test, for continuous variables. Qualitative data were compared by the Chi-square test or Fischer's exact test as required. Survival probability was estimated according to the Kaplan–Meier method, whereas the log-rank test was used for comparison of survival in different subgroups. Univariate and Multivariate analysis was performed using the Cox-regression model to evaluate significant predictors of recurrence and their relative role. Statistical analyses were performed using SPSS 16.0 for Windows software (SPSS Inc, Chicago, Illinois, USA). $P \leq 0.05$ was considered significant.

3. Results

Ninety-seven patients underwent liver resections for CLM over 5 years at our institution; demographic, clinical and histological data are summarized in Table 1. After first liver resection, 6 (5.7%) patients underwent surgery for another resection and 2 (2.9%) had a third operation. Thirteen (13.4%) patients underwent PVE prior to surgery and 11 (11.3%) had extra-hepatic disease. Sixty-four (66%) patients had a CRS $\leq$ 2 whereas 33 (34%) patients had a CRS>2. Among the 105 liver resections, in 52 (49.5%) patients a major hepatectomy was performed, 27 (25.7%) patients underwent a segmentectomy and 26 (24.8%) a wedge resection; in 13 (12.4%) patients a radio-frequency ablation (RFA) was carried out during the operation, as an adjunct to hepatectomy. The median blood loss was 700 ml (IQR 350; 1000 ml) and 32 (30.5%) patients had complications. Bile leak was the commonest complication (10.5%). The median length of hospital stay was 9 days (IQR 7; 15 days) and peri-operative mortality occurred in 6 (5.7%) patients. On pathological examination, the median size of the largest tumour was 5 cm (IQR 2.8; 10 cm) and a R0 resection was confirmed in 76 (78.4%) patients while 21 (21.6%) had a R1 resection. Seventy-nine (81.4%) patients were alive, 17 (17.5%) were deceased and 1 patient (1%) was lost at follow up at the end of June 2009 and 44 (45.4%) patients had a recurrence after curative liver resection for colorectal metastases.

Table 1
Demographic, clinical and histological characteristics of 97 patients with colorectal cancer liver metastases who underwent surgical resection.

Demographic and clinical data	Variable	Total ($n = 97$) *n* (%)
	Gender	
	Male	56 (57.7%)
	Female	41 (42.3%)
	Age	
	Median, years (IQR)	64.6 (57.6; 72.6)
	pre-operative CEA	
	Median, ng/mL (IQR)	9.2 ng/mL (3.1; 53.6)
Primary Tumour	Site	
	Rectum	37 (38.1%)
	Sigmoid Colon	35 (36.1%)
	Right Colon	12 (12.4%)
	Left Colon	7 (7.2%)
	Transverse Colon	6 (6.2%)
	Stage	
	Dukes A	4 (4.1%)
	Dukes B	14 (14.4%)
	Dukes C	34 (35.1%)
	Dukes D	45 (46.4%)
	Nodal status	
	Node negative[a]	25 (25.8%)
	Node positive	72 (74.2%)
	Synchronous metastases	45 (46.4%)
	Metachronous metastases	52 (53.6%)
	Adjuvant chemotherapy	
	Yes	82 (84.5%)
	No	15 (15.5%)
Metastases features	Tumour size	
	Median, cm (IQR)	5 cm (2.8; 10)
	Resection margin	
	R0	76 (78.4%)
	R1	21 (21.6%)
	Grading	
	Well Differentiated	40 (41.2%)
	Moderately Differentiated	51 (52.6%)
	Poorly Differentiated	6 (6.2%)
	Distribution	
	Unilobar	70 (72.2%)
	Bilobar	27 (27.8%)
	Number	
	Solitary	49 (50.5%)
	Multiple	46 (47.4%)

[a] The number of node negative tumours is more than the sum of the Dukes A and Dukes B tumours, as some of the Dukes D tumours were node negative as well.

The 3-and 5-years disease-specific survival from the resection of the primary tumour were 81.3% and 72.6% respectively, whereas the 3-years disease-specific survival from the resection of the liver metastases was 64.5%. The 3-years disease-free survival was 23% with a median of 16.4 months (Fig. 1). On univariate analysis (Table 2), the largest metastasis >5 cm, the presence of extra-hepatic disease and a resection margin $\leq$5 mm were significantly associated with a higher risk of recurrence after curative resection for CLM.

Multivariable analysis confirmed that the presence of a lesion with a diameter > 5 cm, and a resection margin $\leq$5 mm as independent prognostic indicators of recurrence with presence of extra-hepatic disease just reaching the significant threshold (Table 3). The estimated disease-free survival curve based on each factor is shown in Fig. 2. The hazard ratio was slightly, but not significantly higher

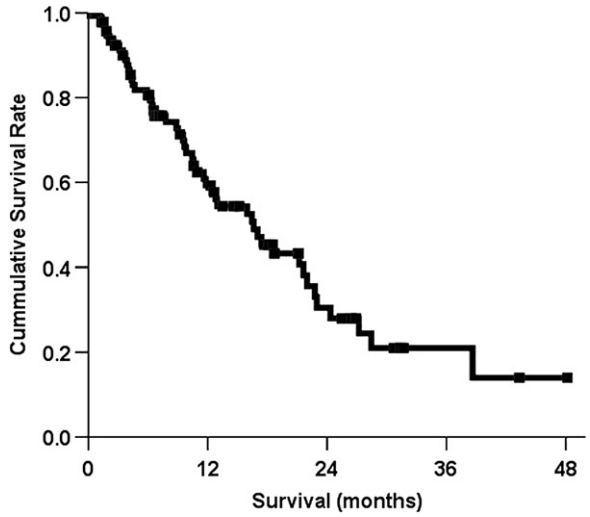

Fig. 1. Disease-free survival of patients ($n = 97$) after curative liver resection for colorectal liver metastases.

in patients with a CRS > 2 than in those with a CRS ≤ 2 (HR 1.72 CI 95% 0.97–3.06).

On the basis of these results, we divided our cohort of patients into two different groups; group A included patients with a largest liver lesion ≤5 cm and group B included patients with a largest liver lesion > than 5 cm Table 4 compares the pre-operative findings between the two groups, which demonstrates no differences between the two groups for most variables. Surprisingly, 85.4% of patients with smaller tumours (Group A) had lymph node involvement at the time of the resection for the primary tumour whereas only 61% of patients with large liver metastasis (Group B) had histologically confirmed lymph node involvement at the time of the primary resection ($p = 0.013$). Within the group of patients with negative lymph nodes at the first diagnosis, 7 (28%) had synchronous metastases whereas 18 (72%) developed metachronous metastases ($p = 0.03$).

Table 2
Univariate analysis of prognostic factors for recurrence after liver resection for CLM.

Variable	HR	95% CI		*p*
Gender (Male vs. Female)	1.39	0.75	2.59	0.30
Age > 60 years	1.69	0.80	3.58	0.17
pre-operative CEA > 200 ng/mL	2.48	0.57	10.74	0.23
Presence of extra-hepatic disease	2.39	1.14	5.02	**0.02**
Microvessel Invasion	1.04	0.13	8.22	0.97
Primary Site Rectum	1.28	0.03	2.48	0.26
Sigmoid Colon	1.12	0.41	3.01	0.83
Left Colon	0.58	0.14	2.45	0.46
Transverse Colon	0.29	0.03	2.48	0.26
Right Colon	reference			
Dukes D	0.42	0.12	1.46	0.17
Dukes C	0.45	0.13	1.59	0.22
Dukes B	0.71	0.18	1.59	0.62
Dukes A	reference			
Primary tumour N1	0.70	0.35	1.40	0.70
Metachronous	0.43	0.70	2.33	0.43
Interval ≤ 12 months	1.16	0.61	2.17	0.66
Size of the largest metastases > 5 cm	2.04	1.10	3.80	***0.03***
Number of metastases > 1	0.97	0.53	1.77	0.92
Grading Poorly Differentiated	2.56	0.83	7.92	0.10
Moderately Differentiated	1.75	0.91	3.66	0.09
Well Differentiated	reference			
Distribution (Bilobar)	0.79	0.41	1.52	0.48
Margin ≤5 mm	1.91	1.06	3.47	***0.03***
CRS > 2	1.72	0.97	3.06	0.07

Table 3
Multivariable analysis of prognostic factors for recurrence after liver resection for CLM.

Variable	HR	95% CI		p
Presence of extra-hepatic disease	2.03	0.99	4.14	0.05
Size of the largest metastases > 5 cm	2.17	1.19	3.96	***0.01***
Margin ≤5 mm	2	1.08	3.69	***0.03***

4. Discussion

Our study confirmed that surgery is an effective treatment for CLM with a 3-years disease-specific survival of 64.5%, consistent with other studies.[24–26] In the current study, a resection margin ≤5 mm, size of the largest liver metastasis > 5 cm, and the presence of extra-hepatic disease were independent predictors of recurrence after curative resection for CLM. Previously, a resection margin less than 1 cm for CLM has been shown to decrease disease-free survival.[14,21,23,27,28] Furthermore, others have found that a resection margin greater than 5 mm is an independent favourable prognostic factor.[15]

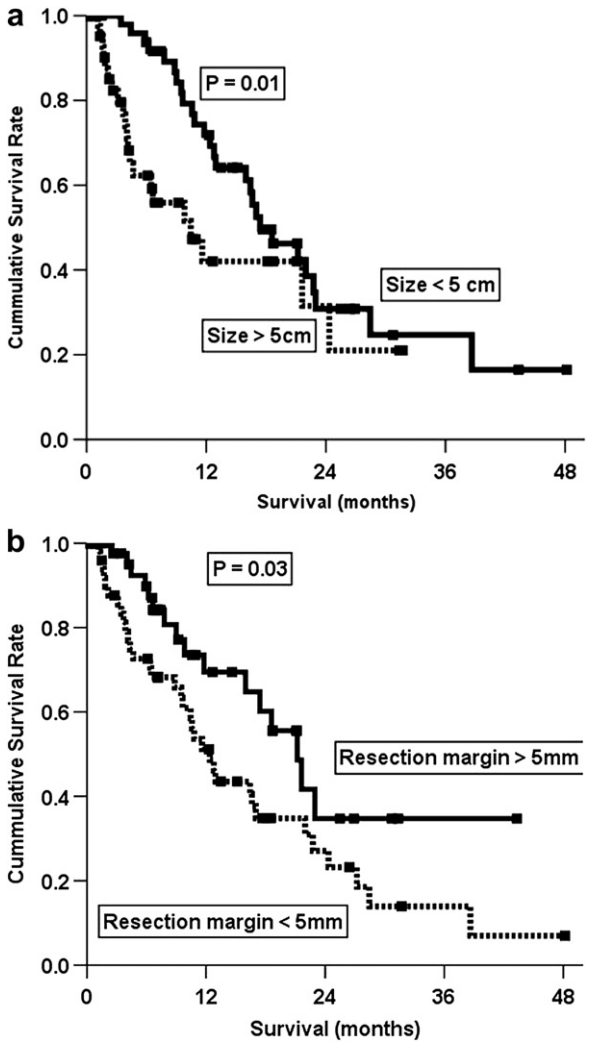

Fig. 2. Comparison of the disease-free survival of patients undergoing liver resection based on the significant prognostic factors. **a)** Patients with largest metastasis ≤5 cm ($n = 50$, continuous line) and patients with largest metastasis >5 cm ($n = 47$, dotted line); ($p = 0.01$). **b)** Resection margin > 5 mm (continuous line) versus resection margin ≤5 mm (dotted line); ($p = 0.03$).

Table 4
Comparison between two groups of patients with the diameter of the largest liver metastasis ≤5 cm (group A) and patients with the diameter of the largest liver metastasis >5 cm (group B).

Variable	Group A ($n = 50$)	Group B ($n = 47$)	p	Test
Men (n)	27 (51.9%)	32 (64%)	0.22	Chi-Square Test
Age (median,IQR)	62.15 years (56.6; 73.16)	67.61 years (53.19; 71.78)	0.29	Mann–Whitney *U* Test
pre-operative CEA (median,IQR)	20.6 ng/mL (3.25; 96.52)	8.5 ng/mL (3.2; 44.2)	0.48	Mann–Whitney *U* Test
Site Primary				
Right Colon	4 (8.3%)	6 (13%)	0.87	Fisher's Exact Test
Transverse Colon	4 (8.3%)	2 (4.3%)		
Left Colon	3 (6.2%)	4 (8.7%)		
Sigmoid Colon	18 (37.5%)	16 (34.8%)		
Rectum	19 (39.6%)	18 (39.1%)		
Dukes A	2 (4.2%)	2 (4.3%)	0.22	Fisher's Exact Test
Dukes B	4 (8.3%)	10 (21.7%)		
Dukes C	21 (43.8%)	13 (28.3%)		
Dukes D	21 (43.8%)	21 (45.7%)		
N1 (primary tumour) N0 (primary tumour)	41 (85.4%) 7 (14.6%)	28 (61%) 18 (39%)	*0.01*	Chi-Square Test
Adjuvant chemotherapy (n)	39 (81.2%)	40 (87%)	0.45	Chi-Square Test
Synchronous presentation Metachronous presentation	21 (43.8%) 27 (56.2%)	21 (45.7%) 25 (54.3%)	0.85	Chi-Square Test
Months from primary to metastases (median)	11 months	12 months	0.58	Mann–Whitney *U* Test
Margin, mm (median,IQR)	4.5 mm (1; 10.75)	8.5 mm (0.88; 13.5)	0.29	Mann–Whitney *U* Test

In the current study we failed to demonstrate that the CRS as proposed by Fong et al.,[1] is a significant predictive factor for recurrence after liver resection for CLM. However, among the five criteria,[1] the largest metastases with a diameter > 5 cm is most frequently found to be a negative prognostic factor[18,25,29–31] and has been confirmed by our cohort of patients. Beyond the study from the Memorial Sloane Kettering,[1] many reports suggested that the diameter of the largest metastasis is a predictive factor of recurrence after surgery.[7,18,25,30] Tanaka et al.,[30] suggested that apart from the size of the metastasis, a short CLM doubling time (<45 days) negatively affects the survival as well.

In order to ascertain the prognostic relevance of this factor, we choose to analyze the pre-hepatectomy factors that could be associated with a larger metastasis size. We compared two groups of patients using 5 cm diameter of the largest metastasis as cut off and found that the median time from diagnosis of the primary tumour and the detection of liver metastases was no different between two groups. This fact seems to demonstrate that the larger lesions grow more quickly than the smaller ones and this could be related to a more aggressive biological behaviour i.e. shorter tumour doubling time. Interestingly, the number of patients without lymph nodes involvement at the time of primary tumour resection is higher in the group with larger CLM and several possible hypotheses could explain this finding.

Firstly, patients with N0 primary colon cancer usually have less stringent follow-up criteria following resection of the primary tumour. The current guidelines for the surveillance and follow-up of patients with colorectal cancer recommend routine clinic visits and CEA measurements without routine hepatic imaging.[32,33] In our two groups, we failed to find a statistically significant difference between the median pre-operative CEA values (Table 4). Therefore, CEA may not predict the size of the metastases and in the absence of a routine surveillance hepatic imaging studies some patients could develop large lesions within a relatively short period of time. In both groups the rate of adjuvant chemotherapy was the same and this reassures us that N0 patients were not under-treated. Perhaps, dedicated protocol use of imaging studies, such as abdominal ultrasound, could detect these metastatic lesion(s) earlier and neo-adjuvant chemotherapy trials for liver resection such as new-EPOC can treat these patients better.

Another possible explanation of larger hepatic metastases with N0 primary may be related to a preferential haematogenous spread for a subgroup of tumours and resulting in a greater size of the final metastatic nodules. The TNM-system of the International Union against Cancer[34] does not allow precise prognostication for an individual patient and to overcome this limitation, molecular characterization of the tumour have been advocated.[35] In order to identify patients with Dukes' B colon cancer at high risk of recurrence, Wang et al.[36] identified a 23-gene signature that predicts recurrence in Dukes' B colon cancer. Moreover, a study from the University of Heidelberg[37] suggested that the detection of circulating tumour cells in blood samples of patients with stage II colorectal cancer can identify patients with a poor outcome. These findings indicate that a particular subgroup of colorectal tumours, though without lymph node metastases, can have an aggressive biological behaviour.

Another possible reason for the association between colorectal N0 tumours and larger size of liver metastases could be the presence of lymph node or hepatic micrometastases. The detection of micrometastases in stage II colorectal cancer is a prognostic tool and can explain the high incidence of recurrence in some patients without lymph nodes metastases after curative resection of the primary colorectal cancer.[38]

Our study has several limitations; first of all, this is a retrospective review of a relatively small series of patients. Secondly, the short follow up does not allow proper evaluation of long term disease-specific survival, although considering the presence of recurrence as an event should not bias our results. Lastly, since many patients were referred from different institutions, they were not followed up with a standard protocol after the primary cancer resection.

In conclusion, we confirmed that the presence of extra-hepatic disease, a resection margin less than 5 mm and a diameter of the largest metastasis more than 5 cm are negative prognostic factors for recurrence after curative resection for CLM. Given the higher number of patients with N0 primary tumour in the group of patients with the larger metastatic lesions, we suggest that perhaps a more routine use of imaging modalities such as abdominal ultrasound may have helped in early detection. Our observations should be validated in multi-centre, prospective studies with uniform post-primary resection surveillance protocol.

Conflict of interest
No conflicts of interest.

Funding
SP is funded by European Society of Surgical Oncology Fellowship and HMK by the UK NIHR Clinician Scientist award.

Ethical approval
None.

Acknowledgements

We thank all members of the Barts and the London HPB centre multi-disciplinary team for their contribution in decision making process.

References

1. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;**230**(3):309–18 [discussion 318–21].
2. D'Angelica M, Brennan MF, Fortner JG, Cohen AM, Blumgart LH, Fong Y. Ninety-six five-year survivors after liver resection for metastatic colorectal cancer. *J Am Coll Surg* 1997;**185**(6):554–9.
3. Malik HZ, Prasad KR, Halazun KJ, Aldoori A, Al-Mukhtar A, Gomez D, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. *Ann Surg* 2007;**246**(5):806–14.
4. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008;**247**(1):125–35.
5. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. *Arch Surg* 2004;**139**(11):1168–72.
6. Arru M, Aldrighetti L, Castoldi R, Di Palo S, Orsenigo E, Stella M, et al. Analysis of prognostic factors influencing long-term survival after hepatic resection for metastatic colorectal cancer. *World J Surg* 2008;**32**(1):93–103.
7. Tanaka K, Shimada H, Ueda M, Matsuo K, Endo I, Togo S. Long-term characteristics of 5-year survivors after liver resection for colorectal metastases. *Ann Surg Oncol* 2007;**14**(4):1336–46.
8. Kato T, Yasui K, Hirai T, Kanemitsu Y, Mori T, Sugihara K, et al. Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. *Dis Colon Rectum* 2003;**46**(Suppl. 10):S22–31.
9. Scheele J, Altendorf-Hofmann A, Grube T, Hohenberger W, Stangl R, Schmidt K. Resection of colorectal liver metastases. What prognostic factors determine patient selection? *Chirurg* 2001;**72**(5):547–60.
10. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996;**77**(7):1254–62.
11. Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* 1994;**116**(4):703–10 [discussion 710–1].
12. Mazzoni G, Tocchi A, Miccini M, Bettelli E, Cassini D, De Santis M, et al. Surgical treatment of liver metastases from colorectal cancer in elderly patients. *Int J Colorectal Dis* 2007;**22**(1):77–83.
13. Bakalakos EA, Kim JA, Young DC, Martin Jr EW. Determinants of survival following hepatic resection for metastatic colorectal cancer. *World J Surg* 1998;**22**(4):399–404 [discussion 404–5].
14. Wray CJ, Lowy AM, Mathews JB, Park S, Choe KA, Hanto DW, et al. The significance and clinical factors associated with a subcentimeter resection of colorectal liver metastases. *Ann Surg Oncol* 2005;**12**(5):374–80.
15. Ambiru S, Miyazaki M, Isono T, Ito H, Nakagawa K, Shimizu H, et al. Hepatic resection for colorectal metastases: analysis of prognostic factors. *Dis Colon Rectum* 1999;**42**(5):632–9.
16. Gomez D, Morris-Stiff G, Wyatt J, Toogood GJ, Lodge JP, Prasad KR. Surgical technique and systemic inflammation influences long-term disease-free survival following hepatic resection for colorectal metastasis. *J Surg Oncol* 2008;**98**(5):371–6.
17. Tanaka K, Shimada H, Fujii Y, Endo I, Sekido H, Togo S, et al. Pre-hepatectomy prognostic staging to determine treatment strategy for colorectal cancer metastases to the liver. *Langenbecks Arch Surg* 2004;**389**(5):371–9.
18. Minagawa M, Yamamoto J, Kosuge T, Matsuyama Y, Miyagawa S, Makuuchi M. Simplified staging system for predicting the prognosis of patients with resectable liver metastasis: development and validation. *Arch Surg* 2007;**142**(3):269–76 [discussion 277].
19. Zakaria S, Donohue JH, Que FG, Farnell MB, Schleck CD, Ilstrup DM, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg* 2007;**246**(2):183–91.
20. Minagawa M, Makuuchi M, Torzilli G, Takayama T, Kawasaki S, Kosuge T, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. *Ann Surg* 2000;**231**(4):487–99.
21. Ohlsson B, Stenram U, Tranberg KG. Resection of colorectal liver metastases: 25-year experience. *World J Surg* 1998;**22**(3):268–76 [discussion 276–7].
22. Capussotti L, Vigano' L, Ferrero A, Lo Tesoriere R, Ribero D, Polastri R. Timing of resection of liver metastases synchronous to colorectal tumor: proposal of prognosis-based decisional model. *Ann Surg Oncol* 2007;**14**(3):1143–50.
23. Viganò L, Ferrero A, Lo Tesoriere R, Capussotti L. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. *Ann Surg Oncol* 2008;**15**(9):2458–64.
24. Okano K, Yamamoto J, Kosuge T, Yamamoto S, Sakamoto M, Nakanishi Y, et al. Fibrous pseudocapsule of metastatic liver tumors from colorectal carcinoma. Clinicopathologic study of 152 first resection cases. *Cancer* 2000;**89**(2):267–75.
25. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;**241**(5):715–722, [discussion 722–4].
26. Nagashima I, Takada T, Adachi M, Nagawa H, Muto T, Okinaga K, et al. Proposal of criteria to select candidates with colorectal liver metastases for hepatic resection: comparison of our scoring system to the positive number of risk factors. *World J Gastroenterol* 2006;**12**(39):6305–9.
27. Wakai T, Shirai Y, Sakata J, Valera VA, Korita PV, Akazawa K, et al. Appraisal of 1 cm hepatectomy margins for intrahepatic micrometastases in patients with colorectal carcinoma liver metastasis. *Ann Surg Oncol* 2008;**15**(9):2472–81.
28. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol*; 2009.
29. Iwatsuki S, Dvorchik I, Madariaga JR. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg* 1999;**189**(3):291–9.
30. Tanaka K, Shimada H, Miura M, Fujii Y, Yamaguchi S, Endo I, et al. Metastatic tumor doubling time: most important prehepatectomy predictor of survival and nonrecurrence of hepatic colorectal cancer metastasis. *World J Surg* 2004;**28**(3):263–70.
31. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *Eur J Surg Oncol* 2008;**34**(1):55–60.
32. Anthony T, Simmang C, Hyman N. Practice parameters for the surveillance and follow-up of patients with colon and rectal cancer. *Dis Colon Rectum* 2004;**47**(6):807–17.
33. Scholefield JH, Steele RJ. Guidelines for follow up after resection of colorectal cancer. *Gut* 2002;**51**(Suppl. 5):V3–5.
34. Sobin LH. *W.C., UICC: TNM classification of malignant tumors*. 6th ed. , London: John Wiley & Sons; 2002.
35. Weitz J, Koch M, Debus J, Höhler T, Galle PR, Büchler MW. Colorectal cancer. *Lancet* 2005;**365**(9454):153–65.
36. Wang Y, Jatkoe T, Zhang Y, Mutch MG, Talantov D, Jiang J, et al. Gene expression profiles and molecular markers to predict recurrence of Dukes' B colon cancer. *J Clin Oncol* 2004;**22**(9):1564–71.
37. Koch M, Kienle P, Kastrati D, Antolovic D, Schmidt J, Herfarth C, et al. Prognostic impact of hematogenous tumor cell dissemination in patients with stage II colorectal cancer. *Int J Cancer* 2006;**118**(12):3072–7.
38. Liefers GJ, Cleton-Jansen AM, van de Velde CJ, Hermans J, van Krieken JH, Cornelisse CJ, et al. Micrometastases and survival in stage II colorectal cancer. *N Engl J Med* 1998;**339**(4):223–8.