Review Article

Colorectal Cancer Liver Metastases – Understanding the Differences in the Management of Synchronous and Metachronous Disease

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Abstract

Introduction: Metastatic disease to the liver in colorectal cancer is a common entity that may present synchronously or metachronously. While increasing surgical experience has improved survival outcomes, some evidence suggest that synchronous lesions should be managed differently. This review aims to update current literature on differences between the outcomes and management of synchronous and metachronous disease. Materials and Methods: Systematic review of MEDLINE database up till November 2008. Results: Discrete differences in tumour biology have been identified in separate studies. Twenty-one articles comparing outcomes were reviewed. Definitions of metachronicity varied from anytime after primary tumour evaluation to 1 year after surgery for primary tumour. Most studies reported that synchronous lesions were associated with poorer survival rates (8% to 16% reduction over 5 years). Sixteen articles comparing combined vs staged resections for synchronous tumour showed comparable morbidity and mortality. Benefits over staged resections included shorter hospital stays and earlier initiation of chemotherapy. Suitability for combined resection depended on patient age and constitution, primary tumour characteristics, size and the number of liver metastases, and the extent of liver involvement. Conclusions: Surgery remains the only treatment option that offers a chance of long-term survival for patients amenable to curative resection. Synchronicity suggests more aggressive disease although a unifying theory for biological differences explaining the disparity in tumour behaviour has not been found. Combined resection of primary tumour and synchronous metastases is a viable option pending careful patient selection and institutional experience. Given the current evidence, management of synchronous and metachronous colorectal liver metastases needs to be individualised to the needs of each patient.

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Introduction

Colorectal cancer (CRC) is one of the commonest cancers worldwide with age standardised incidence rates of 22.8 to 64.2 and 19.0 to 46.7 per 100,000 in males and females, respectively.[1,2] The disease accounts for one of the commonest causes of cancer death and the prognosis is closely related to the extent of disease at presentation as determined by Dukes'[3,4] and American Joint Committee on Cancer (AJCC)[5] classifications. While the prognosis of AJCC Stages I and II CRC is good with 5-year survival rates after treatment of between 72% and 93%,[6] untreated metastatic disease to the liver has corresponding survival rates of only 0-3%.[7-11] In particular, the median survival for patients with untreated colorectal cancer liver metastases (CRLM) ranges from 4.5 to 21 months.[7,11-17] Up to 50% of colorectal metastases occur in the liver only and in about half of these, the appearance is synchronous with the primary tumour. While it is often said that synchronous CRLM are prognostically poorer than metachronous disease, there remains widespread differences in the approach to the management of these two problems and hence the need for a review of this topic.

Materials and Methods

The MEDLINE database was systematically reviewed for evidence up till November 2008. A Pubmed search for terms "colorectal cancer AND liver metastases AND synchronous AND metachronous" yielded 155 results. "Colorectal cancer AND liver metastases AND synchronous" yielded 430 results. This search method includes MeSH terms "colorectal neoplasms", "liver", and "neoplasm metastasis". The following publication types: randomised controlled

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trials, prospective studies, case series, retrospective studies, and pathology studies were reviewed.

Results

Natural History of Synchronous Compared to Metachronous Liver Metastases

Approximately half of all patients with CRC develop metastatic disease, either synchronous or metachronous, with the liver as the most common distant site of involvement (apart from lymph nodes), followed by the lungs, bone and brain in that order. Venous drainage (via the portal system) is the primary mode of spread. This explains in part why distal rectal cancers more often metastasise to the lungs as the inferior rectal vein drains directly into the inferior vena cava instead of the portal system. Hepatic metastases are extremely common; 14.5% to 24% of patients with newly diagnosed colorectal cancer have synchronous liver lesions while a further 8.1% to 20% develop metachronous disease.[11,17,18] With improved surgical techniques, resection of CRLM has now become a viable option even without neoadjuvant chemotherapy, achieving 5 year survival rates of 25% to 40%. Unfortunately due to the unique segmental anatomy of the liver and the need for a critical volume of residual liver function, only an estimated 15% to 23% of all patients with CRLM are amenable to curative resection at first presentation.[19-21] Prognosticating suitability of surgery for patients with CRLM is still contentious and preoperative factors have been investigated extensively in an attempt to allow surgeons and patients to make better informed decisions.

One of these factors is the extent of disease at initial presentation, in particular whether liver metastases have already developed. This was first observed by Ekberg[22] in 1986, who suggested that synchronous liver lesions may have a poorer survival after surgery indicating perhaps a more aggressive form of malignancy. The definition of metachronicity, however, varied between different institutions, ranging from lesions discovered any time after the point of primary tumour evaluation,[23] to 3 months,[24] 6 months,[11] or even up to a year after primary tumour surgery,[25] making exact comparisons of different studies difficult. An attempt to address this issue was made in the 6th edition of AJCC staging manual,[5] where the definition of staging includes the sentence "carried out during the initial evaluation of the patient through the first course of surgery and prior to any definitive treatment or by 4 months after diagnosis, whichever is longer."[26] Interpretation using this definition nonetheless retains heterogeneity in classification since patients do not always decide on surgery at the same time. For a patient who receives an operation within a week after receiving the histological report of malignancy, staging ends a little after 3 months from the date of operation. In comparison, for a patient who decides 6 months after diagnosis that he would want an operation, staging ends at surgery. It may also be difficult to apply practically – to schedule a radiological evaluation for metastases on the exact date projected for each patient.

Reviewing the epidemiology of these lesions, studies specifically investigating these two groups of patients (synchronous versus metachronous liver metastases) have found no differences in gender,[27-29] tumour location,[27,28,30] size of primary tumour,[28,30] size of metastatic lesion,[27,29,30] tumour grading,[30] tumour differentiation[28] and extent of vascular invasion.[27] There was also no observable difference in terms of metastases to regional lymph nodes[27,30] which is an independent poor prognostic factor.[31,32] A single report found that patients with synchronous metastases were younger (58.6 years vs 63.1 years)[30] but this was not observed in other studies.[27-29]

While there were no differences in intrahepatic distribution,[27] metastatic synchronous lesions tended to be more often bilobar[30] and present in significantly greater numbers.[27,30] Interpreting this data requires consideration of the fact that synchronous lesions are possibly detected later in the course of disease. In comparison, metachronous lesions may be picked up earlier during postoperative follow-ups hence present with fewer lesions. In terms of tumour markers, patients with synchronous lesions had higher carcino-embryonic antigen (CEA) levels of 51μg/L compared to 20μg/L (P = 0.012).[29]

Pathological Differences

Differences in tumour biology may explain the observed differences between synchronous and metachronous disease. Several biological peptide markers, like transforming growth factor-α (TGF-α), insulin-like growth factor-II (IGF-II),[33,34] and matrix metalloproteinase 2 (MMP-2),[35,36] have been investigated. Elevation of all three markers by ≥25% predicts a poor outcome and a greater than 99% risk of developing liver metastases after correction for depth of tumour invasion, lymph node involvement, histological grade and patient age.[37] TGF-α , which competes with epithelial growth factor (EGF) and binds to the EGF receptor (EGF-R), was found to be higher in patients with synchronous metastases and predicted shorter survival (P = 0.036), suggesting an unfavourable tumour biology.[38]

Up-regulation of mucin 1 (MUC1)[39,40] and down-regulation of mucin 2 (MUC2),[41] apomucins for epithelial membrane antigen, are aggressive pathological factors in colorectal, pancreatic and biliary tree cancers.[42] The relationship between synchronous liver metastases and MUC1 up-regulation is not clear and may be confounded by an advanced primary tumour, usually pT3 or T4.[40]

Tumour suppressor protein p53 was not found to be related

to unfavourable tumour characteristics but predicts for better survival after partial liver resection.[38] However, absent or low expression of cyclin-dependent kinase inhibitor p27, another tumour suppressor, is associated with aggressive colorectal adenocarcinomas. Its expression was reduced in primary tumours with synchronous lesions compared to metachronous metastases more than 6 months after primary tumour resection (8.3% vs 41.7%).[43]

Gene profiling by Pantaleo et al[44] found that 49 genes were up-regulated in metachronous tumour specimens while 55 genes were up-regulated in synchronous metastases. Further functional analysis of these genes showed that EGF-R was over-expressed in metachronous lesions while the cyclo-oxygenase-2 (COX-2) gene was over-expressed in synchronous lesions.

Histological examination has shown that the incidence of venous invasion is higher in patients with synchronous liver metastases.[45] This is corroborated with findings of increased proliferating cell nuclear antigen (PCNA) and adhesion molecule CD44 expressions, both related to venous invasion, in synchronous liver metastases[46] when compared against primary tumours without metastases. This may however represent a different stage in tumour genesis when the cancer cells acquire further mutations that allow it to metastasise rather than as an intrinsic tumour difference.

On the other hand, there was greater angiogenesis within metachronous lesions compared to synchronous lesions when assessed microscopically for vascularity in the histology specimen. The authors provided two suggestions: (i) a lead time bias as metachronous lesions are diagnosed when they have reached a significant size (when tumours have acquired independent angiogenesis) while synchronous lesions are usually detected earlier, for example during laparotomy, (ii) that synchronous lesions grow faster with necrosis accounting for decreased vascularity.[47]

On a cellular level, host anti-tumour immune response can be assessed by the presence of mature dendritic cells (displaying CD83) at the invasive margin of CRC stroma.[48] A deficient anti-tumour immune response as indicated by CD83+ cell counts of <2 per field prognosticates poorer survival. Interestingly, metachronous liver metastases display higher numbers of CD83+ dendritic cells compared to synchronous metastases. This difference in host immunity between the two groups of patients may account for the poorer survival of the latter group.[49]

Although differences between metachronous and synchronous lesions have been reported in discrete studies at various biological levels, a "unified theory" to explain the patho-physiology of aggressiveness of synchronous lesions rather than malignancy detected at a later stage has yet to be elucidated. Further research in this area may perhaps provide the answer to this question.

Survival Outcomes

Twenty-one articles comparing survival outcomes of patients with synchronous and metachronous liver metastases receiving operations were available. Overall, 5- and 10-year survival rates ranged from 16% to 44% and 20% to 30.9%, respectively (Table 1).[16,18,22,25,27-30,50-62] Meta-analysis was not conducted as the studies were neither randomised nor controlled. As was discussed earlier, there was indeed a vast variability in the definition of metachronicity, ranging from anytime after primary tumour evaluation to one year after surgery for the primary tumour. This plurality greatly impacts the ability to compare the survival outcomes between studies. Nevertheless in accordance with each individual paper's definition, most studies showed a difference in survival favouring metachronous lesions although it did not always reach statistical significance. Studies reporting a statistically significant difference showed a 8% to 16% reduction in 5-year survival rates in the synchronous group.[16,18,25,52,57] Six other studies reported a similar difference that while observable, did not achieve statistical significance.[27,30,53,55,60,61] Ueno et al[25] reported a worse prognosis for synchronous metastases in their multivariate model HR 2.06 (1.07 – 3.96, $P = 0.029$), adjusting for tumour features and number of liver metastases.

A shorter disease-free interval is congruent with a poorer prognosis. Further studies by Tsai et al[30] and Nuzzo et al[61] while not reporting poorer survival, found significant shortening of 5-year disease free survival in the synchronous group by about 18%. Alwan et al[28] also observed slightly higher local recurrence rates in synchronous liver metastases compared to metachronous disease (15.4% vs 9.5%, $P = 0.38$). The same study found more lymph nodes positive for disease in the synchronous group (73.9% vs 59.5%) suggesting more aggressive disease although tumour differentiation was not as evident (81.5% vs 76.2% were moderately well differentiated) as a prognostic separator. Sugihara et al[52] also reported a lower recurrence rate of metachronous metastases in the abdominal cavity (5% vs 25%). The authors however highlight a possibility of a selection bias as patients with metachronous lesions and abdominal cavity involvement have been excluded.

Importantly, and regardless of the above factors, is the finding that a positive tumour margin on resection (R1) is a poor prognostic factor in both groups[27,29,63] reinforcing the importance of adequate tumour clearance. Although evidence for resection margins >1 cm conveying survival benefit has not always been demonstrated,[30,53,58,59] studies reporting the converse for margins of >1 cm[16,22] and >5 mm[27,55] remain, and an inverse linear relationship

Table 1. Comparing Outcomes between Synchronous vs Metachronous Colorectal Liver Metastases

Author, Year	Study Design	Surgery offered (combined colon & liver vs staged)	Definition of syn/ metachronicity	Liver metastases	N	Median duration to diagnosis of metachronous lesions	Overall survival	Disease-free survival	Comments
Coppa, 1985[50]	Single centre case series	Not specified	Not specified	Overall	25	-	25% (5yr) Mean = 28.8 mths	NR	Chemo status not described.
				Synchronous	13	-	66% (5yr) Mean = 32 mths	NR	
				Metachronous	12	Mean = 47 mths (range, 7-96)	0% (5yr) Mean = 24.8 mths *P* = NS	NR	
Ekberg, 1986[22]	Retrospective review	18% had wedge resection with synchronous of primary tumour.	Metachronous: after time of primary tumour evaluation.	Overall	72	-	16% (5 yr) Median = 22 mths	NR	Chemo: 11% received adjuvant cytotoxic chemo. 35% received cytostatic therapy for palliation of recurrent disease.
				Synchronous	41	-	NR	NR	
				Metachronous	31	19 mths (range, 3-87)	Possible improved survival *P* = 0.1	NR	
Nordlinger, 1987[51]	Single centre case series	Combined intestinal and liver resections for 19 patients with easily accessible small synchronous metastases.	Metachronous: after time of primary tumour evaluation.	Overall	80	-	24.9% (5 yr)	20.3% (3yr)	One patient received chemo for ovarian carcinoma. Chemo status otherwise not specified.
				Synchronous	43	-	NR	NR	
				Metachronous	37	23.7 mths (range, 2-70)	NR, *P* = NS	NR	
Sugihara, 1993[52]	Single centre case series	Not specified	Not specified	Overall	107	-	47.9% (5yr)	NR	Chemo status not described.
				Synchronous	65	-	NR	NR	
				Metachronous	42	NR	Higher survival *P* <0.01	NR	
Jatzko, 1995[53]	Single centre case series	Combined if complication-free R0 resection of primary tumour was possible. Elective setting.	Metachronous: after time of primary tumour evaluation.	Overall	66	-	29.6% (5yr)	13.9% (5yr)	Chemo status not described.
				Synchronous	40	-	26.7% (5yr)	10.7% (5yr)	
				Metachronous ≤1yr	9	NR	25.9% (5yr)	18.5% (5yr)	
				Metachronous >1yr	17	NR	43.8% (5yr) *P* = 0.39	26.2% (5yr) *P* = 0.35	
Scheele, 1995[16]	Single centre case series (99.5% follow up)	Combined in 57%, separate operations in 43% of synchronous CRLM.	Metachronous: after time of primary tumour evaluation.	Overall (in study)	434	-	38%, 23%, 17% (5,10,20yr) Median = 39.6 mths	33.6%, 27.8%, 20.9% (5,10,20yr) Median = 25.3 mths	31 patients in trial for HAI with 4x mitomycin and 5FU. 11 had adjuvant chemo after diagnosis of liver metastasis, 4 of them before liver resection. 10 with low and mid rectal cancers had adjuvant radiotherapy. 35 received chemo after cancer relapsed.
				Synchronous	142	-	32%, 19% (5,10yr)	27%, 22% (5,10yr)	
				Metachronous	208	NR	44%, 25% (5,10yr) *P* = 0.014	38%, 33% (5,10yr) *P* = 0.004	

Table 1. Contd.

Author, Year	Study Design	Surgery offered (combined colon & liver vs staged)	Definition of syn/ metachronicity	Liver metastases	N	Median duration to diagnosis of metachronous lesions	Overall survival	Disease-free survival	Comments
Taylor, 1997[54]	Single centre case series (95% follow up)	Metastatectomy separate from colon resection.	Metachronous if after time of primary tumour evaluation.	Overall	123	-	34%, 26% (5, 10yr)	20%, 18% (5, 10yr)	Adjuvant chemo in 60%; no standard criteria.
				Synchronous	43	-	-	NR	
				Metachronous	80	NR	No difference P <0.4	NR	
Rees, 1997[55]	Single centre case series	Resection for primary tumour separate from hepatectomy, 1 patient had resection of CRC with hepatectomy.	Synchronous if ≤3 months after primary bowel surgery.	Overall	91	-	30% (5 yr)	NR	Chemo status not described.
				Synchronous	36	-	25% (5yr)	NR	
				Metachronous	53	NR	45% (5yr), P = 0.081	NR	
Irie, 1999[56]	Single centre case series (98% follow up)	Metastatectomy separate from colon resection.	Synchronous if detected up to time of operation.	Overall	77	-	24.1% (5yr)	NR	Chemo status not described.
				Synchronous	40	-	NR	NR	
				Metachronous	37	NR	NR, P = 0.0015	NR	
Ueno, 2000[25]	Single centre prospective study	Metastatectomy separate from colon resection.	Synchronous if within 12 months after bowel resection.	Overall	85	-	27.9% (5yr)	20.5% (5yr)	43.5% of patients received intra-arterial 5FU.
				Synchronous	59	-	-	NR	
				Metachronous	26	NR	HR 2.36, P = 0.007	NR	
Weber, 2001[57]	Single centre case series	Metastatectomy separate from colon resection.	Not specified	Overall	221	-	34% (5yr)	20% (5yr)	Chemo status not described.
				Synchronous	90	-	30% (5yr)	19% (5yr)	
				Metachronous	131	NR	38% (5yr), P = 0.0429	21% (5yr), P = 0.09	
Bramhall, 2003[58]	Retrospective review	Separate operations	Metachronous: after time of primary tumour evaluation.	Overall	212	-	54%, 28% (3,5yr)	NR	No patients received chemo after liver resection excepting recurrence. No standard protocol. 3 patients participated in a phase1 trial of 5FU.
				Synchronous	51	-	52% (3yr)	NR	
				Metachronous	161	NR	55% (3yr), P = 0.7	NR	
Alwan, 2005[28]	Retrospective review	Separate operations	Metachronous: after time of primary tumour evaluation.	Overall	107	-	NR	NR	Data reported in Disease Free survival refers to local recurrence.
				Synchronous	65	-	NR	Median = 10.2 mths, (range, 3-31)	
				Metachronous	42	19.3 mths, (range, 2.9-62.5)	NR	Median = 16.1 mths (range, 13.5-30) P = 0.38	
Shah, 2006[59]	Case series from 2 university-affiliated hospitals	Metastatectomy separate from colon resection.	Synchronous if within 3mths of bowel resection	Overall	39	-	Median = 87 mths, (range, 60-116)	Median = 19.8 mths, (range, 12.6-25.5)	Metastases refer to both liver and pulmonary lesions. 22 patients received adjuvant chemo after primary colorectal resection.
				Synchronous	11	-	NR	NR	
				Metachronous	28	16.7 mths, (range, 5.5-38)	NR, P = 0.45	NR	

Table 1. Contd.

Author, Year	Study Design	Surgery offered (combined colon & liver vs staged)	Definition of syn/ metachronicity	Liver metastases	N	Median duration to diagnosis of metachronous lesions	Overall survival	Disease-free survival	Comments
Taniai, 2006[27]	Single centre case series	Combined resection offered for synchronous lesions.	Synchronous if within 12 months after bowel resection.	Overall	108	-	41.6, 30.9% (5,10yr)	NR	2 patients underwent chemo prior to metastatectomy due to multiple liver lesions.
				Synchronous	67	-	26.7% (5yr)	NR	
				Metachronous	41	NR	39.2% (5yr) $P = 0.354$	NR	
Manfredi, 2006[18]	Population based cancer registry 1976-2000	Not described	After time of primary tumour evaluation.	Overall having resection for cure	203	-	NR	NR	54% in synchronous group had adjuvant chemo vs 21.5% in metachronous group.
				Synchronous	124	-	10.8% (5yr)	NR	
				Metachronous	79	NR	29% (5yr), $P < 0.001$	NR	
Tsai, 2007[30]	Retrospective review	Combined resections for synchronous lesions.	Synchronous if within 12 months after bowel resection.	Overall	155		41.1% (5yr)	16.8% (5yr)	Patients receiving neoadjuvant chemotherapy were excluded. All others received non-standardized regimen of chemotherapy.
				Synchronous	97	-	34.2% (5yr)	10.1% (5yr)	
				Metachronous	58	21.1 mths, (range, 12-120)	54.6% (5yr) $P = 0.15$	27.9% (5yr) $P = 0.004$	
Wang, 2007[60]	National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database	Not described	At least 180 days after bowel resection.	Overall	923	-	22% (5yr)	NR	35% of metachronous group received adjuvant chemo after primary cancer resection. 8% from both groups received combined FUdR and 5FU therapy after liver resection. 62% of synchronous vs 36% metachronous ($P < 0.001$) received 5FU after liver resection.
				Synchronous	409	-	19% (5yr)	NR	
				Metachronous	514	NR	25% (5yr), $P = 0.312$	NR	
Bockhorn, 2008[29]	Single centre case series	Not described	Synchronous if within 12 months after bowel resection.	Overall in study	NR	-	NR	NR	47% of patients in synchronous group received neoadjuvant chemo - 12 different chemo regimens with varying cycles.
				Synchronous	63	-	47% (5yr)	33% (5yr)	
				Metachronous	63	NR	39% (5yr), $P = 0.78$	13% (5yr), $P = 0.28$	
Nuzzo, 2008[61]	Single centre prospective database	First liver resection only	Not specified	Overall	185	-	37.9%, 22.9%, (5,10yr) Median = 47 mths	29%, 25.6%, (5,10yr) Median = 18.5mths	Chemo status not described.
				Synchronous	66	-	27.7% (5yr)	17% (5yr)	
				Metachronous	119	NR	42.2% (5yr), $P = 0.09$	35.3% (5yr), $P = 0.007$	
Hamady, 2008[62]	Single centrecase series	Not specified	At least 12 months after bowel resection.	Overall	184	-	44%, 36% (5,10yr)	Median = 21 mths	Chemo status not described.
				Synchronous	138	-	NR	NR	
				Metachronous	46	NR	NR, $P = 0.6$	NR	

NR: Not reported; NS: Not specified; HAI: Hept

demonstrated between recurrence and resection margins at subsets of < 1 cm.[61] Nuzzo et al[61] also reported an association between smaller resection margins and synchronous tumours - this may contribute to the poorer prognosis seen in this group of patients. Another possible confounder exists, as patients with R1 resections may possess more extensive disease and in terms of size of tumour and number of metastases.[61,64] Reviewing the above studies listed, this was partially addressed in the multivariate model on patients with synchronous tumours by Taniai et al,[27] demonstrating that a tumour free margin (>5 mm) remained an adverse factor for survival after adjusting for the number of lesions. Resection margins of the primary tumour are also an important factor in prognostication. Knowledge of the presence of liver metastases affects surgeon performance and is related to an increased rate of positive colorectal resection margins, translating into intra-abdominal extra-hepatic recurrence of CRC.[62]

One argument is that measurement of survival for patients with metachronous lesions may be calculated from the onset of primary disease and not hepatic disease, resulting in an increased observed survival.[60] This introduces a study-specific systematic bias that may erroneously report better survival for patients with metachronous disease. Of the studies reviewed, most defined disease free survival as "duration after operation" without specific reference to which operation. It was clearly defined as "duration after hepatectomy" in 7 studies.[22,25,30,56,58-60] One paper distinguished differences in 5- and 10-year disease survival rates (44% and 36% respectively) after liver resection, and 51% and 36% after primary tumour resection.[62] Another argument is the detection bias inherent in patients with metachronous disease as they would ideally have regular follow-up allowing earlier detection of metastases, which is not possible for patients presenting for the first time with synchronous metastases. This however has been addressed with multi-variate analysis by Tsai et al,[30] where synchronicity and stage of primary tumour were found to be independent prognostic factors for recurrence and not related to time of detection, suggesting that synchronicity represented a greater tendency to spread.

Almost all studies agreed that synchronous disease had poorer survival outcomes. Two studies showed the reverse: Coppa et al[50] reported a 66% five-year survival compared to 0% in the metachronous group, and Bockhorn et al[29] with 5-year survival rates of 47% compared to 39%, although both studies did not reach statistical significance.

Controversies in Management

Amongst the earliest of recommendations for technical feasibility for resection is the Ekberg criteria where contraindications to surgery include: (i) the presence of four metastases or more, (ii) presence of extra-hepatic disease, and (iii) if resection margin of less than 1 cm is expected.[22] Other factors that have been considered in deciding operability include (i) location and (ii) size of metastases, (iii) liver reserve after resection, and (iv) surgical opinion on whether all metastases can be removed.[20,31,65-67] Opinion on technical feasibility is otherwise highly institutional and surgeon dependent and will not be discussed in this paper.

Should synchronous tumours be removed at the same setting as the primary tumour? The "cascade" theory suggests that haematogenous metastases spread in a stepwise fashion to the liver before the lungs, and that the latter only occurs after considerable progression of disease. Further delay risks dissemination of cancer cells. Indeed, synchronously detected lesions resected metachronously fare worse than those metachronously detected and resected.[68] Unresected metastases are known to proliferate after resection of primary tumour, as are the vascular density of these metastatic lesions.[69] Net cellular proliferation of liver metastases assessed at least 6 weeks after bowel surgery alone was also greater when compared to metachronous metastases (P = 0.0005).[70] There is a possibility that the primary tumour produces anti-angiogenic molecules other than vascular endothelial growth factor (VEGF) such as angiostatin and with resection, this inhibition is lost resulting in proliferation of metastases.

In order to reap the benefits of early surgery, a curative liver resection must be performed. However, therein lies the problem in determining operability at the point of initial evaluation. If the decision is made for separate operations, 2 approaches may be undertaken – either a staged or a delayed approach. A staged approach refers to first operating on the primary tumour, followed by a second operation for the metastases. This is mainly due to technical considerations or intra-operative findings that curtail a simultaneous operation. A delayed operation, in contrast, includes administration of chemotherapy or other treatment modalities between the two operations.[71] Scheele et al[16] purports enforcing a "test of time" approach of waiting up to 6 months to observe the tumour biology and evolution of metastases as a means of natural selection for operable disease. During this time, a resectable tumour is unlikely to become unresectable but instead allows discrimination of up to 30% of patients with diffuse disease who will not benefit from a liver resection.[24] Mean tumour doubling time has been assessed using serial computed tomography to be 155 ± 34 days for overt metastases and 86 ± 12days for occult lesions not evident at laparotomy.[72] Extrapolation of these figures quantifying tumour growth suggest that the 3 to 6 month wait advocated by these authors may be appropriate for observing the development of metastases and appearance of occult metastases, thereby reducing relapse rates.[73,74] For those patients with synchronous disease still suitable for hepatic resection after the interval, Lambert et al[24] report no

significant difference in survival between them and those who underwent immediate hepatic resection. Lesions larger than 4 cm, however, are considered to have withstood the test of time, having grown to such a size without becoming obviously diffuse or unresectable.

Delaying the liver operation will allow the opportunity for administration of interim chemo-immunotherapy which has been reported to achieve a mean survival of 66 ± 4 months.[75] Although overall survival for patients with a delayed resection may not change with neoadjuvant chemotherapy, it allows identification of patients with biologically aggressive cancer who may otherwise not benefit from a liver operation.[24] Indeed, subgroup analyses by Allen et al[76] showed survival benefit for those whose disease did not progress while on neoadjuvant chemotherapy. It is recommended, during this period of watchful waiting that other investigations such as needle biopsies should not be performed as it risks tumour cell spillage and needle tract or peritoneal seeding.[77]

With increasing surgical experience, morbidity and perioperative mortality rates have decreased to the extent that some centres are now routinely combining the primary tumour resection with liver metastasectomy. There remain some concerns in performing simultaneous operations: (i) Colonic resection may risk intraoperative contamination of the cut liver surface predisposing to intra-abdominal collections. (ii) Portal clamping causes portal hypertension, and together with liver impairment may cause intestinal oedema and compromise the colonic anastomosis. (iii) Small occult metastases may not be evident during the evaluation and therefore not addressed during the operation. (iv) The amount of liver that may be safely resected in a combined operation. Sixteen studies comparing combined versus staged/delayed resections of liver metastases for synchronous disease were available for review (Table 2).[16,23,27,32,71,73,78-87] The proportion of patients with simultaneous operations with rectal cancer as the primary ranged from 12.0% to 62.7%. Two studies explicitly reported the involvement of both colorectal and hepato-biliary specialists in the management of patients.[23,80]

Comparing morbidity and mortality outcomes, 2 papers clearly described the methodology of comparison – that of combined morbidity (from separate colorectal and hepatic resection) of staged patients against those who underwent both procedures simultaneously.[80,83] Morbidity, including minor complications, was reported to range from 5% to 53% with perioperative mortality rates from 0-10%.[23,32,78-87] Both mortality and morbidity were not significantly different between the two approaches in most studies. Thelen et al[84] reported a higher 90-day perioperative mortality rate in combined resections although long-term survival was comparable. Tanaka et al[81] showed that postoperative morbidity was associated with larger liver resections (350g vs 150g, $P < 0.05$). Reddy et al[83] too found significantly raised mortality rates of 8.3% vs 1.4% ($P = 0.04$) when combined with a major hepatectomy (at least 3 segments in accordance with terminology defined by Strasberg[88]). The same study also reported higher morbidity rates in combined procedures though other studies reported comparable morbidity or the opposite.[23,79,84-86] While the most common complications reported are infected intra-abdominal collections and pleural effusions, of relevance is the absence of an increase in risk of complications from infection or anastomotic leak.[23,80]

Long-term outcomes appeared similar between the 2 approaches. None of the studies showed statistically significant differences in survival rates, although Jovine et al[89] suggests that earlier initiation of adjuvant chemotherapy (by performing combined resections) may provide better oncologic results. A planned delayed approach (i.e. primary tumour resection followed by chemotherapy before liver resection) may interfere with the delivery of complete cycles of chemotherapy if morbidity from the first operation is present.[86] Other benefits include reduced total blood loss,[23] and a shorter length of hospital stay.[23,80,83,85,87] Nevertheless, caution needs to be borne in the interpretation of such results. The first is a selection bias as the studies were mainly retrospective reviews of surgical databases and of patients who have had surgery. Although survival outcome was defined as time after hepatectomy,[71,80] survival analyses would not include the subset of patients not suitable for simultaneous resections but subsequently had progression of disease and did not undergo a staged hepatectomy. This will naturally select patients with less aggressive disease into the staged group. The second is a potential bias as simultaneous resections are associated with smaller liver resections with fewer and smaller metastases.[23,81,83]

Summary of Recommendations

Recommendations on surgical treatment for patients with colorectal liver metastases pooled from the various studies are as follows. Results suggest that, if surgically amenable, resection of primary and metastatic tumour should be performed. Synchronicity of metastases may be considered as an adverse prognostic factor. For patients presenting with synchronous metastases, combined surgery for both primary and metastatic lesions may be performed in carefully selected patients. Those best suited for combined resections are younger than 70 years of age[27,81,84] and with good surgical fitness.[77] Relevant to the primary tumour are an adequate tumour-free margin, lesions that are not advanced (T4),[82] less than 4 colorectal lymph node metastases,[31] and histology that is not poorly differentiated or mucinous adenocarcinoma.[27, 81] The site of primary lesion and type of colectomy planned is also of concern. Right-sided

Table 2. Comparing Combined/Simultaneous vs Staged Resections For Synchronous Colorectal Liver Metastases

Author, Year	Study Design	Criteria for Staged/ Combined Surgery	Surgery performed	N	Median duration before surgery	Morbidity	Mortality	Overall survival	Disease free s survival	Comments
Vogt, 1991[78]	Single centre case series	Combined: Minor liver resection with colonic resection.	Overall	36	-	11%	0%	20% (5yr) Median = 28 mths (range, 3-125)	Median =16.5 mths	Chemotherapy status not described.
			Combined	19	-	5%	0%	Median = 18 mths	Median = 7 mths (range, 3-71)	
			Staged	17	2 mths ±1	17.6%	0%	Median = 31 mths *P* = NS	Median = 19 mths (range, 16-47)	
Scheele, 1995[16]	Single centre case series (99.5% follow up)	Not specified	Overall (in study)	434	-	16%	4.4%	38%, 23%, 17% (5,10,20yr) Median = 39.6 mths	33.6%, 27.8%, 20.9% (5,10,20yr) Median = 25.3 mths	Chemotherapy: 31 patients in trial for HAI with 4x mitomycin and 5FU. 11 had adjuvant after diagnosis of liver lesions, 4 of them before liver resection. 10 with low and mid rectal cancers had adjuvant radiotherapy. 35 received chemotherapy after cancer relapsed.
			Combined	74	-	NR	NR	26%,16% (5,10yr)	21%, 17% (5,10yr)	
			Staged	68	R 2-23 wks	NR	NR	40%, 25% (5,10yr), *P* = 0.06	32%, 32% (5,10yr), *P* = 0.09	
Fujita, 2000[32]	Single center case series	Combined: 1) Primary lesion resectable curatively 2) Pre & intra-op examination reveals all liver tumours can be technically resected with adequate conservation of normal parenchyma 3) no extrahepatic metastases.	Overall	97	-	33%	0%	31% (5yr)	NR	5FU given to 44% patients after resection.
			Combined	83	-	NR, higher than staged resection	NR	NR	NR	
			Staged	14	R ≤ 6mths			NR	NR	
Martin, 2003[23]	Prospective single centre database	Not specified	Overall	240	-	NR	NR	NR	NR	Chemotherapy status not described.
			Combined	134	-	48%	4%	NR	NR	
			Staged	106	NR	68%, *P* = 0.003	4%, *P* = NS	NR	NR	
Weber, 2003[79]	Single centre case series	Combined: 1) Less than 4 uni-lobar metastases 2) intra-operatively identified lesions were respectable 3) no contraindications to additional major surgery 4) absence of colorectal tumour complications i.e. obstruction or perforation.	Overall	97	-	NR	NR	Mean = 30 mths (range, 3-91)	NR	Chemotherapy in 44% of patients before hepatectomy and 51% after hepatectomy. Post-op complications include sub-phrenic collection, pleural effusion and pneumonia.
			Combined	35	-	23%	0%	21% (5yr) Median = 35 mths	NR	
			Delayed	62	7 mths ± 6	32%, *P* = 0.33	0%	22% (5yr), *P* = 0.967 Median = 33 mths	NR	

Table 2. Contd.

Author, Year	Study Design	Criteria for Staged/ Combined Surgery	Surgery performed	N	Median duration before surgery	Morbidity	Mortality	Overall survival	Disease free survival	Comments
Chua, 2004[80]	Retrospective review of single centre records	Staged: 1) Patient/surgeon preferred staged resection at pre-op planning 2) diagnosis of hepatic metastases was made intra/ postoperatively 3) hepatectomy required was extensive	Overall	100	-	NR	NR	NR	NR	Chemotherapy status not described.
			Combined	64	-	53%	0%	28.9% (5yr) Median = 27 mths	9.2% (5yr) Median = 13 mths	
			Staged	32	NR	41%, *P* = 0.25	0%	42.9% Median = 34 mths, *P* = 0.52	20.2% (5yr) Median = 13 mths *P* = 0.53	
Tanaka, 2004[81]	Single centre case series	Combined: if the relatively small number of liver neoplasms were considered to be completely removed by a relatively simple hepatectomy procedure, irrespective of primary neoplasm location.	Overall	76	-	NR	NR	NR	NR	Chemotherapy: adjuvant 5FU x 8 cycles. In the delayed group, 18 had chemo (5FU, Folinic acid, cisplatin) before hepatectomy.
			Combined	39	-	28%	0%	68%, 53% (3,5yr)	20%, 16% (3,5yr)	
			Delayed	37	NR	16%	0%	47%, 47%, (3,5yr) *P* = 0.394	35%, 28% (3,5yr) *P* = 0.784	
Minagawa, 2006[71]	Case series from 3 centres	Combined: Regardless of 1) number 2) extent of liver metastases and 3) location of primary cancer. Oncologically radical operation, possibility of preserving ≥40% of normal hepatic parenchyma.	Overall	187	-	NR	NR	NR	NR	Chemotherapy: In the delayed group, 14 had local, 8 had systemic, combined systemic & local in 1, irradiation & systemic in 1, ethanol injection & local in 1, microwave coagulation & local in 1, RFA and systemic in 1.
			Combined	142	-	NR	NR	Median = 3.1 yrs (range, 2.4-4.2)	NR	
			Staged	18	2.0 mths (range, 0.5-15.4)	NR	NR	Median = 2.6 yrs (range, 2.3-7.9), *P* = 0.36	NR	
			Delayed (Prior CRC surgery then chemo or other treatment)	27	6.4 mths (range, 2.3-26.8)	NR	NR	Median = 2.4 yrs (range, 2.0-4.4), *P* = 0.32	NR	
Taniai, 2006[27]	Single centre case series	Combined: for all synchronous metastases. Exclusion criteria not described.	Overall	45	-	NR	NR	NR	NR	2 patients in staged group received adjuvant chemotherapy after primary bowel surgery before hepatectomy.
			Combined	37	-	NR	NR	37.8% (5yr)	NR	
			Staged	8	NR	NR	NR	57.1% (5yr), *P* = 0.66	NR	
Capussotti, 2007[82]	Retrospective review of single centre data	Combined: for all patients except if 1) ASA>3 2) presence of bowel obstruction or perforation 3) when all gross disease could not be removed.	Overall	127	-	NR	NR	NR	NR	Chemotherapy: 68.4% in delayed group received neo-adjuvant. Subsequently, 62.8% of patients from combined group and 66.7% from delayed group received adjuvant treatment (*P* = 0.655). 1 mortality excluded from analysis.
			Combined	70	-	35.7%	0%	30.8% (5yr)	NR	
			Delayed	57	6 mths (range, 1-36)	36.8%, *P* = 0.89	0%	32% (5yr), *P* = 0.406	NR	

Table 2. Contd.

Author, Year	Study Design	Criteria for Staged/ Combined Surgery	Surgery performed	N	Median duration before surgery	Morbidity	Mortality	Overall survival	Disease free survival	Comments
Reddy, 2007[83]	Retrospective review of database from 3 major centres	Not specified	Overall	510	-	NR	NR	NR		Chemotherapy: 60.7% (combined group) had before liver resection vs 79.2% (staged) (P <0.001). Most common complication s were infected intra-abdominal collections and isolated/combined organ failure.
			Combined	135	-	NR	NR	NR	NR	
			Minor hepatectomy	99		33.3%	1.0%			
			Major hepatectomy	36		44.4%	8.3%			
			Staged	475	7 mths (range, 4-11)	NR	NR	NR	NR	
			Minor hepatectomy	184		20.1%, P = 0.02	0.5%, P = 0.7			
			Major hepatectomy	291		26.8%, P = 0.04	1.4%, P = 0.03			
Thelen, 2007[84]	Single centre case series	Combined: not performed if contraindications to additional major surgery i.e. severe CHD, reduced general constitution, severe COPD or complications of colorectal tumour i.e. bowel obstruction or perforation were present. Only minor hepatectomies were combined with rectal primaries.	Overall	219	-	NR	NR	NR	NR	Chemotherapy: From the combined grp, 3 received neoadjuvant, 18 adjuvant, and 1 regional. From the staged grp, 49 received systemic, 2 regional after primary tumour resection. 94 received systemic adjuvant and 4 regional adjuvant after hepatectomy.
			Combined	40	-	18%	10%	53%, 32% (5,10yr)	NR	
			Staged	179	55 days (range, 23-184)	25%, P = 0.166	1.1%, P = 0.012	39%, 26% (5,10yr), P = 0.983	NR	
Yan, 2007[85]	Single centre observational cohort	Combined: whenever practical except when not detected pre-operatively.	Overall	103	-	35%	0%	Median = 37 mths	Median = 28mths	Common complications include wound infection (20%), peri-hepatic fluid collection (13%), other intra-abdominal fluid collection (14%).
			Combined	73	-	32%	0%	36% (5yr), Median = 37 mths	14% (5yr), Median = 28 mths	
			Staged	30	79 days (range, 57-86)	43%	0%	37% (5yr), Median = 36 mths, P = 0.9	14%, Median = 26 mths P = 0.585	
Turrini, 2007[86]	Single centre case series	Combined: 1) no complications of CRC such as bowel obstruction or perforation.	Overall	119	-	NR	NR	NR	NR	Complete chemotherapy delivered in 89% (combined) vs 67% (staged) of patients P = 0.04.
			Combined	57	-	21%	3.5%	32% (5yr)	19 mths	
			Staged	62	Mean=6 mths	31%, P = 0.07	5%, P = 0.09	25% (5yr), P = 0.06	14 mths, P = 0.04	
Vassiliou, 2007[87]	Single centre case series	Combined: 1) if both lesions could be managed through one subcostal/midline incision 2) Trisegmentectomy or biliary reconstruction not anticipated	Overall	103	-	NR	NR	NR	NR	Chemotherapy status not reported. Common post-op morbidity includes chest infection, pleural effusions and sub-phrenic collections.
			Combined	25	-	NR	0%	28% (5yr)	NR	
			Staged	78	(range, 1-3 mths)	NR, P = NS	0%	31% (5yr)	NR	

Table 2. Contd.

Author, Year	Study Design	Criteria for Staged/ Combined Surgery	Surgery performed	N	Median duration before surgery	Morbidity	Mortality	Overall survival	Disease free survival	Comments
Shimizu, 2008[73]	Single centre case series	Combined: 1) synchronous liver resection considered to be possible 2) no extrahepatic lesions present at time of colon surgery	Overall	27	-	NR	NR	NR	NR	Chemotherapy status not described.
			Combined	8	-	NR	NR	50% (5yr)	NR	
			Delayed	19	99 days (range, 53-244)	NR	NR	51.7% (5yr), $P = 0.5078$	NR	

NR: Not reported; NS: Not specified

colectomies can be combined with any liver resection.[77,87] Left-sided colectomies should not be combined with a liver resection greater than a right hemi-hepatectomy.[77] For low anterior resections, the risk of anastomotic leakage and requirement for diverting ileostomies needs to be considered.[77] While not contraindicated, and reports of major hepatectomies and anterior resections performed simultaneously without morbidity or mortality have been published,[66,79,90] caution needs to be taken.

For factors pertaining to the metastatic hepatic lesion(s), combined resections are recommended only if there are 3 or fewer liver metastases,[82] and a minor liver resection (less than 3 segments) is planned.[27,77,78,83,84] In this respect, Tanaka et al[81] recommended simultaneous operations only if 1 hepatic section is involved. Lesions more than 4 cm can be considered as having withstood "the test of time", and combined surgery may be offered.

Candidates not suitable should instead undergo a staged or interval resection of the liver metastases. Benefits include allowing interim chemotherapy,[75] optimisation of surgical fitness, and identification of patients who are unlikely to benefit from an operation.[24,76] However, one consideration particular to this two-stage approach is the psychological burden borne by the patient in knowing that there is still residual tumour in his/her body which has not been removed. Hence a thorough discussion of the benefits and risks of either approach must be made with the patient. Going further, Kim et al[91] have published preliminary results of a series of 10 laparoscopic-assisted combined colon and liver resections with no major morbidity and mortality.

Conclusion

Synchronous CRLM shows a trend towards a slightly poorer survival, suggesting a more aggressive form of disease. Although discrete evidence for biological differences exist, a "unified theory" explaining the disparity in tumour behaviour of synchronous CRLM has yet to be found. Surgery for patients amenable to curative resection remains the only treatment option that can offer a chance of long-term survival that at present ranges from 16% to 44% at 5 years. This can only improve with further developments in chemotherapeutic, immunotherapeutic and targeted therapy agents. Combined resection of primary tumour and synchronous metastases is a viable option. However, the decision to offer such an operation is still not clear and depends on careful patient selection and institutional experience. Given the current evidence, management of synchronous and metachronous CRLM needs to be individualised to the needs of each patient.

REFERENCES

1. Seow AWPK, Chia KS, Shi LM, Lee HP, Shanmugaratnam K. Trends In Cancer Incidence in Singapore 1968 - 2002. Singapore: Singapore

Cancer Registry; 2004. Report No.: 6.

2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.
3. Dukes CE. The classification of cancer of the rectum. J Patho l 1932;35:323-32.
4. Dukes CE. The Surgical Pathology of Rectal Cancer. J Clin Pathol 1949;2:95-8.
5. Greene FL. AJCC Cancer Staging Manual. 6th ed. Chicago, Illinois: Springer, 2002.
6. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst 2004;96:1420-5.
7. Wagner JS, Adson MA, Van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. Ann Surg 1984;199:502-8.
8. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet 1994;343:1405-10.
9. Bengtsson G, Carlsson G, Hafstrom L, Jonsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg 1981;141:586-9.
10. Mancini R, Ettorre G, Vennarecci G, Sperduti I, Garufi C, Esposito A, et al. Personal experience on treatment of colorectal liver metastases: a multidisciplinary approach. J Exp Clin Cancer Res 2003;22(4 Suppl):213-7.
11. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006;93:465-74.
12. Rougier P, Milan C, Lazorthes F, Fourtanier G, Partensky C, Baumel H, et al. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Fondation Francaise de Cancerologie Digestive. Br J Surg 1995;82:1397-400.
13. Luna-Perez P, Rodriguez-Coria DF, Arroyo B, Gonzalez-Macouzet J. The natural history of liver metastases from colorectal cancer. Arch Med Res 1998;29:319-24.
14. Palmer M, Petrelli NJ, Herrera L. No treatment option for liver metastases from colorectal adenocarcinoma. Dis Colon Rectum 1989;32:698-701.
15. Wanebo HJ, Semoglou C, Attiyeh F, Stearns MJ, Jr. Surgical management of patients with primary operable colorectal cancer and synchronous liver metastases. Am J Surg 1978;135:81-5.
16. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg 1995;19:59-71.
17. Ballantyne GH, Quin J. Surgical treatment of liver metastases in patients with colorectal cancer. Cancer 1993;71(12 Suppl):4252-66.
18. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254-9.
19. Silen W. Hepatic resection for metastases from colorectal carcinoma is of dubious value. Arch Surg 1989;124:1021-2.
20. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-53.
21. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.
22. Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hagerstrand I, Ranstam J, et al. Determinants of survival in liver resection for colorectal secondaries. Br J Surg 1986;73:727-31.
23. Martin R, Paty P, Fong Y, Grace A, Cohen A, DeMatteo R, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg 2003;197:233-41; discussion 241-2.
24. Lambert LA, Colacchio TA, Barth RJ, Jr. Interval hepatic resection of colorectal metastases improves patient selection. Arch Surg 2000;135:473-9; discussion 479-80.
25. Ueno H, Mochizuki H, Hatsuse K, Hase K, Yamamoto T. Indicators for treatment strategies of colorectal liver metastases. Ann Surg 2000;231:59-66.
26. Compton CC. Key issues in reporting common cancer specimens: problems in pathologic staging of colon cancer. Arch Pathol Lab Med 2006;130:318-24.
27. Taniai N, Yoshida H, Mamada Y, Matsumoto S, Mizuguchi Y, Suzuki H, et al. Outcome of surgical treatment of synchronous liver metastases from colorectal cancer. J Nippon Med Sch 2006;73:82-8.
28. Alwan M, Stubbs R. Local recurrence in patients with synchronous or metachronous colorectal liver metastases—is there a difference? N Z Med J 2005;118:U1631.
29. Bockhorn M, Frilling A, Fruhauf NR, Neuhaus J, Molmenti E, Trarbach T, et al. Survival of patients with synchronous and metachronous colorectal liver metastases-is there a difference? J Gastrointest Surg 2008;12:1399-405.
30. Tsai MS, Su YH, Ho MC, Liang JT, Chen TP, Lai HS, et al. Clinicopathological features and prognosis in resectable sync hronous and metachronous colorectal liver metastasis. Ann Surg Oncol 2007;14:786-94.
31. 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;142:269-76; discussion 277.
32. Fujita S, Akasu T, Moriya Y. Resection of synchronous liver metastases from colorectal cancer. Jpn J Clin Oncol 2000;30:7-11.
33. Kawamoto K, Onodera H, Kan S, Kondo S, Imamura M. Possible paracrine mechanism of insulin-like growth factor-2 in the development of liver metastases from colorectal carcinoma. Cancer 1999;85:18-25.
34. Li SR, Ng CF, Banerjea A, Ahmed S, Hands R, Powar M, et al. Differential expression patterns of the insulin-like growth factor 2 gene in human colorectal cancer. Tumour Biol 2004;25:62-8.
35. Wagenaar-Miller RA, Gorden L, Matrisian LM. Matrix metalloproteinases in colorectal cancer: is it worth talking about? Cancer Metastasis Rev 2004;23:119-35.
36. Oshima T, Kunisaki C, Yoshihara K, Yamada R, Yamamoto N, Sato T, et al. Clinicopathological significance of the gene expression of matrix metalloproteinases and reversion-inducing cysteine-rich protein with Kazal motifs in patients with colorectal cancer: MMP-2 gene expression is a useful predictor of liver metastasis from colorectal cancer. Oncol Rep 2008;19:1285-91.
37. Barozzi C, Ravaioli M, D'Errico A, Grazi GL, Poggioli G, Cavrini G, et al. Relevance of biologic markers in colorectal carcinoma: a comparative study of a broad panel. Cancer 2002;94:647-57.
38. De Jong KP, Stellema R, Karrenbeld A, Koudstaal J, Gouw AS, Sluiter WJ, et al. Clinical relevance of transforming growth factor alpha, epidermal growth factor receptor, p53, and Ki67 in colorectal liver metastases and corresponding primary tumors. Hepatology 1998;28:971-9.
39. Matsuda K, Masaki T, Watanabe T, Kitayama J, Nagawa H, Muto T, et al. Clinical significance of MUC1 and MUC2 mucin and p53 protein expression in colorectal carcinoma. Jpn J Clin Oncol 2000;30:89-94.
40. Suzuki H, Shoda J, Kawamoto T, Shinozaki E, Miyahara N, Hotta S, et al. Expression of MUC1 recognized by monoclonal antibody MY.1E12 is a useful biomarker for tumor aggressiveness of advanced colon carcinoma. Clin Exp Metastasis 2004;21:321-9.

41. Okano K, Shimoda T, Matsumura Y. Clinicopathologic and immunohistochemical study of early colorectal cancer with liver metastases. J Gastroenterol 1999;34:334-40.
42. Yonezawa S, Sato E. Expression of mucin antigens in human cancers and its relationship with malignancy potential. Pathol Int 1997;47:813-30.
43. Thomas GV, Szigeti K, Murphy M, Draetta G, Pagano M, Loda M. Down-regulation of p27 is associated with development of colorectal adenocarcinoma metastases. Am J Pathol 1998;153:681-7.
44. Pantaleo MA, Astolfi A, Nannini M, Paterini P, Piazzi G, Ercolani G, et al. Gene expression profiling of liver metastases from colorectal cancer as potential basis for treatment choice. Br J Cancer 2008;99:1729-34.
45. Ouchi K, Sugawara T, Ono H, Fujiya T, Kamiyama Y, Kakugawa Y, et al. Histologic features and clinical significance of venous invasion in colorectal carcinoma with hepatic metastasis. Cancer 1996;78:2313-7.
46. Sumiyoshi Y, Yamashita Y, Maekawa T, Sakai N, Shirakusa T, Kikuchi M. Expression of CD44, vascular endothelial growth factor, and proliferating cell nuclear antigen in severe venous invasional colorectal cancer and its relationship to liver metastasis. Surg Today 2000;30:323-7.
47. Mooteri S, Rubin D, Leurgans S, Jakate S, Drab E, Saclarides T. Tumor angiogenesis in primary and metastatic colorectal cancers. Dis Colon Rectum 1996;39:1073-80.
48. Suzuki A, Masuda A, Nagata H, Kameoka S, Kikawada Y, Yamakawa M, et al. Mature dendritic cells make clusters with T cells in the invasive margin of colorectal carcinoma. J Pathol 2002;196:37-43.
49. Miyagawa S, Soeda J, Takagi S, Miwa S, Ichikawa E, Noike T. Prognostic significance of mature dendritic cells and factors associated with their accumulation in metastatic liver tumors from colorectal cancer. Hum Pathol 2004;35:1392-6.
50. Coppa GF, Eng K, Ranson JH, Gouge TH, Localio SA. Hepatic resection for metastatic colon and rectal cancer. An evaluation of preoperative and postoperative factors. Ann Surg 1985;202:203-8.
51. Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. Ann Surg 1987;205:256-63.
52. Sugihara K, Hojo K, Moriya Y, Yamasaki S, Kosuge T, Takayama T. Pattern of recurrence after hepatic resection for colorectal metastases. Br J Surg 1993;80:1032-5.
53. Jatzko GR, Lisborg PH, Stettner HM, Klimpfinger MH. Hepatic resection for metastases from colorectal carcinoma—a survival analysis. Eur J Cancer 1995;31A:41-6.
54. Taylor M, Forster J, Langer B, Taylor BR, Greig PD, Mahut C. A study of prognostic factors for hepatic resection for colorectal metastases. Am J Surg 1997;173:467-71.
55. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 1997;84:1136-40.
56. Irie T, Itai Y, Hatsuse K, Mochizuki H. Does resection of small liver metastases from colorectal cancer improve survival of patients? Br J Radiol 1999;72:246-9.
57. Weber JC, Nakano H, Bachellier P, Oussoultzoglou E, Inoue K, Shimura H, et al. Is a proliferation index of cancer cells a reliable prognostic factor after hepatectomy in patients with colorectal liver metastases? Am J Surg 2001;182:81-8.
58. Bramhall SR, Gur U, Coldham C, Gunson BK, Mayer AD, McMaster P, et al. Liver resection for colorectal metastases. Ann R Coll Surg Engl 2003;85:334-9.
59. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg 2006;202:468-75.
60. Wang X, Hershman DL, Abrams JA, Feingold D, Grann VR, Jacobson JS, et al. Predictors of survival after hepatic resection among patients with colorectal liver metastasis. Br J Cancer 2007;97:1606-12.
61. Nuzzo G, Giuliante F, Ardito F, Vellone M, Giovannini I, Federico B, et al. Influence of surgical margin on type of recurrence after liver resection for colorectal metastases: a single-center experience. Surgery 2008;143:384-93.
62. Hamady ZZ, Malik HZ, Alwan N, Wyatt JI, Prasad KR, Toogood GJ, et al. Surgeon's awareness of the synchronous liver metastases during colorectal cancer resection may affect outcome. Eur J Surg Oncol 2008;34:180-4.
63. Liu CL, Fan ST, Lo CM, Law WL, Ng IO, Wong J. Hepatic resection for colorectal liver metastases: prospective study. Hong Kong Med J 2002;8:329-33.
64. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg 2008;248:626-37.
65. Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509-20; discussion 520-2.
66. Pozzo C, Basso M, Cassano A, Quirino M, Schinzari G, Trigila N, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15:933-9.
67. Poston GJ, Adam R, Alberts S, Curley S, Figueras J, Haller D, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. J Clin Oncol 2005;23:7125-34.
68. Lyass S, Zamir G, Matot I, Goitein D, Eid A, Jurim O. Combined colon and hepatic resection for synchronous colorectal liver metastases. J Surg Oncol 2001;78:17-21.
69. Peeters CF, Westphal JR, de Waal RM, Ruiter DJ, Wobbes T, Ruers TJ. Vascular density in colorectal liver metastases increases after removal of the primary tumor in human cancer patients. Int J Cancer 2004;112:554-9.
70. Peeters CF, de Waal RM, Wobbes T, Westphal JR, Ruers TJ. Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. Int J Cancer 2006;119:1249-53.
71. Minagawa M, Yamamoto J, Miwa S, Sakamoto Y, Kokudo N, Kosuge T, et al. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. Arch Surg 2006;141:1006-12; discussion 1013.
72. Finlay IG, Meek D, Brunton F, McArdle CS. Growth rate of hepatic metastases in colorectal carcinoma. Br J Surg 1988;75:641-4.
73. Shimizu Y, Yasui K, Sano T, Hirai T, Kanemitsu Y, Komori K, et al. Validity of observation interval for synchronous hepatic metastases of colorectal cancer: changes in hepatic and extrahepatic metastatic foci. Langenbecks Arch Surg 2008;393:181-4.
74. Yoshidome H, Kimura F, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, et al. Interval period tumor progression: does delayed hepatectomy detect occult metastases in synchronous colorectal liver metastases? J Gastrointest Surg 2008;12:1391-8.
75. Lygidakis NJ, Singh G, Bardaxoglou E, Dedemadi G, Sgourakis G, Nestoridis J, et al. Two-stage liver surgery for advanced liver metastasis synchronous with colorectal tumor. Hepatogastroenterology 2004;51:413-8.
76. Allen PJ, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. J Gastrointest Surg 2003;7:109-15; discussion 116-7.
77. Scheele J, Rudroff C, Altendorf-Hofmann A. Resection of colorectal liver metastases revisited. J Gastrointest Surg 1997;1:408-22.
78. Vogt P, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. World J Surg 1991;15:62-7.
79. Weber JC, Bachellier P, Oussoultzoglou E, Jaeck D. Simultaneous

resection of colorectal primary tumour and synchronous liver metastases. Br J Surg 2003;90:956-62.

80. Chua HK, Sondenaa K, Tsiotos GG, Larson DR, Wolff BG, Nagorney DM. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Colon Rectum 2004;47:1310-6.
81. Tanaka K, Shimada H, Matsuo K, Nagano Y, Endo I, Sekido H, et al. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery 2004;136:650-9.
82. 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;14:1143-50.
83. Reddy SK, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol 2007;14:3481-91.
84. Thelen A, Jonas S, Benckert C, Spinelli A, Lopez-Hanninen E, Rudolph B, et al. Simultaneous versus staged liver resection of synchronous liver metastases from colorectal cancer. Int J Colorectal Dis 2007;22:1269-76.
85. Yan TD, Chu F, Black D, King DW, Morris DL. Synchronous resection of colorectal primary cancer and liver metastases. World J Surg 2007;31:1496-501.
86. Turrini O, Viret F, Guiramand J, Lelong B, Bege T, Delpero JR. Strategies for the treatment of synchronous liver metastasis. Eur J Surg Oncol 2007;33:735-40.
87. Vassiliou I, Arkadopoulos N, Theodosopoulos T, Fragulidis G, Marinis A, Kondi-Paphiti A, et al. Surgical approaches of resectable synchronous colorectal liver metastases: timing considerations. World J Gastroenterol 2007;13:1431-4.
88. Strasberg SM. Terminology of liver anatomy and liver resections: coming to grips with hepatic Babel. J Am Coll Surg 1997;184:413-34.
89. Jovine E, Biolchini F, Talarico F, Lerro FM, Mastrangelo L, Selleri S, et al. Major hepatectomy in patients with synchronous colorectal liver metastases: whether or not a contraindication to simultaneous colorectal and liver resection? Colorectal Dis 2007;9:245-52.
90. Capussotti L, Ferrero A, Vigano L, Ribero D, Lo Tesoriere R, Polastri R. Major liver resections synchronous with colorectal surgery. Ann Surg Oncol 2007;14:195-201.
91. Kim SH, Lim SB, Ha YH, Han SS, Park SJ, Choi HS, et al. Laparoscopic-Assisted Combined Colon and Liver Resection for Primary Colorectal Cancer with Synchronous Liver Metastases: Initial Experience. World J Surg 2008;32:2701-6.