Surgical resection of colorectal hepatic metastases

CK Leow, WY Lau, AKC Li

The reported median survival of patients with untreated colorectal liver metastases is 10.6 months from the time of diagnosis. Systemic and regional chemotherapy do produce responses in a proportion of patients but with limited prolongation of survival. At present, surgical resection is the only treatment that can cure. The 5-year survival rate following curative hepatic resection for colorectal liver metastases is 30% to 40%. However, only 5% to 10% of all patients with curative resection of their primary colon cancer will develop liver secondaries that are amenable to surgery. Hepatic resection for colorectal liver metastases should be offered to this select group of patients and should only be performed by an experienced surgical team with an operative mortality rate of less than five per cent.

HKMJ 1997;3:50-6

Key words: Colorectal liver metastasis; Surgery

Introduction

Tumours of the colon and rectum are the second leading cause of cancer deaths in Western societies.[1] In Hong Kong, carcinomas of the colon and rectum (including recto-sigmoid) are respectively, the third and seventh leading causes of new cancer cases. In 1991, they accounted for 2139 new cancer cases, second only to the leader, carcinoma of the lungs. While the mortality rate (deaths/100 000 population) for rectal and recto-sigmoid cancers has remained static over a 10-year period (1984 to 1993), the rate for colon carcinoma has gradually increased (8.2 to 12.2 for males, 7.9 to 10.4 for females).[2]

In spite of receiving a 'curative' resection for colorectal carcinoma, 40% to 50% of patients die within five years of surgery. Eighty per cent die, predominantly with liver metastases, within three years.[3] The three most common sites for distant colorectal metastases are the liver, lungs, and regional lymph nodes.[4] Once liver metastases were discovered, the median survival of 2581 patients, reported in 20 studies from around the world, was 10.6 months (range 3.7-24 months).[5] Survival is closely related to the extent of liver involvement. In a retrospective study of 113 patients with liver involvement only, patients with widespread bilateral disease had a mean survival time of 3.1 months, compared with 16.7 months for those with solitary metastases.[6] Furthermore, patients with well differentiated liver secondaries survive twice as long as those with poorly differentiated lesions do—11 months versus 5.5 months.[7]

Since the 1950s, mortality from cancers of the colon and rectum in England and Wales has changed little and accounts for 12% of all deaths from cancer. As the practice of cancer chemotherapy on a large scale only started in the 1950s, chemotherapy has had little impact on the mortality of colon cancer.[8] Systemic 5-fluorouracil (5-FU) with folinic acid, considered an optimum treatment for metastatic colorectal cancer, yielded a 25% response rate and provided median survival of approximately 12 months.[9] In eight randomised studies, regional hepatic arterial therapy with 5-fluoro-2-deoxyuridine (FUDR) has been shown to produce a better response than systemic chemotherapy in treating colorectal liver metastases. However, only two of these studies showed a statistically significant (but moderate) extension of survival to a maximum of 15 months.[10] While new anti-cancer therapeutics such as antibody-directed enzyme prodrug therapy (ADEPT) and polymer drug conjugates[11] may hold promise of potential cure in the future, at present, chemotherapy per se will not cure patients with colorectal hepatic metastases. The only treatment that is curative is surgery.

The detection of liver metastases

Metastatic deposit(s) in the liver can present at the initial laparotomy for primary colonic resection, as a cause

Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
CK Leow, MD, FRCS
WY Lau, MD, FRCS (Edin)
AKC Li, MD, FRCS (Edin)

Correspondence to: Prof AKC Li

of symptoms such as pain, jaundice, and ascites. They also may be found asymptomatically at follow up with the presence of an elevated serum carcinoembryonic antigen (CEA) concentration.

Between 8% to 25% of patients undergoing laparotomy for colonic cancer resection have overt liver metastases.[12] However, operative evaluation by palpation for liver secondaries is very inaccurate. Of 71 patients considered free of metastases at initial laparotomy, post-operative ultrasonography and computer tomography of the liver revealed that 17 (24%) had occult secondaries that were confirmed on clinical follow up. Seventy-four per cent of these metastases were located in segments VI and VII of the liver, an area that is difficult to assess adequately during laparotomy.[3] In a prospective study of 213 patients with colorectal cancer, pre-operative ultrasonography and intra-operative palpation of the liver failed to detect liver metastases (0.3-3.5 cm in size) demonstrated by intra-operative ultrasound in 21 patients (10%).[13]

Patients presenting with an isolated raised CEA level after a 'curative' colonic resection should have the measurement confirmed and then investigated. This includes a chest X-ray, liver ultrasonography, computed tomography (CT) of the abdomen, bone scintigraphy, and colonoscopy to look for recurrence or metastases. When recurrent disease is only confined to the liver, our practice is to perform a hepatic artery angiogram prior to surgical exploration.

The role of intraoperative ultrasound

The detection of liver metastases at laparotomy missed by pre-operative imaging with percutaneous ultrasound and CT scans affect and alter surgical decision-making. The sensitivity of pre-operative ultrasound scan in the detection of colorectal liver metastases can be as low as 41.3%.[14,15] Using dynamic CT, delayed CT, and magnetic resonance imaging can improve the detection rate for hepatic metastases.[16] Currently, CT arterial portography (CTAP) is the most sensitive pre-operative imaging technique for detecting colorectal liver secondaries. Of 56 metastases in 25 patients undergoing hepatectomy, intra-operative ultrasound (IOUS) detected 54 (96%) metastases while pre-operative CTAP detected 51 (91%) metastases.[17] Machi et al showed that IOUS at the time of primary colonic resection had significantly better sensitivity, negative and positive predictive value, and overall accuracy (>90%) in detecting colorectal liver secondaries compared with pre-operative ultrasound, CT, and surgical exploration.[14] The extended follow up of 188 patients for more than 18 months with liver imaging demonstrated that the negative and positive predictive value and overall accuracy of IOUS are maintained and significantly exceed those of pre-operative ultrasound, CT, and surgical exploration.[15]

Approximately 20% of patients with colorectal secondaries selected for exploration and liver resection had their plan of management at operation altered as a result of IOUS findings.[18] This examination enables a spatial assessment of the lesion(s) to be made during surgery. The anatomic relation of the tumour(s) to intrahepatic vessels can be delineated and helps the surgeon decide on the most appropriate type of resection, such as a wedge resection, ultrasonically-guided subsegmentectomy,[19] or lobectomy, without compromising on an adequate resection margin, or leaving insufficient hepatic tissue to sustain life. During cryoablation therapy, IOUS is essential not only to accurately place the cryoprobe within the lesion but also to monitor the extent of ablation by the ice-ball.[20]

At our institution, we routinely perform IOUS examination of the whole liver prior to definitive surgery. The procedure can be performed in five minutes, does not require mobilisation of the whole liver, and complications such as hepatic injuries or infection have not been encountered.

The resection of metastases

There is a dearth of literature as to whether liver resection for colorectal liver metastases and primary colonic resection should be performed at the same operation or on separate occasions. Scheele et al report on 189 patients with synchronous liver metastases; 108 underwent combined excision of the liver mass and primary tumour and 81 had a hepatic resection performed two weeks to 23 months after the initial operation for primary colonic resection.[21] It is reasonable to perform liver resection for a suitably situated metastasis at the time of initial colonic resection if it is only a simple wedge resection or left lateral segmentectomy. Patients requiring more extensive liver resection such as lobectomy should have primary colonic resection only. A delay allows time for investigation of the presence or absence of any extrahepatic disease and to determine resectability. Elapse of time between primary colonic resection and subsequent liver resection is the best selection method for resectability and does not impair the curative po-

tential of a delayed hepatic resection.[22]

While the 30-day mortality rate for resection of liver metastases reported by the Erlangen University Hospital on their 469 patients over a period of 32 years (1960-1992) was only 4.4%, this obscured the fact that their operative mortality has gradually been improving over the years, falling from 11.5% during the first two decades to 3.4% from 1980 onwards. The mortality rate has been only 1.8% in the past three years.[21] Most recent series report mortality rates of 7% to 8%[23-25] but Starzl and colleagues at Pittsburg report a zero mortality in 204 patients.[26]

Survival after resection of metastases

The combined 5-year survival rate from 24 published series involving 1387 patients is 36%.[5] Analysis of the Registry of Hepatic Metastases, which contains records of 859 patients from 24 institutions led Hughes and coworkers to report a 5-year actuarial survival rate of 33% and a 5-year actuarial disease-free survival rate of 21% for those patients who had hepatic resection for colorectal metastases.[27] More recently, the groups from Erlangen and Pittsburg report actual 5-year survival rates of 36.9% +/- 7.0% and 32%, respectively, on a total of 554 patients who underwent hepatic resection with curative intent.[21,26] The overall 5-year tumour-free survival reported from Erlangen is 30% +/- 7.2%.[21] In contrast, only 11 of 1650 patients with untreated colorectal liver metastases have been reported to survive five years and beyond.[27]

The prognostic determinants of survival following resection

The Dukes' staging of the primary colonic tumour has been shown to influence the survival of patients undergoing hepatic resection of colorectal secondaries.[23,26,27] The median survival of patients who had hepatic resection with an initial Dukes' A and B lesion was 125 months compared with 28.6 months in those with Dukes' C lesions.[28] Forty-eight per cent of patients with no mesenteric lymph node involvement at the initial colonic resection were alive at five years following resection of the liver secondaries. The presence, however, of involved mesenteric lymph nodes led to a 5-year survival rate of only 18%.[21] Interestingly, a comparison of those patients who had Dukes' A and B primary colon cancer without liver metastases and those with potentially curative hepatic resections revealed minimal survival differences between the two. This implies that lymph node status at the primary colonic resection is the determining variable in these patients with colorectal cancer, even if there were liver metastases that were resected.[28]

Metachronous liver metastases probably represent a subgroup of favourable, slow-growing lesions, compared with synchronous metastases. While the combined 5-year survival of 433 patients from 11 institutions who had resection of synchronous liver metastases averaged 27% (range, 0%-38%), the average 5-year survival among 555 patients with metachronous lesions was 31% (range, 0%-59%).[5] A single-institution experience, with 142 patients with synchronous lesions and 208 patients with metachronous lesions, confirms that patients with resected metachronous lesions have significantly better 5-year survival rates (43% vs 30%).[21]

The effect on survival of the time interval between resection of the primary colonic lesion and the diagnosis of liver metastases is conflicting. Analysis of the data from the Registry of Hepatic Metastases led Hughes et al to report a 5-year survival rate of 28% in 199 patients who underwent hepatic resection less than 12 months after their colonic resection. In 360 patients who underwent hepatic resection more than one year after their colonic resection, the 5-year survival rate was 40%.[28] More recently, Gayowski et al report that patients with a less than 24-month interval between primary colorectal and hepatic metastases resection experience a poorer outcome.[26] When the interval exceeds four years, the 5-year survival rate following hepatic resection is better than 70%.[12] While Scheele and colleagues report very similar 5-year survival rates for their patients with less than 12 months (44%), 12 to 23 months (46%), and more than 24 months (38%) intervals between colorectal and metachronous liver secondaries resection,[21] Foster and Lundy report improved survival for those with a shorter interval.[29]

Whether the timing of resection of synchronous lesions (at the time of colonic resection or delayed until after the primary colonic resection) would significantly alter survival is a moot point. There is a place for a 'test of time' to allow manifestation of extrahepatic disease or multiple hepatic lesions less than 5 cm in diameter, provided the delay does not compromise technical resectability. There is some evidence in favour of the 'delay' but the result does not reach statistical significance.[21]

Following resection of colorectal liver metastases, Cady and McDermott report that patients with four or

more hepatic metastases resected die of the disease, 80% with further liver metastases. In contrast, only three of 18 patients with one to three metastases resected developed further hepatic lesions.[22] Others have found that patients with three or more metastases resected have significantly worse survival rates.[24,26,27] However, Scheele et al and Fortner et al did not find that the number of metastases resected had a significant effect on prognosis.[21,23] Thirty-two patients with four or more metastases removed followed the same survival course as those with three or fewer metastases excised. Nine are alive without recurrent disease at five to 14 years after liver resection.[21] Instead, the regional spread of disease to adjacent organs or vessels, tumour rupture, or distant metastases adversely affected survival.[23] In addition, the presence of satellite metastases in the subgroup with solitary and multiple metastases was associated with poor survival and tumour-free survival.[21] Satellite metastases are caused by portal vein invasion[19] thus making coincidental invasion of hepatic veins more likely. This results in a higher incidence of subsequent pulmonary metastases in those patients with satellite metastases (45%) than those without (23%).[21]

The evidence supporting the significance of a clear hepatic resection margin is overwhelming.[18,21,26-28] The 5-year survival rate in 152 patients with a clear margin of 1 cm or less was 26% compared with 44% for the 112 patients with a clear margin of more than 1 cm.[28] The median disease-free survival time for those patients with a 0.1 to 0.9 cm margin of clearance was 20 months. Further analysis of this group of patients revealed very similar median survival times for those patients with a clear margin of 0.1 to 0.4 cm (18 months) and 0.5 ot 0.9 cm (21 months). When a clear margin of at least 1 cm is achieved, the median disease-free survival is 32 months.[21] It is generally agreed that a curative resection must achieve a clear resection margin of 1 cm or more.

One explanation for the better patient outcome when comparing size of lesion (very large vs small),[21,30] magnitude of resection (lobectomy vs trisegmentectomies),[31] anatomical versus non-anatomical resection,[28,32] unilobar versus bilobar tumour distribution,[26] and number of metastases (1-2 vs >3 metastases) is the likelihood of obtaining an adequate negative resection margin at operation. It is difficult to place an upper limit on the number of metastases that can be resected. Multiple wedge resections or enucleations are feasible, but in practice, this is achieved only at the expense of an adequate resection margin and is limited by the site and size of the tumours. The chance of performing anatomical resection and obtaining a minimum 1 cm clear margin in a patient with bilobar disease involving more than three moderate-sized metastases is much reduced compared with a patient with unilobar disease and a single large lesion. While some investigators report a 5-year survival rate of 18% in patients with a positive pathological resection margin,[28] most series show that a positive margin precludes 5-year survival.[21,26]

Recurrence of liver metastases following initial liver resection

The most common site of recurrent disease following hepatic resection for liver metastases is the lung, followed by the liver. Sixteen of 45 patients (36%) who had hepatic resection for colorectal metastases developed pulmonary metastases as their first site of recurrence; only eight patients (18%) developed new liver lesions.[33] The incidence of recurrence after resection of hepatic metastases, confined solely to the liver, varies from 5% to 33%.[34-37] The majority of patients with recurrent liver metastases are asymptomatic. Only 9% of patients have specific symptoms related to the presence of the second liver metastases. The recurrent metastases were detected by an increase in CEA level (39%), or by CT scan (44%), and conventional ultrasonography (12%). Only five per cent of the diagnoses of recurrent metastases were made during on exploratory laparotomy.[38]

Re-resection of recurrent liver metastases

Only 7% to 13% of patients who have had liver resection for colorectal metastases undergo repeat resection for recurrence.[36,39-41] The median survival of 66 patients who had repeat liver resection, reported in 10 studies, ranged from 6 to 36 months.[35,41] More recently, Fernandez-Trigo et al report the results of their analysis of the Repeat Hepatic Metastases Registry containing data on 170 patients with repeat liver resection for recurrent metastases. The overall 3- and 5-year survival rates were 45% and 32%, respectively.[38]

The two most important and significant prognostic variables in terms of survival were the presence of extrahepatic disease and residual liver tumour when repeat liver resection was performed. Patients with extrahepatic disease had a 5-year survival rate of 19% while those without had a rate of 36% (P=0.09). Complete resections gave rise to a 36% 5-year survival rate whereas presence of residual liver disease following resection reduced the survival rate to 17% (P=0.01). Those patients with a disease-free interval of less than one year between liver resections and those having

anatomic resection instead of wedge resection enjoyed better 5-year survival rates but the results did not reach statistical significance. Dukes' staging of the primary colonic tumour did not predict survival following repeat liver resection for metastases.[38]

The effectiveness of cryosurgery of liver metastases

Cryosurgery (the use of low temperature for cellular destruction) is another therapy available for the treatment of colorectal liver metastases. Its ability to cause focal, in situ destruction of tissue is ideal for treating patients who are unsuitable candidates for major hepatic resection either due to the extent of the intrahepatic disease, poor liver reserve (i.e. cirrhosis), or because of comorbid conditions. In those patients with three or fewer non-resectable lesions owing to their positions or distributions, cryoablation may offer similar results to surgical resection.[42] Eighteen of 24 patients with colorectal liver metastases treated with cryosurgery achieved an overall and disease-free survival rates of 78% and 39%, respectively. Twenty-five per cent of the patients failed treatment because of residual disease.[43]

Technical and temporal constraints are the major limitations of cryosurgery. At present, adequate treatment can only be delivered to lesions smaller than 5 cm in diameter[20] and the optimum number of lesions for treatment is four; treating patients with more than four lesions is controversial.[42] For optimum treatment, each lesion requires double freeze/thaw cycles and each cycle takes approximately 25 minutes, depending on the size of the lesion.[43] Thus the procedure is slow, frquently taking more than four hours to complete.[44] Although the mortality and morbidity associated with hepatic cryotherapy is low, frequent myoglobinuria and clinical renal failure in patients treated by cryosurgery is the most worrying problem.[45]

The development of liver recurrence or extrahepatic disease in 68% of patients with colorectal liver metastases treated by cryoablation probably implies that cryosurgery alone is inadequate and should be combined with systemic adjuvant therapy.[43] A recent retrospective study of patients with non-resectable colorectal liver metastases shows a 2-year survival rate for patients who receive cryotherapy and hepatic artery chemotherapy of 21% compared with 12.5% for those treated with cryotherapy alone.[46]

To prove the rationale that cryosurgery ablates all gross disease and adjuvant hepatic artery chemotherapy destroys all microscopic residual tumour will require future, well conducted, randomised, prospective trials.

The role of adjuvant chemotherapy after resection of liver metastases

Up to one third of patients with curative resection of colorectal liver metastases will experience recurrence within the liver remnant.[34-37] Theoretically, post-operative adjuvant chemotherapy should eradicate any foci of microscopic metastatic disease within the resected liver thus reducing the recurrence rate and improving long term survival. The initial result of a randomised prospective trial of adjuvant regional chemotherapy and hepatic resection for colorectal liver secondaries demonstrated a trend towards better survival in those patients treated with hepatic resection and adjuvant continuous hepatic artery infusion of fluorodeoxyuridine (FUDR).[47] Unfortunately, a subsequent follow up report by the same investigators failed to confirm their initial observation. Although the disease-free interval was significantly extended from 8.7 months to 30.7 months in those patients who received adjuvant chemotherapy after hepatic resection of a solitary metastasis, this advantage did not translate into a survival advantage.[48]

Following curative resection of colorectal liver metastases, adjuvant hepatic arterial 5-FU infusion administered to 18 patients seems to have reduced the incidence of recurrent disease when compared with historical controls treated with surgery alone.[49] A retrospective study involving 102 patients showed that median unadjusted survival times for patients who received adjuvant 5-FU and folinic acid chemotherapy and for patients who had surgery only were 35 and 25 months, respectively.[50] A further 15 studies, involving a total of 504 patients, report that those patients who received adjuvant therapy following resection of hepatic metastases had an overall median survival of 31 to 51 months, compared with 22 to 37 months in those who underwent resection only.[51] The efficacy of adjuvant chemotherapy following liver resection is suggested but has not yet been confirmed.

The potential benefit of chemotherapy must be weighed against the not inconsiderable risks of complications from intra-arterial adjuvant chemotherapy, which include cholecystitis, chemical hepatitis, sclerosing cholangitis, gastric and duodenal ulcerations, diarrhoea, and neutropenia.[47-49,51]

In the United States, 5-FU plus levamisole is the current standard adjuvant treatment for Dukes' C

colorectal cancer as this regimen significantly improves recurrence-free and overall survival.[52] European cooperative study groups, however, are still conducting trials on the efficacy of various permutations of adjuvant therapy with 5-FU/folinic acid/levamisole in the treatment of colorectal cancer.[53] In these countries, doubt still remains and there is no consensus that adjuvant treatment is of benefit.[54] Similarly, the role of adjuvant chemotherapy after resection of colorectal liver metastases is still unsettled and we await the results of the three European trials conducted by the European Organization for Research and Treatment of Cancer (EORTC), Gastro-Intestinal Tract Cancer Cooperative Group (GITCCG) and Arbeitsgemeinschaft Leber Metastasen (ALM) with keen interest.[53]

Conclusion

The effectiveness of any treatment for colorectal liver metastases should be measured against the natural history of untreated cancer. At present, surgical resection of colorectal liver secondaries is the only effective therapeutic modality that can cure a substantial proportion of patients, with a 5-year survival rate approaching 40%.[21,30,31,55] Sixteen to 22% of patients who develop recurrent disease after curative resection for colorectal carcinoma will only develop liver metastases.[5] Unfortunately, only 5% to 10% of all patients with 'curative' resection of their primary colon cancer will have colorectal liver secondaries that are amenable to resection.

As the mortality of a standard liver resection, performed by an experienced team in an otherwise healthy patient, is 2% or less,[21,26] one must ask the question of how far one can proceed and how liberal one can be with performing liver resections. Technically, surgical procedures can go up to the stage of ante-situ or ex-situ resection[56] and even to orthotopic liver transplantation.[36]

Those patients who initially have well confined primary colorectal tumours resected, develop one to three unilobar liver metastases that are amenable to resection with an adequate resection margin, and have no evidence of extrahepatic disease, a 'curative' hepatic resection can be performed with the expectation of a good chance for extended life or cure. The prospects are poor for patients who have extrahepatic metastases, numerous metastases involving both lobes, large lesions encroaching on major hepatic veins or bile ducts or lesions that are sited so as to preclude resection with a clear margin. Some surgeons consider the presence of even one of these factors to be an absolute contraindication to hepatic resection.[30] Although few of these patients will live beyond three years even if all macroscopic disease is removed, palliative surgery should be considered and selectively offered for symptomatic relief and a hope for life. Therapeutic success cannot be measured only in terms of months or years of life when comfort may be of equal importance. The quality of daily life is more real for most patients than is a prediction of longevity. The desire to practice surgical science must be tempered with humanity.

To quote MA Adson: "We cannot always act so that hope might triumph over judgement, but we must not ignore patients' need for hope when operative risk and morbidity are low, when there are no therapeutic alternatives, and when, at times, palliative efforts may give rise to cure. We should hope to blend our science and our humanity into an art that our patients can perceive as grace."[34]

References

1. Haller DG. An overview of adjuvant therapy for colorectal cancer. Eur J Cancer 1995;31A(7/8):1255-63.
2. Hong Kong Government Department of Health. Annual Report, 1993-1994. Hong Kong. 1994.
3. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. Br J Surg 1986;73:732-5.
4. Welch JP, Donaldson GA. The clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg 1979;189:496-502.
5. Ballantyne GH, Quin J. Surgical treatment of liver metastases in patients with colorectal cancer. Cancer 1993; 71(Suppl):4252S-4266S.
6. Wood CB, Gillis CR, Blumgart LH. A retrospective study of the natural history of patients with liver metastases from colorectal cancer. Clin Oncol 1976;2:285-8.
7. Pestana C, Reitemeier RJ, Moertel CG, Judd ES, Dockerty MB. The natural history of carcinoma of the colon and rectum. Am J Surg 1964;108:826-9.
8. Cancer Research Campaign. Facts on cancer. London: CRC, 1993. Factsheet 18.3.
9. Advanced Colorectal Cancer Meta-analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992;10:896-903.
10. Kemeny NE. Regional chemotherapy of colorectal cancer. Eur J Cancer 1995;31A(7/8):1271-6.
11. Connors TA, Duncan R, Knox RJ. The chemotherapy of colon cancer. Eur J Cancer 1995;31A(7/8):1373-8.
12. Saenz NC, Cady B, McDermott WV, Steele GD. Experience with colorectal carcinoma metastatic to the liver. Surg Clin North Am 1989;69(2):361-70.
13. Olsen AK. Intraoperative ultrasonography and the detection of liver metastases in patients with colorectal cancer. Br J Surg 1990;77:998-9.
14. Machi J, Isomoto H, Yamashita Y, Kurohiji T, Shirouzu K, Kahegawa T. Intraoperative ultrasonography in screening for liver metastases from colorectal cancer: comparative accuracy with traditional procedures. Surgery 1987;101:678-84.

15. Machi J, Isomoto H, Kurohiji T, et al. Accuracy of intraoperative ultrasonography in diagnosing liver metastases from colorectal cancer: evaluation with postoperative follow-up results. World J Surg 1991;15:551-7.
16. Heiken JP, Weyman PJ, Lee JK, et al. Detection of focal hepatic masses: prospective evaluation with CT, delayed CT, CT during arterial portography, and MR imaging. Radiology 1989;171:47-51.
17. Soyer P, Levesque M, Elias D, Zeitoun G, Roche A. Detection of liver metastases from colorectal cancer: comparison of intraoperative US and CT during arterial portography. Radiology 1992;183:541-4.
18. Cady B, Stone MD, McDermott WV, et al. Technical and biological factors in disease-free survival after hepatic resection for colorectal cancer metastases. Arch Surg 1992;127:561-9.
19. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet 1985;161:346-50.
20. Bayjoo P, Jacob G. Hepatic cryosurgery: biological and clinical considerations. J R Coll Surg Edinb 1992;37:369-72.
21. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg 1995;19:59 -71.
22. Cady B, McDermott WV. Major hepatic resection for metachronous metastases from colon cancer. Ann Surg 1985;201:204-9.
23. Fortner JG, Silva JS, Golbey RB, Cox EB, Maclean BJ. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. Ann Surg 1984;199:306-16.
24. van Ooijen B, Wiggers T, Meijer S, et al. Hepatic resections for colorectal metastases in The Netherlands: a multi-institutional 10-year study. Cancer 1992;70:28-34.
25. Petrelli N, Gupta B, Piedmonte M, Herrera L. Morbidity and survival of liver resection for colorectal adenocarcinoma. Dis Colon Rectum 1991;34:899-904.
26. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 1994;116:703-11.
27. Registry of Hepatic Metastases. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Surgery 1988;103:278-88.
28. Hughes K, Scheele J, Sugarbaker PH. Surgery for colorectal cancer metastatic to the liver: optimizing the results of treatment. Surg Clin North Am 1989;69(2):339 -59.
29. Foster JH, Lundy J. Liver metastases. Curr Probl Surg 1981;18:157-202.
30. Ekberg H, Tranberg KG, Andersson R, et al. Determinants of survival in liver resection for colorectal secondaries. Br J Surg 1986;73:727-31.
31. Iwatsuki S, Esquivel CO, Gordon RD, Starzl TE. Liver resection for metastatic colorectal cancer. Surgery 1986;100:804-10.
32. Scheele J, Stangl R, Altendorf-Hoffman A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 1990;77:1241-46.
33. Fortner JG. Recurrence of colorectal cancer after hepatic resection. Am J Surg 1988;155:378-82.
34. Adson MA. Resection of liver metastases - when is it worthwhile? World J Surg 1987;11:511-20.
35. Bozetti F, Bignami P, Montalto F, Doci R, Gennari L. Repeated hepatic resection for recurrent metastases from colorectal cancer. Br J Surg 1992;79:146-8.
36. Vaillant JC, Belladur P, Nordlinger B, et al. Repeat liver resection for recurrent colorectal metastases. Br J Surg 1993;80:340-4.
37. Sugihara K, Hojo K, Moriya Y, Yamasaki S, Kosuga T, Takayama T. Pattern of recurrence after hepatic resection for colorectal metastases. Br J Surg 1993;80:1032-5.
38. Fernandez-Trigo V, Shamsa F, Sugarbaker PH, and other members of the Repeat Hepatic Metastases Registry. Repeat liver resections from colorectal metastasis. Surgery 1995;117:296-304.
39. Griffith KD, Sugarbaker PH, Chang AE. Repeat hepatic resections for colorectal metastases. Surgery 1990;107:101-4.
40. Stone MD, Cady B, Jenkins RL, McDermott WV, Steele GD. Surgical therapy for recurrent liver metastases from colorectal cancer. Arch Surg 1990;125:718-22.
41. Gouillat C, Ducerf C, Patensky C, Benlieux J, Berard PH., Pouyet M. Repeated hepatic resections for colorectal metastases. Eur J Surg Oncol 1993;19:443-7.
42. Morris DL, Horton MD, Dilley AV, Warlters A, Clingan PR. Treatment of hepatic metastases by cryotherapy and regional cytotoxic perfusion. Gut 1993;34:1156-7.
43. Ravikumar TS, Kana R, Cady B, Jenkins R, Clouse M, Steele G. A 5-year study of cryosurgery in the treatment of liver tumors. Arch Surg 1991;126:1520-4.
44. Horton MD, Warlters A, Dilley AV, Clingan PR, Morris DL. Survival after hepatic cryotherapy for hepatic metastases [abstract]. Br J Surg 1992;79:452A.
45. Onik G, Rubinsky B, Zemel R, et al. Ultrasound guided hepatic cryosurgery in the treatment of metastatic colon carcinoma. Cancer 1991;67:901-7.
46. Preketes AP, Caplehorn JR, King J, Clingan PR, Ross WB, Morris DL. Effect of hepatic artery chemotherapy on survival of patients with hepatic metastases from colorectal carcinoma treated with cryotherapy. World J Surg 1995;19:768-71.
47. Kemeny MM, Goldberg D, Beatty JD, et al. Results of a prospective randomized trial of continuous regional chemotherapy and hepatic resection as treatment of hepatic metastases from colorectal primaries. Cancer 1986;57:492-8.
48. Wagman LD, Kemeny MM, Leong L, et al. A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver. J Clin Oncol 1990;8:1885-93.
49. Curley SA, Roh MS, Chase JL, Hohn DC. Adjuvant hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases. Am J Surg 1993;166:743-8.
50. Donato N, Dario C, Giovanni S, et al. Retrospective study on adjuvant chemotherapy after surgical resection of colorectal cancer metastatic to the liver. Eur J Surg Oncol 1994;20:454-60.
51. Patt YZ, McBride CM, Ames FC, et al. Adjuvant perioperative hepatic arterial mitomycin C and floxuridine combined with surgical resection of metastatic colorectal cancer in the liver. Cancer 1987;59:867-73.
52. Metzger U, Gross TH., Honegger HP. Adjuvant treatment for colorectal cancer: 'State of the art' - messages from recent trials. Eur J Surg Oncol 1995;21:341-6.
53. Pahlman L. Open trials in colorectal cancer. Eur J Surg Oncol 1995;21:347-51.
54. van Triest B, van Groeningen CJ, Pinedo HM. Current chemotherapeutic possibilities in the treatment of colorectal cancer. Eur J Cancer 1995;31A(7/8):1193-7.
55. Butler J, Attiyeh FF, Daly JM. Hepatic resection for metastases of the colon and rectum. Surg Gynecol Obstet 1986;162:109-13.
56. Pichlmayr R, Grosse H, Hauss J, Gubernatis G, Lamesch P, Bretschneider HJ. Technique and preliminary results of extracorporeal liver surgery (bench procedure) and of surgery on the in situ perfused liver. Br J Surg 1990;77:21-6.