Current Controversies in the Surgical Management of Colorectal Cancer Metastases to the Liver

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Abstract

Surgical resection offers the best opportunity for cure in patients with colorectal cancer metastasis to the liver, with 5 year survival rates of up to 58% following resection. However, only a small percentage of patients are eligible for resection at the time of diagnosis and the average recurrence rate is still high. Consequently, research endeavors have focused on methods aimed at increasing the number of patients eligible for surgical resection, refining the selection criteria for surgery, and improving the disease-free and overall survival time in these patients. Improvements in imaging techniques and the increasing use of FDG-PET allow more accurate preoperative staging and superior identification of patients likely to benefit from surgical resection. Advances in the use of neoadjuvant chemotherapy allow up to 38% of patients previously considered unresectable to be significantly downstaged and eligible for hepatic resection. Many reports have critically evaluated the surgical techniques applied to liver resection, the concurrent or alternative use of local ablative therapies, such as radiofrequency ablation, and the subsequent use of adjuvant chemotherapy in patients undergoing surgical resection for hepatic metastases.

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Colorectal cancer accounts for the third most common malignancy in western countries. In patients with colorectal cancer, up to 25% will have liver metastases at diagnosis and more than 70% of all patients will develop hepatic metastases during the course of disease [1]. Currently, the standard of care and only potential curative therapy for colorectal liver metastases is hepatic resection of the metastatic lesions.

Improvements in surgical and anesthetic technique, imaging modalities, low operative mortality rates, careful patient selection, and the impact of modern downstaging chemotherapy regimens have all contributed to the current management of patients with colorectal liver metastases. When hepatic metastases are resected, the 5 year survival rate is up to 58% in selected patients [2]. Furthermore, advances in chemotherapy regimens using newer agents have promoted a better response rate in patients with colorectal liver metastases and have made previously unresectable patients eligible for surgery. Yet, the appropriate combination of chemotherapeutic regimens, its sequence (neoadjuvant vs. adjuvant approach), the surgical strategy (anatomic vs. non-anatomic), the use of local ablative therapy, and specific indications are still unclear. In this article, we will review some of the above controversies in the management of colorectal liver metastases.

Current staging: The role of and drawbacks of PET-CT

Preoperative imaging plays a crucial role in patient selection for hepatic resection. Traditionally, computed tomography was the modality of choice for detecting hepatic metastases; however, historical data showed that when the decision to perform partial hepatectomy is based solely on CT findings, 42% of patients are found to be unresectable at the time of laparotomy [3]. This ratio has improved with the progress and accuracy of CT technology but is still far from acceptable. The advent of positron emission tomography using fluoro-18-deoxyglucose has provided a new and complementary imaging and diagnostic modality in colorectal cancer metastases.

Multiple reports have shown FDG-PET to be a good diagnostic modality with a high sensitivity and specificity for detecting hepatic and especially extrahepatic disease [4-6]. A meta-analysis by Wiering et al. [5] demonstrated a pooled sensitivity and specificity with FDG-PET of 88.0% and 96.1%, respectively for hepatic lesions, and 91.5% and 95.4%, respectively for extrahepatic lesions. FDG-PET showed superior sensitivity and specificity in detecting extrahepatic disease compared to CT (91.5% vs. 60.9% sensitivity, 95.4% vs. 91.1% specificity). Similarly, Truant and colleagues [4] found comparable sensitivity by PET and CT in identifying intrahepatic lesions (79% for both), but the sensitivity of FDG (63%) was more than twice that of CT (25%) in detecting extrahepatic, specifically intra-abdominal, lesions. Moreover, FDG-PET identified unsuspected extrahepatic metastases missed by conventional imaging in 21.5% of patients with FDG-PET-positive liver lesions [6].

The ability of FDG-PET to detect occult disease prevents unnecessary surgery in 21.5% of patients [6] and changes the overall management in 25% [5]. FDG-PET alters the target population for surgery, improving mean survival time in patients undergoing surgery, while providing potential for alternate therapies in patients with unresectable disease.

Despite these benefits, the various shortcomings in the use of FDG-PET must be considered. Patients undergoing extensive chemotherapy may develop FDG-PET negativity during treatment [7,8] due to a significantly decreased tumor FDG uptake and tumor cell hexokinase phosphorylating activity [9]. Furthermore,

PET = positron emission tomography
FDG = fluoro-18-deoxyglucose

FDG-PET failed to identify 37% of lesions in patients treated with chemotherapy compared to 23% of undetected lesions in patients without preoperative treatment. Due to its decreased sensitivity during chemotherapy, PET should not be used as the sole determinant for the presence of cancer. In addition, the inability of PET to detect metastatic liver lesions smaller than 1 cm [4], poor visualization of mucinous tumors [8], failure to reveal anatomic details [4], and limited spatial resolution [6] make tumor site localization difficult and may lead to underestimation of the hepatic tumor burden.

FDG-PET functions as a key imaging modality in the workup, diagnosis and treatment of patients with colorectal liver metastases. Despite its superior sensitivity in detecting extrahepatic lesions, it is necessary to recognize the pitfalls of FDG-PET and utilize additional imaging modalities. The use of image overlays, combining results of PET and high resolution spiral CT may increase the accuracy of preoperative staging before hepatic resection [10]. We are therefore convinced that PET is mandatory in the evaluation and staging of colorectal liver metastases.

Traditional risk factors, selection criteria, indications and contraindications are being challenged and need revalidation

Neoadjuvant vs. adjuvant chemotherapy in resectable disease

Surgical resection is the standard of care and best treatment for resectable liver metastases. However, in 80–90% of patients liver metastases are unresectable at the time of diagnosis. The introduction of oxaliplatin-based chemotherapy has changed the prognosis of these patients, increasing the response rate and median survival. Multiple studies have demonstrated that neoadjuvant chemotherapy allows 12.5–38% of patients previously considered unresectable to be significantly downstaged and eligible for hepatic resection [11,12] with overall 5 year survival rates similar to that of patients who underwent primary resection [13].

Neoadjuvant chemotherapy

Patients with resectable colorectal liver metastases can undergo either immediate resection or a delayed resection after a course of neoadjuvant chemotherapy. According to Allen and co-researchers [14], overall 5 year survival was similar in patients with clinically resectable metastatic disease with and without neoadjuvant chemotherapy prior to resection (52% vs. 38% respectively, $P = 0.35$). However, they did find that patients within the neoadjuvant group whose disease remained stable without progression while receiving chemotherapy experienced significantly improved survival as compared to patients who did not receive chemotherapy (85% vs. 35%, $P = 0.03$) [14]. Similar findings by Capussotti et al. [13] demonstrated that the combination of neoadjuvant chemotherapy and liver resection increases survival compared to chemotherapy alone, but rarely provides cure.

Despite the survival benefits, recent studies have demonstrated that prolonged neoadjuvant systemic chemotherapy induces pathological changes in the liver that may increase morbidity and mortality after major resection [15,16]. Karoui and associates [15] found a significantly higher morbidity rate in patients who received systemic chemotherapy prior to liver resection compared to those who did not (38% vs. 13.5%). Preoperative chemotherapy was significantly associated with sinusoidal dilation, atrophy of hepatocytes, and/or hepatocytic necrosis [15]. Furthermore, a recent study by Vauthey et al. [16] reports a significant risk of hepatotoxicity, such as the induction of chemotherapy-associated steatohepatitis, and increased 90 day mortality following hepatic surgery with the use of neoadjuvant chemotherapy.

A recent report from the Memorial Sloane-Kettering Cancer Center demonstrates another promising aspect of the neoadjuvant approach. In their series, patients whose disease progressed while on chemotherapy had a significantly worse survival compared to patients who responded [17]. Further investigation is necessary to evaluate if the response to neoadjuvant treatment seen on imaging is a significant and effective predictor of survival.

Adjuvant chemotherapy

Following hepatic resection, postoperative or adjuvant chemotherapy is used to increase survival and decrease the rate of metastatic recurrence. Recently, the first randomized clinical trial comparing surgery alone to surgery plus adjuvant chemotherapy provided clear evidence that adjuvant chemotherapy is beneficial in the setting of colorectal liver metastases. In this study, Portier and team [18] randomly assigned 173 patients to receive surgery and observation or surgery plus 6 months of systemic adjuvant chemotherapy. Results demonstrated a significantly improved 5 year disease-free survival in the surgery plus chemotherapy group compared to surgery alone (33.5% vs. 26.7%, $P = 0.028$), with a trend towards increased overall 5 year survival [18].

Despite the use of neoadjuvant chemotherapy, the metastatic recurrence rate after hepatic resection has been high overall, ranging from 66% to 80% [11,13]. One study reported significantly higher recurrence rates in patients receiving neoadjuvant chemotherapy compared to primary resection without chemotherapy (94% vs. 66.4%) [13]. Another study determined that adjuvant chemotherapy does not decrease the metastatic recurrence rate in the remnant liver [19]. This may be related to the concept of complete clinical response and the vanishing of metastatic lesions following chemotherapy. In patients with a complete clinical response to chemotherapy according to CT imaging, *in situ* recurrence was observed in 78% of patients after one year due to non-visible but persistent viable tumor cells or microscopic disease [20]. Therefore, it is important for the surgeon to consider resecting the sites of these vanished lesions in order to reduce the risk of metastatic recurrence.

Both neoadjuvant and adjuvant chemotherapy have been shown to improve survival in the setting of colorectal liver metastases and therefore should be utilized in the face of resectable disease. Although neoadjuvant chemotherapy downstages liver metastases and increases patient eligibility for surgery, a multicenter randomized control trial is needed to truly evaluate the benefits of its use. The recent publication of a randomized clinical trial proving adjuvant chemotherapy beneficial compared to surgery alone warrants its application [18]. It is now clear that while tailoring the treatment plan for the individual patient, potential risks and benefits of neoadjuvant strategy should be balanced carefully. Influencing factors include the extent of resection, the oncological prognosis, body mass index, and other co-morbidities such as diabetes and steatohepatitis.

Surgical strategy: a question of adequate margins

Since hepatic resection of metastases offers the greatest opportunity for patient survival, resection strategy is very important to achieve an overall goal of metastatic resection, negative histological margins, and the preservation of enough functional liver parenchyma for regrowth and hepatic survival. The two principal techniques are non-anatomic (wedge) resection and anatomic resection. Wedge resections with narrow margins are most often done for small, peripheral or isolated metastases. The segmental or anatomic approach involves the resection of defined anatomic segments of the liver typically performed for large, deeply situated, or multiple-clustered metastases [21]. Some authors suggest that one surgical technique is superior to the other, while others conclude that there are no differences.

Superior survival and a lower incidence of positive surgical margins have been reported in patients undergoing anatomic resection compared to patients undergoing wedge resection for colorectal metastases. A study of 267 patients at Memorial Sloane-Kettering comparing resection techniques concluded that patients undergoing anatomic segmental resection had significantly fewer positive surgical margins (2% vs. 16%, $P < 0.001$), significantly longer survival (55 months vs. 38 months, $P = 0.015$) and significantly longer disease-free interval (58% vs. 43%, $P = 0.014$) compared to patients undergoing wedge hepatectomy [22]. The increased use of parenchyma-sparing segmental resections for liver metastases has been associated with an improvement in perioperative results and a downward trend in operative mortality, blood loss, use of blood products, and hospital stay [23]. Other studies, however, report similar rates of positive margins and similar outcome in patients treated with wedge resection or anatomic resection. A recent study at the MD Anderson Cancer Center found an identical 8.3% incidence of positive margins after both types of resection with no difference in overall recurrence rates, patterns of recurrence or complication rate, and a comparable 5 year survival of 60% [21]. Similar findings by Kokudo and team [24] demonstrated no significant difference in patient survival or recurrence rates according to surgical procedure.

It has been established that histological liver resection margin involvement is a significant predictor of survival and disease-free survival after surgery. A positive hepatic resection margin has been associated with a higher incidence of surgical margin postoperative recurrence and lower survival rate. However, recent studies have demonstrated that the width of the resection margin does not affect the rate and pattern of recurrence or rate of survival [25,26].

The techniques used in parenchymal dissection are a key factor impacting the potential for minimal margins, yet adequate R0 resection. While in earlier series, surgeons applied rough instrument crushing techniques, the use of more controlled and fine tissue dissectors, such as the CUSA or water jet aspirators, allows guided and precise resection even in close proximity to the lesions and in the depth of liver.

The type of resection chosen for a particular patient should be based on the intrahepatic location of the lesions, the quality of liver tissue, and the goal of preserving an adequate volume of functional liver parenchyma. Since margin width does not affect survival or recurrence, we can safely perform a limited wedge resection with narrow margins to preserve a maximal amount of liver parenchyma that will become the functional liver remnant. Protection of the liver decreases operative morbidity and maintains future re-resection as a viable option. We conclude that there is no need to adhere to anatomic resection in the treatment of colorectal liver metastases.

Progress is ongoing in the imaging, chemotherapeutic regimens and surgical techniques in the battle against colorectal metastases to the liver

Local ablation therapy vs. surgical resection

The majority of patients with primary or metastatic malignancies confined to the liver are not candidates for curative resection because of tumor location, multifocality, proximity of the tumor to vessels, or inadequate functional hepatic reserve. For these patients alternative treatment approaches, such as radiofrequency ablation therapy, are being explored to control and potentially cure primary and secondary liver disease. RFA uses high frequency alternating current to produce thermal energy that destroys tumors by denaturing proteins. Previous studies have discussed the efficacy and safety of RFA in the treatment of colorectal liver metastases, and demonstrated acceptable local recurrence and short-term survival rates [27,28]. Here, the efficacy and long-term survival rates compared to surgical resection will be reviewed.

An original series by Pawlik et al. [27] at MD Anderson evaluated the combined treatment of surgical resection and RFA in patients with hepatic malignancies without extrahepatic disease,

RFA = radiofrequency ablation therapy

finding comparable morbidity and mortality rates with a recurrence rate of 56.9% at 21.3 months. The number and size of tumors treated with RFA did not affect time to recurrence, but patients with more than 10 treated tumors had a significantly shorter time to recurrence [27]. In a follow-up study at the same institution, recurrence and survival were compared in patients with resection alone (190, 45%), patients with combined resection and RFA (101, 24%), and those with RFA alone (57, 14%). Overall survival rate was highest after resection (58% at 5 years), but there was no survival difference for patients treated with RFA + resection versus RFA alone, although these were significant risk factors for decreased survival compared with resection alone [29]. Elias and co-workers [30] also concluded that a combination of surgery, RFA and chemotherapy is optimal, providing an increased 3 year survival rate of 47%. However, multiple reports have indicated a significantly higher rate of metastatic recurrence, specifically local and intrahepatic recurrence, with RFA [29].

Decision making and patient care mandate careful assessment of the risks and benefits and a reasonable balance must be attained between surgical feasibilities and oncological justifications

The use of RFA in combination with surgical resection allows the surgeon to ablate small lesions while removing the larger lesions. In general, adding RFA to the hepatic resection is well tolerated and adds minimal complexity to the operation. RFA plus resection confers a morbidity and mortality similar to surgical resection if performed by experienced hands. However, RFA is inferior for local control of metastases, systemic spread, and long-term survival. Thus, in resectable cases and mainly in the treatment of solitary hepatic metastases, the application of local ablative therapy cannot be recommended as primary treatment. RFA provides survival slightly superior to that of non-surgical chemotherapy treatment and therefore can be used as a palliative modality in selected patients. Based on the current data, we conclude that RFA should be reserved only for non-resectable lesions and non-operable high risk patients.

Repetitive resection: the role of re-resection

Although hepatic resection is performed with curative intent, 60–70% of patients may develop recurrent disease within the first 2 years, one-third of which recurs in the liver [31]. Only a subset (10–15%) of these patients are candidates for re-resection [32]. Improvements in surgical techniques, perioperative management and safety of liver resections have paved the way for more frequently performed repeat hepatic resection in patients with isolated hepatic recurrence.

In well-selected patients, repeat hepatectomy provides similar long-term survival to primary hepatectomy, without increasing postoperative morbidity and mortality [33-35]. A study by Pessaux et al. [33] showed overall 5 year survival rates of 33%, 21% and 36% respectively after a first, second and third hepatectomy. Similarly, Shaw and collaborators [34] demonstrated comparable 5 year survival rates after repeat and single hepatectomy: 1, 3 and 5 year survival rates were 94, 68 and 44%, compared with 89.3, 51.7 and 29.5%, respectively.

In an analysis of patients undergoing a third hepatectomy, Adam et al. [36] concluded that a third hepatectomy is safe, with complication rates and survival benefit similar to first and second hepatectomies. Following third hepatectomy, overall 5 year survival was 32% and disease-free survival 17%. Survival compared favorably to that of patients with recurrence following a second hepatectomy who could not be operated (5% at 3 years), patients who failed to be resected (15% at 2 years, $P = 0.0001$), and patients who underwent only two hepatectomies (27% at 5 years). When estimated from the time of the first hepatectomy, survival was 65% at 5 years for the 60 patients who underwent three hepatic resections [36]. Due to comparable survival rates, some investigations strongly support aggressive surgical management in selected patients with intrahepatic recurrence.

Since only a subset of patients are eligible for re-resection, prognostic indicators of survival are important for determining patient eligibility and probable success following repeat liver resection. The factors predicting survival in repeat hepatectomy are: the curative nature of first and second hepatectomies, an interval between the two procedures of more than 1 year, the number of recurrent tumors, serum carcinoembryonic antigen levels, and the presence of extrahepatic disease [37]. Optimal selection for long-term survival after repeat resection includes patients with a low tumor load, no extrahepatic disease, and removal of all visible tumors during the second hepatectomy [35,38].

The patients eligible for re-resection constitute a highly selective group of patients who have already survived chemotherapy and primary resections. Criteria for the selection of patients who will be successful in re-resection are not well established. Despite the numerous studies showing survival comparable to first and second liver resections, the role of repeat liver surgery in patients with intrahepatic recurrence is controversial due to the questionable survival benefit and additional risks of re-resection. There is a need for a large-scale prospective randomized control trial to determine the true survival advantage or disadvantage of re-resection. Furthermore, uniform protocols must be established to standardize the treatment of patients with recurrent hepatic disease. Until then, it is the important balance between surgical feasibility and oncologic justification that must guide clinicians in determining the appropriate treatment strategy for their patients.

Extrahepatic disease

Traditionally, extrahepatic disease was a contraindication to hepatic resection. However, various institutions have recently reported extended hepatic resections with removal of adjacent

intra-abdominal and intrathoracic organs, such as diaphragm, bowel, lung and pancreas [32].

Patients with extrahepatic disease have significantly poorer survival than patients without extrahepatic disease [37,39]. In one study of 14 patients with synchronous extrahepatic disease who underwent a second liver resection, the 3 year survival rate was 32%, compared to 63% in patients without extrahepatic disease. At 5 years, there were no survivors in this group compared to 54% of patients without extrahepatic disease [37]. Despite these findings, a multivariate analysis by Adam et al. [36] found that extrahepatic disease was not independently associated with decreased survival and therefore re-resection cannot be excluded as an option in patients with extrahepatic disease. Careful assessment of the risks and benefits for each individual patient is important in the decision to resect extrahepatic disease since there are no prospective randomized trials to guide our practice.

Summary

There is ongoing progress in the imaging, chemotherapeutic regimens and surgical techniques in the battle against colorectal metastases to the liver. Current results are better than historical controls but are far from satisfactory. There is a shortage of clear data from well-designed and randomized controlled studies, and many aspects and dilemmas have yet to be resolved. Traditional risk factors, selection criteria, indications and contraindications are being challenged and need revalidation. Decision making and patient care mandate careful assessment of the risks and benefits for each individual patient, and a reasonable balance must be attained between surgical feasibilities and oncological justifications.

References

1. Taylor I. Liver metastases from colorectal cancer: lessons from past and present clinical studies. *Br J Surg* 1996;83:456–60.
2. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002;235:759–66.
3. Steele G, Bleday R, Mayer RJ, Lindblad A, Petrelli N, Weaver D. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: gastrointestinal tumor study group protocol 6584. *J Clin Oncol* 1991;9:1105–12.
4. Truant S, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. *Br J Surg* 2005;92:362–9.
5. Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. *Cancer* 2005;104:2658–70.
6. Zhuang H, Sinha P, Pourdehnad M, Duarte PS, Yamamoto AJ, Alavi A. The role of positron emission tomography with fluorine-18-deoxyglucose in identifying colorectal cancer metastases to liver. *Nucl Med Commun* 2000;21:793–8.
7. Lubezky N, Metser U, Geva R, et al. The role and limitations of 18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan and computerized tomography (CT) in restaging patients with hepatic colorectal metastases following neoadjuvant chemotherapy: comparison with operative and pathological findings. *J Gastrointest Surg* 2007;11:472–8.
8. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg* 2004;240:438–47; discussion 447–50.
9. Akhurst T, Kates TJ, Mazumdar M, et al. Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. *J Clin Oncol* 20051;23:8713–16.
10. Tzimas GN, Koumanis DJ, Meterissian S. Positron emission tomography and colorectal carcinoma: an update. *J Am Coll Surg* 2004;198:645–52.
11. Adam R, Delvart V, Pascal G, 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.
12. Giachetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999;10:663–9.
13. Capussotti L, Muratore A, Mulas MM, Massucco P, Aglietta M. Neoadjuvant chemotherapy and resection for initially irresectable colorectal liver metastases. *Br J Surg* 2006;93:1001–6.
14. 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.
15. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal metastases. *Ann Surg* 2006;243.
16. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;24:2065–72.
17. Kornprat P, Jarnagin WR, Gonen M, et al. Outcome after hepatectomy for multiple (four or more) colorectal metastases in the era of effective chemotherapy. *Ann Surg* 2007;14:1151–60.
18. Portier G, Elias D, Bouche O, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *J Clin Oncol* 2006;24:4976–82.
19. Kokudo N, Seki M, Ohta H, et al. Effects of systemic and regional chemotherapy after hepatic resection for colorectal metastases. *Ann Surg Oncol* 1998;5:706–12.
20. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006;24:3939–45.
21. Zorzi D, Mullen JT, Abdalla EK, et al. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. *J Gastrointest Surg* 2006;10:86–94.
22. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. *J Gastrointest Surg* 2000;4:178–84.
23. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002;236:397–407.
24. Kokudo N, Tada K, Seki M, et al. Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma. *Am J Surg* 2001;181:153–9.
25. Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP. Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1 cm rule. *Eur J Surg Oncol* 2006;32:557–63.
26. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin

status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;241:715–22; discussion 722–4.
27. Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol* 2003;10:1059–69.
28. Bachar GN, Greif F, Mor E, Tur Kaspa R, Belenky A. Radiofrequency ablation for the management of liver tumors. *IMAJ* 2003:5:496–500.
29. Abdalla E, Vauthey J, Ellis L, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818–27.
30. Elias D, Baton O, Sideris L, et al. Hepatectomy plus intraoperative radiofrequency ablation and chemotherapy to treat technically unresectable multiple colorectal liver metastases. *J Surg Oncol* 200590:36–42.
31. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery* 1991;110:13–29.
32. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? *J Clin Oncol* 2005;23:8490–9.
33. Pessaux P, Lermite E, Brehant O, Tuech JJ, Lorimier G, Arnaud JP. Repeat hepatectomy for recurrent colorectal liver metastases. *J Surg Oncol* 2006;93:1–7.
34. Shaw IM, Rees M, Welsh FK, Bygrave S, John TG. Repeat hepatic resection for recurrent colorectal liver metastases is associated with favourable long-term survival. *Br J Surg* 2006;93:457–64.
35. Petrowsky H, Gonen M, Jarnagin W, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann Surg* 2002;235:863–71.
36. Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases: the third hepatectomy. *Ann Surg* 2003;238:871–83; discussion 883–4.
37. Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg* 1997;225:51–62.
38. Sugarbaker PH. Repeat hepatectomy for colorectal metastases. *J Hepatobiliary Pancreat Surg* 1999;6:30–8.
39. Jenkins LT, Millikan KW, Bines SD, Staren ED, Doolas A. Hepatic resection for metastatic colorectal cancer. *Am Surg* 1997;63:605–10.

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