Chapter 1

General introduction and outline of the thesis

Surgical treatment of colorectal liver metastases

The prevalence of colorectal cancer is among the highest of malignancies in the western world.[1] Hepatic metastases will eventually develop in as many as 50-80% of colorectal cancer patients and the liver is the sole site of dissemination in 30%.[2,3] When untreated, the presence of liver metastases is associated with a very poor prognosis.[4-6] Novel chemotherapy regimes using oxaliplatin or irinotecan have doubled the median overall survival from 10 to 20 months, but still, virtually all patients will eventually succumb to their disease within 5 years.[7-10]
Currently, surgical resection remains the only hope for cure, offering 5 and 10-year survival rates of 30-40% and 20-25% respectively in selected patient groups.[11-14] Recent developments have made an increasing number of patients amenable to this potentially curative treatment.[15-17] For instance, although approximately 10-15% of patients are regarded eligible for an intentionally curative resection upon presentation, oxaliplatin or irinotecan-based neoadjuvant chemotherapy has increased resectability rates with an estimated 10-15%.[18-20] Moreover, multiple metastases or simultaneous resection of limited extrahepatic metastases is now no longer regarded as a contra-indication for hepatic resection, as long as an R0 resection can be achieved.[21-26] Finally, due to technical advances (e.g. portal vein embolization[27,28]) and a more aggressive approach (including two staged resections[29,30] and repeat hepatic resection[31-33]), an increasing number of patients may be offered long-term survival by partial liver resection.
Despite these advances, still many patients with hepatic metastases are not candidates for surgical resection because of extensive disseminated disease, an expected inadequate postoperative hepatic reserve or a poor medical condition. For nonresectable metastases confined to the liver, thermal destruction therapies, such as radiofrequency ablation (RFA) or laser-induced thermotherapy (LITT), have emerged as effective strategies to achieve tumor clearance. With 3-year survival rates of 37-58%, these treatments have generated encouraging results and potentially increase life-expectancy in selected patients.[34-40]

Recurrences and the importance of residual micrometastases

Unfortunately, even after an apparently radical tumor removal or complete tumor destruction, the majority of patients (about two-thirds) develop recurrent disease within the first two years after surgery, predominantly in the liver.[14,41,42] Intrahepatic recurrences may either develop from circulating tumor cells that are released into the circulation through surgical manipulation or from pre-existent microscopic tumor residues in the liver. In hepatic surgery, circulating tumor cells are detected peri-operatively in 15-44% of patients.[43-45] However, the majority of circulating tumor cells have limited life-span, and thus, due to this metastatic inefficiency their detection is of limited prognostic value.[46-50]
In contrast, residual microscopic tumor cell deposits that are undetected at the time of surgery are a more likely source for tumor recurrence, as they have already passed the first steps of the metastatic process. Intrahepatic micrometastatic colorectal cancer lesions are detected in 26-70% of randomly selected biopsies and are strongly associated with a poor outcome.[51-54] Moreover, two other obvious sources for residual metastatic disease are micro-satellite lesions and a positive resection margin, which are both highly indicative for early tumor recurrence.

In thermal destruction therapies, residual tumor tissue may be caused by incomplete heat-destruction, resulting in the development of local recurrences around the thermally induced lesion in up to 60% of treated tumors.[42,55,56] Insufficient heat-diffusion at the tumor periphery may cause unsuccessful treatment, especially in tumors greater than 4 centimeter or during the percutaneous approach.[35,57-59] Local recurrence may also develop from viable tumor cells that survive around blood vessels due to the cooling effect of the blood stream, i.e. the 'heat sink' effect.[60-63]
Thus, the development of recurrent disease is strongly associated with the presence of intrahepatic residual micrometastatic disease. The biological behavior of these micrometastases largely determines the time to develop recurrence, which is crucial for the further course of the disease and ultimately has great impact on patient survival.

Surgery-induced tumor growth

Despite the curative intent of surgery, it has been long suggested that surgical trauma may enhance the outgrowth of cancer cells.[64] Pre-existent micrometastases may stay dormant for years due to balanced apoptosis and proliferation and angiogenesis suppression,[65] until surgically induced micro-environmental stimuli may evoke their uncontrolled growth early in the postoperative period. The first experimental evidence of surgery-induced tumor growth originates from 1959 by Fisher and Fisher, showing enhanced micrometastasis outgrowth after subsequent relaparotomies and organ manipulation.[66] Many experimental studies on accelerated tumor growth and clinical reports on early recurrence after surgery have been reported since.[67-71] As neovascularization (or angiogenesis) is an integral part of physiological tissue repair, it has been implicated in the generation of the unfavorable side-effects of oncological surgery.[72]
Other than surgical injury and wound healing in general, some procedures related to hepatic surgery have been specifically associated with enhanced tumor growth and early tumor recurrence, such as blood transfusion and hepatectomy.[73-78] This thesis focuses on two particular surgical interventions that may adversely affect outcome by stimulating tumor growth following hepatic surgery: vascular clamping and thermal destruction therapy.

Vascular clamping and ischemia/reperfusion during hepatic surgery

The prime concern of hepatic surgeons is to safely perform a curative resection, without excessive blood loss. Intra-operative hemorrhage during hepatectomy is common, often necessitating blood transfusion, which is associated with unfavorable short and long-term outcome.[73-76] Therefore, approaches to reduce intra-operative blood loss are applied worldwide and include vascular clamping methods.[79-82]
During thermal destruction therapies, hepatic blood flow transports heat away from the probe resulting in a smaller lesions, known as the 'heat sink' effect. For this reason, vascular clamping is advised by many authors, as it reduces dissipation of the generated heat, providing increased destruction volumes and greater tumor free margins.[56,83-85]
A major disadvantage of temporary vascular clamping is ischemia and subsequent reperfusion injury to the remaining liver parenchyma.[86] The local events after ischemia/reperfusion (I/R) that induce liver tissue damage are complex, but can grossly be divided in two distinct phases. In the acute phase, oxygen radicals, proteases and inflammatory

cytokines are generated shortly after reperfusion and contribute to early hepatocellular damage.[87] The late phase is characterized by an imbalance of vasoconstrictors (e.g. endothelin-1) and vasodilators (e.g. nitric oxide), causing microcirculatory disturbances and prolonged tissue hypoxia.[88-91] Moreover, the accumulation of neutrophils induces delayed perfusion failure by plugging of the hepatic sinusoids, which further aggravates the ischemic damage and finally results in microscopic tissue necrosis.[92] Consequently, I/R may contribute to postoperative liver dysfunction and morbidity. Several therapeutic strategies have been successfully developed to prevent liver tissue damage following I/R.[93,94]

The degree of ischemic injury largely depends on the type and duration of vascular occlusion and is influenced by several (patho)physiological parameters, including hemodynamic stability, body temperature, age, gender and the presence of underlying liver disease.[95-100]

Several different clamping techniques have been described, each with its advantages and disadvantages with respect to hemodynamic stability, the duration of the procedure, the amount of blood loss and the magnitude of I/R damage.[79-82] Although the vascular clamping technique used during hepatic surgery depends on the individual surgeon's judgment and preference, good knowledge of all the benefits and drawbacks of the different techniques available is a prerequisite for appropriate individualized application of vascular clamping during hepatic resection and thermal ablation.

Vascular clamping techniques

Portal triad clamping, i.e. the Pringle Maneuver, is the oldest and the simplest technique first described in 1909 by James Hogarth Pringle.[101] The Pringle Maneuver results in complete arterial and portal inflow occlusion, leaving back flow from the hepatic veins intact. For more complex major liver resections, inflow occlusion may be combined with occlusion of the supra and infrahepatic inferior caval vein, resulting in total vascular occlusion.[102,103] When caval flow is preserved, inflow occlusion combined with selective control of major hepatic veins results in selective vascular exclusion. In addition, selective hemihepatic or segmental vascular occlusion techniques have been successfully developed to minimize ischemic damage to the contralateral lobe. Selective clamping of the portal, arterial or venous flow has also been described. Portal clamping may be advantageous in thermal destruction techniques, as it provides an increase in lesion size, but minimizes ischemic injury.[83,85,104,105] Finally, as a result of several advances in parenchymal transection devices, improved visualization of hepatic vascularization by intra-operative ultra-sonography, and the maintenance of low central venous pressure, major liver resection may even be performed without vascular clamping.

Vascular clamping may be applied either continuously or intermittently. Intermittent clamping allows the liver parenchyma to be reperfused shortly in-between clamping periods, which protects against ischemic damage.[106-108] Moreover, the application of a short occlusion period before prolonged vascular clamping, called ischemic preconditioning, can render liver tissue less vulnerable to a sustained ischemic insult by triggering hepatocellular defense mechanisms.[86,109,110]

Peri-operative tolerance to hepatic ischemia also correlates with the duration of vascular occlusion. In general, occlusion periods of up to 60 minutes for continuous clamping, and 120 minutes for intermittent clamping can be safely performed in normal livers, i.e. without major postoperative morbidity or mortality.[111-113]

In recent years, the adverse effects of I/R resulting from vascular clamping on hepatocellular function have been well documented. Strikingly, the influence of I/R on the outgrowth of residual colorectal micrometastases has been underexposed. We performed an extensive systematic review among more than 1500 papers, searching for all studies comparing different clamping techniques and all papers describing prognostic factors of recurrence and survival after partial liver resection for colorectal liver metastases, and found only four studies evaluating long-term outcome after vascular clamping.[114-117] The patient groups included and the clamping techniques studied were highly heterogeneous and the studies lacked a sufficiently detailed evaluation to draw any firm conclusion. Moreover, the only preclinical studies available show that I/R, when applied prior to a challenge with tumor cells, stimulates tumor cell adhesion and promotes the incidence of metastases formation.[118,119] However, these studies may only be relevant for the implantation of tumor cells that are shed into the blood circulation during surgical manipulation. It is currently unknown how I/R, such as frequently encountered during liver surgery, affects the outgrowth of pre-existent hepatic micrometastases and how this influences the time to develop (liver) recurrence and survival.

Outline and central questions of this thesis

The central theme of this thesis is surgery-induced tumor growth. In **chapter 2**, the role of angiogenesis (in response to tissue injury and hypoxia) in surgery-induced tumor growth is reviewed and its mechanistic overlap with tumor associated neovascularization is discussed. In this review, we also address the influence of antiangiogenic therapy on angiogenesis-dependent phenomena such as wound repair, healing of intestinal anastomoses and liver regeneration.
The impact of two key procedures in hepatic surgery on the outgrowth of micrometastases have been examined in detail in this work. We mainly focused on the adverse effects of I/R resulting from vascular clamping on the outgrowth of existent hepatic colorectal micrometastases (**chapters 3-8**). In addition, the effects of thermal destruction therapy on the outgrowth of perilesional micrometastatic tumor cell deposits was studied (**chapter 9**).

The studies presented in this thesis were guided by the following research questions:

- **I** How often and to what extent are vascular clamping methods currently used by hepatic surgeons in and around Europe? (**chapter 3**)
- **II** Does I/R resulting from vascular inflow occlusion promote the outgrowth of residual micrometastases in the liver and how does this affect prognosis? (**chapters 4 and 5**)
- **III** How does ischemia time affect the outgrowth of micrometastases after I/R? (**chapter 6**)
- **IV** Are the adverse effects of vascular clamping on tumor growth influenced by age, gender and hepatic steatosis? (**chapters 5 and 6**)
- **V** What alternative clamping methods can be used to circumvent the putative adverse effects of vascular clamping on tumor growth? (**chapters 4 and 7**)
- **VI** What mechanisms contribute to the stimulated micrometastasis outgrowth after I/R and how can these be mediated by pharmacological interventions? (**chapters 4 and 8**)
- **VII** Does thermal ablation, which is associated with pathophysiological events similar to I/R, also stimulate the outgrowth of residual tumor cell deposits and how can this be inhibited? (**chapter 9**)

To study the effects of I/R on metastasis outgrowth a standardized murine model of partial hepatic I/R with pre-established colorectal micrometastases was developed (**chapters 4,6-8**). As hypotension, systemic anoxia and hypothermia all may affect I/R damage, special attention was paid to anesthetic management, hemodynamic stability and body temperature in this model. Similarly, two animal models with established colorectal micrometastases were used to study the effect of radiofrequency ablation and laser-induced thermotherapy on the outgrowth of tumor cell clusters at the lesion periphery. Finally, the preclinical studies were strengthened by a descriptive survey (**chapter 3**) and a retrospective patient analysis (**chapter 5**).

References

1. GLOBOCAN 2002, Cancer Incidence, mortality and prevalence worldwide (2002 estimates). http://www-dep.iarc.fr/ [16 September 2005]
2. Pickren JW, Tsukada Y, Lane WW. Liver metastases. Analysis of autopsy data. In Weiss L, Gilber HA (eds). Liver metastases. Boston, USA: GK Hall; 1982:2-18.
3. Gilbert JM. Distribution of metastases at necropsy in colorectal cancer. Clin Exp Metastasis 1983; 1:97-101.
4. Bengmark S, Hafstrom L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer 1969; 23:198-202.
5. Wood CB, Gillis CR, Blumgart LH. A retrospective study of the natural history of patients with liver metastases from colorectal cancer. Clin Oncol 1976; 2:285-288.
6. Gray BN. Colorectal cancer: the natural history of disseminated disease. Aust N Z J Surg 1980; 50:643-646.
7. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000; 355:1041-1047.
8. Holen KD, Saltz LB. New therapies, new directions: advances in the systemic treatment of metastatic colorectal cancer. Lancet Oncol 2001; 2:290-297.
9. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004; 22:23-30.
10. Goldberg RM. Therapy for metastatic colorectal cancer. Oncologist 2006; 11:981-987.
11. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999; 230:309-318.
12. Scheele J, Altendorf-Hofmann A. Resection of colorectal liver metastases. Langenbecks Arch Surg 1999; 384:313-327.
13. Fioole B, Liem MS, Hennipman A, Borel Rinkes IH. Partial liver resections: mortality, morbidity and risk factors for postoperative complications in 133 patients/137 operations; Utrecht University Medical Center 1991/2000. Ned Tijdschr Geneeskd 2002; 146:210-213.
14. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006; 94:982-999.
15. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J Clin Oncol 2005; 23:8490-8499.
16. Wicherts DA, de Haas RJ, Borel Rinkes IH, Voest EE, van Hillegersberg R. Better treatment for patients with colorectal liver metastases. Ned Tijdschr Geneeskd 2006; 150:345-351.
17. Fahy BN, Jarnagin WR. Evolving techniques in the treatment of liver colorectal metastases: role of laparoscopy, radiofrequency ablation, microwave coagulation, hepatic arterial chemotherapy, indications and contraindications for resection, role of transplantation, and timing of chemotherapy. Surg Clin North Am 2006; 86:1005-1022.
18. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, Kunstlinger F, Levi F, Bismuth F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001; 8:347-353.

19. Selzner M, Clavien PA. Resection of hepatic tumors: special emphasis on neoadjuvant and adjuvant therapy. In Clavien PA (ed). Malignant liver tumors: current and emerging therapies. Sudbury, Massachusets, USA: Jones and Bartlett Publishers; 2004:153-169.
20. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2005; 23:2038-2048.
21. Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg 2000; 231:743-751.
22. Jaeck D. The significance of hepatic pedicle lymph nodes metastases in surgical management of colorectal liver metastases and of other liver malignancies. Ann Surg Oncol 2003; 10:1007-1011.
23. Elias D, Sideris L, Pocard M, Ouellet JF, Boige V, Lasser P, Pignon JP, Ducreux M. Results of R0 resection for colorectal liver metastases associated with extrahepatic disease. Ann Surg Oncol 2004; 11:274-280.
24. Elias D, Benizri E, Pocard M, Ducreux M, Boige V, Lasser P. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. Eur J Surg Oncol 2006; 32:632-636.
25. Shah SA, Haddad R, Al Sukhni W, Kim RD, Greig PD, Grant DR, Taylor BR, Langer B, Gallinger S, Wei AC. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg 2006; 202:468-475.
26. Avital I, DeMatteo R. Combined resection of liver and lung metastases for colorectal cancer. Thorac Surg Clin 2006; 16:145-55.
27. Imamura H, Shimada R, Kubota M, Matsuyama Y, Nakayama A, Miyagawa S, Makuuchi M, Kawasaki S. Preoperative portal vein embolization: an audit of 84 patients. Hepatology 1999; 29:1099-1105.
28. Denys A, Madoff DC, Doenz F, Schneider F, Gillet M, Vauthey JN, Chevallier P. Indications for and limitations of portal vein embolization before major hepatic resection for hepatobiliary malignancy. Surg Oncol Clin N Am 2002; 11:955-968.
29. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 2000; 232:777-785.
30. Jaeck D, Bachellier P, Nakano H, Oussoultzoglou E, Weber JC, Wolf P, Greget M. One or two-stage hepatectomy combined with portal vein embolization for initially nonresectable colorectal liver metastases. Am J Surg 2003; 185:221-229.
31. Sugarbaker PH. Repeat hepatectomy for colorectal metastases. J Hepatobiliary Pancreat Surg 1999; 6:30-38.
32. Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, Encke A, Blumgart L, Fong Y. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. Ann Surg 2002; 235:863-871.
33. Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases: the third hepatectomy. Ann Surg 2003; 238:871-883.
34. Heisterkamp J, van Hillegersberg R, IJzermans JN. Interstitial laser coagulation for hepatic tumours. Br J Surg 1999; 86:293-304.
35. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, Cova L, Halpern EF, Gazelle GS. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 2001; 221:159-166.
36. Choi H, Loyer EM, DuBrow RA, Kaur H, David CL, Huang S, Curley S, Charnsangavej C. Radio-frequency ablation of liver tumors: assessment of therapeutic response and complications. Radiographics 2001; 21:S41-S54.
37. Mutsaerts EL, van Coevorden F, Krause R, Borel Rinkes IH, Strobbe LJ, Prevoo W, Tollenaar RA, van Gulik TM. Initial experience with radiofrequency ablation for hepatic tumours in the Netherlands. Eur J Surg Oncol 2003; 29:731-734.
38. Nikfarjam M, Christophi C. Interstitial laser thermotherapy for liver tumours. Br J Surg 2003; 90:1033-1047.
39. Garcea G, Lloyd TD, Aylott C, Maddern G, Berry DP. The emergent role of focal liver ablation techniques in the treatment of primary and secondary liver tumours. Eur J Cancer 2003; 39:2150-2164.
40. McKay A, Dixon E, Taylor M. Current role of radiofrequency ablation for the treatment of colorectal liver metastases. Br J Surg 2006; 93:1192-1201.
41. 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; 80:1032-1035.
42. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004; 239:818-825.
43. Weitz J, Koch M, Kienle P, Schrodel A, Willeke F, Benner A, Lehnert T, Herfarth C, von Knebel DM. Detection of hematogenic tumor cell dissemination in patients undergoing resection of liver metastases of colorectal cancer. Ann Surg 2000; 232:66-72.
44. Uchikura K, Ueno S, Takao S, Miyazono F, Nakashima S, Tokuda K, Nakajo A, Matsumoto M, Aiko T. Perioperative detection of circulating cancer cells in patients with colorectal hepatic metastases. Hepatogastroenterology 2002; 49:1611-1614.
45. Vlems FA, Diepstra JH, Punt CJ, Ligtenberg MJ, Cornelissen IM, van Krieken JH, Wobbes T, van Muijen GN, Ruers TJ. Detection of disseminated tumour cells in blood and bone marrow samples of patients undergoing hepatic resection for metastasis of colorectal cancer. Br J Surg 2003; 90:989-995.
46. Fidler IJ. Metastasis: guantitative analysis of distribution and fate of tumor embolilabeled with 125 I-5-iodo-2'-deoxyuridine. J Natl Cancer Inst 1970; 45:773-782.
47. Weiss L. Inefficiency of metastasis from colorectal carcinomas. Relationship to local therapy for hepatic metastasis. Cancer Treat Res 1994; 69:1-11.
48. Ishii S, Mizoi T, Kawano K, Cay O, Thomas P, Nachman A, Ford R, Shoji Y, Kruskal JB, Steele G, Jr., Jessup JM. Implantation of human colorectal carcinoma cells in the liver studied by in vivo fluorescence videomicroscopy. Clin Exp Metastasis 1996; 14:153-164.
49. Patel H, Le Marer N, Wharton RQ, Khan ZA, Araia R, Glover C, Henry MM, Allen-Mersh TG. Clearance of circulating tumor cells after excision of primary colorectal cancer. Ann Surg 2002; 235:226-231.
50. Vlems FA, Ruers TJ, Punt CJ, Wobbes T, van Muijen GN. Relevance of disseminated tumour cells in blood and bone marrow of patients with solid epithelial tumours in perspective. Eur J Surg Oncol 2003; 29:289-302.
51. Nanko M, Shimada H, Yamaoka H, Tanaka K, Masui H, Matsuo K, Ike H, Oki S, Hara M. Micrometastatic colorectal cancer lesions in the liver. Surg Today 1998; 28:707-713.
52. Yokoyama N, Shirai Y, Ajioka Y, Nagakura S, Suda T, Hatakeyama K. Immunohistochemically detected hepatic micrometastases predict a high risk of intrahepatic recurrence after resection of colorectal carcinoma liver metastases. Cancer 2002; 94:1642-1647.
53. Schimanski CC, Linnemann U, Galle PR, Arbogast R, Berger MR. Hepatic disseminated tumor cells in colorectal cancer UICC stage 4 patients: prognostic implications. Int J Oncol 2003; 23:791-796.
54. Linnemann U, Schimanski CC, Gebhardt C, Berger MR. Prognostic value of disseminated colorectal tumor cells in the liver: results of follow-up examinations. Int J Colorectal Dis 2004; 19:380-386.

55. Scaife CL, Curley SA. Complication, local recurrence, and survival rates after radiofrequency ablation for hepatic malignancies. Surg Oncol Clin N Am 2003; 12:243-255.
56. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005; 242:158-171.
57. Kuvshinoff BW, Ota DM. Radiofrequency ablation of liver tumors: influence of technique and tumor size. Surgery 2002; 132:605-611.
58. Goldberg SN. Science to practice: can we differentiate residual untreated tumor from tissue responses to heat following thermal tumor ablation? Radiology 2005; 234:317-318.
59. van Duijnhoven FH, Jansen MC, Junggeburt JM, van Hillegersberg R, Rijken AM, van Coevorden F, van der Sijp Jr, van Gulik TM, Slooter GD, Klaase JM, Putter H, Tollenaar RA. Factors influencing the local failure rate of radiofrequency ablation of colorectal liver metastases. Ann Surg Oncol 2006; 13:651-658.
60. Isbert C, Roggan A, Ritz JP, Muller G, Buhr HJ, Lehmann KS, Germer CT. Laser-induced thermotherapy: intra- and extralesionary recurrence after incomplete destruction of experimental liver metastasis. Surg Endosc 2001; 15:1320-1326.
61. Machi J, Uchida S, Sumida K, Limm WM, Hundahl SA, Oishi AJ, Furumoto NL, Oishi RH. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. J Gastrointest Surg 2001; 5:477-489.
62. Bowles BJ, Machi J, Limm WM, Severino R, Oishi AJ, Furumoto NL, Wong LL, Oishi RH. Safety and efficacy of radiofrequency thermal ablation in advanced liver tumors. Arch Surg 2001; 136:864-869.
63. Lu DS, Raman SS, Limanond P, Aziz D, Economou J, Busuttil R, Sayre J. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. J Vasc Interv Radiol 2003; 14:1267-1274.
64. Deelman HT. The part played by injury and repair in the development of cancer. Br Med J 1927; 1:872.
65. Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. Nat Med 1995; 1:149-153.
66. Fisher B, Fisher ER. Experimental evidence in support of the dormant tumor cell. Science 1959; 130:918-919.
67. Dvorak HF. Tumors: wounds that do not heal. Similarity between tumor stroma generation and wound healing. N Engl J Med 1986; 315:1650-1658.
68. Baker DG, Masterson TM, Pace R, Constable WC, Wanebo H. The influence of the surgical wound on local tumor recurrence. Surgery 1989; 106:525-532.
69. Berends FJ, Kazemier G, Bonjer HJ, Lange JF. Subcutaneous metastases after laparoscopic colectomy. Lancet 1994; 344:58.
70. Reilly WT, Nelson H, Schroeder G, Wieand HS, Bolton J, O'Connell MJ. Wound recurrence following conventional treatment of colorectal cancer. A rare but perhaps underestimated problem. Dis Colon Rectum 1996; 39:200-207.
71. Hofer SO, Molema G, Hermens RA, Wanebo HJ, Reichner JS, Hoekstra HJ. The effect of surgical wounding on tumour development. Eur J Surg Oncol 1999; 25:231-243.
72. McNamara DA, Harmey JH, Walsh TN, Redmond HP, Bouchier-Hayes DJ. Significance of angiogenesis in cancer therapy. Br J Surg 1998; 85:1044-1055.
73. Stephenson KR, Steinberg SM, Hughes KS, Vetto JT, Sugarbaker PH, Chang AE. Perioperative blood transfusions are associated with decreased time to recurrence and decreased survival after resection of colorectal liver metastases. Ann Surg 1988; 208:679-687.
74. Rosen CB, Nagorney DM, Taswell HF, Helgeson SL, Ilstrup DM, van Heerden JA, Adson MA. Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. Ann Surg 1992; 216:493-504.
75. Busch OR, Hop WC, Marquet RL, Jeekel J. The effect of blood transfusions on survival after surgery for colorectal cancer. Eur J Cancer 1995; 31A:1226-1228.
76. Kooby DA, Stockman J, Ben Porat L, Gonen M, Jarnagin WR, Dematteo RP, Tuorto S, Wuest D, Blumgart LH, Fong Y. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg 2003; 237:860-869.
77. de Jong KP, Slooff MJ, de Vries EG, Brouwers MA, Terpstra OT. Effect of partial liver resection on tumour growth. J Hepatol 1996; 25:109-121.
78. Drixler TA, Borel Rinkes IH, Ritchie ED, van Vroonhoven TJ, Gebbink MF, Voest EE. Continuous administration of angiostatin inhibits accelerated growth of colorectal liver metastases after partial hepatectomy. Cancer Res 2000; 60:1761-1765.
79. Belghiti J, Marty J, Farges O. Techniques, hemodynamic monitoring, and indications for vascular clamping during liver resections. J Hepatobiliary Pancreat Surg 1998; 5:69-76.
80. Abdalla EK, Noun R, Belghiti J. Hepatic vascular occlusion: which technique? Surg Clin North Am 2004; 84:563-585.
81. Smyrniotis V, Farantos C, Kostopanagiotou G, Arkadopoulos N. Vascular control during hepatectomy: review of methods and results. World J Surg 2005; 29:1384-1386.
82. Dixon E, Vollmer CM Jr, Bathe OF, Sutherland F. Vascular occlusion to decrease blood loss during hepatic resection. Am J Surg 2005; 190:75-86.
83. Albrecht D, Germer CT, Isbert C, Ritz JP, Roggan A, Muller G, Buhr HJ. Interstitial laser coagulation: evaluation of the effect of normal liver blood perfusion and the application mode on lesion size. Lasers Surg Med 1998; 23:40-47.
84. Patterson EJ, Scudamore CH, Owen DA, Nagy AG, Buczkowski AK. Radiofrequency ablation of porcine liver in vivo: effects of blood flow and treatment time on lesion size. Ann Surg 1998; 227:559-565.
85. Wiersinga WJ, Jansen MC, Straatsburg IH, Davids PH, Klaase JM, Gouma DJ, van Gulik TM. Lesion progression with time and the effect of vascular occlusion following radiofrequency ablation of the liver. Br J Surg 2003; 90:306-312.
86. Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. Am J Physiol Gastrointest Liver Physiol 2003; 284:G15-G26.
87. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 1985; 312:159-163.
88. Goto M, Takei Y, Kawano S, Nagano K, Tsuji S, Masuda E, Nishimura Y, Okumura S, Kashiwagi T, Fusamoto H. Endothelin-1 is involved in the pathogenesis of ischemia/reperfusion liver injury by hepatic microcirculatory disturbances. Hepatology 1994; 19:675-681.
89. Vollmar B, Glasz J, Post S, Menger MD. Role of microcirculatory derangements in manifestation of portal triad cross-clamping-induced hepatic reperfusion injury. J Surg Res 1996; 60:49-54.
90. Pannen BH, Al Adili F, Bauer M, Clemens MG, Geiger KK. Role of endothelins and nitric oxide in hepatic reperfusion injury in the rat. Hepatology 1998; 27:755-764.
91. Scommotau S, Uhlmann D, Loffler BM, Breu V, Spiegel HU. Involvement of endothelin/nitric oxide balance in hepatic ischemia/reperfusion injury. Langenbecks Arch Surg 1999; 384:65-70.
92. Jaeschke H, Smith CW. Mechanisms of neutrophil-induced parenchymal cell injury. J Leukoc Biol 1997; 61:647-653.
93. Cryer HG. Therapeutic approaches for clinical ischemia and reperfusion injury. Shock 1997; 8:26-32.

94. Selzner N, Rudiger H, Graf R, Clavien PA. Protective strategies against ischemic injury of the liver. Gastroenterology 2003; 125:917-936.
95. Heijnen BH, Elkhaloufi Y, Straatsburg IH, van Gulik TM. Influence of acidosis and hypoxia on liver ischemia and reperfusion injury in an in vivo rat model. J Appl Physiol 2002; 93:319-323.
96. Choi S, Noh J, Hirose R, Ferell L, Bedolli M, Roberts JP, Niemann CU. Mild hypothermia provides significant protection against ischemia/reperfusion injury in livers of obese and lean rats. Ann Surg 2005; 241:470-476.
97. Gasbarrini A, Simoncini M, Di Campli C, De Notariis S, Colantoni A, Pola P, Bernardi M, Gasbarrini G. Ageing affects anoxia/reoxygenation injury in rat hepatocytes. Scand J Gastroenterol 1998; 33:1107-1112.
98. Harada H, Pavlick KP, Hines IN, Hoffman JM, Bharwani S, Gray L, Wolf RE, Grisham MB. Selected contribution: Effects of gender on reduced-size liver ischemia and reperfusion injury. J Appl Physiol 2001; 91:2816-2822.
99. Behrns KE, Tsiotos GG, DeSouza NF, Krishna MK, Ludwig J, Nagorney DM. Hepatic steatosis as a potential risk factor for major hepatic resection. J Gastrointest Surg 1998; 2:292-298.
100. Selzner N, Selzner M, Jochum W, Amann-Vesti B, Graf R, Clavien PA. Mouse livers with macrosteatosis are more susceptible to normothermic ischemic injury than those with microsteatosis. J Hepatol 2006; 44:694-701.
101. Pringle JH. Notes on the arrest of hepatic haemorrhage due to trauma. Ann Surg 1909; 48:541-549.
102. Belghiti J, Noun R, Zante E, Ballet T, Sauvanet A. Portal triad clamping or hepatic vascular exclusion for major liver resection. A controlled study. Ann Surg 1996; 224:155-161.
103. Kimura F, Miyazaki M, Suwa T, Sugiura T, Shinoda T, Itoh H, Nakagawa K, Ambiru S, Shimizu H, Yoshitome H. Evaluation of total hepatic vascular exclusion and pringle maneuver in liver resection. Hepatogastroenterology 2002; 49:225-230.
104. Heisterkamp J, van Hillegersberg R, Mulder PG, Sinofsky EL, IJzermans JN. Importance of eliminating portal flow to produce large intrahepatic lesions with interstitial laser coagulation. Br J Surg 1997; 84:1245-1248.
105. Aschoff AJ, Merkle EM, Wong V, Zhang Q, Mendez MM, Duerk JL, Lewin JS. How does alteration of hepatic blood flow affect liver perfusion and radiofrequency-induced thermal lesion size in rabbit liver? J Magn Reson Imaging 2001; 13:57-63.
106. van Wagensveld BA, van Gulik TM, Gelderblom HC, Scheepers JJ, Bosma A, Endert E, Gouma DJ. Prolonged continuous or intermittent vascular inflow occlusion during hemihepatectomy in pigs. Ann Surg 1999; 229:376-384.
107. Belghiti J, Noun R, Malafosse R, Jagot P, Sauvanet A, Pierangeli F, Marty J, Farges O. Continuous versus intermittent portal triad clamping for liver resection: a controlled study. Ann Surg 1999; 229:369-375.
108. Man K, Fan ST, Ng IO, Lo CM, Liu CL, Yu WC, Wong J. Tolerance of the liver to intermittent pringle maneuver in hepatectomy for liver tumors. Arch Surg 1999; 134:533-539.
109. Yadav SS, Sindram D, Perry DK, Clavien PA. Ischemic preconditioning protects the mouse liver by inhibition of apoptosis through a caspase-dependent pathway. Hepatology 1999; 30:1223-1231.
110. Clavien PA, Selzner M, Rudiger HA, Graf R, Kadry Z, Rousson V, Jochum W. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. Ann Surg 2003; 238:843-850.
111. Kahn D, Hickman R, Dent DM, Terblanche J. For how long can the liver tolerate ischaemia? Eur Surg Res 1986; 18:277-282.
112. Delva E, Camus Y, Nordlinger B, Hannoun L, Parc R, Deriaz H, Lienhart A, Huguet C. Vascular occlusions for liver resections. Operative management and tolerance to hepatic ischemia: 142 cases. Ann Surg 1989; 209:211-218.
113. Quan D, Wall WJ. The safety of continuous hepatic inflow occlusion during major liver resection. Liver Transpl Surg 1996; 2:99-104.
114. Buell JF, Koffron A, Yoshida A, Hanaway M, Lo A, Layman R, Cronin DC, Posner MC, Millis JM. Is any method of vascular control superior in hepatic resection of metastatic cancers? Longmire clamping, pringle maneuver, and total vascular isolation. Arch Surg 2001; 136:569-575.
115. Topal B, Kaufman L, Aerts R, Penninckx F. Patterns of failure following curative resection of colorectal liver metastases. Eur J Surg Oncol 2003; 29:248-253.
116. Laurent C, Sa Cunha A, Couderc P, Rullier E, Saric J. Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. Br J Surg 2003; 90:1131-1136.
117. Laurent C, Sa Cunha A, Rullier E, Smith D, Rullier A, Saric J. Impact of microscopic hepatic lymph node involvement on survival after resection of colorectal liver metastasis. J Am Coll Surg 2004; 198:884-891.
118. Ku Y, Kusunoki N, Shiotani M, Maeda I, Iwasaki T, Tominaga M, Kitagawa T, Fukumoto T, Suzuki Y, Kuroda Y. Stimulation of haematogenous liver metastases by ischaemia-reperfusion in rats. Eur J Surg 1999; 165:801-807.
119. Doi K, Horiuchi T, Uchinami M, Tabo T, Kimura N, Yokomachi J, Yoshida M, Tanaka K. Hepatic ischemia-reperfusion promotes liver metastasis of colon cancer. J Surg Res 2002; 105:243-247.