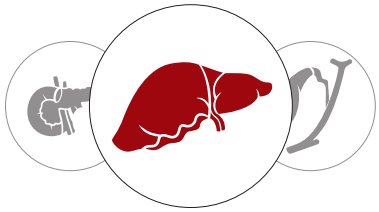

BÖLÜM 15

Kolorektal Kanser Karaciğer Metastazı

Serdar ŞENOL [1]

ÖZET

Kolorektal kanserler Amerika Birleşik Devletleri ve Avrupa'da üçüncü en sık görülen kanser türüdür. Kansere bağlı ölümler içinde ikinci sıradadır. Kolorektal kanserlerin en sık metastaz yaptığı organ karaciğerdir. Tanı konulan hastaların %25'inde tanı sırasında, yarıya yakınında da hastalık seyri sırasında karaciğer metastazı teşhisi konulur. Tercih edilen tedavi, cerrahi olmakla birlikte hastaların sadece %20'si cerrahiye uygun olarak kabul edilir. Tedavi edilmeyen kolorektal kanser karaciğer metastazlı hastaların medyan sağkalımı sadece 6.9 ay iken rezeksiyon uygulanabilen hastalarda bu süre 35 ay, 5 yıllık sağkalım %30-57 olarak bildirilmiştir. Cerrahi müdahalenin etkinliği göz önüne alındığında, karaciğer rezeksiyonu endikasyonlarının genişlemesine neden olmuştur. Geleneksel olarak karaciğer metastazı için rezeksiyon endikasyonları tümörün sayısına, büyüklüğüne ve parankim içindeki dağılımına göre belirlenirdi. Güncel yaklaşımda ise R0 rezeksiyon sağlanırken biliyer drenaj, vasküler inflow /outflowun korunduğu yeterli karaciğer hacminin idame ettirilebilmesi temel yaklaşım halini almıştır.

Kolorektal Kanser Karaciğer Metastazlı Hastaların Preoperatif Değerlendirmesi

Görüntüleme yöntemleri

Hepatik metastazların dağılımının, ekstrahepatik hastalık varlığının değerlendirilmesi ve cerrahi planının oluşturulması preoperatif radyolojik çalışmaların amaçlarını oluşturur (1-3). Çoğu vakada rezektabilitenin değerlendirmesi için batın, pelvis, ve toraks bilgisayarlı tomografisi (BT) yeterli olur. Şüpheli vakalarda manyetik rezonans görüntüleme (MRI) çalışmalara eklenebilir (4-7). Ancak subsantimetrik lezyonların ve neoadjuvan tedavi sonrası hastaların değerlendirilmesinde MRI daha duyarlıdır (8-10).

Pozitron emisyon tomografisi- bilgisayarlı tomografi (PET-CT)'nin BT'ye ya da MRI'ye ek

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den temizlenmesi, planlanan transeksiyon hattı boyunca karaciğerin bölünmesi ve kontralateral portal venin ligasyonudur. 7-14 gün sonra cerrahinin ikinci aşaması olan tamamlayıcı hemihepatektomiye olanak sağlayacak olan FLR'nin hızlı hipertrofisi sağlanır (107).

28 %'lik majör komplikasyon oranı ve 12 %'lik 90 günlük mortalite oranı ile bu teknik ilgi çektiği kadar tartışmalara da yol açmıştır (108). Yeni bir tekniğe adaptasyon, kötü hasta seçimi gibi nedenler, sonuçların kötü olması ile sonuçlanmış olabilir ve daha sonra yapılan çalışmalarda daha iyi ancak hala yüksek 90 günlük mortalite oranları bildirildi. Ana neden, hastaların %75'inde izlenen hepatektomi sonrası karaciğer yetmezliği (PHI) idi (109). ALPPS ile iki aşamalı cerrahinin karşılaştırıldığı çalışmada (107), ALPPS FLR hacminde daha hızlı artışa yol açar, rezeksiyon aşamasına geçebilen hasta oranı daha fazladır. Ancak bu durum artmış morbidite ve mortalite ile gölgelenir.

Ablatif tedavi seçenekleri ile kombine edilmiş olan yaklaşımlar iki aşamalı olan cerrahinin tek aşamalı hale gelmesini ve karaciğer parankiminin korunmasını sağlayabilirler. Aşamalı cerrahiyle elde edilebilen sonuçların düşük komplikasyon ve mortalie oranları ile elde edilebileceği gösterilmiştir (110). Intraoperatif ya da perkütan ablatif tedavi yöntemleri, bilober karaciğer metastazlı hastaların tedavisinde, multidisipliner yaklaşımlar arasında düşünülmelidir (111).

Perioperatif Morbidite ve Mortalite

Son yıllardaki cerrahi teknik, anestezi ve yoğun bakım olanaklarındaki gelişmelere paralel olarak majör hepatektomi dahil olmak üzere kolorektal kanser karaciğer metastaz cerrahi mortalitesi hızla azalmıştır. Memorial Sloan Kettering'te uygulanan son 20 yıla ait 4000 karaciğer rezeksiyonun değerlendirmesinde postoperatif komplikasyon oranın 50%'den 20%'ye, 90 günlük mortalite oranının ise 5%'ten 1.6%'ya gerilediği bildirilmiştir (112). Karaciğer cerrahisi sonrası en sık görülen komplikasyonlar, enfeksiyöz olanlardır. Sepsis, organ boşluk enfeksiyonları, septik şok en sık görülenleridir. Hepatobiliyer cerrahinin, postoperatif dönemdeki en önemli komplikasyonlarından olan biliyer fistüller enfeksiyöz komplikasyonların gelişiminde önemli role sahiptir. Uzun abdominal insizyon hattı, 48 saati geçen uzamış entübasyon artmış akciğer komplikasyonları ile ilişkilendirilir.

Postoperatif morbidite ve mortalite riski, FLR'nin hacim ve fonksiyonu ile doğrudan ilişkilidir (61). FLR'nin 20%'nin altında olması halinde majör komplikasyon oranı 47%'ye, mortalite 13%'e yükselir (63). Var olan karaciğer hastalığı ya da kemoterapiye bağlı olarak hepatik steatoz, FLR hacim ve fonksiyonunun daha fazla olmasını gerektirir. Normal fonksiyonlara sahip karaciğer için gerekli olan 20%'lik eşik FLR değeri, şiddetli karaciğer hasarı olanlarda 30%, sirotik hastalık durumunda da 40% olması gerekir (113). Karaciğer fonksiyonunun potansiyel olarak değerli bir göstergesi, indosiyanin yeşiline benzer bir bileşik kullanılarak uygulanan, 99mTc-Mebrofenin Hepatobiliyer Sintigrafisidir (114). Ana avantajı, diğer yöntemlerden farklı olarak total karaciğer yerine FLR'nin fonksiyonunu gösterebilmesidir.

KAYNAKLAR

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBO-CAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
3. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006;244(2):254-9.
4. Sjovall A, Jarv V, Blomqvist L, et al. The potential for improved outcome in patients with hepatic metastases from colon cancer: a population-based study. Eur J Surg Oncol. 2004;30(8): 834–41.
5. Hackl C, Neumann P, Gerken M, et al. Treatment of colorectal liver metastases in Germany: a ten-year populationbased analysis of 5772 cases of primary colorectal adenocarcinoma. BMC Cancer. 2014;14:810
6. Engstrand J, Nilsson H, Stromberg C, et al. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer. 2018;18(1):78.
7. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectalliver metastasis:an international multi-instutional analysis of 1699 patients Ann Surg. 2009;250(3):440-8.

8. Van Cutsem E, Cervantes A, Adam R, et al. ESMO censensus guidelines for the managment of patients with metastatic colorectal cancer. Ann Onc. 2016;27(8):1386-422.
9. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1261-8.
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed September 1, 2021.
11. Kulemann V, Schima W, Tamandl D, et al. Preoperative detection of colorectal liver metastases in fatty liver: MDCT or MRI? Eur J Radiol. 2011;79(2):e1-6.
12. Erturk SM, Ichikawa T, Fujii H, et al. PET imaging for evaluation of metastatic colorectal cancer of the liver. Eur J Radiol. 2006;58(2):229-35
13. Bipat S, van Leeuwen MS, Comans EF, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology. 2005;237(1):123-31.
14. Bonanni L, De'liguori Carino N, Deshpande R, et al. A comparison of diagnostic imaging modalities for colorectal liver metastases. Eur J Surg Oncol. 2014;40(5):545-550.
15. Jones RP, Jackson R, Dunne DF, et al. Systematic review and meta-analysis of follow-up after hepatectomy for colorectal liver metastases. Br J Surg. 2012;99(4):477-86.
16. Jones RP, Brudvik KW, Franklin JM, et al. Precision surgery for colorectal liver metastases: Opportunities and challenges of omics-based decision making. Eur J Surg Oncol. 2017;43(5):875-83.
17. Tzeng CW, Cooper AB, Vauthey JN, et al. Predictors of morbidity and mortality after hepatectomy in elderly. HPB (Oxford). 2014;16(5):459-68.
18. Nardo B, Serafini S, Ruggiero M, et al. Liver resection for metastases from colorectal cancer in very elderly patients: New surgical horizons. Int J Surg. 2016;33 Suppl 1:S135-41.
19. Hata T, Mise Y, Ono Y, et al. Multidisciplinary treatment for coloreactal liver metastases in elderly patients. World J Surg Oncol. 2020;18(1):173
20. Scherman P, Syk I, Holmberg E, et al. Influence of primary tumour and patient factors on survival in patients undergoing curative resection and treatment for liver metastases from colorectal cancer. BJS Open. 2020;4(1):118-32
21. Tan KK, de Lima Lopes Jr G, Sim R. How uncommon are isolated lung metastases in colorectal cancer? A review from data base of 754 patients over 4 years. J Gastrointest Surg. 2009;13(4):642-8
22. Noren A, Eriksson HG, Olsson LI. Selection for surgery and survival of synchronous colorectal liver metastases; a nationwide study. Eur J Cancer. 2016;53:105-14.
23. Brule SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer. 2015;51(11):1405-14.
24. Gervaz P, Usel M, Rapiti E, et al. Right colon cancer: left behind. 2016;42(9):1343-9.
25. Meguid RA, Slidell MB, Wolfgang CL, et al. Is there a difference in survival between right- versus left-sided colon cancers? Ann Surg Oncol. 2008;15(9):2388-94.
26. Makowiec F, Menzel M, Bronsert P, et al. Does the site of primary coloreactal cancer influence the outcome after resection of isolated liver metastases? Dig Liver Dis. 2018;50(10):1088-1092.
27. Cardona K. Mastrodomenico P, D'Amico F, et al. Detailed pathologic chaacteristics of the primarycoloractal tumor independently predict outcome after hepatectomy for metastases. Ann Surg Ocolo. 2013;20(1):148-54.
28. Adam R, Bhangui P, Poston G, et al. Is Perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? Ann Surg. 2010;252(5):774-87.
29. Kuo IM, Huang SF, Chiang JM, et al. Clinical features and prognosis in hepatectomy for colorectal cancer with centrally located liver metastasis. World J Surg Oncol. 2015;13:92.
30. van der Geest LG, Lam-Boer J, Koopman M, et al. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clin Exp Metastasis. 2015; 32: 457-65.
31. Adam R, de Gramont A, Figueras J, et al. of the EGOSLIM (Expert Group on OncoSurgery management of Lıver Metastases) group. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev. 2015; 41: 729-41.
32. Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multiinstitutional study of patterns of recurrence. Surgery. 1986;100(2):278-84
33. Elias D, Ouellet JF, Bellon N, et al. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg. 2003;90(5):567-74.
34. Hwang M, Jayakrishnan TT, Green DE, et al. Systematic review of outcomes of patients undergoing resection for colorectal liver metastases in the setting of extra hepatic disease. Eur J Cancer. 2014;50(10):1747-57.
35. Galandiuk S, Wieand HS, Moertel CG, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet. 1992;174(1):27-32.
36. Maithel SK, Ginsberg MS, D'Amico F, et al. Natural history of patients with subcentimeter pulmonary nodules undergoing hepatic resection for metastatic colorectal cancer. J Am Coll Surg. 2010;210(1):31-8.
37. Choi DJ, Kwak JM, Kim J, et al. Preoperative chest computerized tomography in patients with locally advanced mid or lower rectal cancer: its role in staging and impact on treatment strategy. J Surg Oncol. 2010;102(6):588-92.
38. Brent A, Talbot R, Coyne J, et al. Should indeterminate lung lesions reported on staging CT scans influence the management of patients with colorectal cancer ? Colorectal Dis. 2007; 9(9) :816-8
39. Downs-Canner S, Bahar R, Reddy SK, et al. Indeterminate pulmonary nodules represent lung metastases in a significant portion of patients undergoing liver resection for malignancy. J Gastrointest Surg. 2012;16(12):2256-9.

40. Gomez D, Kamali D, Dunn WK, et al. Outcomes in patients with indeterminate pulmonary nodules undergoing resection for colorectal liver metastases. HPB (Oxford). 2012;14(7):448-54.
41. Dave RV, Pathak S, White AD, et al. Outcome after liver resection in patients presenting with simultaneous hepatopulmonary colorectal metastases. Br J Surg. 2015;102(3):261-8.
42. Mise Y, Kopetz S, Mehran RJ, et al. Is complete liver resection without resection of synchronous lung metastases justified? Ann Surg Oncol. 2015; 22(5):1585-92.
43. Welter S, Jacobs J, Krbek T, et al. Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. Eur J Cardiothorac Surg. 2007;31(2):167-72.
44. Adam R, de Haas RJ, Wicherts DA, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol. 2008;26(22):3672-80.
45. Chua TC, Morris DL. Colorectal liver metastases with extrahepatic disease--a new criteria for oncologic resection? J Gastrointest Cancer. 2012;43(3):502-4.
46. Kianmanesh R, Scaringi S, Sabate JM, et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. Ann Surg. 2007;245(4):597-603.
47. Chua TC, Yan TD, Zhao J, et al. Peritoneal carcinomatosis and liver metastases from colorectal cancer treated with cytoreductive surgery perioperative intraperitoneal chemotherapy and liver resection. Eur J Surg Oncol. 2009;35(12):1299-305.
48. Elias D, Benizri E, Pocard M, et al. Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer. Eur J Surg Oncol. 2006;32(6):632-6.
49. Adam R, de Haas RJ, Wicherts DA, et al. Concomitant extrahepatic disease in patients with colorectal liver metastases: when is there a place for surgery? Ann Surg. 2011; 253(2):349-59.
50. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309-18
51. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007-16.
52. Poultsides GA, Bao F, Servais EL, et al. Pathologic response to preoperative chemotherapy in colorectal liver metastases: fibrosis, not necrosis, predicts outcome. Ann Surg Oncol. 2012;19(9):2797-804.
53. Blazer DG, 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol. 2008;26(33):5344-51
54. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol. 2008;26(11):1830-5.
55. Egger ME, Cannon RM, Metzger TL, et al. Assessment of chemotherapy response in colorectal liver metastases in patients undergoing hepatic resection and the correlation to pathologic residual viable tumor. J Am Coll Surg. 2013;216(4):845-5
56. Vigano L, Capussotti L, De Rosa G, et al. Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. Ann Surg. 2013;258(5):731-40
57. Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA. 2014;311(18):1863-9.
58. Lake ES, Wadhwani S, Subar D, et al. The influence of FDG PET-CT on the detection of extrahepatic disease in patients being considered for resection of colorectal liver metastasis. Ann R Coll Surg Engl. 2014;96(3):211-5
59. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010;257(3):674-84.
60. Lau LF, Williams DS, Lee ST, et al. Metabolic response to preoperative chemotherapy predicts prognosis for patients undergoing surgical resection of colorectal cancer metastatic to the liver. Ann Surg Oncol. 2014 ;21(7):2420-8.
61. Thirunavukarasu P, Aloia TA: Preoperative Assessment and Optimization of the Future Liver Remnant. Surg Clin North Am. 2016;96(2):197-205.
62. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14(12):1208-15.
63. Abdalla EK. Resection of colorectal liver metastases. J Gastrointest Surg. 2011 ;15(3):416-9.
64. Brudvik KW, Kopetz SE, Li L, et al. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg. 2015;102(10):1175-83.
65. Knijn N, Mekenkamp LJ, Klomp M, et al. KRAS mutation analysis: a comparison between primary tumours and matched liver metastases in 305 colorectal cancer patients. *Br J Cancer* 2011; 104: 1020-1026
66. Zimmitti G, Shindoh J, Mise Y, et al. RAS mutations predict radiologic and pathologic response in patients treated with chemotherapy before resection of colorectal liver metastases. Ann Surg Oncol. 2015; 22: 834-42.
67. Brudvik KW, Kopetz SE, Li L, et al. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg. 2015; 102: 1175-1183
68. Passot G, Denbo JW, Yamashita S, et al. Is hepatectomy justified for patients with RAS mutant colorectal liver metastases? An analysis of 524 patients undergoing curative liver resection. Surgery. 2017; 161: 332-340.
69. Richman SD, Seymour MT, Chambers P, et al. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the

MRC FOCUS trial. J Clin Oncol. 2009; 27(35):5931-7.
70. Karagkounis G, Torbenson MS, Daniel HD, et al. Incidence and Prognostic Impact of KRAS and BRAF Mutation in Patients Undergoing Liver Surgery for Colorectal Metastases. Cancer. 2013;119(23):4137-44.
71. Schirripa M, Bergamo F, Cremolini C, et al. BRAF and RAS mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. Br J Cancer. 2015; 112(12):1921-8.
72. Løes IM, Immervoll H, Sorbye H, et al. Impact of KRAS, BRAF, PIK3CA, TP53 status and intraindividual mutation heterogeneity on outcome after liver resection for colorectal cancer metastases. Int J Cancer. 2016; 139(3): 647-56.
73. Ursem C, Atreya CE, Van Loon K. Emerging treatment options for BRAF-mutant colorectal cancer. Gastrointest Cancer. 2018;8:13-23.
74. Chun YS, Passot G, Yamashita S, et al. Deleterious Effect of RAS and Evolutionary High-risk TP53 Double Mutation in Colorectal Liver Metastases. Ann Surg. 2019;269(5):917-23.
75. Yamashita S, Chun YS, Kopetz SE, et al. APC and PIK3CA Mutational Cooperativity Predicts Pathologic Response and Survival in Patients Undergoing Resection for Colorectal Liver Metastases. Ann Surg. 2020;272(6):1080-5.
76. Mostert B, Jiang Y, Sieuwerts AM, et al. KRAS and BRAF mutation status in circulating colorectal tumor cells and their correlation with primary and metastatic tumor tissue. Int J Cancer. 2013;133(1):130-41.
77. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007; 25(13):1670-6.
78. Fakih MG. Metastatic colorectal cancer: current state and future directions. J Clin Oncol. 2015; 33(16):1809-24.
79. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol. 2008; 26(11):1830-5.
80. Passot G, Soubrane O, Giuliante F, et al. Recent Advances in Chemotherapy and Surgery for Colorectal Liver Metastases. Liver Cancer. 2016; 6(1):72-9.
81. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408-17.
82. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(10):1626-34.
83. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11(1):38-47.
84. Ye LC, Liu TS, Ren L, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol. 2013;31(16):1931-8.
85. Wong R, Cunningham D, Barbachano Y, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. Ann Oncol. 2011; 22(9):2042-8.
86. Schwarz RE, Berlin JD, Lenz HJ, et al. Systemic cytotoxic and biological therapies of colorectal liver metastases: expert consensus statement. HPB (Oxford). 2013;15(2):106-15.
87. Vigano L, Capussotti L, De Rosa G, et al. Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. Ann Surg. 2013;258(5):731-40.
88. 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(13):2065-72.
89. White MA, Fong Y, Singh G: Chemotherapy-Associated Hepatotoxicities. Surg Clin North Am. 2016;96(2):207-17.
90. Adams RB, Aloia TA, Loyer E, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB (Oxford). 2013;15(2):91-103.
91. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg. 2010;14(11):1691-700.
92. Owen JW, Fowler KJ, Doyle MB, et al. Colorectal liver metastases: disappearing lesions in the era of Eovist hepatobiliary magnetic resonance imaging. HPB(Oxford). 2016;18(3):296-303.
93. 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(24):3939-45.
94. Passot G, Odisio BC, Zorzi D, et al. Eradication of Missing Liver Metastases After Fiducial Placement. J Gastrointest Surg. 2016;20(6):1173-8.
95. Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev. 2015;41(9):729-41.
96. Martin R, Paty P, Fong Y, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg. 2003;197(2):233-41
97. Martin RC, Augenstein V, Reuter NP, et al. Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. J Am Coll Surg. 2009;208(5):842-50
98. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol. 2011;29(8):1083-90.
99. Chua TC, Liauw W, Chu F, et al. Summary outcomes of two-stage resection for advanced colorectal liver metastases. J Surg Oncol. 2013;107(2):211-6.
100. Tsai S, Marques HP, de Jong MC, et al. Two-stage strategy for patients with extensive bilateral colorectal liver metastases. HPB (Oxford). 2010;12(4):262-9

101. Simoneau E, Hassanain M, Shaheen M, et al. Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases. Br J Surg. 2015;102(10):1240-9.
102. Shindoh J, Tzeng CW, Aloia TA, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. Br J Surg 2013; 100(13):1777-83.
103. Ribero D, Abdalla EK, Madoff DC, et al. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg. 2007;94(11):1386-94.
104. Leung U, Simpson AL, Araujo RL, et al. Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure. J Am Coll Surg. 2014;219(4):620-30.
105. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. J Am Coll Surg. 2013;216(2):201-9.
106. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405-14.
107. Eshmuminov D, Raptis DA, Linecker M, et al. Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy. Br J Surg. 2016;103(13):1768-1782.
108. Bertens KA, Hawel J, Lung K, et al. ALPPS: challenging the concept of unresectability--a systematic review. Int J Surg. 2015;13:280-7.
109. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. Ann Surg. 2015;262(5):780-5.
110. Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol. 2003;10(9):1059-69.
111. de Jong MC, van Vledder MG, Ribero D, et al. Therapeutic efficacy of combined intraoperative ablation and resection for colorectal liver metastases: an international, multi-institutional analysis. J Gastrointest Surg. 2011;15(2):336-44.
112. Kingham TP, Correa-Gallego C, D'Angelica MI, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. J Am Coll Surg. 2015;220(4):471-9.
113. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg. 2007; 94(3):274-86.
114. Hoekstra LT, de Graaf W, Nibourg GA, et al. Physiological and biochemical basis of clinical liver function tests: a review. Ann Surg. 2013; 257(1):27-36.