



# Treatment Options for Resectable Colorectal Liver Metastases in the Presence of Extrahepatic Disease

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Traditionally, extrahepatic disease (EHD) was considered a contraindication to resection of colorectal liver metastases (LM) [1, 2]. Nevertheless, widespread improvement in surgical morbidity and mortality, as well as improved efficacy of chemotherapeutic agents, has driven increased interest in surgical metastasectomy with the intent of improved survival and potential cure [3, 4]. In patients that undergo complete resection of LM and EHD, recurrence is expected 80–95% of the time [5–8]. Therefore, recurrence is the norm, and care must be taken to select patients who are most likely to benefit from surgical resection. However, recent evidence has shown that long-term survival is possible in selected patients with resected LM and EHD.

Various factors have been found to be predictive of a poor outcome in this patient population. Having multiple sites of EHD predicts worse survival, and the total number of metastatic lesions (both within the liver and outside) is inversely related to survival [3, 5, 9]. Other factors that have been shown to be negative predictors of long-term survival in patients with LM and synchronous EHD are size of LM > 3 cm, more than five LM, and disease progression on neoadjuvant therapy [6]. In the largest meta-analysis to date, patients with more than one site of EHD had a median survival of only 17 months, which is comparable to chemotherapy alone [9]. Incomplete surgical resection with both microscopic (R1) and grossly (R2) positive margins also precludes long-term survival and should be avoided [5, 8, 9].

This chapter endeavors to review the clinical evidence behind metastasectomy in the setting of LM and EHD and to provide clinical guidelines on when surgery should be considered.

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## Pulmonary Metastases

### Background

The lung is the second most common location of metastases in patients with colorectal cancer (CRC) after the liver, and the most common extra-abdominal site. During the course of their disease, 10–20% of patients will develop pulmonary metastases (PM), with synchronous presentation being most common [10–12]. Isolated PM is a less common situation occurring only 2–8% of the time [11, 13]. Patients with rectal cancer have a higher likelihood of developing lung metastases in comparison to those with a colon primary. It is important to note that only a small proportion of patients with PM have disease amenable to surgical resection, as the majority present with multiple, bilateral nodules, or have limited pulmonary function that impedes their ability to tolerate extensive surgery.

### Evidence for Pulmonary Metastasectomy

Historically, untreated patients with metastatic CRC have a median survival of 8 months [14]. Although modern chemotherapy has prolonged the median overall survival (OS) to 24–28 months, 5-year survival in the absence of surgery remains rare [15]. These less-than ideal results generated interest in surgical metastasectomy in patients with isolated PM from CRC [16]. A multitude of predominantly retrospective studies have demonstrated favorable 5-year OS of 27–68% in patients who underwent pulmonary metastasectomy for isolated PM [17–20]. However, it deserves mention that pulmonary metastasectomy for CRC has been criticized by some individuals who raise concerns regarding the inherent selection bias of small retrospective series, and a positive citation bias, with studies that show benefit being cited more frequently [21–23]. There is no doubt that the patients with CRC who benefit from pulmonary resection are a highly selected group, and meticulous patient selection likely factors in the positive results seen with PM. In an attempt to better address the question of whether pulmonary metastasectomy is beneficial to the population at large, a multi-center, randomized control trial of lung resection versus active monitoring is currently underway, with an estimated completion date of 2020 [24, 25].

### Pulmonary and Hepatic Metastases

The focus of this chapter is the management of LM in the setting of EHD. Traditionally, extrapulmonary sites of disease were considered a contraindication to lung resection. However, over the past decade, this dogma has been challenged. Therefore, it is worthwhile to review the evidence for lung resection specifically in the setting of synchronous or metachronous liver metastases (LM) (Table 13.1). The 5-year OS for patients with resected liver and lung metastases ranged from 20% to 61% (all studies in the table).

In a study using the LiverMetSurvey registry, patients with resected, isolated LM were compared to those who had both LM and PM resected, and those who had LM resected with unresected PM. There was no statistically significant difference in 5-year

**Table 13.1** Retrospective studies of patients undergoing resection for metastatic CRC to both liver and lungs

First author	Year	Sample size ( <i>n</i> )	Median survival (months)	5-year overall survival (%)
Kobayashi [26]	1999	47	NR	31
Nagakura [27]	2001	27	NR	27
Mineo [28]	2003	29	41	51
Shah [29]	2006	39	42	NR
Miller [30]	2007	131	40	31
Takahashi [31]	2007	30	39	58
Lee [32]	2008	32	NR	61
Barlow [33]	2009	16	17	20
Neeff [34]	2009	44	NR	42
Limmer [35]	2010	17	98	55
Brouquet [36]	2011	112	NR	50
Gonzalez [37]	2012	27	46	39
Andres [38]	2015	149	NR	45
Leung [6]	2017	57	54	32
Rajakannu [7]	2018	150	76	60

NR not reported

OS between the patients with resected liver-only disease and those with resected lung and liver metastases (51.5% versus 44.5%,  $p = 0.08$ ); however, the patients with unresected PM had a significantly worse 5-year OS (14.3%,  $p = 0.001$ ) [38]. A recent meta-analysis by Hwang et al. summarized the outcomes of patients with CRC and EHD. The authors demonstrated that patients with PM had a median survival of 45 months, which was superior to that for patients with peritoneal carcinomatosis (PC) (29 months) and lymph nodes outside of the primary drainage basin (26 months) [39].

Patients with hepatic and pulmonary metastases that are limited and amenable to resection have a favorable outcome, which is comparable to patients with resected isolated liver disease. Nevertheless, recurrence is common, which explains the discrepancy between disease-free survival (DFS) and OS in many studies [7, 28]. A 10-year OS of up to 35% has been reported, and recent studies have demonstrated that 20% of patients undergoing both hepatic and pulmonary resection for CRC can achieve long-term cure [7].

## Mediastinal and/or Hilar Lymph Node Metastases

Generally, most surgeons do not undertake systematic lymph node dissection at the time of pulmonary metastasectomy [40]. The prevalence of lymph node metastases (LNM) in patients undergoing PM is 22.4% [41]. LNM are more often detected in patients with rectal cancer as compared to colon cancer, patients requiring anatomical lung resections, and those with greater number of lung metastases [20, 41]. There are conflicting results with regards to whether having LNM independently portends a worse survival, and there is no compelling evidence that removal of clinically negative nodes improves survival in patients undergoing PM [20, 41]. Still, many studies demonstrate inferior outcomes in patients with clinically positive mediastinal or hilar lymph nodes, and surgical resection should be recommended with caution in this patient population [20, 41].

## Prognostic Factors

Various prognostic indicators for poor survival in the setting of PM have been reported in the literature. Significant discrepancy between the various small retrospective studies exists, and a universally accepted risk score has not been established. Rectal primary has been shown to be predictive of worse OS than colon primary [20, 41, 42]. The timing of disease presentation is important, with both synchronous disease and a short disease-free interval (<24 months) between the first and second metastasectomies being independently predictive of worse survival [7, 30, 31]. An elevated prelung resection carcinoembryonic antigen (CEA) level has been demonstrated to be negatively prognostic in both isolated PM and hepatic and pulmonary metastases, although the absolute cut-off value differs between studies [7, 31, 42, 43]. There have been conflicting results regarding the significance of the number of lung metastases, with some studies demonstrating equitable survival regardless of the number of lung lesions [29, 32, 41, 43, 44]. In a recent study of 150 patients with both PM and LM, no LM-related factor was independently predictive of survival, indicating that PM, being the more distant metastases, may be the driving factor of prognosis [7].

## Conclusion

In the setting of previously resected or resectable LM, surgery should be offered to patients with limited pulmonary metastases that are amenable to surgical metastasectomy. Recurrence postsurgery is commonplace, but nevertheless, cure can be achieved in this patient population [7]. Although not an absolute contraindication to surgical resection, patients with mediastinal lymph node metastases, multiple bilateral pulmonary nodules, short disease-free interval, and more than one site of EHD should be cautiously considered prior to embarking on surgical resection. In patients with risk factors predicting poor outcome, chemotherapy should be considered prior to selection for surgery. If a patient presents with synchronous lung and liver metastases, there is no evidence to recommend which organ should be resected first. However, it would be reasonable to recommend resecting the organ with the greatest burden of disease first, because if an R0 resection cannot be achieved, resection of the other site is strongly discouraged.

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## Peritoneal Metastases

### Background

Both the peritoneal surface and the liver are common sites of spread of colon cancer; however, only a small subset of patients present with both peritoneal carcinomatosis (PC) and LM. In a Dutch review of patients with CRC, only 2% had both PC and LM [45]. It is more common for patients with PC to also have LM (34%), whereas only 11% of those with LM had concomitant PC [45]. The median OS in the patient population with both LM and PC in the absence of curative-intent treatment is 5 months [45].

## Evidence for Resection of Peritoneal Disease

Within the medical community, concern has been raised about the paucity of phase III trials to support benefit to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). There has been one randomized trial published consisting of 105 patients comparing standard approach (systemic chemotherapy +/-palliative surgery) to aggressive cytoreduction with HIPEC followed by systemic chemotherapy [46]. This trial demonstrated improved survival in those who underwent cytoreduction and HIPEC (22.3 versus 12.6 months,  $p = 0.032$ ); however, the authors cautioned that patients with involvement of six or more regions of the abdominal cavity, and those who had grossly inadequate cytoreduction, had a dismal prognosis [46]. The PRODIGE 7 trial, which as of the time of print, has only been published in abstract form is a randomized trial comparing cytoreductive surgery and HIPEC with oxaliplatin to cytoreductive surgery alone. The authors report no difference in median OS between the HIPEC and non-HIPEC arms (41.7 versus 41.2 months,  $p = 0.995$ ) [47]. Despite the scarcity of randomized trials, a multitude of observational trials support the principle that in highly selected patients, resection of PC combined with HIPEC results in increased survival over palliative treatments alone, and median OS of 21–63 months has been reported [48, 49]. The American Society of Peritoneal Surface Malignancies (ASPSM) multi-institutional study reported a median OS of up to 86 months and a 5-year OS of 58% in patients with favorable histology and minimal burden of disease [48]. Liver resection of CRC metastasis has also been demonstrated to increase survival over palliative treatments and is accepted as standard of care. However, the treatment of LM in the setting of PC still presents a clinical conundrum.

## Peritoneal Disease in the Presence of Hepatic Metastases

There are no randomized trials to inform clinicians on the benefit of resection of LM and PC in patients with CRC, but observational series suggest a potential benefit over palliative treatments in select patients. Leung et al. identified 33 patients with concomitant LM and PC treated over a 10-year time period—the median OS was 40 months and the 5-year OS was 42% [6]. In a case–control study, 37 patients with both PC and LM treated with liver resection, and cytoreductive surgery with HIPEC, were matched to 61 patients with PC alone. The 3-year OS was significantly lower in those with both LM and PC (40% versus 66%.  $p = 0.04$ ) [50]. In this small series, independent predictors of lower survival included a high peritoneal carcinomatosis index (PCI) ( $>12$ ), the presence of LM, positive nodal status, and patients not receiving adjuvant chemotherapy [50]. The authors concluded that patients with limited PC and less than three LM stood to benefit the most from an attempt at curative surgical resection. Conversely, a small non-matched comparison of 16 patients with treated PC and LM and 39 patients with treated PC without hepatic involvement showed no difference in survival between the groups (median OS 36 months) [51]. However, the lower PCI scores and shorter procedural duration in the group with hepatic involvement reveal the highly selected nature of this cohort and significant potential for selection bias. A similar study comparing 36 patients with treated PC and LM and 42

patients with treated PC in the absence of LM showed median OS of 24 and 46 months, respectively, with more than three LM and more than seven PCI being associated with decreased survival [52]. A systematic review and meta-analysis of these and other published cohorts failed to demonstrate a statistically significant improved OS in patients with PC and LM from CRC treated with curative-intent surgery compared to palliative chemotherapy (HR 1.24, 95%CI 0.96–1.60) [53].

The unexpected finding of PC at the time of a planned liver resection of LM from CRC is another clinical conundrum for which high-level evidence to guide clinical decision-making is lacking. A French study suggested that intraoperative discovery of unexpected PC occurs in 3% of patients undergoing liver resection for CRC [54]. In this series, only patients found to have very minimal peritoneal disease (PCI < 2) underwent curative-intent surgery; this highly selected group had a median OS of 42 months and 5-year OS of 18% [54].

## Conclusion

Although long-term survival is possible with curative-intent treatment of PC and LM, the benefit of aggressive surgical intervention appears to be limited to a highly selected group of patients with minimal disease burden. Although clinical factors such as less than 12 PCI and less than three liver metastases have been proposed as selection criteria, the exact criteria beyond which the survival benefit of curative-intent surgery exceeds the risk of added morbidity have yet to be defined or prospectively validated.

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## Metastases to Abdominal Lymph Nodes

### Background

Colorectal cancer LM can spread to locoregional lymph nodes, including porta hepatis nodes, and from there to more distant celiac, para-aortic and retroperitoneal lymph nodes [55]. This phenomenon of “remetastasis” has traditionally been associated with extremely poor prognosis and has largely been considered a contraindication to curative hepatic resection [56, 57]. With the advent of modern chemotherapeutic regimens, numerous investigators have reexamined the role of curative liver resection in the context of lymph node metastasis (LNM). More specifically, the recent literature has focused upon three main questions: (1) the role of routine porta hepatis lymphadenectomy, (2) the management of macroscopic porta hepatis LNM identified preoperatively, or intraoperatively, and (3) the management of celiac, para-aortic and retroperitoneal LNM.

### Occult Porta Hepatis Lymph Node Metastases

The incidence of occult microscopic porta hepatis LNM from metastatic CRC has been estimated at 11–27% [58–62]. These data have been derived largely from

series where a prophylactic porta hepatis lymphadenectomy was carried out systematically in all patients undergoing liver resection. Elias et al. conducted one of the first such studies, where 100 consecutive patients underwent curative liver resection and wide lymphadenectomy along the porta hepatis and celiac artery [58]. None of these patients had macroscopic or palpable metastatic lymph nodes. The authors reported that 14% of patients had microscopically involved metastatic lymph nodes, most commonly along the transverse portion of the common hepatic artery. Microscopic lymph node involvement was noted to be associated with the number of liver metastases, a higher CEA level, and the extent of hepatectomy required.

Similarly, Laurent et al. reported a 15% incidence of occult lymph node metastasis among 156 patients undergoing curative-intent liver resection for colorectal metastasis [63]. Disease recurrence occurred in 91% among those with microscopic lymph node disease, compared to 59% among those without lymph node involvement ( $p = 0.003$ ). The 5-year overall survival was significantly worse among those with lymph node involvement (43% vs. 5%,  $p < 0.001$ ).

In contrast to the above data, Grobmyer et al. examined perihepatic lymph nodes in 100 consecutive patients with both LM and primary hepatic tumors, some of whom had preoperative suspicion of nodal involvement [60]. Among those, 15% had metastatic lymph nodes, of which 87% had suspicion of involvement on preoperative CT and/or PET scan, while the other 13% were clinically palpable at surgical exploration. Among those patients with negative preoperative CT and PET scans, as well as negative manual exploration, none had microscopically involved lymph nodes. Thus, the authors argued against routine lymph node harvest in the context of negative preoperative CT and PET scans. Rather, a recommendation for selective sampling was made. These recommendations must be interpreted in the context of a more recent multicenter randomized controlled trial that demonstrated that the routine use of PET scan prior to liver resection was largely ineffective at altering surgical management [64].

## Portal Versus Retroperitoneal Lymph Node Metastases

The oncologic outcomes of liver resection for colorectal metastasis with concomitant metastatic lymph node excision have been widely studied. In a recent systematic review, Hadden et al. identified 21 relevant publications pertaining to 559 patients with nodal disease [9]. Proportional meta-analysis of these manuscripts revealed pooled 3-year and 5-year OS of 35% (95% CI 29–41%,  $I^2 = 15\%$ ) and 15% (95% CI 11–20%,  $I^2 = 27\%$ ), respectively. The authors argued that these data support the use of radical surgery for colorectal liver metastases with concomitant LNM, as pooled survival outcomes exceeded those reported in modern series of patients receiving systemic chemotherapy alone. An acknowledged limitation of this paper was the inability to pool for oncologic differences between distinct lymph node basins (i.e., portal pedicle vs. para-aortic).

More recently, Leung et al. have reported their 10-year data on 219 patients who underwent liver resection with concurrent EHD treated with resection [6]. A total of 40 (18%) patients had portal LNM, defined as nodes along the hepatic artery proper, portal vein, and common hepatic artery. In this series, patients with portal LNM had



a median OS of 24 months, as well as 3- and 5-year OS rates of 32% and 14%, respectively. No patient survived to 10 years following resection. Portal LNM was identified as an extrahepatic disease site carrying a particularly poor prognosis. A clinical risk score was devised, including liver metastases >3 cm, having more than five liver metastases, and site of EHD (portal/retroperitoneal nodes or multiple sites). Patients with 3/3 clinical risk points all died or recurred within 6 months and had a median recurrence-free survival of 1.4 months. The authors of this paper thus argued that liver resection with concurrent EHD resection should be highly selected, particularly as it pertains to patients with metastatic portal lymph nodes. It may be particularly inadvisable to pursue resection in patients with 3/3 clinical risk points.

Jaeck et al. were the first to differentiate oncologic outcomes between those with metastatic lymph nodes located in the porta hepatis and celiac axis, arguing that liver resection should only be considered among those with porta hepatis nodal involvement and not among those with celiac disease (3-year overall survival 38% versus 1-year OS 0%) [61]. Similarly, Adam et al. reported on 47 patients who had concurrent liver resection and regional LNM [65]. Not surprisingly, OS was significantly worse among patients with LNM (5-year overall survival 53% versus 18%,  $p < 0.001$ ). More importantly, lymph node location strongly affected survival: those with porta hepatis lymph nodes achieved a 5-year overall survival of 25% compared to those with both celiac and para-aortic nodes, whose overall survival is 0% ( $p = 0.001$ ).

Another multi-institutional study reported data on 171 patients who had a liver resection and extrahepatic metastasectomy [5]. Among those, 41 had portal LNM, leading to a median OS of 23 months and 3-year and 5-year OS of 43% and 27%, respectively. Most importantly, this study separated portal from aortocaval LNM, reporting a significantly different median survival of 13 months, 3-year OS of 22%, and 5-year OS of 7% ( $p = 0.001$ ). In light of the above series, it is interesting to note that the recent series by Leung et al. did not find a difference in survival between patients who had portal versus retroperitoneal LNM [6]. This finding is inconsistent with that of other series. It may be related to varying definitions of anatomic lymph node locations, as it can sometimes be difficult to differentiate between lymph node sites within retrospective surgical datasets.

## Conclusion

In summary, the possibility of LNM, particularly within the porta hepatis, should be considered in every patient undergoing liver resection for CRC metastases. A thorough preoperative imaging assessment of lymph nodes draining the liver is recommended for every patient. Routine systematic lymph node harvest is unlikely to be necessary in the context of modern imaging techniques. Liver resection should be considered selectively in patients with porta hepatis LNM who also have a limited disease burden within the liver and no additional sites of EHD. Liver resection cannot be recommended in the context of retroperitoneal/para-aortic/cealic lymph node metastases, or among patients with additional sites of EHD.



## Other Sites of Disease

### Background

CRC metastases to distant solid organs, outside of the lung and liver, are rare, and as such, robust clinical recommendations are not possible. Much of the literature existing on rare sites of EHD is based on case series or single institution retrospective reviews, both of which are significantly impacted by substantial selection bias. The largest meta-analysis on surgical resection of EHD examined 2308 patients who underwent resection for EHD, and only 4% had metastases to infrequent sites such as bone, brain, ovary, and adrenal gland [9].

### Adrenal Gland

The adrenal gland is an uncommon location for CRC to metastasize, and it is seldom the only metastatic site of disease [66]. The current literature consists primarily of case reports of CRC metastases and case series of adrenal metastases from all tumor types. One such case series reported 3-year OS and 5-year OS of 50% and 40%, respectively, in patients undergoing adrenalectomy for metastases from all primary sites, of which the majority were non-small-cell lung cancer and RCC [66]. Only 10.3% of patients in this study had CRC metastases to the adrenal gland. In the absence of robust data, recommendations for or against adrenal metastasectomy for CRC cannot be made. However, a survival benefit in select patients without other sites of EHD can be reasonably inferred.

### Ovary

Ovarian metastases occur in approximately 2–8% of women with CRC, and 50–70% of these patients also have extra-ovarian metastases [67, 68]. There is some evidence that ovarian metastases may be less responsive to chemotherapy when compared to other sites of CRC metastases [69]. The reported prognosis is highly variable, with median OS ranging from 28 to 82 months [6, 8, 68]. Historically, some surgeons advocated for prophylactic oophorectomy in all postmenopausal women undergoing bowel resection for CRC. However, this practice has not been demonstrated to impact survival, and in the absence of clinical indications, prophylactic oophorectomy is not recommended [70, 71]. Given the relatively low surgical morbidity, and the potential for long-term survival, resection of ovarian metastases in the setting of resectable LM is indicated, especially if an ovarian metastasis is the only site of EHD.

### Bone

The reported incidence of bone metastases in CRC is in the range of 5–7%, with signet-ring cell subtype of CRC more commonly behaving in this fashion [72, 73]. Bone metastases are rarely an isolated site of CRC disease, and the median OS is

between 5 and 7 months [74, 75]. The prognosis is highly variable in patients with isolated bone metastases, and treatment with radiation or surgery can be considered, especially for symptom control on a case-by-case basis.

## Brain

Brain metastases from CRC is fortuitously rare, with a reported incidence of only 0.3–0.6%, and this is more common when the primary disease is located in the rectum [76, 77]. Typically, brain metastases occur late in the disease course when patients often have numerous other sites of metastatic CRC and as such confer a uniformly dismal prognosis. In patients with CRC brain metastases, only 2–10% have isolated brain lesions [78–80]. The decision to pursue local treatment depends on the patient's performance status, number and location of lesions, the presence of leptomeningeal disease, and whether or not there are other sites of disease [81]. In general, however, even with aggressive local treatment consisting of whole brain radiation, stereotactic radiation, or surgery, the OS is dismal ranging from 12 to 15 months, and long-term survival greater than 5 years is observed in less than 4% [82–86]. Often times, the decision to treat brain metastases is driven by objectionable symptoms than an intention to alter survival. In the absence of more compelling survival benefit, routine cerebral metastasectomy in the setting of LM cannot be recommended.

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## Summary

There has been increasing enthusiasm for surgical resection in patients with both resectable LM and EHD, despite having been previously considered a contraindication to surgery. Certainly, it has been demonstrated that in carefully selected patients, medium- to long-term survival, and even cure, can be achieved. However, much of the surgical evidence for resection of EHD in the setting of resectable hepatic disease is based upon single-center, retrospective studies, and as such, the possibility of significant selection and publication bias exists. Patients with metastatic CRC should be always discussed in a multidisciplinary setting prior to embarking on treatment. Moreover, patients should be properly informed that the majority of individuals who undergo aggressive surgical treatment of LM in the setting of EHD will recur. Surgical resection should be offered to selected patients who are the most likely to benefit from metastasectomy. Those individuals with poor prognostic indicators such as multiple sites of EHD, a high metastatic burden, retroperitoneal or celiac axis LNM, brain or bone metastases, progression on neoadjuvant systemic therapy, and short disease-free intervals should not be offered resection.

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## References

1. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery*. 1991;110(1):13–29.
2. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, et al. Liver resection for colorectal metastases. *J Clin Oncol*. 1997;15(3):938–46.

3. Elias D, Sideris L, Pocard M, Ouellet JF, Boige V, Lasser P, et al. Results of R0 resection for colorectal liver metastases associated with extrahepatic disease. *Ann Surg Oncol*. 2004;11(3):274–80.
4. Elias D, Ouellet JF, Bellon N, Pignon JP, Pocard M, Lasser P. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg*. 2003;90(5):567–74.
5. Pulitano C, Bodingbauer M, Aldrighetti L, de Jong MC, Castillo F, Schulick RD, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2011;18:1380–8.
6. Leung U, Gonen M, Allen PJ, Kingham TP, DeMatteo RP, Jarnagin WR, et al. Colorectal cancer liver metastases and concurrent extrahepatic disease treated with resection. *Ann Surg*. 2017;265:158–65.
7. Rajakannu M, Magdeleinat P, Vibert E, Ciaccio O, Pittau G, Innominato P, et al. Is cure possible after sequential resection of hepatic and pulmonary metastases from colorectal cancer. *Clin Colorectal Cancer*. 2018;17(1):41–9.
8. Carpizo D, Are C, Jarnagin W, DeMatteo R, Fong Y, Gonen M, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. *Ann Surg Oncol*. 2009;16:2138–46.
9. Hadden WJ, de Reuver PR, Brown K, Mittal A, Samra JS, Hugh TJ. Resection of colorectal liver metastases and extra-hepatic disease: a systematic review and proportional meta-analysis of survival outcomes. *HPB*. 2016;18:209–20.
10. August DA, Ottow RT, Sugarbaker PH. Clinical perspectives of human colorectal cancer metastasis. *Cancer Metastasis Rev*. 1983;3(4):303–24.
11. Mitry E, Guiu B, Coscinea S, Jooste V, Faivre J, Bouvier AM. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. *Gut*. 2010;59(10):1383–8.
12. Labianca R, Beretta GD, Kildani B, Milesi L, Merlin F, Mosconi S, et al. Colon cancer. *Crit Rev Oncol Hematol*. 2010;74(2):106–33.
13. Tan KK, Lopes Gde L, Sim R. How uncommon are isolated lung metastases in colorectal cancer? A review from database of 754 patients over 4 years. *J Gastrointest Surg*. 2009;13(4):642–8.
14. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. *Colorectal Cancer Collaborative Group*. *BMJ*. 2000;321(7260):531–5.
15. Bendell J. Optimum chemotherapy for metastatic colorectal cancer. *Lancet*. 2006;368(9552):2039–41.
16. Thomford NR, Woolner LB, Clagett OT. The surgical treatment of metastatic tumors in the lungs. *J Thorac Cardiovasc Surg*. 1965;49:357–63.
17. Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, Yasumitsu T, et al. Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg*. 2004;78(1):238–44.
18. McCormack PM, Burt ME, Bains MS, Martini N, Rusch VW, Ginsberg RJ. Lung resection for colorectal metastases. 10-year results. *Arch Surg*. 1992;127(12):1403–6.
19. Gonzalez M, Poncet A, Combesure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol*. 2013;20(2):572–9.
20. Meimarakis G, Spelsberg F, Angele M, Preissler G, Fertmann J, Crispin A, et al. Resection of pulmonary metastases from colon and rectal cancer: factors to predict survival differ regarding to the origin of the primary tumor. *Ann Surg Oncol*. 2014;21:2563–72.
21. Primrose J, Treasure T, Fiorentino F. Lung metastasectomy in colorectal cancer: is this surgery effective in prolonging life? *Respirology*. 2010;15(5):742–6.
22. Van Raemdonck D. Pulmonary metastasectomy: common practice but is it also best practice? *Future Oncol*. 2015;11(2 Suppl):11–4.
23. Treasure T. Metastasectomy for colorectal cancer: are there clothes on the emperor? *J R Soc Med*. 2017;100(6):227–30.
24. Migliore M, Milosevic M, Lees B, Treasure T, Di Maria G. Finding the evidence for pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. *Future Oncol*. 2015;11(2 Suppl):15–8.

25. ClinicalTrials.gov [Internet] A randomized trial of pulmonary metastasectomy in colorectal cancer (PulMiCC) Available from: <https://clinicaltrials.gov/ct2/show/NCT01106261>.
26. Kobayashi K, Kawamura M, Ishihara T. Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. *J Thorac Cardiovasc Surg.* 1999;118(6):1090–6.
27. Nagakura S, Shirai Y, Yamato Y, Yokoyama N, Suda T, Hatakeyama K. Simultaneous detection of colorectal carcinoma liver and lung metastases does not warrant resection. *J Am Coll Surg.* 2001;193(2):153–60.
28. Mineo TC, Ambrogi V, Tonini G, et al. Long term results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. *J Am Coll Surg.* 2003;197:386–91.
29. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. *J Am Coll Surg.* 2006;202(3):468–75.
30. Miller G, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. *J Am Coll Surg.* 2007;205(2):231–8.
31. Takahashi S, Nagai K, Saito N, Konishi M, Nakagohri T, Gotohda N, et al. Multiple resections for hepatic and pulmonary metastases of colorectal carcinoma. *Jpn J Clin Oncol.* 2007;37(3):186–92.
32. Lee WS, Yun HR, Yun SH, Chun HK, Lee WY, Kim SJ, et al. Treatment outcomes of hepatic and pulmonary metastases from colorectal carcinoma. *J Gastroenterol Hepatol.* 2008;23(8pt2):e367–72.
33. Barlow AD, Nakas A, Pattenden C, Martin-Ucar AE, Dennison AR, Berry DP, et al. Surgical treatment of combined hepatic and pulmonary colorectal cancer metastases. *Eur J Surg Oncol.* 2009;35(3):307–12.
34. Neeff H, Horth W, Makowiec F, Fischer E, Imdahl A, Hopt UT, et al. Outcome after resection of hepatic and pulmonary metastases of colorectal cancer. *J Gastrointest Surg.* 2009;13(10):1813–20.
35. Limmer S, Oevermann E, Killaitis C, Kujath P, Hoffmann M, Bruch HP. Sequential surgical resection of hepatic and pulmonary metastases from colorectal cancer. *Langenbeck's Arch Surg.* 2010;395(8):1129–38.
36. Brouquet A, Vauthey JN, Contreras CM, Walsh GL, Vaporciyan AA, Swisher SG, et al. Improved survival after resection of liver and lung colorectal metastases compared with liver-only metastases: a study of 112 patients with limited lung metastatic disease. *J Am Coll Surg.* 2011;213(1):62–9.
37. Gonzalez M, Robert JH, Halkic N, et al. Survival after lung metastasectomy in colorectal cancer patients with previously resected liver metastases. *World J Surg.* 2012;36(2):386–91.
38. Andres A, Mentha G, Adam R, Gerstel E, Skipenko OG, Barroso E, et al. Surgical management of patients with colorectal cancer and simultaneous liver and lung metastases. *BJS.* 2015;102:691–9.
39. Hwang M, Jayakrishnan TT, Green DE, George B, Thomas JP, Groeschl RT, et al. Systematic review of outcomes of patients undergoing resection for colorectal liver metastases in the setting of extra hepatic disease. *E J Cancer.* 2014;50(10):1747–57.
40. Internullo E, Cassivi SD, Van Raemdonck D, Friedel G, Treasure T, ESTS Pulmonary Metastasectomy Working Group. Pulmonary metastasectomy: a survey of current practice amongst members of the European Society of Thoracic Surgeons. *J Thorac Oncol.* 2008;3:1257–66.
41. Bolukbas S, Sponholz S, Kudelin N, Eberlein M, Schirren J. Risk factors for lymph node metastases and prognosticators of survival in patients undergoing pulmonary metastasectomy for colorectal cancer. *Ann Thorac Surg.* 2014;97:1926–32.
42. Suzuki H, Kiyoshima M, Kitahara M, Asato Y, Amemiya R. Long-term outcomes after surgical resection of pulmonary metastases from colon cancer. *Ann Thorac Surg.* 2015;99:434–40.
43. Yokoyama S, Mitsuoaka M, Kinugasa T, Hashiguchi T, Matsumoto R, Murakami D, et al. Survival after initial lung metastasectomy for metastatic colorectal cancer in the modern chemotherapeutic era. *BMC Surg.* 2017;17(1):54.
44. Reddy RH, Kumar B, Shah R, Mirsadraee S, Papagiannopoulos K, Lodge P, et al. Staged pulmonary and hepatic metastasectomy in colorectal cancer—is it worth it? *Eur J Cardiothorac Surg.* 2004;25:151–4.
45. Thomassen I, van Gestel YR, Lemmens VE, de Hingh IH. Incidence, prognosis, and treatment options for patients with synchronous peritoneal carcinomatosis and liver metastases from colorectal origin. *Dis Colon Rectum.* 2013;56(12):1373–80.

46. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol.* 2003;21(20):3737–43.
47. Quenet F, Elias D, Roca L, Goere D, Ghouti L, Pocard M, Facy O, Arvieux C, Lorimier G, Pezet D, Marchal F, Loi V, Meeus P, De Forges H, Stanbury T, Paineau J, Glehen O. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *J Clin Oncol.* 2018;36(18\_suppl):LBA3503.
48. Esquivel J, Lowy AM, Markman M, Chua T, Pelz J, Baratti D, et al. The American Society of Peritoneal Surface Malignancies (ASPSM) multiinstitution evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1,013 patients with colorectal cancer with peritoneal carcinomatosis. *Ann Surg Oncol.* 2014;21(13):4195–201.
49. Huang CQ, Min Y, Wang SY, Yanf XJ, Liu Y, Xiong B, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for peritoneal carcinomatosis from colorectal cancer: a systematic review and meta-analysis of current evidence. *Oncotarget.* 2017;18(33):55657–83.
50. Maggiori L, Goere D, Viana B, Tzani D, Dumont F, Honore C, et al. Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? A case-control study. *Ann Surg.* 2013;258(1):116–21.
51. Chua TC, Yan TD, Zhao J, Morris DL. 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.
52. Alzahrani N, Ung L, Valle SJ, Liauw W, Morris DL. Synchronous liver resection with cytoreductive surgery for the treatment of liver and peritoneal metastases from colon cancer: results from an Australian Centre. *ANZ J Surg.* 2017;87(11):E167–E72.
53. de Cuba EMV, Kwakman R, Knol DL, Bonjer HJ, Meijer GA, te Velde EA. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases. *Cancer Treat Rev.* 2013;39(4):321–7.
54. Allard MA, Adam R, Ruiz A, Vibert E, Paule B, Levi F, et al. Is unexpected peritoneal carcinomatosis still a contraindication for resection of colorectal liver metastases? *Eur J Surg Oncol.* 2013;39(9):981–7.
55. Moszkowicz D, Cauchy F, Dokmak S, Belghiti J. Routine pedicular lymphadenectomy for colorectal liver metastases. *J Am Coll Surg.* 2012;214:e39–45.
56. August DA, Sugarbaker PH, Schneider PD. Lymphatic dissemination of hepatic metastases: implications for follow-up and treatment of patients with colorectal cancer. *Cancer.* 1985;55:1490–4.
57. Carpizo DR, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. *Lancet Oncol.* 2009;10:801–9.
58. Elias D, Saric J, Jaeck D, Arnaud JP, Gayet B, Rivoire M, et al. Prospective study of microscopic lymph node involvement of the hepatic pedicle during curative hepatectomy for colorectal metastases. *Br J Surg.* 1996;83:942–5.
59. Ercolani G, Grazi GL, Ravaioli M, Grigioni WF, Cescon M, Gardini A, et al. The role of lymphadenectomy for liver tumors: further considerations on the appropriateness of treatment strategy. *Ann Surg.* 2004;239:202–9.
60. Grobmyer SR, Wang L, Gonen M, Fong Y, Klimstra D, D'Angelica M, et al. Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. *Ann Surg.* 2006;244:260–4.
61. Jaeck D, Nakano H, Bachellier P, Inoue K, Weber JC, Oussouzloglou E, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. *Ann Surg Oncol.* 2002;9:430–8.
62. Pindak D, Pavlendova J, Tomas M, Dolnik J, Duchon R, Pechan J. Selective versus routine lymphadenectomy in the treatment of liver metastasis from colorectal cancer: a retrospective cohort study. *BMC Surg.* 2017;17(1):34.
63. 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;198:884–91.
64. Moulton CA, Gu CS, Law CH, Tandan VR, Hart R, Quan D, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized controlled trial. *JAMA.* 2014;311:1863–9.

65. Adam R, de Haas RJ, Wicherts DA, Aloia TA, Delvart V, Azoulay D, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? *J Clin Oncol.* 2008;26:3672–80.
66. Rosso AE, Untch BR, Kris MG, Chou JF, Capanu M, Coit DG. Adrenal metastasectomy in the presence and absence of extraadrenal metastatic disease. *Ann Surg.* 2019;270(2):373–7.
67. Banerjee S, Kapur S, Moran BJ. The role of prophylactic oophorectomy in women undergoing surgery for colorectal cancer. *Color Dis.* 2005;7(3):214–7.
68. Lee SJ, Lee J, Lim HY, Kang WK, Choic CH, Lee JW, et al. Survival benefit from ovarian metastasectomy in colorectal cancer patients with ovarian metastasis: a retrospective analysis. *Cancer Chemother Pharmacol.* 2010;66(2):229–35.
69. Goere D, Daveau C, Elias D, Boige V, Tomasic G, Bonnet S, et al. The differential response to chemotherapy of ovarian metastases from colorectal carcinoma. *Eur J Surg Oncol.* 2008;34:1335–9.
70. Sieleznoff I, Salle E, Antoine K, Thirion X, Brunet C, Sastre B. Simultaneous bilateral oophorectomy does not improve prognosis of postmenopausal women undergoing colorectal resection for cancer. *Dis Colon Rectum.* 1997;40(11):1299–302.
71. Young-Fadok TM, WolV BG, Nivatvongs S, Metzger PP, Ilstrup DM. Prophylactic oophorectomy in colorectal carcinoma: preliminary results of a randomized, prospective trial. *Dis Colon Rectum.* 1998;1:277–83.
72. Katoh M, Unakami M, Hara M, Fukuchi S. Bone metastasis from colorectal cancer in autopsy cases. *J Gastroenterol.* 1995;30:615–8.
73. Kanthan R, Loewy J, Kanthan SC. Skeletal metastases in colorectal carcinomas: a Saskatchewan profile. *Dis Colon Rectum.* 1999;42:1592–7.
74. Roth ES, Fetzer DT, Barron BJ, Joseph UA, Gayed IW, Wan DQ. Does colon cancer ever metastasize to bone first? A temporal analysis of colorectal cancer progression. *BMC Cancer.* 2009;9:274.
75. Nozue M, Oshiro Y, Kurata M, Seino K, Koike N, Kawamoto T, et al. Treatment and prognosis in colorectal cancer patients with bone metastasis. *Oncol Rep.* 2002;9:109–12.
76. Cascino TL, Leavengood JM, Kemeny N, Posner JB. Brain metastases from colon cancer. *J Neuro-Oncol.* 1983;1:203–20.
77. Schouten LJ, Rutten J, Huvencuers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer.* 2002;94:2698–705.
78. Alden TD, Gianino JW, Saclarides TJ. Brain metastases from colorectal cancer. *Dis Colon Rectum.* 1996;39:541–5.
79. Damiens K, Ayoub JP, Lemieux B, Aubin F, Saliba W, Campeau MP, et al. Clinical features and course of brain metastases in colorectal cancer: an experience from a single institution. *Curr Oncol.* 2012;19:254–8.
80. Kye BH, Kim HJ, Kang WK, Cho HM, Hong YK, Oh ST. Brain metastases from colorectal cancer: the role of surgical resection in selected patients. *Color Dis.* 2012;14:e378–85.
81. Vatandoust S, Price TJ, Karapetis CS. Colorectal cancer: metastases to a single organ. *World J Gastroenterol.* 2015;21(41):11767–76.
82. Hammoud MA, McCutcheon IE, Elsouki R, Schoppa D, Patt YZ. Colorectal carcinoma and brain metastasis: distribution, treatment, and survival. *Ann Surg Oncol.* 1996;3:453–63.
83. Farnell GF, Buckner JC, Cascino TL, O'Connell MJ, Schomberg PJ, Suman V. Brain metastases from colorectal carcinoma. The long term survivors. *Cancer.* 1996;78:711–6.
84. Suzuki Y, Yamaguchi T, Matsumoto H, Nakano D, Honda G, Shinoura N, et al. Prognostic factors and treatment effects in patients with curatively resected brain metastasis from colorectal cancer. *Dis Colon Rectum.* 2014;57:56–3.
85. Aprile G, Zanon E, Tuniz F, Iaiza E, De Pauli F, Pella N, et al. Neurosurgical management and postoperative whole-brain radiotherapy for colorectal cancer patients with symptomatic brain metastases. *J Cancer Res Clin Oncol.* 2009;135:451–7.
86. Wronski M, Arbit E. Resection of brain metastases from colorectal carcinoma in 73 patients. *Cancer.* 1999;85:1677–85.