Colorectal Liver Metastases

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Introduction

The liver is the most common site of metastases from colorectal cancer (CRC) [1]. Approximately 15% of patients with CRC present with synchronous liver metastases, and 15% of patients will develop metachronous metastases to the liver [2]. Of the patients who develop liver metastases, up to 80% have unresectable disease at presentation [3, 4]. Modern systemic chemotherapy has increased the median survival of non-resected patients to 22 months [5], but patients who undergo complete resection can achieve 5-year survival up to 47–58% [3, 6–8], with 10-year survival up to 28% [3, 9, 10].

Prognostic Variables

Various clinical risk scores have been developed to help clinicians estimate survival outcomes for individual patients (see Table 7.1). One of the most commonly used is the Clinical Risk Score (Fong Criteria) which takes into account the size and number of CRLM, serum CEA, primary tumor nodal status, and disease-free interval [11, 12]. This was recently modified to include the CRLM RAS status [13], which

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Table 7.1 Risk scores predicting survival and recurrence in patients with CRLM

Study	Variables	Score	5-year OS (%)
Clinical risk score Fong et al., 1999 [11]	Node positive primary Size > 5 cm >1 lesion CEA level > 200 ng/mL Disease-free interval < 12 months	0 1 2 3 4 5	60 44 40 20 25 14
Modified clinical score Brudvik et al., 2019 [13]	Node positive primary Size > 5 cm RAS mutation	0 1 2 3	78 46 23 17
Basingstoke predictive index Rees et al., 2008 [22]	Node positive primary (2 points) Primary tumor differentiation (moderate: 2; poor: 4 points) CEA level, ng/mL (6–60:1; >60: 3 points) Size, cm (5–10: 2; >10: 7 points) Positive resection margin (11 points) Extrahepatic metastasis (4 points)	0 5 10 15 20 25 30	64 49 34 21 11 5 2
Nordlinger et al., 1996 [23]	Age > 60 years		2-year OS (%)
	Size > 5 cm Extension of primary into serosa Lymphatic spread Disease-free interval ≤ 2 years ≥4 lesions Resection margin < 1 cm	0–2 3–4 5–7	79 60 43

Abbreviations: *OS* overall survival, *CEA* carcinoembryonic antigen

has been consistently shown to predict earlier systemic recurrence and shorter overall survival [14–16]. Additional prognostic variables that have recently emerged include the following:

- Embryologic origin of primary tumor: Midgut-derived colon cancers (SMA distribution; right colon and hepatic flexure) are more often of mucinous histology and likely to harbor BRAF mutations compared to tumors arising from the hindgut (IMA distribution; left colon, sigmoid, rectum) [17]. Midgut origin is also associated with worse response to preoperative chemotherapy and shorter overall and recurrence-free survival; this association may persist even after controlling for RAS mutation status [6, 18].
- Response to chemotherapy: Poor pathologic response to preoperative chemotherapy has been consistently associated with shorter overall and recurrence-free survival, and is considered a relative contraindication to surgery [19, 20]. A similar trend is now emerging for patients who respond to chemotherapy, but exhibit disease progression shortly after chemotherapy cessation [21].

Table 7.2 Overview of work-up and follow-up of patients with CRLM

Work-up	Follow-up
Labs: Serum CEA LFTs **Imaging**: CT chest, abdomen, pelvis Consider MRI with liver-specific contrast agent (e.g., gadoxetic acid) **Colonoscopy** within the preceding 18 months	Every 3–6 months for the first 2 years then every 6 months thereafter: CT chest, abdomen, pelvis Serum CEA Colonoscopy at 1 year

Abbreviations: *CEA* carcino-embryonic antigen, *LFT* liver function test

Management of CRLM

Initial Work-Up

Initial liver imaging usually consists of CT (ideally 4-phase: precontrast, arterial, portal, and delayed venous; see Table 7.2). MRI (especially with hepatocyte-specific contrast, i.e., gadoxetic acid) may be beneficial for macrosteatotic livers, the detection of subcentimeter nodules, and in the post-chemotherapy setting [24]. PET does not result in change in management in >90% of cases and is not routinely recommended [25]. Ultrasound is routinely performed intra-operatively to confirm extent of disease and delineate transection margins [26]. Further, ultrasound may have enhanced diagnostic value with the addition of IV contrast [27, 28].

Surgical Considerations in Resectable CRLM

The goal of surgical resection in CRLM is to remove all the tumors with ≥1 mm margin, while preserving as much liver remnant as possible [8]. Compared to anatomic liver resection, parenchymal-sparing resection has similar long-term oncologic outcomes, while maximizing the functional liver remnant, and is now considered standard of care [29–32].

- Intra-operative ultrasound (IOUS) is crucial for planning of a liver resection. IOUS is sensitive and specific (98% and 95%, respectively) for the detection of CRLM ≥5 mm [33], and it is also used to precisely characterize the intrahepatic vascular anatomy and delineate the transection margins in parenchymal-sparing resections [26, 34].
- Laparoscopic resection in selected patients in centers with expertise in minimally invasive surgery [35, 36] is oncologically similar to open hepatectomy, with potential improvement in some perioperative outcomes [37–39].
- Every attempt should be made to minimize perioperative transfusions [40, 41] and postoperative complications [42, 43], as they have been associated with poor oncologic outcomes.

Table 7.3 Overiew of sequencing of surgical management for synchronous CRLM

Strategy	Management [48]
Simultaneous resection	1. Uncomplicated colon resection + liver resection 2. Complicated colon resection + limited liver resection
Staged resection	1. Complicated rectal resection, extensive colon resection 2. Major liver resection (>3 segments)
Primary first	Traditional approach **Advantage**: Avoids potential complications from primary disease (bleeding, perforation) **Disadvantage**: Postoperative complications can delay resection of hepatic disease
Liver resection first	Consider in Extensive hepatic disease with asymptomatic primary Patients with rectal primary who have received radiation (due to planned wait time of 8–12 weeks after chemoradiation before primary is resected) **Advantages**: Early control of CRLM with opportunity to eradicate all hepatic disease. Complications from primary resection will not delay/prevent resection of metastatic disease **Disadvantages**: Primary may progress to unresectability or complications from progression may develop. Patient may have unnecessary liver resection, delaying palliative systemic treatment

- Enhanced Recovery After Surgery (ERAS) protocols allow for earlier recovery and shorter length of hospital stay after liver resection [44–46]. The use of medial open transversus abdominis plane (MOTAP) catheters results in decreased opioid requirements and shorter length of stay [47].

Management of Synchronous CRLM

The presence of synchronous CRLM (diagnosed at or before diagnosis of primary) portends worse prognosis than metachronous, especially late metachronous (>12 months of diagnosis of primary) disease. The selection and sequence of therapies in the treatment of colorectal cancer with synchronous CRLM is a complicated process and should be discussed in a multidisciplinary cancer setting (see Table 7.3). General considerations include the following:

- Is the primary symptomatic?
- Are the CRLM resectable?
- Where is the bulk of the disease?

Assessment of Resectability of CRLM [24]

The assessment for resectability of CRLM is based on oncologic (tumor biology) and technical (tumor location/size/number) criteria (see Table 7.4).

Table 7.4 Assessment of resectability of CRLM

Oncologic criteria	Technical criteria
1. Prior to considering resection of CRLM, pretreatment radiological staging is required to assess for the presence and extent of intrahepatic and extrahepatic disease. 2. Patients harboring limited extrahepatic disease, particularly in the lungs, or with reasonable expectations for long-term control should be considered for a liver resection. 3. For patients with significant progression of metastatic disease during treatment with optimal systemic therapy, consider deferring surgical resection until disease control is achieved with other systemic or regional therapies.	1. Resectability is defined by the ability to achieve an R0 margin with acceptable morbidity/mortality. 2. The technical feasibility of liver resection is based on three criteria related to the liver remnant after resection: (a) The anticipated ability to preserve adequate future liver remnant (FLR) volume (20% in normal liver and 30% in pretreated liver with chemotherapy). (b) The anticipated ability to preserve adequate vascular inflow, outflow, and biliary drainage. (c) The demonstrated ability of the FLR to adequately function based on the appropriate regenerative response after portal vein embolization in patients with a marginal FLR volume and/or underlying liver disease.

Expanding Resectability of CRLM

One of the major factors that precludes resectability of CRLM is inadequate liver remnant, and therefore several strategies have been developed in an attempt to maximize the future liver remnant (FLR) and shrink tumor burden [49]. The FLR is calculated using volumetric CT or MRI and is a function of anticipated remnant liver volume and body surface area, a surrogate of total liver volume [50, 51]. Systemic chemotherapy is usually administered in conjunction with these strategies.

- Local ablation (microwave or radiofrequency) can be employed at the time of liver resection for lesions that are not amenable to resection. Overall the evidence on long-term oncologic outcomes is conflicting in retrospective series, but outcomes appear similar when applied to small lesions [52–54].
- Portal vein embolization (PVE) is a percutaneous modality to increase the FLR. In principle, embolization of the right portal vein induces hypertrophy of the left hemiliver and atrophy of the right hemiliver. This is typically performed in anticipation of an extended right hepatectomy [55].
- Two-stage hepatectomy is a strategy employed in patients with significant bilobar disease, and has gained wider acceptance when used in conjunction with PVE [56]. During the first stage, parenchymal-sparing resections of the left lobe are aimed to clear the left hemiliver of any disease. This is followed by right PVE (or right portal vein ligation), and the left hemiliver is then allowed to hypertrophy for 4–6 weeks. If on repeat volumetric CT the new FLR is deemed adequate, a right hepatectomy is then performed. This strategy allowed complete resection of the CRLM in 69–75% of patients in retrospective series, and 5-year survival reached 32–51% [57–60].

- Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) is an unproven technique performed in few centers [61]. During the first stage, parenchymal-sparing resections of the left lobe are aimed to clear the left hemiliver of any disease. At the same time, the right portal vein is ligated/embolized and the parenchyma between segments 4A/B and the left lateral segment is divided. This induces accelerated hypertrophy of the remnant liver and the patient receives volumetric CT at regular intervals postoperatively until the FLR reaches 30%; at that time the deportalized right lobe is removed [61]. While this technique may result in faster and perhaps greater left lobe hypertrophy, it has not been widely adopted due to preliminary results of high morbidity and mortality, as well as poor oncologic outcomes [61–63]. A recent RCT from Norway (LIGRO trial) showed promising short-term outcomes (better resection rates than two-stage hepatectomy/PVE with comparable morbidity/mortality), but long-term results are pending [64]. ALPPS can also be considered as a salvage option in patients who do not achieve adequate FLR after PVE [65].

Management of Unresectable CRLM

The primary treatment for patients with unresectable CRLM is systemic chemotherapy. Rarely, unresectable patients may be downsized to resectable/borderline resectable disease with chemotherapy alone (see below, "Role of systemic chemotherapy") [66]. In selected patients with liver-only metastatic disease that is unresectable due to the location or extent of the lesions, the following liver-directed strategies can be employed:

- Hepatic artery infusion pump (HAIP) therapy is used in specialized centers [67]. A catheter is surgically placed in the proper hepatic artery (via the gastroduodenal artery), connected to a subcutaneous reservoir, and FUDR is administered through the pump, typically in combination with systemic chemotherapy. This combination can convert unresectable to resectable/ablatable disease in 25–50% of patients [68, 69].
- Liver transplantation is currently being revisited as an option in patients with unresectable liver-only metastatic disease [70]. Small series reported 5-year OS 50–56% with acceptable morbidity [71–73], and there are currently 4 open trials investigating this topic.

Role of Systemic Chemotherapy

In the setting of resectable CRLM, the role of systemic chemotherapy is controversial (see Table 7.5). The EORTC Intergroup Trial 40,983 reported marginally better PFS, but no difference in OS with perioperative FOLFOX [74, 75]. Pseudoneoadjuvant chemotherapy can also be used as a test for the biology of the disease

Table 7.5 RCTs examining perioperative chemotherapy for CRLM

Study	Methods	Results
EORTC intergroup trial 40,983 Nordlinger et al. [74, 75]	RCT – Perioperative FOLFOX (6 + 6 cycles) vs surgery alone ($N = 364$)	Perioperative chemotherapy increased PFS (3-year PFS: 38.2% vs 30.3%); no difference in OS (5-year OS: 51.2% vs 47.8%) [intention-to-treat population]. The chemotherapy arm had more postoperative complications (25% vs 16%)
EPOC trial, Primrose et al. [79, 80]	RCT – Perioperative chemotherapy (FOLFOX, CAPOX, or FOLFIRI) with vs without cetuximab in KRAS wild-type patients ($N = 336$)	Terminated early. Addition of cetuximab to perioperative chemotherapy decreased PFS (median 14.1 vs 20.5 months); no difference in OS (39.1 months vs not reached). On longer follow-up [80], the cetuximab group had shorter OS (median 55.4 vs 81 months) but similar PFS (15.5 vs 23.9 months)
EXPERT trial, Mise et al. [81]	RCT – Perioperative FOLFOX + cetuximab (6 + 6 cycles) vs adjuvant FOLFOX (12 cycles) in KRAS wild-type patients	Terminated early due to slow accrual ($N = 77$). No difference in PFS (3-year PFS 30% vs 35%) or OS (3-year OS 74% vs 86%)

Abbreviations: *RCT* randomized controlled trial, *PFS* progression-free survival, *OS* overall survival

and possibly prevent an operation in patients with overly aggressive disease. On the other hand, pseudo-neoadjuvant chemotherapy could render treated metastases invisible to imaging ("ghost" metastases) [76], and the chemotherapy-induced hepatotoxicity (especially if >6 cycles or pre-existing liver disease) may increase perioperative morbidity and mortality [77]. In this context, pseudo-neoadjuvant chemotherapy should be mostly considered in patients at higher risk of progression to assess biology of the disease.

The addition of epidermal growth factor receptor (EGFR) inhibitors (cetuximab, panitumumab) has generally improved oncologic outcomes in RAS and BRAF wild-type patients with metastatic colorectal cancer [78]. In the setting of resectable CRLM, the new EPOC trial initially showed shorter PFS (no difference in OS) when cetuximab was added to perioperative chemotherapy in mostly RAS wild-type patients; on longer follow-up the cetuximab group had shorter OS [79, 80]. Another similar trial from Japan (EXPERT trial) showed no difference in OS or PFS, but was terminated early due to slow accrual [81].

The use of chemotherapy in the adjuvant setting is also controversial. A pooled analysis of 2 small RCTs explored the benefit of systemic FU-based chemotherapy and suggested a trend towards longer progression-free (median 27.9 vs 18.8 months,

Table 7.6 RCTs comparing pseudo-neoadjuvant chemotherapy regimens with intent to convert unresectable/not optimally resectable CRLM to resectable

Study	Methods	Results
OLIVIA trial Gruenberger et al. [83]	RCT phase II – Pseudo-neoadjuvant bevacizumab + FOLFOX vs FOLFOXIRI ($N = 80$)	R0 resection rate of 23% vs 49%, median PFS 11.5 vs 18.6 months
CELIM trial Folprecht et al. [84, 85]	RCT phase II – Pseudo-neoadjuvant cetuximab + FOLFOX vs FOLFIRI ($N = 111$)	R0 resection rate of 38% vs 30%, KRAS WT patients had higher response rate. Median PFS 11.2 vs 10.5 months, median OS 35.8 vs 29 months (no difference)
Ye et al. [86]	RCT – Pseudo-neoadjuvant chemotherapy (FOLFIRI/FOLFOX) with vs without cetuximab in KRAS WT patients ($N = 138$)	Addition of cetuximab increased objective response rates (57.1% vs 29.4%) and R0 resection rate (25.7% vs 7.4%)

Resection rates should be interpreted with caution as the criteria of upfront unresectability were variable and no longer apply

Abbreviations: *RCT* randomized controlled trial, *WT* wild type, *OS* overall survival, *PFS* progression-free survival

$p = 0.058$) and overall survival (median 62.2 vs 47.3 months, $p = 0.095$) in the chemotherapy arm [82]. Although the difference was not statistically significant, these trials used suboptimal regimens by modern standards. Pending future randomized studies, adjuvant chemotherapy is usually considered in patients with high risk for recurrence despite inconclusive evidence.

In the setting of unresectable CRLM, systemic chemotherapy is the primary treatment. Several studies have investigated different regimens with intent to convert unresectable CRLM to resectable, but the results have been inconsistent, and the interpretation of conversion rates should take into consideration the variability in the definition of "unresectable" and "not optimally resectable" CRLM among the studies (see Table 7.6) [83–90]. In this setting, the addition of EGFR (for RAS/BRAF wild-type patients) or vascular endothelial growth factor (VEGF) inhibitors (bevacizumab) to standard doublet chemotherapy may improve objective response and R0 resection rates.

Special Notes

- Hold chemotherapy 3–4 weeks prior to liver resection.
- Hold bevacizumab for 6 weeks prior to liver resection to reduce the risk of bleeding [91].

Table 7.7 Local therapy modalities for CRLM

Local therapy.	Mechanism	Advantage	Disadvantage
Radiofrequency ablation (RFA) [54]	Direct current transmission into tissue	Can be used for selected patients with otherwise unresectable disease (due to patient or disease factors) or to clear liver to extend resectability	Unpredictable results as functions on impedance which changes during ablation Incomplete ablation with lesions >3 cm. Cannot be used near large vessels or portal structures due to heat sink and potential damage to structures
Microwave ablation (MWA) [94]	Microwave energy agitates water molecules to create heat	As above. More uniform/predictable ablation zone and shorter time than RFA	Limit on size of treatable lesions
Stereotactic ablative radiotherapy (SABR/SBRT) [95–97]	Delivery of high doses of radiation to a focused target. Role in patients unfit for surgery with oligometastatic CRLM	Limited evidence – Retrospective series of patients with oligometastatic CRLM reported median OS 31.5 months with acceptable morbidity. No randomized data available	Not widely available
Irreversible electroporation (IRE) [98]	Electric pulses cause permeabilization of membranes of tumor and parenchymal cells. Role under investigation	Limited evidence – Retrospective series report IRE is safe in perivascular liver tumors. No efficacy data available	Not used in patients with pacemakers or arrhythmias. Requires general anesthesia

Local Therapies

Local therapies can be used in conjunction with liver resection for borderline resectable CRLM (discussed above), or in the setting of unresectable CRLM, usually in combination with systemic chemotherapy (see Table 7.7) [92]. A recent phase II trial (EORTC 40004 CLOCC) randomized 119 patients with up to 9 unresectable CRLM to systemic chemotherapy vs chemotherapy and aggressive local therapies (radiofrequency ablation ± wedge liver resections), and reported a survival benefit in the combined therapy arm (5- and 8-year OS 43.1% and 35.9% vs 30.3% and 8.9%, respectively) [93].

Regional Therapies

Regional therapies are geared towards treating the entire liver. The indications include unresectable CRLM, technically resectable CRLM in patients unfit for hepatectomy, and second-line treatment after progression of the liver disease through systemic chemotherapy. There are varying degrees of evidence supporting the use of different regional therapies (see Table 7.8).

Table 7.8 Regional therapy modalities for CRLM

Regional therapy	Technique & setting	Evidence	Disadvantages
Hepatic artery infusion pump (HAIP) therapy [67]	Surgically placed catheter into proper hepatic artery with subcutaneous reservoir. Role in unresectable CRLM and in the adjuvant setting	HAIP with systemic chemotherapy can convert 25–50% of unresectable CRLM to resectable/ablatable [68, 69]. HAIP in the adjuvant setting is controversial; small trials reported a survival benefit with the addition of HAIP to systemic chemotherapy (older regimens) [99, 100], especially in patients in high risk for recurrence [101], but whether HAIP offers any benefit in conjunction with modern chemotherapy has not been thoroughly evaluated [102]	Requires multidisciplinary team with expertise in hepatobiliary surgery, medical oncology, interventional radiology, nuclear medicine, and nursing. Not widely available
DEBIRI (drug-eluting bead, irinotecan) TACE (transarterial chemotherapy) [103–105]	Transarterial embolization with drug-eluting beads with irinotecan. Role in unresectable CRLM	In a phase III RCT, patients with unresectable CRLM treated with DEBIRI vs FOLFIRI had longer OS (median 22 vs 15 months), with a sustained improvement in quality of life [105]	Not widely available

Table 7.8 (continued)

Regional therapy	Technique & setting	Evidence	Disadvantages
Yttrium-90 radioembolization [106–108] (SIRT, selective internal radiotherapy)	High-dose radiation delivered via the hepatic artery with microspheres. Role in unresectable CRLM	A phase III RCT reported no benefit in OS with the addition of Y-90 to FU in patients with unresectable CRLM (median OS 10 vs 7.3 months) [107]. A combined analysis of 3 multicenter phase III RCTs reported no benefit in OS with the addition of Y-90 to FOLFOX in patients with unresectable CRLM (median OS 22.6 vs 23.3 months) [108]	Short-term restriction in patient exposure to friends/family due to radiation. Not widely available

Abbreviations: *RCT* randomized controlled trial, *OS* overall survival, *FU* fluorouracil

Extrahepatic Metastases (EHM)

The presence of EHM used to be a contraindication for liver resection for concurrent CRLM, but this is no longer the case. Several series and a phase II trial have demonstrated long-term survival in selected patients with EHM who undergo complete resection of the CRLM and the EHM (see Table 7.9) [109–111]. All cases of CRLM with limited EHM should be reviewed at a multidisciplinary cancer conference and preoperative/perioperative systemic chemotherapy should be considered. Surgical management and outcomes vary depending on the site of EHM:

- Lungs: Subcentimeter pulmonary nodules (SPN) do not alter long-term prognosis, and therefore should not preclude liver resection. Lung metastases have an indolent course; for larger pulmonary nodules, staged resection of tumors in the liver and lung if they are resectable with R0 intent (liver resection first, followed by lung resection) [112]. Selected patients may achieve long-term survival (5-year OS 32–74%) [7, 111, 113, 114].
- Peritoneum: Peritoneal metastases have variable biologic behavior. Potential liver resection should be assessed in conjunction with a peritoneal malignancy program. Selected patients may achieve long-term survival (5-year OS 26–42%) [111, 114].
- Ovaries: Ovarian metastases are considered equivalent to limited peritoneal disease. Resection should be considered if complete resection can be achieved. Selected patients may achieve long-term survival (5-year OS 34%) [111].

Table 7.9 Surgical management of extrahepatic metastases

Study	Methods	Results
Toronto phase II trial, Wei et al. [109]	Phase II trial ($N = 26$) CRLM and EHM resection (lung, portal LN, peritoneum, adrenals, other)	Median OS and RFS 38 and 5 months, respectively. Major morbidity 19%, mortality 4%, QoL returned to baseline 1 year post-treatment
MSKCC study, Leung et al. [111]	Retrospective review ($N = 219$) CRLM and synchronous EHM resection (lung, portal/retroperitoneal LN, peritoneum, ovaries, other)	Median OS and RFS 34.4 and 8 months, respectively. 3 poor prognostic factors: CRLM >3 cm, >5 CRLM, and unfavorable EHM site; 5-year OS ranged from 43% (0 factors) to 0% (3 factors)
French study, Adam et al. [7]	Retrospective review ($N = 186$) Liver resection and EHM resection (lung, LN, peritoneum, other)	5 poor prognostic factors: EHM other than lung, EHM concomitant to CRLM recurrence, CEA ≥ 10 ng/mL, ≥ 6 CRLM, and right colon; 5-year OS ranged from 64% (0 factors) to 0% (>3 factors). Overall 5-year OS 28% (33% for isolated lung mets)
International study, Pulitano et al. [114]	Retrospective review ($N = 171$) CRLM and EHM resection (lung, peritoneum, portal LN, aortocaval LN, other)	5-year OS 26%; OS worse with R1 resection, multiple sites of EHM and location (aortocaval LN worst)

Abbreviations: *EHM* extrahepatic metastases, *LN* lymph node, *OS* overall survival, *RFS* recurrence-free survival, *QoL* quality of life

- Portal and retroperitoneal lymph nodes: Metastasis to portal and retroperitoneal lymph nodes is believed to represent a re-metastasis from the CRLM and thus an indicator of more aggressive biological behavior. Long-term outcomes are generally poor (5-year OS 14–21%) [111, 115–117]. It is often considered a relative contraindication to liver resection, although resection can be considered in patients with limited lymph node involvement (especially for portal rather than para-aortic nodes) and good response to systemic chemotherapy [112, 115–118].

Toronto Pearls

- If there is any doubt about the volume of future liver remnant, obtain formal volumetrics and consider preoperative portal vein embolization.
- When performing liver resections, use the principle of parenchyma-sparing surgery as a guide.
- Resection of all visible disease is the goal: use systemic therapy sparingly and with this ultimate goal always in mind.

- Subcentimeter pulmonary nodules are very common and do not affect prognosis; ignore them.
- Blood loss and transfusion are associated with adverse perioperative outcomes and long-term disease recurrence: incorporate preoperative, operative, and postoperative strategies to reduce bleeding and transfusion.
- The role of pseudo-neoadjuvant therapy is to assess biology of disease; select agents to minimize hepatotoxicity (FOLFOX) and limit the duration to 4 cycles.

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