Management of Colorectal Cancer with Hepatic Metastasis

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Colorectal cancer has become one of the leading causes of cancer-related death worldwide. In Thailand, colorectal cancer (CRC) was the most commonly reported gastrointestinal malignancy by the National Cancer Center in 2010. It is the second most commonly diagnosed malignancy in men after lung cancer and in women after breast and cervical cancer.[1] Median survival of stage IV CRC without any kind of treatment has been reported to be around 5 to 6 months.[2, 3] The liver appears to be the most common organ of distant metastatic spread from colorectal cancer. Approximately 25% of patients present with synchronous disease and an additional 30% to 40% will develop hepatic metastases during the course of their disease.[4] In addition, liver metastases are found in over 50% of patients who die from CRC and hepatic involvement is the most implicated reason for their death.[5] This review will attempt to give an overview of the treatment alternatives in CRC patients with liver metastasis, with a focus on the updated rationales as well as controversial and current trends in the multidisciplinary approach.

Preoperative hepatic assessment using appropriate hepatic imaging is a crucial step to achieve the most beneficial treatment outcomes. Identifying the best imaging modality to determine hepatic metastasis has been the subject of many studies. Ward, et al.[6] performed the prospective evaluation of hepatic imaging studies in the detection of colorectal metastasis including an intravenously administered lipid contrast agent that enhances liver parenchyma on computed tomography (CT) scans (EOE-CT), arterial portography (AP-CT), delayed CT scanning (DS-CT), T1- and T2-weighted magnetic resonance imaging (MRI) (T1-MRI, T2-MRI). The authors demonstrated that the T1-MRI examination proved to be the best hepatic imaging study in the detection of colorectal metastases. More recent meta-analysis from the Netherlands group[7] performed a systematic review to obtain the sensitivity estimates of CT, MRI and fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) for detection of colorectal liver metastases. Sixty one relevant articles were included. They reported that FDG PET was the most accurate modality by showing the most sensitivity estimates on both per-patient basis and per-lesion basis. Moreover, the study performed by Engledow et al.[8] which enrolled 64 consecutive patients with CRC liver metastases demonstrated that the addition of PET/CT scans led to management changes in over one-third of the patients. Using PET/CT scans, they were able to find the disease upstaging in 20 patients (31%) and downstaging in two patients (3%).

Whether or not to perform preoperative biopsy of detected suspected liver lesion is still the subject of debate. The survival after liver resection was substantially diminished compared with well matched patients in whom no biopsy or fine needle aspira-

tion cytogy (FNAC) had been attempted.[9] Jones et al.[10] analyzed 598 consecutive patients undergoing radical resection of colorectal liver metastases between 1986 and 2003. The authors examined specifically the 90 patients in whom diagnostic biopsy had been performed before the referral. Tumor seeding at the site of biopsy was histologically confirmed in 17 patients (19%). The authors also found that biopsy of liver metastases conferred significant poorer long-term survival on patients after liver resection ($p = 0.008$). They concluded that preoperative liver biopsy was not justified in patients with potentially resectable disease. This finding has been confirmed by other studies.[11, 12] Consultation with a specialist hepatobiliary surgical team is recommended before a *"tissue diagnosis"* is attempted in such patients.[9]

Among the current treatment alternatives for CRC with liver metastasis, hepatic resection has been established as the standard therapy offering a chance for cure for well-selected resectable metastases, over the last two decades[13] Many studies have shown that resection offers the only chance of long-term survival and cure in highly-selected patients.[14-17] Robertson et al.[18] reported long term outcomes after hepatic resection in an national experience study that analyzed Medicare enrollees (age > 63 years old) who were admitted to hospital in the United States of America between January, 2002 and December, 2004. A total of 306,061 patients were diagnosed with colorectal cancer, 3,957 patients with liver metastasis were identified and underwent hepatic resection. The 5-year survival rate was 25.5%. The authors concluded that subgroups at high risk for worse outcomes included the extreme elderly and those undergoing synchronous colon and hepatic resection. Other reports also demonstrated similar findings, whereby poorer long term outcomes were associated with synchronous liver metastases as compared to metachronous liver metastases.[19, 20] However, a better long term outcomes were demonstrated in an earlier report by a group of surgeons from Johns Hopkins Hospital in 2002.[17] Over a 16-year period, 226 patients undergoing curable liver resection for CRC with liver metastasis were reviewed. The median survival was 46 months, and a 5-year survival rate was 40%. They found significantly better overall and disease-free survival in the recent time period when compared with the earlier period; 58% (133 patients, 1993-1999) vs. 31% (93 patients, 1984-1992). The authors also pointed that the independent factors associated with improved survival included number of metastatic tumor < 3, negative resection margin, and carcinoembryonic antigen (CEA) < 100 ng/mL. Comparisons were made between time periods, only resection type (anatomical vs. non-anatomical), and the use of intra-operative ultrasound differed between the early and recent time periods. In addition, more effective peri-operative medical antitumor therapy (e.g. chemotherapy) and better patient selection were also responsible for significant improvement in long term outcomes. Most studies suggest poor prognostic

indicators including extrahepatic disease, 4 or more lesions, bilateral lesions, and a surgical margin less than 1 cm; therefore, these factors were long considered relative contraindications to hepatectomy. In contrast, more recent research suggests that a wider range of patients may benefit from liver resection.

Several published literature has described factors identified as predictors for long term survival after hepatic resection. Wagner et al.[21] reported in 1984 that differences in survival depend on the extent of liver metastases-patients with solitary metastasis have a median survival of 21 months, those with unilobar oligometastases have a median survival of 15 months, and those with widespread bilobar disease have a median survival of less than 12 months. Nordlinger et al.[16] proposed a simple prognostic scoring system to select patients who were likely to benefit from surgery. Data from 1,568 patients with resected liver metastasis from CRC were analyzed with multivariate analysis. The authors found independent predictors of overall survival after hepatic resection included age, primary tumor stage, disease free interval of less than 12 months, preoperative CEA levels, number and size of metastatic tumors, and presence of extrahepatic disease. Furthermore, the surgical resection margin is also considered to be one of the important prognostic factors. A consensus stated that surgical margin positivity results in a worse outcome as compared to the patients with negative resection margins, however the extent of negative margins remains controversial. A recent meta-analysis performed using 18 studies by Dhir et al.[22] demonstrated the result of a total of 4,821 CRC with liver metastasis patients undergoing hepatic resection with negative resection margin to determine whether negative resection margins of 1 cm or more confer any survival advantage over negative resection margin of less than 1 cm. The authors concluded that among patients undergoing hepatic resection for colorectal cancer with liver metastasis, a negative margin of 1 cm or more conferred a survival advantage when compared with sub centimeter negative margins (46% vs. 38%; OR = 0.773; 95% CI, 0.638-0.938; $p = 0.009$). Other authors have however concluded that the width of negative margin has no influence on the outcome.[23-26] Gomez et al.[27] recently failed to identify a relevant prognostic scoring system to predict the patient outcomes following hepatic resection. They found that the published studies had been inconsistent in identifying these variables as independent predictors of survival on multi-variable analyses in different datasets, which suggested that certain prognostic variables may be more significant in certain patient groups. The explanation for this observation may involve suboptimal number of patients, limitation of the data available for analysis, and an insufficient follow up.

Despite an improvement in preoperative imaging, better surgical resection together with modern chemo-

therapy, up to two-thirds of patient's still experience recurrence of the disease which is most commonly found in the liver and lungs after hepatectomy.[28-36] Adequate surveillance protocols after hepatic resection are essential which should (ideally) be designed for each individual patient depending on the risks of recurrence. Many researchers had been investigating prognostic scoring systems to predict recurrence.[14, 16, 22, 27, 37] However there is currently no standard prognostic scoring system that has been generally accepted. Apart from the potential risk factors to predict recurrences, cost benefit analysis must also be carefully considered to determine the frequency of radiological imaging. The fact is that the first two years following hepatic resection have been recognized as when the disease is most likely to re-cur.[15] Bhattacharjya et al.[38] proposed an intensive follow up after hepatic resection using serial tumor marker estimations and contrast-enhanced CT of the chest and abdomen. This prospective study of 76 consecutive patients undergoing potentially curative resections of colorectal liver metastases was performed in a single unit where all the patients were followed up with a protocol of 3 monthly CEA and carbohydrate antigen 19-9 estimations and contrast-enhanced spiral CT of the chest, abdomen and pelvis for the first 2 years following surgery and 6 monthly thereafter. The median period of follow-up was 24 months (range 18–60). Nineteen patients developed isolated liver recurrence, of which 8 developed within 6 months of liver resection and none of which were resectable. Five of the 11 recurrences (45%) after 6 months were resectable. The authors found that the use of computerized tomography (CT) scan or tumor markers alone would have failed to demonstrate early recurrence. A combination of tumor markers and CT scan detected significantly more ($p < 0.05$) recurrence than either modality alone. They concluded that the tumor markers and CT scan should be used in combination in the follow-up of patients with resected colorectal liver metastases.

Patients with disease recurrence following resection of liver metastasis were considered to have poor prognosis. With development in hepatobiliary surgery, nowadays repeated liver resection can be offered with curative intent in properly selected patients with recurrent hepatic metastatic disease. Several reports have demon-strated a 5-year survival following repeat hepatic resection of up to 45%[39,40]; however the efficacy in 5-year survival typically decreases with each resection.[41] It is also recommended to preserve of at least two contiguous liver segments with adequate vascular inflow/outflow, biliary drainage, and an adequate hepatic remnant as defined as greater than 20-25% in a healthy liver.[42] The benefit of adjuvant chemotherapy following complete surgical resection among CRC with liver metastasis remains inconclusive and requires further evaluation. Nevertheless some published data supports the superiority of this adjuvant chemotherapy.[43, 44]

Kemeny et al.[45] conducted an intergroup study of 109 CRC patients with one to three potentially resectable liver metastases. Fifty and six patients were randomized to receive surgery alone (control group). Fifty and three patients underwent surgical resection followed by adjuvant chemotherapy which was postoperative hepatic arterial floxuridine combined with intravenous continuous-infusion fluorouracil. They found that 4-year recurrence-free rate was 25% for the control group and 46% for the chemotherapy group ($p = 0.04$). The 4-year liver recurrence-free rate was 43% in the control group and 67% in the chemotherapy group ($p = 0.03$). The median survival of the 75 assessable patients was 49 months for the control arm and 63.7 months for the chemotherapy arm ($p = 0.60$). The authors stated that adjuvant intra-arterial and intravenous chemotherapy was beneficial in prolonging time to recurrence and preventing hepatic recurrence after hepatic resection of CRC. Furthermore, the presence of extrahepatic disease at the time of surgery is independently associated with a poorer prognosis.[41] The resection of concurrent pulmonary and hepatic metastases can also be undertaken in highly selected patients and still yield 5-year survival rates at or above 50%.[46] However, the outcomes have been poor for lymph node metastatic involvement; hence surgical resection in this group of patients is contraindicated. The survival benefit from surgical resection can be expected in younger patients whose lymph node metastasis response to or stabilized by neoadjuvant chemotherapy.[47]

To date, there is no strong evidence to support the use of neoadjuvant chemotherapy in resectable liver lesion. Current reports demonstrated that even with the best chemotherapy regimen, 20% of the patients had disease progressed while 50% of the patients experienced partial response.[48] Neoadjuvant chemotherapy on the other hand is recommended for those patients who have unresectable liver lesions. This will enhance the chance of curative resection. One study[49] analyzed 701 consecutive patients with unresectable liver metastases who were treated with neoadjuvant chemotherapy and found that 13.5% of these patients were resectable on the reevaluation. In addition, the authors also demonstrated that 5-year survival rates were 60% for large tumors, 49% for ill-located lesions, 34% for multinodular disease and 18% for liver metastases with extrahepatic disease. A more recent study from a North Central Cancer Treatment Group[50] described that after a median of 6 months of chemotherapy, 60% of the patients had tumor reduction by serial imaging, and 40% underwent curative liver resection. This concurs with the findings of other studies.[51] Nordlinger et al.[52] performed an interesting intercon-tinental (Europe, Australia, and Hong Kong) study recruiting 364 patients (78 hospitals) with histologically proven colorectal cancer and up to four liver metastases. Patients were randomly assigned to either six cycles of FOLFOX4 before and six cycles after surgery (182 patients) or to surgery alone (182 patients). In the

perioperative chemotherapy group, 151 (83%) patients were resected after a median of six (range 1-6) preoperative cycles and 115 (63%) patients received a median six (1-8) postoperative cycles. 152 (84%) patients were resected in the surgery group. The absolute increase in rate of progression-free survival at 3 years was 7.3% (from 28.1% to 35.4%, $p = 0.058$) in randomized patients; 8.1% (from 28.1% to 36.2%, $p = 0.041$) in eligible patients; and 9.2% (from 33.2% to 42.4%, $p = 0.025$) in patients undergoing resection. The authors concluded that perioperative chemotherapy with FOLFOX4 was compatible with major liver surgery and reduced the risk of events of progression-free survival in eligible and resected patients. The efficacy of a regimen can be enhanced to induce sufficient tumor regression to permit R0 resection by combining targeted agents.[53-56] The most recent study published in 2012 by Bokemeyer et al.[53] analysing the pooled radomized clinical trials (CRYSTAL and OPUS) of 845 patients with KRAS wild-type tumors. The authors demonstrated a significant improvement in overall survival ($p = 0.0062$), progression-free survival ($p < 0.001$) and overall-recurrent rates ($p < 0.0001$) in cetuximab combined with chemotherapy group. They also confirmed that the consistency of the benefit obtained across all efficacy end-points from adding cetuximab to first-line chemotherapy in patients with KRAS wild-type metastatic CRC. Folprecht et al.[57] described that chemotherapy with cetuximab yielded high response rates compared with historical controls, and led to significantly increased resectability in multi-center (17 centers in Germany and Austria) randomized trial of 111 patients. Patients with non-resectable liver metastases (technically non-resectable or > 5 metastases) were randomly assigned to receive cetuximab with either FOLFOX6 (oxaliplatin, fluorouracil, and folinic acid) or FOLFIRI (irinotecan, fluorouracil, and folinic acid). The study showed the increase of resectability rates from 32% at baseline to 60% after chemotherapy ($p < 0.0001$). Perioperative chemotherapy can be administered in selected patients in order to improve long term treatment outcomes.[52] Furthermore, the addition of targeted agents had also shown significantly increase in resectability of the CRC with liver metastases.[53, 57]

While surgical resection is considered the gold standard for the treatment of CRC with liver metastases, other alternatives which also have an impact on survival such as radiofrequency ablation[58], cryotherapy and other ablative therapy[59] may be indicated for those patients who are not surgical candidates for various reasons, such as the lesion being anatomically ill-located, the functional hepatic reserve after a resection being insufficient, the patient's co-morbidities inhibiting a major operation, or presence of extrahepatic metastases, all of which can further decrease the likelihood of cure. Radiofrequency ablation (RFA) produces localized tumor destruction by generating a high-frequency alternating current which converses to heat that subsequently evaporates intracellular

water and leads to irreversible cellular changes, including intracellular protein denaturation, melting of membrane lipid bilayers, and coagulative necrosis of individual tumor cells. It has been applied in metastatic CRC to reduce the survival gap between resectable and unresectable disease. The first randomized study on the efficacy of RFA reported by a group from the Netherlands[60] randomly assigned 119 patients with non-resectable CRC liver metastases between systemic treatment (n = 59) or systemic treatment plus RFA (±resection) (n = 60). 30-month overall servial (OS) rate was 61.7% for combined treatment, and 57.6% for systemic treatment. Progression-free survival rate at 3 years for combined treatment was 27.6% compared with 10.6% for systemic treatment only ($p = 0.025$). The authors suggested that RFA plus systemic treatment resulted in significant longer progression-free survival; however the effect of RFA on overall survival remains uncertain. Although RFA has been established as a safe, well tolerated, easily repeated and less invasive procedure[61, 62], Wu et al.[58] again stated in the meta-analysis of 647 patients from 17 studies that hepatic resection was related to superior long term outcomes when compared to RFA in the treatment of CRC liver metastases. On the other hand, cryotherapy uses extremely low temperatures to destroy malignant tissue. A retrospective study conducted by Rivoire et al.[63] reviewed 131 patients with unresectable CRC liver metastases. After 3-6 months of systemic chemotherapy, 57 patients were considered candidates for curative liver resection. Surgery alone was performed in 33 patients (25%) or cryotherapy associated with resection in 24 patients (18%). After a median follow-up of 48 months were similar in both groups: 37% in the resection group and 36% in the cryotherapy plus resection group. They noted that the combination of neoadjuvant chemotherapy, cryotherapy, and liver resection constitutes promising treatment outcomes for patients with advanced CRC with liver involvement.

A new tissue ablation technique, irreversible electroporation (IRE) which was first reported in the early seventies[64-67], is associated with an increase in cell membrane permeability after microseconds to milliseconds of the electrical fields (high-voltage direct current, up to 3 kV) are applied. The increase in membrane permeability is associated with the formation of nanoscale defects (pores) in the cell membrane. These changes in membrane permeability have led to the naming of the process *"electroporation"*. The defects (pores) do not reseal, and are known to cause *"irreversible electroporation"*. As a result, the eventual cell death occurs due to loss of the cell's homeostatic mechanisms.[68] Unlike other ablative techniques, IRE can ablate the tissue without thermal effects[69] and the extent of tissue ablation can be predicted with mathematical analysis[70], therefore IRE can be applied in those lesions adjacent to blood vessels in the liver; it also demonstrates a decrease in size of treatment zone as early as 1 month following treatment. Several ongoing studies using this novel technology will

soon provide more information on its safety and efficacy for future applications.

Summary

Even though surgical resection has become the optimal, indeed only treatment modality associated with long term survival in the CRC patient with liver metastasis,

a multidisciplinary approach is essential to increase potentials for cure. The aims of liver resection are to remove all macroscopic disease, to achieve clear resection margins and to leave sufficient functioning liver. Multiple randomized control trials are ongoing to evaluate both conventional and newer approaches to improve the treatment outcomes.

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