

Commentary

Role of chemotherapy for treatment of colorectal liver metastasis in modern era of liver surgery. Current data and clinical practice in 2017

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Surgical resection is the only potentially curative treatment for colorectal liver metastasis (CLM) with reported 5-year survival rates of 30-40% [1]. At least 50% of all patients with colorectal cancer develop liver metastasis during their lifetime. Despite negative margins during liver resection, recurrent disease in the liver remains common. In the 1970's when liver resections were historically performed without use of chemotherapy, the five-year overall survival after complete tumor resection was less than 20% [2]. Perioperative chemotherapy, mainly in the adjuvant setting, has then been employed as a method to decrease tumor recurrence and increase overall survival post liver resection. Because promising outcomes were seen with the use of chemotherapy in patients with unresectable or borderline resectable liver metastases, concept of neoadjuvant chemotherapy for resectable colorectal liver metastasis has gained popularity among hepatobiliary surgeons and medical oncologists. However, the role of neoadjuvant chemotherapy for resectable colorectal liver metastasis is still controversial. Only limited data is available on the literature regarding this issue. We aimed to summarize current clinical evidence of utilizing neoadjuvant chemotherapy for patients with resectable CLM.

In the original Intergroup trial report published by Nordlinger *et al.* which compared outcomes of perioperative chemotherapy and liver resection versus liver resection alone, only 63% of patients in chemotherapy group actually received the adjuvant chemotherapy. Of those who received adjuvant chemotherapy, only 70% completed their treatment [3]. A significant number of patients did not receive or complete their chemotherapy due to postoperative complications, intolerable toxic effects of chemotherapy, disease progression while on chemotherapy, and patient refusal. However, potential advantages of administering neoadjuvant chemotherapy in resectable cases are early treatment of micrometastatic disease, reduction of tumor volume/size (which often translates to optimum liver parenchymal preservation), and selection (subsequent exclusion from liver resection) of patients with rapidly progressing tumor which indicates aggressive tumor biology.

A systematic review of all currently available evidence since year 2000 was performed. All English literatures, which described comparative outcomes of liver resection for colorectal metastasis with and without neoadjuvant chemotherapy were reviewed. Studies containing patients with unresectable metastatic disease or borderline resectable disease were excluded since the use of chemotherapy in these patients had been uniformly accepted to be beneficial. Only one randomized clinical trial study has been published regarding the use of perioperative chemotherapy for resectable colorectal liver metastasis. However, this study by Nordlinger *et al* was not specifically

designed to differentiate clinical outcomes between neoadjuvant and adjuvant chemotherapy in combination with surgical resections³. Patients who received neoadjuvant chemotherapy prior to their liver resections were found to have an increased 3-year progression free survival. Overall survival, however, was not affected by administration of neoadjuvant chemotherapy. A follow-up study five years later by the same group failed to show prolongation of progression-free and overall survival in patients who received neoadjuvant chemotherapy prior to liver resections. Other studies are retrospective in nature with highly heterogeneous reported data points. A careful analysis must be employed during interpretation, since many of the published reports have obvious selection biases. Patients with more than two hepatic tumors and/or unfavorable tumor locations, larger/borderline resectable, bilateral lesions, short disease free interval, and higher clinical risk score tend to be started on neoadjuvant chemotherapy to evaluate their in vivo response, prior to liver resection. Those with single lesion located peripherally were scheduled for immediate liver resections followed by postoperative chemotherapy. Previously published studies that reported overall 3- and 5-year survival outcomes in neoadjuvant group and non-neoadjuvant group are summarized in Table 1 [3-10]. Only a single study which was published by Tanaka *et al* in 2003 demonstrated significant 5-year overall survival benefit in patients who received neoadjuvant chemotherapy for resectable colorectal liver metastasis (38.9% versus 20.7%, $p=0.039$) [4].

Despite potential advantages of neoadjuvant chemotherapy for resectable liver lesions, this method of administration also comes with potential disadvantages. Liver damages in the form of hepatic steatosis/steatohepatitis secondary to irinotecan and sinusoidal obstruction (hepatic veno-occlusive disease) secondary to oxaliplatin are well known complications. These chemotherapy regimens induce parenchymal changes that could increase postoperative morbidity. Approximately 7-10% of patients who undergo neoadjuvant chemotherapy progress to unresectable disease, which exclude them from a potentially curative surgical treatment. Furthermore, neoadjuvant chemotherapy may also lead to disappearance of small metastases on radiological imaging, which could result in technically more difficult curative operation.

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Table 1. Survival outcomes in studies reporting effects of neoadjuvant chemotherapy in patients with resectable colorectal liver metastasis

Study	Author	Year	Neoadjuvant Group	Surgery Group	Neoadjuvant Group	Surgery Group	P-Value
			3 year OS	3 year OS	5 year OS	5 year OS	
1	Tanaka et al	2003	67%	51.80%	38.90%	20.70%	0.039
2	Scoggins et al	2009	nr	nr	nr	nr	ns
3	Boostrom et al	2009	62%	63%	48%	45%	ns
4	Pinto et al	2012	59%	71%	43%	55%	ns
5	Oh et al	2012	44%	67%	nr	nr	ns
6	Nordlinger et al	2013	nr	nr	51.20%	47.80%	ns
7	Araujo et al	2013	78%	74%	74%	56%	ns
8	Zhu et al	2014	69%	nr	52%	48%	ns

ns = no significance
OS = overall survival
nr = details not reported

Notably, administration of neoadjuvant chemotherapy was associated with a trend toward higher rate of postoperative complications (37.2% versus 24%, $p=0.006$). Therefore, age, comorbidities, and patient characteristics should all be taken into consideration, in order to optimize the usefulness of preoperative chemotherapy.

Thus far, neoadjuvant chemotherapy was found to improve 3-year progression free survival in only one prospective randomized study. While postoperative chemotherapy has been the standard of care for colorectal liver metastasis, data on the usefulness of neoadjuvant chemotherapy in resectable lesions is still currently nonconclusive. Neoadjuvant chemotherapy has been widely administered in the United States by community medical oncologists for resectable colorectal liver metastasis, even before referring the patient to a liver surgeon or a multidisciplinary discussion. There has been no consensus or guideline in regard to the most effective combination of drugs and schedule of administration. Different chemotherapeutic protocols are used in different institutions. Folfox and folfiri have been widely administered, but combinations of oxaliplatin, fluoropyrimidine, leucovorin, capecitabine, irinotecan, and monoclonal antibodies are also commonly used in many hepatobiliary centers (both community and academic). Consequently, response rates to the neoadjuvant regimens are variable (ranging from 33% to 61%) with disease progression rates ranging from 7% to 47% [5]. In conclusions, neoadjuvant chemotherapy is currently the standard of care for borderline resectable liver metastasis from colorectal cancer. In cases of resectable lesions, however, there have been no convincing prospective randomized clinical trial which shows superiority when compared to straight liver resection, even though neoadjuvant chemotherapy is given widely in clinical practice for patients with resectable lesions. Prospective randomized trial would be important to objectively determine benefits of neoadjuvant chemotherapy in resectable liver metastasis from colorectal cancer.

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