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Commentary

In Defense of Hepatic Arterial Infusion for Hepatic Metastases of Colorectal Cancer

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Dr. Nancy Kemeny is a medical oncologist with a special expertise in treating colorectal cancer. During 35 years at Memorial Sloan-Kettering Cancer Center (MSKCC), she has conducted some of the first studies using drugs such as irinotecan and oxaliplatin, which are now widely used in patients with colorectal cancer, and has investigated many other drugs as well. Her main research has been on regional therapy, involving administering drugs directly into the liver through a pump. With investigators at MSKCC, she has used regional therapy in patients with liver metastases to downstage disease so that liver resection may become possible in unresectable patients and used regional therapy to decrease recurrence after liver resection. In addition to her clinical and research responsibilities at MSKCC, she is a Professor of Medicine at the Weill Medical College of Cornell University. She served as a member of the Oncology Drug Advisory Committee, and held various positions at ASCO, including Director, and Chairperson of the Membership Committee. In addition, she was Principal Investigator of a National CALGB protocol evaluating regional liver therapy versus systemic therapy in patients whose disease spread from the colon to the liver. She is also a scientific reviewer for many journals and on the editorial board of 3 journals.

The recently published NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for the treatment of colorectal carcinoma[1] are excellent and comprehensive, but I believe that one area deserves more comprehensive review: the use of hepatic arterial infusion (HAI) for the treatment of liver only metastases. I believe 3 circumstances exist in which HAI therapy may be considered. The first is after liver resection. Four randomized controlled trials address the use of HAI therapy after hepatic resection, and 3 of the 4 showed a significant increase in hepatic and overall disease-free survival (Table 1).[2–6] The Memorial Sloan-Kettering Cancer Center (MSKCC)[2] study randomized 156 patients after hepatic resection to continuous HAI of floxuridine (FUDR) and dexamethasone (Dex) combined with systemic infusion of fluorouracil (5FU) and leucovorin (LV) versus systemic infusion of 5FU/LV alone for 6 months. Updated results after a median follow-up of 10 years reported survival rates of 41% and 27% at 10 years and progression-free survivals of 31.3 and 17.2 months for the HAI + systemic infusion and systemic infusion alone groups, respectively (P = .02).[3]

An ECOG study[4] randomized 100 patients to HAI FUDR + systemic 5FU infusion versus no further therapy after liver resection and showed an increase in progression-free survival. A randomized study of 122 patients from Greece[5] reported a significant improvement in disease-free survival for HAI plus chemo-immunotherapy versus systemic infusion alone, although this was not seen in a German study[6] that compared 5FU HAI administered through a port instead of a pump. House et al.[7] evaluated patients who underwent liver resection between 2001 and 2005 and compared patients treated with HAI plus modern systemic chemotherapy versus systemic therapy alone. They reported improved survival (Figure 1) for those who received HAI.

HAI may also be considered as second-line therapy; studies show significant response rates and survival with this approach. In one study using HAI FUDR/Dex plus systemic oxaliplatin and irinotecan, the response rate in second-line therapy was 88% with a 35-month median survival.[8] When compared with second-line systemic therapy, which has a low response rate and survival, HAI therapy seems to be superior and should be part of the treatment plan for patients with liver-only disease (Table 2).[9–15]

A third circumstance in which HAI should be considered is in the neoadjuvant (preoperative) setting to shrink hepatic metastases and make liver resection possible.

Table 1 Randomized Studies After Liver Resection: HAI + Systemic Infusion Versus Systemic Infusion Along or Control

		Disease-Free Survival				
		2-Year (%)		5-Year (%)		
Studies	#	HAI	Systemic infusion	HAI	Systemic Infusion	*P* Value
MSKCC[2]	156	55	45	40	30	0.02
ECOG[4]	75	60	40	40	20*	0.03
Lorenz et al.[6]	186	median	median	20	12.6*	NS
Lygidakis et al.[5]	122	66	48	60	35	0.0002

Abbreviations: HAI, hepatic arterial infusion; MSKCC, Memorial Sloan-Kettering Cancer Center; NS, not significant.
*No treatment in control arm.

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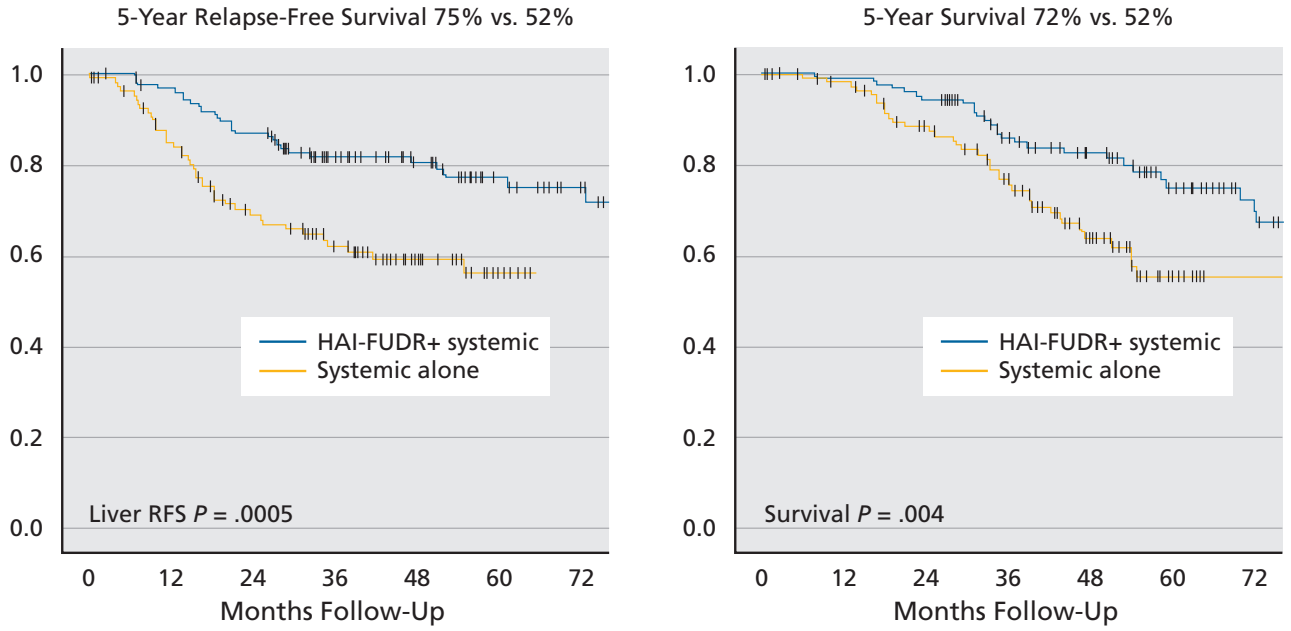

Figure 1 Between 2001 and 2005, 25 patients underwent resection of liver metastases followed by HAI FUDR + systemic infusion. Results were compared with those of 125 consecutive patients who received adjuvant folfox or folfiri after resection with a median follow-up of 43 months.
Abbreviations: FUDR, floxuridine; HAI, hepatic arterial infusion; RFS, relapse-free survival.
From House MG, Kemeny N, Jarnagin WR, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer [abstract]. Presented at the 2009 Gastrointestinal Cancer Symposium; January 15–17, 2009; San Francisco, California. Abstract 383.

Table 2 Second-Line Therapy for Metastatic Colorectal Cancer

Systemic Infusion	No. Patients	% Response	1-Year Survival (%)
CPT-11[9]	205	11	46
CPT + 225[9]	218	23	—
Folfox[10]	289	20	40
Folfox + bevacizumab[11]	290	22	55
CPT-11 + 225 + bevacizumab[12]	45	35	—
HAI + Systemic Infusion			
HAI FUDR + systemic CPT-11[15]	56	74	84
HAI FUDR + systemic oxaliplatin + CPT-11[8]	47	92	87
HAI oxaliplatin + systemic FU/LV[13]	28	64	82
HAI FUDR + mitomycin-C[14]	37	70	—

Abbreviations: HAI, hepatic arterial infusion; FUDR, floxuridine; FU, fluorouracil; LV, leucovorin.

In several systemic therapy–alone chemotherapy trials for patients with liver metastases that cannot be resected, the rate of conversion to resection is 15% to 30% in chemotherapy-naïve patients and less than 20% in previously treated patients. After concurrent neoadjuvant HAI and systemic therapy in a study of 49 patients, 57% of chemotherapy-naïve patients and 38% of previously treated patients were able to undergo resection.[8]

These data show the effectiveness of HAI therapy in patients with liver metatases, warranting broader consideration of this treatment option among certain patients with advanced colorectal cancer.

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