Liver Resection and HIPEC

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Introduction

Synchronous intra-parenchymal hepatic involvement (HI) in patients with peritoneal disease (PD) has traditionally served as a contraindication for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) on the basis that HI represents a systemic rather than locoregional disease. In recent years, however, multidisciplinary management of peritoneal cancers has evolved, with the addition of modern systemic chemotherapy to surgical resection resulting in improved survival in carefully selected patients with HI or PD. Several studies have also demonstrated the feasibility and safety of combined liver resection with CRS/HIPEC in well-selected patients with synchronous HI and PD. Despite growing evidence that acceptable long-term outcomes are achievable, however, concerns over the safety of synchronous hepatic resection and CRS/HIPEC have persisted due to the relative magnitude of both procedures. This chapter examines the perioperative considerations and outcomes of liver resection as a component of CRS/HIPEC.

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Preoperative Considerations

Incidence

Synchronous HI and PD are most commonly found in patients with colorectal or high-grade appendiceal (HGA) primaries, but the true incidence of combined HI and PD is unknown. Most studies demonstrate between 8% and 45% of patients with colorectal cancer have both HI and PD, but these studies investigate only patients who undergo liver resection and CRS/HIPEC, excluding patients who were not candidates for resection [1–6]. However, Franko et al. compared patients with PD from colorectal cancer who underwent CRS/HIPEC to those who received systemic chemotherapy alone [7]. In patients who underwent CRS/HIPEC, 15% had HI and PD; in those who received systemic chemotherapy alone, 35% had HI and PD, giving perhaps a better estimate of the true incidence of HI and PD.

Evaluating patients with HI and PD can be challenging due to the inability of CT imaging to detect all PD. In a study conducted by Jacquet and colleagues, sensitivity of CT scan in determining disease was 70–88%, depending on the region of the abdomen. Moreover, the false negative ranged from 20% to 28% [8]. An additional study by Denzer et al. showed PD on exploration in 100% of patients with a wide range of histologically proven malignancy in whom an earlier CT showed only 47.8% with PD. [9] Allard et al.

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examined the rate of unexpected PD at the time of liver resection for colorectal HI. Of 1340 patients with a planned liver resection, 42 (3%) had unexpected PD. [10] Thus, more HI and PD may exist than is captured, because not every patient will undergo surgical exploration and have the presence or absence of PD confirmed.

Preoperative Evaluation

When considering liver resection as part of CRS/HIPEC, like any patient with HI or peritoneal involvement, a thorough preoperative evaluation is imperative. At our institution, we perform a complete history and physical examination, measure relevant serum tumor markers, as well as obtain a CT scan of the chest, abdomen, and pelvis and a dedicated liver MRI [2]. Eligibility for CRS/HIPEC includes a histologic or cytologic diagnosis of peritoneal carcinomatosis, potentially resectable or resected primary lesion, debulkable PD based on imaging, absence of extra-abdominal disease, and complete recovery from any previous radiation or chemotherapy [2]. The biological behavior of the tumor should also be considered, such that only patients who show a response or no progression on preoperative chemotherapy are eligible for operative resection. When considering HI, whether superficial or parenchymal, disease must be considered resectable by standard definitions of colorectal liver metastases [11]. Thus, all HI must be resectable with a negative margin which allows for preservation of at least two functional liver segments with intact portal and arterial inflow, venous outflow, and biliary drainage [11].

For patients with colorectal and HGA lesions, we recommend 3 months of preoperative first-line systemic chemotherapy with FOLFOX or FOLFIRI with or without bevacizumab [2]. In our experience with 108 combined liver resections and CRS/HIPEC, all patients with HI due to colorectal or HGA adenocarcinoma received first-line chemotherapy prior to referral. In addition, 31% received second-line chemotherapy, and 13% received third-line chemotherapy prior to CRS/HIPEC [2]. In a study by Berger et al., 56.6% of patients undergoing liver resection with CRS/HIPEC for a variety of primary peritoneal involvement received at least one line of preoperative systemic chemotherapy [1].

Operative Technique and Findings

The goal of CRS/HIPEC, with or without HI, is to remove all gross disease. At our institution, we start with a midline laparotomy incision and proceed to quantify the distribution of disease using the peritoneal carcinomatosis index (PCI) [12]. We perform a routine supracolic omentectomy and resection of the primary if not previously completed. Peritoneal stripping and resection of intra-abdominal organs are performed only as indicated by presence of visible disease [13]. Liver resections range from superficial liver capsule stripping to anatomic resection based on the extent of disease. HI is defined as superficial for cases in which HI is not invading Glisson's capsule, or parenchymal for cases with parenchymal invasion. Parenchymal invasion can occur via hematogenous spread identified on preoperative CT scan or through direct invasion from intraperitoneal dissemination [2]. Hemostasis of raw liver surface is achieved with electrocautery or argon beam coagulation. Although several chemotherapeutic agents are used, most patients receive Mitomycin C using a closed abdomen technique [13]. Other chemotherapeutic agents are used based on primary tumor and previous systemic therapy.

In our series of CRS/HIPEC performed between 1991 and 2013, 108 of 1067 (10.1%) CRS/HIPEC procedures included a liver resection, and this represent one of the largest series of published combined liver resections and CRS/HIPEC [2]. The majority of HI was due to a colorectal primary (39.0%), followed by appendiceal (32.9%), mesothelioma (4.9%), ovarian (4.9%), and gastric (2.4%). Other primaries represented 15.9% of HI. Of the liver resections performed, 89.9% ($N = 97$) were subsegmental resections; more than one liver resection was performed in 28.7% of cases ($N = 31$). Parenchymal involvement was found in 22.2%

of patients (N = 24), and the mean volume of parenchyma resected was 87.3 cm^3 [2]. Patients with colorectal primaries were more likely to have parenchymal disease compared to patients with appendiceal primaries (37.5% versus 6.7%, respectively; $p < 0.001$) [2]. All of the patients with parenchymal disease with an appendiceal primary were high-grade lesions; low-grade appendiceal (LGA) lesions were only caused superficial disease confined to the liver capsule.

In a similar study by Berger et al., 269 CRS/HIPEC were performed at a single institution, with 103 procedures including a liver resection (38.3%) [1]. A similar distribution of primaries was found compared to our study, but more parenchymal resections were performed (44.7%, N = 46). In their series, they performed 31 subsegmental resections, 10 segmentectomies, 2 right hepatectomies, 2 central hepatectomies, and 1 left hepatectomy [1]. Likewise, Saxena and colleagues performed 936 CRS/HIPEC procedures, with 132 (14%) including liver resection [14]. Similar to Berger et al., 54% of liver resections had intra-parenchymal metastases with a wide variety of primaries.

Multiple other smaller series have similar resection profiles but only include patients with colorectal primaries [4, 6, 15–19], so a distinction between superficial liver capsule stripping and parenchymal resection is not drawn. Several studies include radiofrequency ablation (RFA) and cryoablation as an adjunct to or in place of liver resection [6, 17–20], so results have to be interpreted with caution, as RFA alone carries a different complication profile than liver resection.

Outcomes

Feasibility and survival from an early series of liver resection and CRS with intraperitoneal chemotherapy (IPIC) were reported by Elias et al. [21] They studied 12 patients with HI due to multiple primaries, 9 patients of which underwent major hepatectomy in addition to CRS. All patients underwent IPIC for 5 days postoperatively. There were no perioperative deaths, and morbidity was largely attributed to transient bile leaks (33%). At 14-month median follow-up, there was no recurrent disease reported, leading the authors to conclude that despite the magnitude of both procedures, the combination of liver resection and IPIC was safe in well-selected patients.

In continuation of their work, the same group compared 37 patients with synchronous HI and PD who underwent liver resection and some form of IPIC (early postoperative, intra-operative HIPEC, or combination) with colorectal cancer as the main primary to 61 patients with PD without HI who underwent some form of IPIC [16]. They demonstrated that a PCI of 12 or greater and number of liver metastases (LM) were independent risk factors for poor OS. Median OS was 76 months for patients with a PCI less than 12 and no LM, and 40 months for patients with a PCI less than 12 and 1 or 2 LM. If the PCI was 12 or more, median OS dropped to 21–29 months, regardless of the number of LM. Because the odds ratio for PCI was higher than the odds ratio for presence of LM, Maggiori et al. concluded that the presence of LM was not the most important prognostic factor for OS but rather the PCI itself [16]. They proposed that aggressive surgical resection for patients with HI and PD should be limited to patients with a PCI less than 12 and less than 3 areas of HI. Saxena and colleagues had similar findings [14]. Median OS in patients with 1, 2–3, and ≥4 areas of HI was 37.5, 46.6, and 14.5 months, respectively, and these differences were significant. Moreover, the median OS in patients undergoing liver resection had a steep drop with increasing PCI, with 92.5, 27.4, and 19.7 months OS for PCI ≤ 5, PCI 6–10, and PCI ≥ 11, respectively [14].

Multiple other studies have continued to evaluate the overall morbidity, mortality, and survival of liver resection and CRS/HIPEC. Most are small cohort studies comparing patients with colorectal primaries with HI and PD who underwent liver resection and CRS/HIPEC to patients with PD who underwent CRS/HIPEC. Major complication rates (Clavien-Dindo Grades III and IV) [22] range from 31% to 45% in patients with HI and 11% to 42% in patients without HI, with conflicting results on whether these

differences are significant [4, 6, 14, 18, 20]. Thirty-day mortality was relatively low, ranging from 0% to 7.1% in patients with HI and 0.6% to 8.3% in patients without HI, with no significant difference found in any studies [4, 6, 14, 18–20]. Median OS ranged from 13 to 36.1 months in patients with HI, and from 15.8 to 45.5 months in patients without HI when measured from time of surgery [4–6, 14, 18–20]. Berger et al. reported a median OS of 45.1 months for patients with HI, and 73.5 months without HI, when measured from date of diagnosis [1]. They also separately reported median OS with a HGA primary, demonstrating a median OS of 42.0 months with HI. In those without HI, median OS had not been reached [1]. Overall, however, these ranges can be difficult to interpret due to the wide variability in PCI, HI, type of liver resection, and single institution nature of each study.

A recent study performed by Cloyd et al. examined the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database to evaluate liver resection and CRS/HIPEC in a nationally representative cohort [3]. Of 1168 patients who underwent CRS/HIPEC, 100 (8.6%) also underwent synchronous liver resection. The most common primary diagnosis was unspecified (65.3%), distantly followed by appendiceal and colorectal. They demonstrated a significantly higher complication rate, longer LOS, and re-operation rate in patients who underwent liver resection with CRS/HIPEC compared to CRS/HIPC alone [3]. As a result, they suggested that patients with HI and PD may therefore benefit from a staged operative approach rather than combined liver resection and CRS/HIPEC [3].

In our own institutional series, we compared 99 patients who underwent 108 liver resections as part of CRS/HIPEC to 957 patients with no HI who underwent CRS/HIPEC with primaries and liver resections as noted above [2]. We found no statistically significant difference in minor (Clavien-Dindo Grades I and II) or major complications between the two groups (Table 16.1), and no significant difference in 30-day mortality was found in patients with or without HI (6.5% vs. 2.8%, $p = 0.07$). Additionally, there were no significant differences in operative time, length of hospital stay, length of intensive care unit stay, or 30-day readmission in patients who underwent liver resection compared to those who did not. Even when stratifying by the type of HI (superficial versus parenchymal) and extent of liver resection (subsegmental versus anatomic), there were no differences in minor complications, major complications, mortality, or 30-day readmission.

Table 16.1 Morbidity and mortality after cases of CRS/HIPEC for patients with or without hepatic involvement and partial hepatectomy

	No hepatic involvement	Hepatic involvement	P-value
	($n = 957$)	($n = 108$)	
Minor morbidity, *n* (%)	342 (35.7)	30 (27.8)	0.11
Major morbidity, *n* (%)	215 (22.5)	20 (18.5)	0.39
30-day mortality, *n* (%)	27 (2.8)	7 (6.5)	0.07
30-day readmission, *n* (%)	354 (37.0)	30 (27.8)	0.07
Operation time, mean (SD) hours	8.5 (3.1)	8.8 (3.2)	0.41
Length of hospital stay, mean (SD) days	14.2 (16.2)	13.6 (16.4)	0.71
Intensive care unit stay, mean (SD) days	3.3 (9.0)	3.5 (7.6)	0.92

SD standard deviation

Median follow-up for patients with HI in our series was 49.4 months and 49.9 months without HI. For patients with LGA primaries, median OS was 42.1 months for patients with HI and 95.5 months for patients without HI ($p = 0.03$) (Fig. 16.1). Median OS for patients with LGA primaries and complete cytoreduction (R0/R1) was not reached, regardless of HI ($p = 0.55$). For patients with colorectal primaries and complete cytoreduction, median OS was 21.2 months for those with HI and 33.6 months without HI ($p = 0.03$) (Fig. 16.2). Regardless of resection status, patients with colorectal primaries with parenchymal HI had no difference in survival compared to those with superficial HI (19.2 versus 21.2 months, $p = 0.97$).

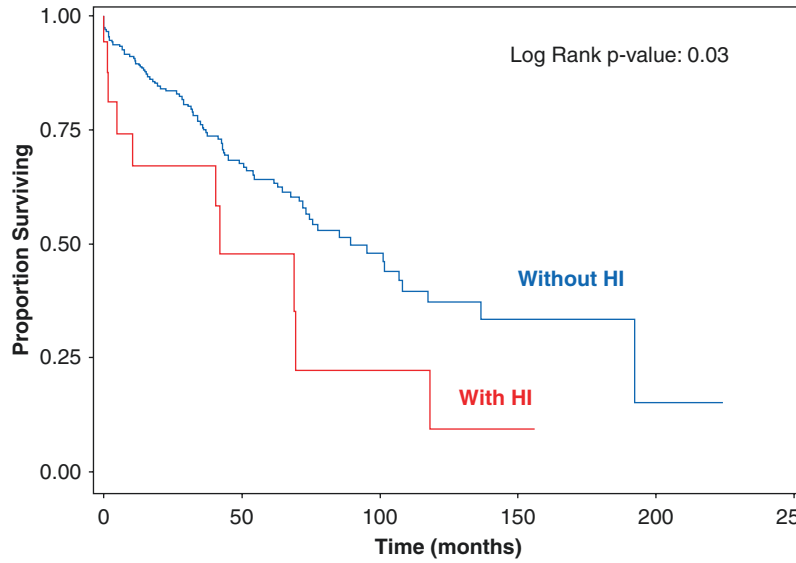

Fig. 16.1 Median overall survival after CRS/HIPEC with and without hepatic involvement (HI) for patients with low-grade appendiceal (LGA) cancer who underwent complete cytoreduction

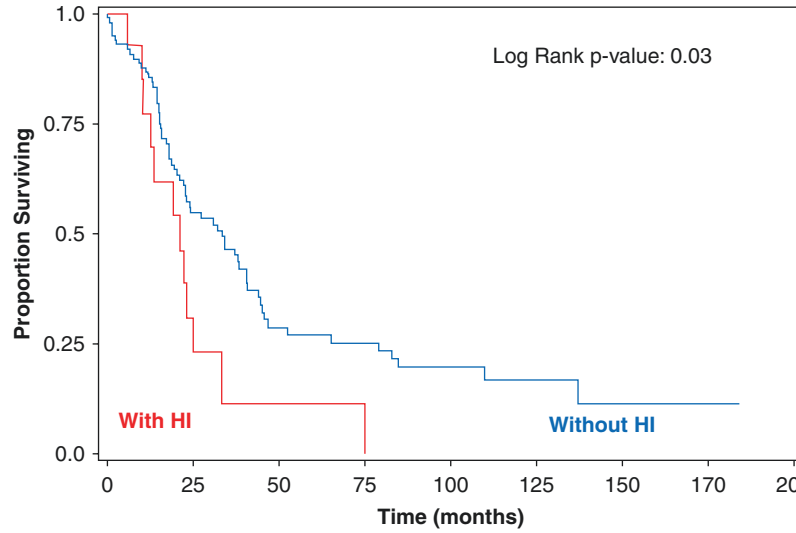

Fig. 16.2 Median overall survival after CRS/HIPEC with and without hepatic involvement (HI) for patients with colorectal cancer who underwent complete cytoreduction

When a complete cytoreduction was obtained, there was no significant difference in recurrence rates for patients with colorectal primaries or LGA primaries based on HI (Table 16.2). Despite similar recurrence rates, however, median time to recurrence was shorter in patients with HI than in those without HI (6.8 versus 12.0 months, $p = 0.001$) (Fig. 16.3). Of those with HI who recurred, only 12.5% had high-grade lesions, but 71.9% had lymph node involvement. For patients with LGA primaries, there was no difference in median time to recurrence with or without HI (118.9 versus 128.3 months, $p = 0.23$). There was no difference in site of recurrence (liver, peritoneal, or extra-abdominal) for colorectal primaries or LGA primaries regardless of HI (Table 16.2).

Discussion

Surgical management of patients with synchronous HI and PD remains controversial, with the majority of experience stemming from single institution studies [1, 2, 4–7, 14, 16, 18–20].

Table 16.2 Disease recurrence after complete CRS/HIPEC

	No hepatic involvement	Hepatic involvement	P-value
	(*n* = 433)	(*n* = 37)	
Recurrence, n/N (%)			
Colorectal	57/107 (53.3)	11/17 (64.7)	0.44
Low-grade appendix	20/118 (16.9)	2/5 (40.0)	0.22
Median time to recurrence, months			
Colorectal	12.0	6.8	0.001
Low-grade appendix	128.3	118.9	0.23
Site of recurrence, n/N (% of recurrence)			
Liver			
Colorectal	22/57 (38.6)	2/11 (18.2)	0.30
Low-grade appendix	6/20 (30.0)	1/2 (50.0)	1.00
Peritoneum			
Colorectal	21/57 (36.8)	5/11 (45.5)	0.74
Low-grade appendix	13/20 (65.0)	1/2 (50.0)	1
Extra-abdominal			
Colorectal	14/57 (24.6)	4/11 (36.4)	0.46
Low-grade appendix	1/20 (5.0)	–	1

Its study can be challenging due to the uncommon nature of the disease process, in addition to the difficulties in detecting PD on imaging. Moreover, both HI and PD can present with a diverse set of disease distribution, with small lesions that are unresectable and large burdens of disease that can be completely removed, making quantifying and comparing patients additionally complex. Most studies also include a variety of primaries with differing biologic machinery and methods of dissemination.

Based on our institutional data and work by others, we regard liver resection as part of CRS/HIPEC as another form of metastasectomy that is safe and feasible in well-selected patients. CRS/HIPEC carries a known complication rate of 25–41% [23], and our study and others found major morbidity rates equal to or less than this even with the inclusion of liver resection. No studies have demonstrated a statistically significant increase in 30-day mortality in patients undergoing liver resection with CRS/HIPEC, although OS is dependent on type of primary, PCI, and completeness of cytoreduction.

Not all HI with PD is equal. HI from LGA primaries is significantly different from that of colorectal primaries. Patients with LGA primaries often present with a large volume of disease

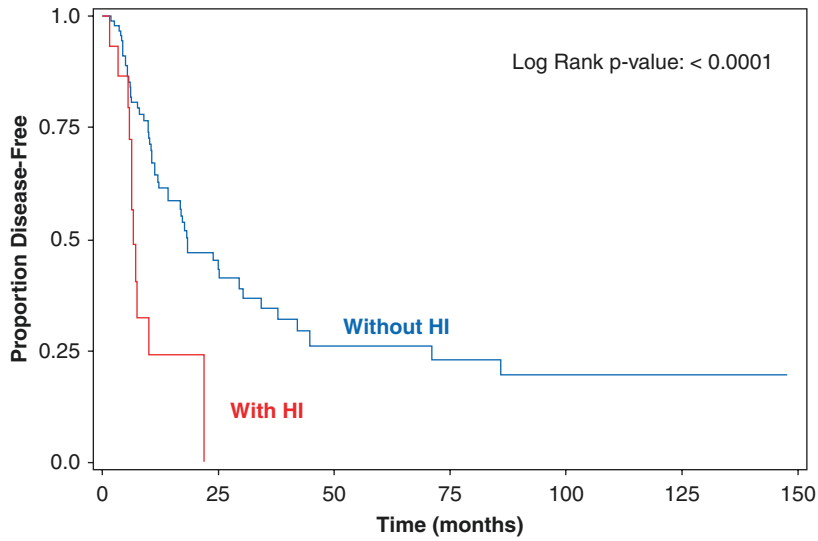

Fig. 16.3 Median disease-free survival for patients with colorectal cancer after CRS/HIPEC with complete cytoreduction. HI hepatic involvement

involving the liver capsule, but this represents true peritoneal surface disease, rarely invades the parenchyma and has no effect on DFS or OS after a complete cytoreduction. Thus, for LGA, HI may function as a marker of greater disease volume. When incomplete cytoreductions were included our analysis, the decreased survival observed likely reflected the effect of residual peritoneal surface disease on survival, and not the effect of the HI itself. In LGA primaries, superficial HI alone should not be considered a contraindication to resection.

On the contrary, colorectal disease is typically parenchymal and indicates aggressive biologic behavior affecting DFS and OS, even with a complete cytoreduction. Additionally, 36% of patients will develop extra-abdominal systemic failure [2], and a PCI of 12 or greater, or 3 or more areas of HI with a colorectal primary predict poor OS [16]. Therefore, in patients with colorectal primaries, and similarly HGA lesions, we perform liver resection and CRS/HIPEC only in patients who receive upfront systemic chemotherapy, have no evidence of progression of disease on repeat imaging, and who have a low volume of resectable disease. In these cases, CRS functions as any other metastasectomy, while any role that HIPEC may have is probably related to controlling local recurrence within the peritoneal cavity.

With modern systemic chemotherapy resulting in improved survival outcomes, it is tempting to compare OS of CRS/HIPEC to systemic chemotherapy alone; however, this is not an accurate comparison. The survival benefit provided by CRS/HIPEC and liver resection is not in lieu of that provided by systemic chemotherapy, but is additive to it. A more appropriate comparison could be drawn between liver resection with CRS/HIPEC and second- or third-line chemotherapy, where median survival for second-line chemotherapy is 10–14 months, and for third-line is less than 3 months [24–26], as compared to the 13–35 months achievable through liver resection and CRS/HIPEC.

Due to the relative magnitude of both procedures and high complication profile, previous studies have cautioned against simultaneous resection or advocated for a staged approach with large resections [3, 5]. Recently, Cloyd et al. have proposed a staged approach to resection, as in colorectal cancer, due to high postoperative morbidity, increased operative times, and longer LOS in patients with HI compared to patients who undergo CRS/HIPC without liver resection [3]. However, a comparison of synchronous resection and staged resection has never been completed. Additionally, this study included a heterogenous cohort, with unknown PCIs and the majority of patients with an unknown primary. As PCI was unknown, increased operative time, LOS, and morbidity may be related to the extent of cytoreductive surgery, rather than liver resection itself. Moreover, while a staged approach may be possible for a small subset of colorectal primaries, for LGA primaries where the liver disease is superficial, a staged operative approach would be contraindicated.

Conclusions

Synchronous HI and PD is not an absolute contraindication to CRS/HIPEC in appropriately selected patients. In patients with LGA primaries, HI is generally superficial and functions as a marker for greater volume of disease, rather than contraindication to resection. In patients with colorectal or HGA primaries, HI is associated with decreased DFS and OS, but with the addition of preoperative systemic chemotherapy, a meaningful survival benefit can still be achieved with CRS/HIPEC. In our opinion, this benefit is predominantly derived from surgical resection, while HIPEC may have an effect in delaying local recurrence in the peritoneal cavity. In all colorectal cancer cases, CRS/HIPEC should not be offered when a complete macroscopic cytoreduction cannot be achieved.

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