

The role of liver transplantation for hilar cholangiocarcinoma

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BACKGROUND: Hilar cholangiocarcinoma is a devastating disease. Surgery is the only potentially curative modality. However, the results of surgical resection for hilar cholangiocarcinomas are disappointing. The introduction of liver transplantation for this condition has brought new hope for the management of this disease. The aim of this review is to discuss the role of liver transplantation in this disease.

DATA SOURCES: A MEDLINE search was conducted for the articles on liver transplantation for hilar cholangiocarcinoma. Their results have been compiled and compared with the existing literature on resection for this disease.

RESULTS: The earlier series on liver transplantation for hilar cholangiocarcinoma were not encouraging because of poor patient selection. The Mayo Clinic protocol of neoadjuvant chemoradiation followed by liver transplantation has shown remarkable success (survival at 1-, 3-, and 5-year post-transplantation being 92%, 82%, and 82%, respectively). With better patient selection and integration of neoadjuvant chemoradiation, the long-term survival is superior to that of the patients who undergo resection, as shown by the published literature on resection. The limitations of organ availability can be overcome by the living donor liver transplantation programme. This review article discusses the rationale, pros and cons of liver transplantation vis-à-vis resection for hilar cholangiocarcinoma.

CONCLUSIONS: Liver transplantation, especially living donor liver transplantation, is a new and exciting alternative to resection for hilar cholangiocarcinoma. Integration of neoadjuvant chemoradiation has the potential to further improve the curative potential of liver transplantation. The strategy of combining neoadjuvant chemoradiation and liver transplantation brings new hope for the treatment of this difficult disease.

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KEY WORDS: liver transplantation;
hilar cholangiocarcinoma;
neoadjuvant chemoradiation.

Introduction

Hilar cholangiocarcinoma is one of the most formidable solid organ malignancies to treat and has poor long-term outcome. Surgical resection offers the only potentially curative approach for this disease. The anatomical location of this tumor, with its proximity to major vascular structures in the hepatic hilum, makes surgical extirpation technically demanding. Complicating the surgery further are the related medical problems in a jaundiced patient like coagulopathy, impaired liver functions, and possible sepsis. Not surprisingly, less than 20% of patients with hilar cholangiocarcinoma are amenable to a potentially curative resection.^[1] Those who undergo resection have a 5-year survival ranging from 11% to 40%.^[2-7]

The major challenge in the surgical resection for this disease is the proximity of the tumor to the major vessels of the hepatic hilum and its potential to extend into either or both lobes of the liver as well as the caudate lobe. A better understanding of the pattern of spread of these tumors has led several surgeons to extend the resection to include the caudate lobe and to perform right or left hepatectomy depending on the principal tumor location. The addition of systematic lymph node dissection addresses the potential for lymphatic spread.

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Rationale for liver transplantation (LT) and early results

Despite these conceptual and technical advances, resectional surgery for hilar cholangiocarcinoma has several inherent limitations:

1. Patients with Bismuth type IV tumors (extending to both lobes of the liver) remain unresectable despite the fact that they may not have other extrahepatic disease.

2. Patients with hilar cholangiocarcinoma arising in the setting of primary sclerosing cholangitis (PSC) will tolerate resection poorly because of the underlying liver impairment.

3. Invasion of the main portal vein or common hepatic artery, tumor extension into one lobe of the liver with invasion of the contralateral branch of the portal vein or hepatic artery are factors that render the tumor unresectable.

4. Dissection in the hepatic hilum has the potential to cause tumor spillage. Extrapolating data from other malignancies, tumor spill is an adverse prognostic factor.^[8]

5. Although longitudinally clear margins can be achieved with appropriate resection, a clear circumferential margin is often not achievable. The status of circumferential margin has been shown to be a very important prognostic factor for local recurrence in many tumors, especially rectal cancer, where the technique of mesorectal excision has significantly decreased local recurrence rates.^[9,10]

LT has brought new hope for solving the issues outlined above. Early experiences with LT for this disease were disappointing because of poor patient selection and mixture of patients with both intrahepatic and extrahepatic/hilar cholangiocarcinomas, thus making the data difficult to interpret. As both these entities are quite distinct and have different therapeutic challenges, a combined result of both these tumors is not accurately representative of the results of either of

them. Table 1 depicts the reports of LT for hilar cholangiocarcinomas prior to 2000.

In the European transplant registry data,^[11] none of the 38 patients with hilar cholangiocarcinoma survived 5 years after LT. Among the other larger series focusing on hilar cholangiocarcinomas, the one from Hannover^[13] reported a 5-year survival of 17.1%. In the report from the University of Pittsburgh,^[14] the 5-year survival after LT was 36.2%, but that after a more aggressive cluster abdominal transplantation was only 9.1%. Neuhaus et al^[15] described the results of the extensive procedure of LT and partial pancreatectomy (LTPP) as a so-called "no-touch technique" for the resection of hilar cholangiocarcinoma. Although 14 of the 15 patients who underwent LTPP had R0 resection, the 5-year survival was a modest 38%. These results led to disappointment with LT as a treatment modality for hilar cholangiocarcinomas.

The new approach (integration of neoadjuvant chemoradiation) and results since 2000

In 2000, a group from Mayo Clinic presented their exciting preliminary result of their protocol of neoadjuvant chemoradiation followed by LT in 11 patients with hilar cholangiocarcinoma.^[16] All 11 patients were alive and only one had recurrent disease at the time of publication of the article. Three patients had less than 1 year of follow-up while the other patients had a follow-up of 17 to 83 months.

Following the Mayo Clinic preliminary report, more centers published their results of LT for hilar cholangiocarcinomas.^[17-19] The results of the publications since 2000 are summarized in Table 2.

Besides the Mayo Clinic, the University of Nebraska^[18] also used the protocol of neoadjuvant chemoradiation preceding LT. As evident from Tables 1 and 2, the results of the Mayo Clinic are far superior to other series, and thus deserve further discussion.

Table 1. Results of LT for hilar cholangiocarcinoma in studies published before 2000

Institution	Year	n	Patient survival (%)			Tumor-free survival (%)		
			1-yr	3-yr	5-yr	1-yr	3-yr	5-yr
European Transplant Registry ^[11]	1987	38	40	16 (2-yr)	0	-	-	-
Kings College, London, UK ^[12]	1988	13	30	10	10	-	-	-
Hochschule Hannover, Germany ^[13]	1996	25	60	21.4	17.1	-	-	-
University of Pittsburgh, USA ^[14]	1998	27 (LT)	59.3	36.2	36.2	-	-	-
		11 (Cluster)	54.6	9.1	9.1	-	-	-
Humboldt University, Berlin, Germany ^[15]	1999	15 (LTPP)	-	-	38	-	-	-

LT: liver transplantation; Cluster: abdominal cluster transplantation; LTPP: LT with partial pancreatectomy.

Table 2. Results of LT for hilar cholangiocarcinoma in studies published since 2000

Institution	Year	n	Patient survival (%)			Tumor-free survival (%)		
			1-yr	3-yr	5-yr	1-yr	3-yr	5-yr
Mayo Clinic, Rochester, USA ^[16]	2000	11	100	-	-	90.9	-	-
University of California, LA, USA ^[17]	2001	9	86	31	-	57	57	-
University of Nebraska Medical Center, Omaha, USA ^[18]	2002	11	-	-	45	-	-	-
Spanish experience (multicenter) ^[19]	2004	36	82	53	30	-	-	-
Mayo Clinic, Rochester, USA ^[20]	2005	38	92	82	82	-	-	-

Patients enrolled: Unresectable HC or HC in the setting of PSC



Diagnosis established by any of the following

- Intraluminal brush cytology / biopsy
- CA 19.9 > 100 ng/ml in the setting of a radiographic malignant stricture
- Biliary aneuploidy demonstrated with digital image analysis (DIA) and fluorescent in-situ hybridization (FISH)



Staging investigations

- CT scan of chest and abdomen
- Liver ultrasound
- Bone scan
- Endoscopic ultrasound with FNAC of suspicious lymph nodes



Exclusion criteria

- Previous chemotherapy/radiotherapy
- Uncontrolled infection
- Previous malignancy (other than skin or cervical cancer) within preceding 5 years
- Medical comorbidity precluding transplantation
- Extrahepatic disease (including regional nodal metastasis)
- Operative biopsy or attempted resection



EBRT 4500 cGy, 150 cGy twice daily+bolus 5-FU iv (500 mg/sqm/d)×3 days



Intraluminal boost using transcatheter Iridium-192 brachytherapy wire (2000 - 3000 cGy at 1 cm radius)



Infusional 5-FU (225 mg/sqm/d) daily or oral Capecitabine 2000 mg/sqm/d in 2 divided doses, 2 out of every 3 weeks; continued till transplantation



Exploratory laparotomy

- Right or bilateral subcostal incision
- Thorough abdominal exploration with biopsy of any abnormal lymph nodes or nodules
- Palpation of the hilum to determine inferior extension of tumor
- Examination of caudate to assess resectability with caval-sparing hepatectomy
- Biopsy of lymph nodes overlying common hepatic artery at the take-off of the gastroduodenal artery and others along the common bile duct (CBD) above duodenum
- Extrahepatic metastases, lymph node metastases, and local extension of disease to adjacent organs or tissues precluded liver transplantation



Liver transplantation

Fig. Selection and treatment schema (Mayo Clinic protocol).^[16, 20]

The selection and treatment schema in the Mayo Clinic protocol is described in Fig.

In the updated series from the Mayo Clinic,^[20] 71 patients entered the transplant treatment protocol and received chemoradiation. Five patients died and another 4 had disease progression beyond transplant criteria during or after the completion of chemoradiation. Sixty-one patients underwent

operative staging, and 14 (23%) had findings precluding subsequent transplantation. Eventually, 38 patients underwent LT. Three patients died of surgical complications. One-, 3-, and 5-year recurrence rates following transplantation were 0%, 5%, and 12% respectively. Patient survivals at 1, 3, and 5 years after transplantation were 92%, 82%, and 82%, respectively. These were superior to the non-

transplanted group (*vide infra*).

The investigators compared their results of LT with the results of resection of hilar cholangiocarcinoma in the same institution. During the same period, 54 patients were explored for resection and 26 underwent successful resection with patient survival rates of 82%, 48%, and 21% at 1, 3, and 5 years respectively. To account for the confounding factors of nodal metastasis and R+ resections in the resection group, the authors did a subset analysis of the patients with R0 resection and node-negative disease after resection and found that their 1-, 3-, and 5-year survival rates were 87%, 53%, and 18%, respectively. These results were quite similar to the resection group as a whole and significantly inferior to the transplantation group. To account for the mortality related to the neoadjuvant treatment and exclusion of the patients based on the laparotomy findings, the outcome of all the 71 patients enrolled in the transplant protocol was analyzed. The survival at 1, 3, and 5 years for this whole group were 79%, 61%, and 58%, respectively. These results were also superior to the survival rates in the resection group.

The excellent results of the Mayo Clinic group can be attributed to a number of factors. The fact that only 38 of the 71 patients enrolled in transplantation protocol actually had transplantation reflects the rigorous selection of these patients. The selection process included a mandatory exploratory laparotomy, which excluded 23% of patients from future transplantation. It should also be noted that patients with regional lymph node metastases were also excluded from transplantation. While the authors have emphasized the importance of exploratory laparotomy, the routine use of such invasive procedure purely for patient selection raises some concern. In the era of positron emission tomography (PET) scan and with advances in laparoscopic evaluation using laparoscopic ultrasound, these modalities could perhaps replace the mandatory laparotomy.

Neoadjuvant and adjuvant treatment has had a significant impact on the treatment of many solid tumors. Although many studies have demonstrated the potential efficacy of radiotherapy with or without chemotherapy as palliative therapy,^[21] adjuvant therapy,^[22] and neoadjuvant therapy^[23] before conventional resection, the exact role of such treatment is not well established for hilar cholangiocarcinoma. Extrapolating the benefit of neoadjuvant treatment in other malignancies to hilar cholangiocarcinoma is a logical attempt to improve the treatment of this disease.

Neoadjuvant chemoradiation for hilar cholangiocarcinoma is limited by its toxicity, especially hepatotoxicity. Major liver resections may not be safe after such treatment as the remnant radiated liver is likely to be suboptimal. LT following neoadjuvant chemoradiation is not limited by hepatotoxicity as the diseased and radiated liver is replaced by a new liver. Thus, combining neoadjuvant therapy with a more radical surgery like LT is a further attempt at achieving the aim of cure.

Transplantation or resection?

Surgical resection has been the standard of care for hilar cholangiocarcinoma. The anatomy of the hepatic hilum and the pattern of spread of hilar cholangiocarcinoma are such that the addition of liver resection is often essential to achieve clear margin. Indeed, routine liver resection has been shown to improve survival over bile duct resection alone. In a report from the Memorial Sloan-Kettering Cancer Center,^[5] negative margins could be achieved in 84% of patients who underwent hepatectomy as compared to 56% of patients who did not have hepatectomy. The 5-year survival in the liver resection group in this series was 39%, while none of the patients who did not have liver resection survived for 5 years.

The extent of liver resection varies with different centers. As the concepts and techniques have evolved, caudate lobe resection along with right or left hepatectomy (based on the principal tumor location) is now considered a standard. Extended resection including right trisegmentectomy and portal vein resection has been proposed by Neuhaus et al^[24] who have reported a 5-year survival of 72% for patients who underwent R0 resection using this strategy. Hepatectomy with portal vein resection has been shown to be safe in experienced centers and can offer a long-term survival in some patients with advanced tumors.^[25] Preoperative portal vein embolization has the potential benefit of allowing such extended resection by causing hypertrophy of the proposed remnant liver.^[26]

LT has several benefits over conventional resection for hilar cholangiocarcinoma. It is not limited by the traditional criteria of unresectability like bilobar extension of tumor or encasement of major vessels. Without the need to dissect the porta hepatis in the region of tumor, there is decreased possibility of tumor spillage and a higher chance of achieving a clear margin (longitudinal and circumferential). In addition, patients with hilar cholangiocarcinoma with

Table 3. Advantages and disadvantages of resection and liver transplantation for hilar cholangiocarcinoma

Approaches	Advantages	Disadvantages
Resection	No issue of donor organ No concern of immunosuppression	Criteria for resectability more stringent Patients with underlying Primary Sclerosing Cholangitis tolerate resection poorly Increased possibility of tumor spill Increased possibility of positive margins especially circumferential margin Difficult to integrate neoadjuvant chemoradiation
Liver transplantation	Criteria for resectability liberal Reduced possibility of tumor spill Reduced possibility of positive margin Not limited by hepatotoxicity of neoadjuvant chemoradiation	Organ availability (Living donor liver transplantation may overcome this limitation) Concern that lifelong immunosuppression may lead to long-term recurrence Neoadjuvant treatment necessitates biliary stenting in all cases, a procedure with its own risks

underlying PSC tolerate resection poorly and LT is an attractive option as it aims at the treatment of the tumor as well as the underlying liver disease. Of the 38 patients who underwent transplantation for hilar cholangiocarcinoma in the Mayo Clinic series, 22 (58%) had underlying PSC.^[20] As has been discussed earlier, major liver resection after neoadjuvant chemoradiation may not be safe. LT on the other hand, is not limited by the hepatotoxicity of the neoadjuvant treatment. Thus, with the integration of neoadjuvant treatment, LT may be a safer procedure than major liver resection.

The most important disadvantage of LT protocol for hilar cholangiocarcinoma is the limited availability of cadaveric donor organs. The remarkable progress of living donor LT (LDLT) in the recent years has made the long waiting lists for transplantation redundant in centers actively engaged in LDLT. With improvements in surgical techniques and increased experience, morbidity and mortality for both donor and recipient can be minimized.^[27] LDLT thus can be a viable option for patients with hilar cholangiocarcinoma.

Despite the obvious advantages of the strategy of neoadjuvant chemoradiation and LT in the treatment of hilar cholangiocarcinoma, certain concerns remain. Use of neoadjuvant treatment necessitates preoperative biliary stenting in all cases, a procedure that has its own potential of morbidity and mortality. This concern has been highlighted in his editorial by Bismuth^[28] who emphasizes the need for a randomized controlled trial of transplantation, with and without chemoradiation in these patients.

The advantages and disadvantages of the approaches of resection and transplantation are summarized in Table 3.

Overall, the results of LT integrated with neoadjuvant chemoradiation have been superior to the published literature on resection for hilar cholangiocarcinoma. The experience from the Mayo Clinic clearly provides a new way forward for the unfortunate patients with this devastating disease.

Conclusions

LT overcomes many limitations of resectional treatment for hilar cholangiocarcinoma. The integration of neoadjuvant chemoradiation has a potential to improve the oncologic results even further. The advent of LDLT has removed the restriction of cadaveric organ availability and provides a viable option for the treatment of this disease. The excellent long-term result of LT following neoadjuvant chemoradiation in this setting therefore promises to be an exciting new option and deserves greater application and consideration.

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