

REVIEW ARTICLE

Liver transplantation for non-hepatocellular carcinoma malignancy

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Abstract

Liver transplantation (LT) for hepatocellular carcinoma is effective for selected patients. LT for other malignancies like cholangiocarcinoma (CCA), hepatoblastoma (HB), hepatic epithelioid hemangioepithelioma (HEHE), angiosarcoma (AS), and neuroendocrine tumors (NET) is being defined. For CCA, series that did not emphasize highly selected early stage disease and neoadjuvant or adjuvant chemoradiation had an average 5-year survival of 10%. However, emphasizing neoadjuvant radiation and chemosensitization in operatively confirmed stage I or II hilar CCA has led to improved 5-year survival, up to 82%. LT is indicated under strict research protocols at selected centers, for patients with early stage CCA and anatomically unresectable (Bismuth type IV) lesions. HB is typically sensitive to cisplatin-based chemotherapy. LT plays a role as primary surgical therapy for those individuals in whom tumors remain unresectable after chemotherapy or as rescue therapy for those who are incompletely resected, recur after resection, or develop hepatic insufficiency after chemotherapy and/or resection. Long-term survival is reported at 58–88%. HEHE is a multifocal tumor that lies somewhere between benign hemangiomas and malignant AS. The extensive multifocal nature makes resection difficult and LT an attractive option. Series on LT for HEHE report overall survival of 71–78% at 5 years. However, AS is an aggressive tumor and LT is contraindicated. For NET, resection of the primary tumor and all gross metastatic disease is reported to provide 5-year survival of 70–85%. LT has been employed for some patients for unresectable tumors or for palliation of medically uncontrollable symptoms with 5-year survival reported between 36% and 80%.

Key Words: *liver transplantation, malignancy, cholangiocarcinoma, hepatoblastoma, hepatic epithelioid hemangioendothelioma, angiosarcoma, neuroendocrine tumors, carcinoma*

Introduction

Liver transplantation (LT) has become an effective and widely accepted treatment for hepatocellular carcinoma (HCC), providing good long-term disease-free and overall survival as appropriate criteria evolved to select patients. The indications for LT have also developed for less common hepatic tumors, achieving acceptable results, perhaps surrounded by more controversy and evolving later. These other malignancies including cholangiocarcinoma, hepatoblastoma, hepatic epithelioid hemangioendothelioma, angiosarcoma, and metastasis from neuroendocrine tumors, all of which are the topic of this article, occur more frequently in non-cirrhotic liver than HCC. This fact sometimes makes obtaining a graft at an appropriate time from an oncologic point of view

more difficult than for HCC. Understanding treatment options, the pathology of various tumors, the tumor stage, size, number and location, the patient's underlying condition, and the resources available are keys to selecting the optimal treatment choice for each patient. This article focuses on the transplantation option.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common primary hepatobiliary malignancy in the United States [1]. Worldwide, it accounts for 3% of all primary gastrointestinal malignancies and 10% of primary hepatobiliary malignancies [2]. CCA is notoriously difficult to treat as it often presents in advanced stages where it is not amenable to resection.

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Reports of 5-year survival following resection range from 8% to 44% [3].

With few long-term survivors after resection, attempts at cure of CCA were made in the early LT experience. One early aggregation of patients in 1991 from the University of Cincinnati tumor registry revealed 2- and 5-year survival rates of 30% and 17%, respectively [4]. This was confirmed in 2000 by the same group examining the results of 207 patients undergoing liver transplantation for cholangiocarcinoma. This revealed an overall 1-, 2-, and 5-year survival rate of 72%, 48%, and 23%, respectively [5]. These series did not analyze peripheral and central CCA separately.

The Hannover experience reported in 1989 showed similar results, with only 1 of 10 patients with intrahepatic cholangiocarcinoma and 10 of 20 patients with proximal bile duct cholangiocarcinomas surviving to 1 year [6]. A series out of the University of Pittsburgh examining 20 patients transplanted for intrahepatic CCA identified a 5-year survival rate of only 18% [7]. The King's College experience reported similar results with almost universal disease recurrence and death within 3 years of transplantation for patients with both peripheral and central CCA [8]. The results of these early series, which did not emphasize highly selected early stage disease and neoadjuvant or adjuvant radiation and chemotherapy, had an average 1-, 3-, and 5-year survival of 43%, 30%, and 10%, respectively [9]. A more recent review of Spanish centers identified a 5-year survival of 30% for patients transplanted with hilar CCA and 42% for peripheral CCA. A summary of selected series is given in Table I. These studies, among others, established CCA as a poor indication in general for transplantation due to high disease recurrence with few long-term survivors. In addition, the poor results with transplantation for peripheral CCA have not exceeded conventional surgery, leading to the abandonment of transplantation for known peripheral CCA.

Table I. Survival after liver transplantation for cholangiocarcinoma.

Author	Year	Institution	n	Survival			
				1-year	2-year	3-year	5-year
O'Grady et al. [38]	1988	King's College	26	34%	15%	8%	5%
Ringe et al. [6]	1989	Hannover	30	38%	32%	–	14%
Penn [4]	1991	Cincinnati registry	109	–	30%	–	4%
Nashan et al. [39]	1996	Hannover	10	30%	–	–	10%
Goss et al. [10]	1997	UCLA (known)	4	33%	33%	–	0%
Goss et al. [10]	1997	UCLA (incidental)	10	90%	–	83%	83%
Iwatsuki et al. [40]	1998	Pittsburgh	27	60%	36%	36%	36%
Bismuth [41]	2000	Paul Brousse	9	–	–	33%	–
Meyer et al. [5]	2000	Cincinnati registry	207	72%	48%	–	23%
Shimoda et al. [42]	2001	UCLA	25	71%	–	35%	–
Robles et al. [43]	2004	Spanish centers (hilar)	36	82%	–	53%	30%
Robles et al. [43]	2004	Spanish centers (peripheral)	23	77%	–	65%	42%
Ghali et al. [44]	2005	Canadian centers (incidental)	10	90%	–	30%	–

Note that in the study by Goss et al., incidental CCAs treated with transplantation had a 5-year survival of 83% (incidental CCA were lesions <1 cm that were discovered on pathologic examination of the explanted liver) [10]. However, patients in this same study with known CCA had a 5-year survival of 0%. This observation helped stimulate a more selective approach to transplantation for CCA.

Highly selected patients with CCA found in the study by DeVreede et al. demonstrated an 80% 5-year survival [11]. Ten of the 11 patients transplanted were stage I and II patients. They all underwent external beam irradiation plus bolus 5-fluorouracil (5-FU), followed by brachytherapy with iridium plus 5-FU infusion, followed by exploratory laparotomy, and finally a continuous 5-FU infusion until transplantation. Sudan et al., using a protocol of intense brachytherapy and 5-FU, reached a 3- and 5-year survival of 45% in 11 transplanted patients [12]. And more recently, the Mayo group reported a protocol utilizing neoadjuvant external beam radiation therapy, chemosensitization with infusional 5-FU and oral capecitabine, and intraluminal brachytherapy. Eligible patients had to have operatively confirmed, stage I or II unresectable hilar CCA or CCA arising in the setting of primary sclerosing cholangitis prior to orthotopic liver transplantation. Of the 38 patients undergoing transplantation, improved survival was demonstrated; 92% at 1 year, 82% at 3 years, and 82% at 5 years. Additionally, 1-, 3-, and 5-year recurrence rates were also improved at 0%, 5%, and 12%, respectively [13]. The studies shown in Table II indicate that LT for early stage hilar CCA in selected individuals can be effective and should be considered as part of a research protocol in certain centers.

Hepatoblastoma

Hepatoblastoma (HB) is the most common primary malignant hepatic tumor in the pediatric population, with the incidence peaking in the first 3 years of life.

Table II. Survival after liver transplantation for cholangiocarcinoma in which early stage disease and neoadjuvant or adjuvant radiation and chemotherapy are emphasized.

Author	Year	Institution	n	Survival			
				1-year	2-year	3-year	5-year
DeVreede et al. [11]	2000	Mayo	11	100%	100%	100%	80%
Sudan et al. [12]	2002	Nebraska	11	55%	45%	45%	–
Rea et al. [13]	2005	Mayo	38	92%	–	82%	82%

Approximately 60% of patients are unresectable at the time of diagnosis [14]. These tumors are typically very sensitive to cisplatin-based chemotherapy. Therefore, the cornerstone of therapy is neoadjuvant chemotherapy in an attempt to decrease tumor bulk to allow patients to become candidates for resection. When followed after surgical resection, an 80% 5–10-year disease-free survival has been demonstrated [15]. LT plays a role as primary surgical therapy for those individuals afflicted with HB in whom tumors are unresectable after chemotherapy. Additionally, LT plays a role as rescue therapy for patients who are incompletely resected, recur after resection, or develop hepatic insufficiency after chemotherapy and/or resection.

Otte et al. [16] reviewed the world experience with LT for HB, collecting data from 24 centers (12 in North America, 10 in Europe, 1 in Japan, and 1 in Australia). They found that the overall survival at 6 years post transplant was 82% for primary transplant recipients and 30% for rescue transplant recipients. These positive results for LT for HB have been supported by subsequent studies. A smaller series from the University of Cincinnati had an 88% overall survival rate with the lone death occurring 7 years after rescue transplantation from post-transplant lymphoproliferative disorder [14]. A recent review of the United Network for Organ Sharing database of 135 patients undergoing LT for HB also demonstrated good long-term results. The reported 1-, 5-, and 10-year survival rate was 71%, 61%, and 58%, respectively [17]. The largest single institution series of living donor liver transplantation for HB is from Kyoto University Hospital in Japan [18]. A 72%

overall survival was demonstrated in 14 patients (7 primary transplant, 7 rescue) at a median follow-up of 42 months. Results of selected series are shown in Table III. Based on these reports and others, LT for HB has become a widely accepted indication for LT if the tumor is unresectable after chemotherapy or as a rescue therapy for residual disease after resection or for hepatic insufficiency after chemotherapy and/or resection.

Hepatic epithelioid hemangioendothelioma and angiosarcoma

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare, multifocal tumor arising from the vascular endothelium, predominantly effecting females (1.6:1). HEHE is an enigmatic tumor with unpredictable malignant behavior that lies somewhere in the spectrum between benign hemangiomas and malignant angiosarcomas (AS) [19]. Due to the multifocal nature of disease, HEHE can often be misdiagnosed as metastatic disease. The lesions are bilobar in almost all cases and number an average of 15 or more [20]. Chemotherapy and radiation appear to offer little benefit. Some patients have had long-term survival with no therapy [21], while others succumb within months from rapid progression. Distinction between these two clinical courses is difficult to predict, necessitating intervention. Resection is therefore indicated but the extensive multifocal nature of the disease can make surgical resection quite difficult and has made LT the more attractive option.

Most series on LT for HEHE are small, but show favorable outcomes. One of the larger series to date includes 16 patients who underwent transplantation for HEHE at the University of Pittsburgh. Overall survival was 100%, 88%, and 71% at 1, 3, and 5 years. Disease-free survival was 81%, 69%, and 60% at 1, 3, and 5 years, respectively [22]. Interestingly, the presence of extrahepatic disease at the time of transplantation did not effect survival time. A series from Heidelberg of three patients who received LT for HEHE (two cadaveric grafts, one living donor graft) reported no deaths with a follow-up of 13, 13, and 151 months, respectively [23]. Finally, the European Liver Transplant Registry contains 51 patients that were transplanted for HEHE with a 5- and 10-year survival of 87% and 78%, respectively [20]. There

Table III. Summary of selected results of liver transplantation for hepatoblastoma.

Center	Period	n	Overall survival (%)
Pittsburgh [45]	1989–1998	12	83
Omaha [16]	1986–1999	10	70
UCLA [16]	1984–2001	16	75
Brussels [16]	1987–2001	10	70
Birmingham, UK [46]	1991–2000	14	79
London, UK [47]	1992–2001	11	100
Baylor [48]	1984–2000	9	66
SIOPEL-1 [16]	1990–2001	12	66
UNOS review [17]	1987–2004	135	66

Table IV. Results of selected series for liver transplantation for metastatic neuroendocrine tumors.

Reference	Year	<i>n</i>	1-year survival (%)	5-year survival (%)	Actuarial 5-year disease-free survivors
Lang et al. [33]	1997	12	83	83	1
Olausson et al. [34]	2002	9	89	–	0
Rosenau et al. [35]	2002	19	89	80	3
Florman et al. [32]	2004	11	73	36	1

was no difference in survival from the presence of extrahepatic disease in adults, although some required additional pulmonary resections. These reports and others have made HEHE an acceptable indication for LT, even in the face of extrahepatic disease.

The vascular endothelium is also the point of origination for AS. Unlike HEHE, however, AS is a very aggressive tumor and is a contraindication to LT. The outlook for patients transplanted in which AS is found incidentally is ominous. One report from the United Network for Organ Sharing database on seven transplant patients in whom AS was incidentally discovered demonstrated a mean survival of 262 days [24]. There were 17 patients in the European Liver Transplant Registry who had undergone transplantation for angiosarcoma with a median survival of only 7 months [20]. Reports like this have led to abandonment of liver transplant in the setting of AS. It is an absolute contraindication.

Neuroendocrine tumors (NET)

Variable 5-year survival for untreated liver metastasis from NET has been reported, centering on 30–40%, and for carcinoid tumors a slightly more favorable prognosis [25]. Because these tumors are characteristically relatively slow growing and treatment response rates are quite different from a comparable tumor load of other types of metastasis, these patients deserve careful and thoughtful consideration of aggressive medical and surgical therapy. For example, functional hormonal blockade and/or tumor debulking or ablation can produce improved quality and length of life by decreasing the levels of circulating hormones produced by the tumor and the resulting symptoms.

It is commonplace for liver metastases of NET to be bilobar and patients with NET can have a miliary pattern of disease and often present with distant disease. Therefore, only about 10–20% of patients will be candidates for resection, and even then total resection is not often accomplished. In general, palliative resection of hepatic metastases is believed to be a worthwhile endeavor if 80–90% of the gross hepatic tumor mass can be successfully resected and the surgical risk is very low [26]. Symptomatic improvement can be expected in the majority of these patients and the duration of the clinical response is felt

to be inversely proportional to the amount of residual tumor following resection [27,28].

LT has been employed for some patients for unresectable tumors or for palliation of medically uncontrollable symptoms. This is currently the only metastatic indication for LT [29]. A total of 103 patients reported in the world literature transplanted for metastatic NET were reviewed in 1998 by Lehnert [30]. The 2- and 5-year survival rates were 60% and 47%, respectively. Factors associated with worsened survival on multivariate analysis were age >50 years and combined upper abdominal exenteration. Other factors that have been proposed in selecting patients for transplantation are progression of liver tumors, the absence of extrahepatic disease proven over a 6-month period, and excessive hormonal symptoms refractory to medical therapy [31].

Florman et al. [32] reported an overall survival of 73% and 36% at 1 and 5 years, respectively, with a mean follow-up of 34 months. Lang et al. [33] reported an actuarial survival of 75%, with a median follow-up of 55 months; 58% of these patients developed recurrence. Two other publications demonstrated good short-term survival, each 89% at 1 year [34,35]. These results are summarized in Table IV. These authors suggest that cure for metastatic NET to the liver is unlikely. Furthermore, due to overall reported results, they recommend that liver transplantation should be withheld until all other avenues of treatment have been explored and deemed unsuccessful. Sutcliffe et al. [29] recommend using the Milan criteria for assessing the suitability of LT in the setting of metastatic NET, although these criteria have not been validated. Furthermore, they suggest that results could also be improved if primary resection is undertaken prior to transplantation and if patients are transplanted early in their clinical course when the presence of extrahepatic disease is less likely.

Primary NET of the liver are even rarer than their metastatic counterparts. There have been fewer than 60 reported cases in the world literature, with the largest series to date consisting of 8 patients, 2 of whom required transplantation due to unresectable disease [36]. Both of these patients had successful outcomes with survival of 45 and 95 months, respectively.

Metastatic disease

Metastatic disease to the liver is very rarely an indication for LT, except in the setting of NET. However, in 2005, successful long-term outcome following LT for metastatic gastrointestinal stromal tumors in two patients was reported [37]. Both patients were alive without evidence of recurrence at 48 and 69 months, respectively.

Summary

In conclusion, LT for early stage hilar CCA in selected individuals can be effective and should be considered an indication for transplantation as part of a research protocol in certain centers following neoadjuvant chemoradiation.

For HB, the role of LT is twofold. First, transplantation is reserved for patients who are still unresectable after neoadjuvant therapy. Second, LT plays a role as rescue therapy for patients who are incompletely resected, recur after resection, or develop hepatic insufficiency after chemotherapy and/or resection. HEHE is an acceptable indication for LT. Transplantation is indicated for patients even with extrahepatic disease, at least in adults. Angiosarcoma is an absolute contraindication to LT. Neuroendocrine tumors, whether metastatic or arising from the liver, can be treated with LT when unresectable or when medical management of symptoms cannot be achieved. Best results will be achieved with patients age <50 years, primary tumor completely resected; absence of extrahepatic disease proven over a 6-month period; and excessive hormonal symptoms refractory to medical therapy.

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