Review Article

Pediatric liver transplantation for hepatoblastoma

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Abstract: Hepatoblastoma is the most common pediatric liver tumor and is usually diagnosed before five years of age. Treatment consists of a combination of chemotherapy and surgery, with the goal being attainment of complete local control by surgical resection and eradication of any extrahepatic disease. Neoadjuvant chemotherapy is utilized and is often beneficial in rendering tumors resectable; however, prolonged chemotherapy administration attempting to render tumors resectable by conventional resection should be avoided. For patients whose tumors are too extensive to be conventionally resected, liver transplantation can be curative and remains the treatment of choice for eligible patients otherwise incurable by conventional resection.

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Hepatoblastoma is the most common pediatric liver tumor and is usually diagnosed before five years of age. It accounts for 1.2% of malignancies in patients less than 15 years of age (1). Recent studies report an increasing incidence of hepatoblastoma in the U.S. from 0.6 to 1.2 per million (2,3). Typically, patients present with an abdominal mass and elevated AFP. Increased risk for development of hepatoblastoma is associated with Beckwith-Wiedemann Syndrome, Familial Adenomatous Polyposis Coli, maternal tobacco exposure and very low birthweight (4-6). Treatment consists of a combination of chemotherapy and surgery, with the goal being attainment of complete local control by surgical resection and eradication of any extrahepatic disease.

Staging

By the surgery based Evans staging system, staging was based upon exploratory surgery at diagnosis for all patients. Stage I and II tumors are those resected at diagnosis with microscopically negative and positive margins, respectively. Stage III and IV tumors are unresectable at diagnosis without and with metastatic disease, respectively. The current COG protocol, AHEP0731, uses a risk stratification scheme that is a hybrid of the old Evans system and PRE-TEXT (Pretreatment Extent of disease) used to define the timing and extent of surgical resection (7). In PRE-TEXT, the tumor group (I, II, III, IV) defines the extent of hepatic parenchymal involvement and the PRE-TEXT annotation factors (V, P, E, F, R, C, N, M denoting hepatic veins or vena cava, portal vein, extrahepatic, multifocal, tumor rupture, caudate lobe, lymph node and metastatic disease, respectively) define unique tumor characteristics and the extent of extrahepatic disease. PRE-TEXT I and II tumors have 3 and 2 adjoining sections free of tumor, respectively, and are usually resectable at diagnosis or after neoadjuvant chemotherapy depending on vascular involvement. For PRE-TEXT III and IV tumors, only one or two

nonadjoining sections or none, respectively, are free of tumor and major vessel involvement is common. When the vessels or all sections remain involved after chemotherapy the tumor may not be resectable. Recently, the Childhood Hepatic tumors International Collaboration (CHIC) was formed and developed a new risk stratification and staging system based on PRE-TEXT that will be the basis of the upcoming international liver tumors trial.

Resectability

Complete resection is a critical component for cure in the treatment of hepatoblastoma; however, 60% of tumors are unresectable at the time of diagnosis (8). Neoadjuvant chemotherapy is utilized and is often beneficial in rendering tumors resectable. Commonly, two adjuvant cycles of chemotherapy are reserved for administration post-operatively. Ortega *et al*. reported 20% of initially unresectable tumors remained unresectable after neoadjuvant chemotherapy. Otte *et al*. reported a need for liver transplantation for approximately 15% of patients with initially unresectable tumors (9).

Historical perspective: liver transplantation for hepatoblastoma

For patients whose tumors are too extensive to be conventionally resected, liver transplantation can be curative and has become an integral component of current treatment algorithms. In a recent study based on United Network for Organ Sharing (UNOS) registry data, the frequency of liver transplantation for hepatoblastoma increased from five in 1990 to 43 in 2013 (10). A review by Cruz *et al*. of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry [1975–2007], UNOS [1988–2010] and Children's Hospital of Pittsburgh database [1987–2011] revealed a 20-fold increase in liver transplantation for hepatoblastoma over a 32-year period during which the frequency of hepatoblastoma cases increased 4-fold (11). The authors reported an increase in referral rate for liver transplantation for hepatoblastoma from 5% in early 1990s to 20% after 2004.

Indications for liver transplantation for hepatoblastoma

The Children's Oncology Group (COG) recommends that only tumors where a segmentectomy or hemihepatectomy can be performed with a 1 cm tumor free margin on the middle hepatic vein and portal bifurcation be performed at diagnosis (1). Generally accepted indications for liver transplantation for hepatoblastoma include unifocal POST-TEXT IV (PRE-TEXT classification following chemotherapy) tumors and/or POST-TEXT III or IV with persistent widespread multifocality or major vessel involvement. Ideally, before a transplant there would be some response to chemotherapy. Depending on the surgeon, patients with POST-TEXT III tumors with major vascular involvement may be considered for an extreme conventional resection (conventional resection with major vascular reconstruction) instead of liver transplantation (7). In the nearly completed Childrens Oncology Group study AHEP0731, results are being analyzed for patients with POST-TEXT III with venous involvement and POST-TEXT IV tumors comparing conventional resection versus liver transplantation.

Contraindications to liver transplantation for hepatoblastoma

Transplant is contraindicated in the presence of any active regional or distant metastatic disease not cleared by chemotherapy or surgery (12,13). The treatment strategy for a patient who present with lung metastases with locally advanced tumors where liver transplantation is necessary to achieve tumor extirpation remain the most challenging subset population. Cruz *et al*. found that in their analysis of the Children's Hospital of Philadelphia data, extrahepatic disease present prior to liver transplantation (but which had cleared by CT scan prior to transplant) was the main risk factor for recurrent hepatoblastoma post transplantation (11). Other analyses have found that risk of recurrence was similar for those who cleared with chemotherapy versus resection (10,14,15). Recommendations for bilateral lung palpation at the time of thoracotomy for persistent pulmonary disease following neoadjuvant chemotherapy remain controversial (1).

Liver transplantation in multifocal hepatoblastoma

Transplantation versus resection for patients with multifocal disease remains controversial with some recommending transplantation and others advocating for conventional resection when intrahepatic metastases clear with neoadjuvant chemotherapy (7,15-20). For

patients with POST-TEXT IV multifocal tumors without metastatic disease after neoadjuvant chemotherapy, liver transplantation is clearly indicated (1).

Timing of liver transplantation

Prolonged chemotherapy administration attempting to render tumors resectable by conventional resection should be avoided. Several studies indicate that continuing to administer chemotherapy after four cycles does not increase the likelihood of conventional resectability of the tumor (21,22). In such patients, where liver transplantation is required to achieve local control, transplantation after four cycles of neoadjuvant chemotherapy is ideal (7). Unfortunately, this is not always possible due to unpredictable factors such as deceased organ donor availability. Héry *et al*. reviewed their experience with liver transplantation for hepatoblastoma and reported a wait time of 1–50 days for liver transplant (median 16 days); the authors concluded that delays in timing from last chemotherapy to transplant should be kept as short as possible (15). The concept of early referral for consultation (including consultation via telephone, email or other communication) for liver transplantation versus extreme liver resection was introduced by the current COG protocol AHEP0731 and the feasibility and outcome of this approach has been a major objective of that study. The goal is to decrease excessive toxicity due to prolonged chemotherapy and improve survival. In addition, Otte and others have shown that survival is higher (approximately 80% versus 30–40%) for patients who undergo primary liver transplantation (no attempt at conventional resection) as opposed to those in whom liver transplantation is utilized in the salvage setting (13,15,23-25).

Donor source

Utilization of living versus cadaveric donors for liver transplantation is dependent on the provider's/institution's approach. Benefits of living donor liver transplantation include control of the timing of transplantation resulting on potentially shorter wait times thereby eliminating dependence on cadaveric liver availability, but engender risk of a major operative procedure to a healthy donor (11,15). Benefits to cadaveric donor transplantation include longer blood vessels from cadaveric donor grafts that allow for easier vascular reconstruction (15). Interestingly, Pham *et al.* reported increased recurrence rate for those who waited longer on the liver transplantation list for a cadaveric donor liver (mean time of 31 versus 15 days for those with recurrence versus those without, respectively) (10).

Complications of liver transplantation

Peri- and post-operative complications following liver transplantation include primary nonfunction, hepatic artery and portal vein thrombosis, bleeding, bile leak, infection, acute cellular rejection, long term immunosuppressive medication complications, post transplant lymphoproliferative disease and chronic rejection (14). Cruz *et al*. reported an increased risk of hepatic artery thrombosis in patients with hepatoblastoma undergoing liver transplantation compared to those receiving liver transplants for other conditions (11); however, the PLUTO registry did not find any increase in incidence of this complication (26). Héry *et al*. reported no post-operative mortality in the month post transplant in 13 pediatric patients receiving liver transplantation for hepatoblastoma (15). Four patients experienced complications (bile leak in one patient, arterial thrombosis followed by re-transplantation in three patients). Of 30 patients undergoing liver transplantation for hepatoblastoma at a single institution, four patients developed hepatic artery and/or portal vein thrombosis with all four requiring retransplantation (10). Second malignancies were infrequently reported with one patient with Burkitt Lymphoma four years after surgery (15).

Survival following liver transplantation for hepatoblastoma

Survival results from different institutional reports of liver transplantation for hepatoblastoma are difficult to compare given the inability to compare by patient specifics such as PRE-TEXT/POST-TEXT grouping, chemotherapy regimens, age, comorbidities, timing of transplant from last chemotherapy, utilization of adjuvant chemotherapy post transplantation and status of metastatic disease at the time of transplant. Upon review of 292 patients (in 29 separate publications) with hepatoblastoma who underwent liver transplantation, 76% of patients were alive at the time of publication (*Table 1* and *Table S1*). Of note, some manuscripts reviewed were not included when patients with hepatoblastoma were unable to be separately identified or when it was unclear if the patients had been previously reported. Of 41 patients (with details reported) with rescue liver transplantation after initial attempt at resection, seventeen

Table 1 Patients with HBL who underwent liver transplantation

Reference	Publication date/era	# of patients with hepatoblastoma	Surviving at time of report (%)
Heimann *et al*. (27)	1987/NR	1	100
Ringe *et al*. (28)	1989/1972–1987	2	50
Jenkins *et al*. (29)	1989/1983–1987	3	100
Olthoff *et al*. (30)	1990/1984–1989	1	100
Koneru *et al*. (31)	1991/Pre-1988	12	50
Tagge *et al*. (32)	1992/1980–1990	6	83
Lockwood *et al*. (33)	1993/NR	1	100
Superina *et al*. (34)	1996/ NR	3	67
Bilik *et al*. (35)	1997/1986–1997	4	100
Goss *et al*. (36)	1998/1984–1997	4	75
Al-Qabandi *et al*. (37)	1999/1991–1997	8	63
Dower *et al*. (38)	2000/1995	1	100
Pimpalwar *et al*. (23)	2002/1991–2000	7	86
Srinivasan *et al*. (39)	2002/1992–2001	13	85
Molmenti *et al*. (40)	2002/1984–2000	9	67
Cillo *et al*. (41)	2003/1990–2003	7	71
Otte (13)	2004/1990–1994	61	67
Kasahara *et al*. (42)	2005/1990–2004	14	71
Mejia *et al*. (43)	2005/1985–2003	10	70
Chen *et al*. (44)	2006/1987–2005	7	86
Casas-Melley *et al*. (45)	2007/2001–2005	8	75
Faraj *et al*. (46)	2008/1993–2007	13	92
Kosola *et al*. (47)	2010/1990–2007	6	67
Zsíros *et al*. (48)	2010/1998–2004	31	74
Héry *et al*. (15)	2011/2001–2009	13	77
Kim *et al*. (49)	2011/1991–2009	5	100
Ismail *et al*. (50); Kaliciński *et al*. (51)	2012/1990–2010	12	67
Pham *et al*. (10)	2015/1997–2014	30	87

HBL, hepatoblastoma; NR, not reported.

were alive (41%) compared with 85% of 175 patients with primary liver transplantation. Post-transplant chemotherapy appeared to have been administered for 140 patients; however, it is difficult to assess any relation to outcome given that details were not reported for many patients and many confounding factors exist (for some patients, chemotherapy was given after transplantation for recurrent disease, whereas others did not include these specifics).

Conclusions

Liver transplantation can be curative in certain patients in whom conventional resection is not possible. Early consultation with pediatric liver transplantation specialists is

critical in the management of patients with hepatoblastoma who are most likely to need liver transplantation or extreme liver resection and is important for facilitating timely resection by either conventional resection or liver transplantation (7). Though not without its complications (and lifelong immunosuppression), liver transplantation remains the treatment of choice for eligible patients otherwise incurable by conventional resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Clinical characteristics of patients with HBL who underwent liver transplantation

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Yale, USA	1987/NR	NR	No	VCR, CTX, doxo	No	Primary	NR	VCR, CTX, doxo, 5FU, bleo, cis	Pulm met at 7 months post LT, resected. Alive, NED 34 months post LT	(27)
Germany	1989/1972–1987	NR	NR	NR	NR	NR	NR	NR	Alive NED, 6 years post LT	(28)
Germany	1989/1972–1987	NR	NR	NR	NR	NR	NR	NR	Died of sepsis early post LT	(28)
Boston, USA	1989/1983–1987	NR	NR	NR	NR	NR	NR	NR	Alive NED, 9 months	(29)
Boston, USA	1989/1983–1987	NR	NR	NR	NR	NR	NR	NR	Alive NED, 33 months	(29)
Boston, USA	1989/1983–1987	NR	NR	NR	NR	NR	NR	NR	Alive NED, 7 years 2 months	(29)
UCLA, USA	1990/1984–1989	NR	No	NR	No	NR	NR	NR	Alive NED, 5.5 years post LT	(30)
USA	1991/Pre-1988	NR	No	Yes	No	Rescue	NR	No	Died PCP 9 mo post LT	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Rescue	NR	Yes	DOD 23 mo post LT	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Rescue	NR	No	Died of hep art thrombosis 15 days post LT	(31)
USA	1991/Pre-1988	NR	No	No	No	Primary	NR	No	Died of hep art thrombosis 4 mo post LT	(31)
USA	1991/Pre-1988	NR	No	No	No	Primary	NR	No	Alive NED, 66 mo	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Rescue	NR	No	DOD 4 mo	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Primary	NR	Yes	Alive NED, 30 mo	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Primary	NR	No	Alive NED, 43 mo	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Primary	NR	Yes	Alive NED, 32 mo	(31)
USA	1991/Pre-1988	NR	No	No	No	Primary	NR	Yes	Alive NED, 24 mo	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Primary	NR	No	DOD 35 days post LT	(31)
USA	1991/Pre-1988	NR	No	Yes	No	Primary	NR	Yes	Alive NED, 70 months post LT; (pulm rec @ 7 mo, resected)	(31)
Pittsburgh, USA	1992/1980–1990	NR	No	NR	NR	NR	NR	NR	Alive	(32)
Pittsburgh, USA	1992/1980–1990	NR	No	NR	NR	NR	NR	NR	Alive	(32)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Pittsburgh, USA	1992/1980–1990	NR	No	NR	NR	NR	NR	NR	Alive, 13 months	(32)
Pittsburgh, USA	1992/1980–1990	NR	No	NR	NR	NR	NR	NR	Alive, 5 months	(32)
Pittsburgh, USA	1992/1980–1990	NR	Yes	NR	NR	NR	NR	NR	Alive, 36 months	(32)
Pittsburgh, USA	1992/1980–1990	NR	Yes	NR	NR	NR	NR	NR	Died, 1 month	(32)
Leeds, England	1993/NR	NR	Yes	Cis, doxo, carbo, VP16	No (radio)	Primary	NR	NR	Alive, NED 35 months post LT	(33)
Toronto, Canada	1996/NR	NR	No	Cis, doxo	No	Primary	NR	No	Alive NED, 2.5 years	(34)
Toronto, Canada	1996/NR	NR	Yes	Cis, doxo	Yes (radio), but resected & neg on repeat scan and surgery	Primary	NR	No	Alive NED, 2.0 years	(34)
Toronto, Canada	1996/NR	NR	Yes	Yes	Yes (radio); No (biopsy)	Rescue	NR	NR	Poor disease control pre-LT; DOD 3 months post LT	(34)
Toronto, Canada	1997/1986–1997	NR	No	Yes	NR	Primary	NR	No	Alive	(35)
Toronto, Canada	1997/1986–1997	NR	No	Yes	NR	Primary	NR	No	Alive	(35)
Toronto, Canada	1997/1986–1997	NR	No	Yes	No	Primary	NR	No	Alive NED, 2.5 years [same pt as above in (34)]	(35)
Toronto, Canada	1997/1986–1997	NR	Yes	Yes	As above	Primary	NR	No	Alive NED, 2.0 years [same pt as above in (34) Superina]	(35)
Toronto, Canada	1997/1986–1997	NR	Yes	Yes	As above	Rescue	NR	NR	DOD 3 months post LT [Same pt as above in (34)]	(35)
UCLA, USA: 4 pts	1998/1984–1997	NR	NR	NR	NR	NR	NR	NR	75% survival (4 pts)	(36)
Birmingham, England	1999/1991–1997	IV	NR	Cis, doxo	No	Primary	Cad	NR	Alive, 82 months; retransplant @ 6 years related to hep art thrombosis	(37)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Birmingham, England	1999/1991–1997	II	NR	Cis, doxo	No	Primary	Cad	NR	Died with pulm met (+ FAP), unclear if 2nd neoplasm, 70 months	(37)
Birmingham, England	1999/1991–1997	III	NR	Cis, doxo + other	No	Rescue	Cad	NR	AFP elevated at LT; DOD, 23 months	(37)
Birmingham, England	1999/1991–1997	IV	NR	Cis, doxo	No	Primary	Cad	NR	Alive, 36 months	(37)
Birmingham, England	1999/1991–1997	IV	NR	Cis, doxo + other	No	Primary	Cad	NR	Alive, 9 months	(37)
Birmingham, England	1999/1991–1997	IV	NR	Cis, doxo, carbo	No	Primary	Cad	NR	Alive, 22 months	(37)
Birmingham, England	1999/1991–1997	IV	NR	Ciis, doxo + other	No	Rescue	Cad	NR	Alive, 12 months	(37)
Birmingham, England	1999/1991–1997	IV	NR	Cis, doxo, carbo	No	Primary	Cad	NR	Died of infection, 1 month	(37)
Edmonton, Canada	2000/1995	NR	Yes	Carbo, VCR, 5FU, cis, VP16, doxo, ifos	No (radio)	Rescue	Living	Cis, doxo	Alive NED, 38 months	(38)
Birmingham, England	2002/1991–2000	III	No	Yes	No	Primary	NR	NR	Alive NED	(23) [new patients not previously reported in (37)]
Birmingham, England	2002/1991–2000	IV	No	Yes	No	Primary	NR	NR	Alive NED	(23)
Birmingham, England	2002/1991–2000	IV	No	Yes	No	Primary	NR	NR	Alive NED	(23)
Birmingham, England	2002/1991–2000	IV	No	Yes	No	Primary	NR	NR	Alive NED	(23)
Birmingham, England	2002/1991–2000	IV	No	Yes	No	Primary	NR	NR	Alive NED	(23)
Birmingham, England	2002/1991–2000	NR	Yes (relapse)	Yes	No (cleared by surgery)	Rescue	NR	NR	Alive NED, 3 years post LT	(23)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Birmingham, England	2002/1991–2000	NR	NR	Yes	No	Rescue	NR	NR	DOD 23 months post LT	(23)
UK	2002/1992–2001	III	No	VCR, cis, 5FU	No	Primary	Cad	No	Alive NED, 9 years	(39,46)
UK	2002/1992–2001	IV	No	Cis, carbo, doxo	No	Primary	LRLT	Cis, carbo, doxo	Alive NED, 3.8 years	(39,46)
UK	2002/1992–2001	III	No	Cis, carbo, doxo	No	Rescue	Cad	No	Died of respiratory failure 3 weeks post LT	(39,46)
UK	2002/1992–2001	IV	No	Cis, carbo, doxo	No	Primary	LRLT	Cis, carbo, doxo	Alive NED, 3.5 years	(39,46)
UK	2002/1992–2001	III	No	Cis, doxo	No	Primary	Cad	No	Alive NED, 7.5 years	(39,46)
UK	2002/1992–2001	IV	No	Cis, carbo, doxo	No	Primary	Cad	Cis, carbo, doxo	Alive NED, 4.8 years	(39,46)
UK	2002/1992–2001	III	No	Cis, doxo	No	Primary	Cad	Carbo, doxo	Alive NED, 2.4 years	(39,46)
UK	2002/1992–2001	III	No	Cis, carbo, doxo	No	Primary	Living	No	Alive NED, 1.2 years	(39,46)
UK	2002/1992–2001	III	No	Cis, carbo, doxo	No	Primary	Cad	Cis	Alive NED, 1.9 years	(39,46)
UK	2002/1992–2001	III	No	Cis, carbo, doxo	No	Primary	Living	Cis, carbo, doxo	Alive NED, 2 years	(39,46)
UK	2002/1992–2001	III	No	Cis, carbo, doxo	No	Primary	Cad	Cis, carbo, doxo	Alive NED, 2.3 years	(39,46)
UK	2002/1992–2001	IV	Yes	Cis, carbo, doxo	No (radio)	Primary	Cad	Cis, CTX,VP16	Alive with pulm mets, 8 months post LT	(39,46)
UK	2002/1992–2001	IV	No	Cis, carbo, doxo	No	Primary	Cad	Cis, carbo, doxo	Alive NED, 1 month post LT	(39,46)
Dallas, USA	2002/1984–2000	NR	NR	CTX, doxo	No	Rescue	NR	No	Alive NED	(40)
Dallas, USA	2002/1984–2000	NR	NR	Cis, VCR, 5FU, MTX	No	Rescue	NR	No	Died of PCP 2.5 years post LT	(40)
Dallas, USA	2002/1984–2000	NR	NR	Cis, VCR, 5FU	No	Primary	NR	No	Died early post LT due to hep art thrombosis	(40)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Dallas, USA	2002/1984–2000	NR	NR	Cis, VCR, 5FU	No	Rescue	NR	Cis, VCR, VP16	Alive NED	(40)
Dallas, USA	2002/1984–2000	NR	NR	Cis, doxo	No	Primary	NR	Cis, VCR, 5FU	Alive NED	(40)
Dallas, USA	2002/1984–2000	NR	NR	Carbo, VCR, 5FU, cis, VP16	No	Primary	NR	No	Died due to sepsis 8 days post LT	(40)
Dallas, USA	2002/1984–2000	NR	NR	Cis, VCR, 5FU, VP16	No	Primary	NR	Cis, VCR, 5FU	Alive NED	(40)
Dallas, USA	2002/1984–2000	NR	NR	Cis, VCR, 5FU, carbo	No	Primary	NR	Carbo, VCR, 5FU	Alive NED	(40)
Dallas, USA	2002/1984–2000	NR	NR	Cis, VCR, 5FU, doxo, MTX, irino , CTX, topo	No	Primary	NR	Doxo, irino	Alive 1 year post LT; + margins, elevated AFP at LT; dev'd pulm met	(40)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Rescue	Cad	NR	Died 6 mos post LT	(41)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Primary	LR	NR	DOD 60 mos post LT	(41)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Primary	Cad	NR	Local recurrence @ 100 mos post LT, s/p resection, chemo & brachytherapy; survived @ 108 mos post LT.	(41)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Primary	Cad	NR	Alive, NED	(41)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Primary	Cad	NR	Alive, NED	(41)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Primary	Cad	NR	Alive, NED	(41)
Padua, Italy	2003/1990–2003	NR	No	SIOPEL-1	No	Primary	Cad	NR	Alive, NED	(41)
SIOPEL-1	2004/1990–1994	IV	Yes	Cis, doxo	No	Rescue	Cad	NR	Alive NED 115 months post LT; colon carcinoma at 9 years post LT, alive at last contact	(13)
SIOPEL-1	2004/1990–1994	II	No	Cis, doxo	No	Rescue	Cad	NR	DOD, 24 months post LT	(13)
SIOPEL-1	2004/1990–1994	IV	Yes	Cis, doxo	No	Primary	Cad	NR	Alive NED, 120 months post LT	(13)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
SIOPEL-1	2004/1990–1994	IV	No	Cis, doxo	No	Primary	Cad	NR	Alive NED, 122 months post LT; Retransplanted 6 years post LT related to art thrombosis.	(13)
SIOPEL-1	2004/1990–1994	IV	No	Cis, doxo	No	Primary	Cad	NR	Alive NED, 125 months post LT	(13)
SIOPEL-1	2004/1990–1994	IV	No	Cis, doxo	No	Primary	Cad	NR	Alive NED, 119 months post LT	(13)
SIOPEL-1	2004/1990–1994	II	Yes	Cis, doxo	No	Rescue	Cad	NR	Died related to art thrombosis at 6 days post LT	(13)
SIOPEL-1	2004/1990–1994	IV	Yes	Cis, doxo	No	Rescue	Cad	NR	Alive NED, 52 months post LT	(13)
SIOPEL-1	2004/1990–1994	III	No	Cis, doxo	No	Primary	Cad	NR	DOD, 70 mo post LT	(13)
SIOPEL-1	2004/1990–1994	IV	No	Cis, doxo	No	Primary	Cad	NR	Alive, NED 98 months post LT	(13)
SIOPEL-1	2004/1990–1994	III	No	Cis, doxo	No	Rescue	Cad	NR	Died of sepsis, 48 months post LT	(13)
SIOPEL-1	2004/1990–1994	IV	Yes	Cis, doxo	No	Primary	Cad	NR	Alive, NED 92 months post LT	(13)
Omaha: 10 pts	2004/1986–1999	NR	NR	NR	NR	Primary (6 pts), rescue [4]	Cad [8], Living [2]	3 of 10 pts	70% OS	(13)
Madrid: 8 pts	2004/1986–2001	NR	NR	NR	NR	Primary (7 pts), rescue [1]	Cad [7], Living [1]	7 of 8 pts	75% OS	(13)
Bergamo: 4 pts	2004/1988–2000	NR	NR	NR	NR	Primary (3 pts), rescue [1]	Cad [4]	No	25% OS	(13)
Coop. German group: 4 pts	2004/1989–2001	NR	NR	NR	NR	Primary (4 pts)	Cad [4]	No	100% OS	(13)
Kyoto: 8 pts	2004/1990–2001	NR	NR	NR	NR	Primary (4 pts), rescue [4]	Living [8]	6 of 8 pts	62% OS	(13)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Padova: 5 pts	2004/1994–1999	NR	NR	NR	NR	Primary (5 pts)	Cad [4], Living [1]	3 of 5 pts	80% OS	(13)
Paris: 3 pts	2004/1996–2001	NR	NR	NR	NR	Primary (1 pt), rescue [2]	Cad [3]	No	33% OS	(13)
Torino: 1 pt	2004/1999	NR	NR	NR	NR	Primary (1 pt)	Cad [1]	No	100% OS	(13)
Chicago: 2 pts	2004/1999–2001	NR	NR	NR	NR	Primary (1 pt), rescue [1]	Cad [2]	No	50% OS	(13)
Brisbane: 3 pts	2004/1999–2001	NR	NR	NR	NR	Primary (1 pt), rescue [2]	Cad [3]	No	66% OS	(13)
Boston: 1 pt	2004/2001	NR	NR	NR	NR	Primary [1]	Living [1]	Yes	100% OS	(13)
Kyoto, Japan	2005/1990–2004	III	NR	Cis/doxo	NR	Primary	Living	CTX, 5FU	DOD 280 days post LT	(42)
Kyoto, Japan	2005/1990–2004	IV	NR	Cis/doxo	NR	Rescue	Living	CTX, carbo, VP16, mel	DOD 960 days post LT	(42)
Kyoto, Japan	2005/1990–2004	IV	NR	Cis/doxo	NR	Primary	Living	Carbo, VP16, 5FU	DOD 330 days post LT	(42)
Kyoto, Japan	2005/1990–2004	III	NR	None	NR	Primary/post Kasai	Living	Carbo, doxo	Alive NED 81 months	(42)
Kyoto, Japan	2005/1990-2004	IV	NR	Cis/doxo	NR	Rescue	Living	Carbo, doxo	Alive NED 794 months	(42)
Kyoto, Japan	2005/1990–2004	IV	NR	Cis/doxo	NR	Primary	Living	Cis, doxo	Alive NED 67 months	(42)
Kyoto, Japan	2005/1990–2004	III	NR	Cis/doxo, VP16	NR	Rescue	Living	CTX	Alive NED 55 months	(42)
Kyoto, Japan	2005/1990–2004	IV	NR	Cis/doxo	NR	Rescue	Living	No	Alive NED 42 months	(42)
Kyoto, Japan	2005/1990–2004	IV	NR	Cis/doxo	NR	Primary	Living	Cis, doxo	Alive NED 36 months	(42)
Kyoto, Japan	2005/1990–2004	III	NR	Cis/doxo	NR	Rescue	Living	Carbo, VP16	Alive NED 21 months	(42)
Kyoto, Japan	2005/1990–2004	IV	NR	Cis/doxo	NR	Rescue	Living	Irino	DOD 202 days post LT	(42)
Kyoto, Japan	2005/1990–2004	III	NR	Cis/doxo, VP16	NR	Rescue	Living	Irino	Alive NED 17 months	(42)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Kyoto, Japan	2005/1990–2004	III	NR	Cis/doxo	NR	Primary	Living	Irino	Alive NED 8 months	(42)
Kyoto, Japan	2005/1990–2004	III	NR	Cis/doxo	NR	Primary	Living	Irino	Alive NED 6 months	(42)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, 5FU, VCR	No	Primary	Cad	No	Alive NED	(43)
San Antonio, USA	2005/1985–2003	NR	NR	No	No	Primary	Cad	No	Alive NED	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo, bleo, 5FU, VCR	No	Rescue	Cad	Cis, 5FU, VCR (for rec)	DOD 14 months	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo	No	Primary	Cad	Cis, doxo	Alive NED	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo	No	Rescue	Cad	Cis, doxo (for rec)	DOD 38 months	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo	No	Primary	LRLT	Cis, doxo (for rec)	Alive at 480 months; pulm mets resected ×3 & chemo	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo, mito	No	Rescue	Cad	No	Alive NED	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo	No	Rescue	Cad	Cis, doxo (for rec)	DOD 4 months	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, doxo	No	Primary	Cad	Cis, doxo	Alive NED	(43)
San Antonio, USA	2005/1985–2003	NR	NR	Cis, 5FU, VCR	No	Primary	Living	Cis, doxo	Alive NED	(43)
St. Louis, USA	2006/1987–2005	NR	NR	Cis, 5FU, VCR	NR	Primary	Cad	NR	Alive	(44)
St. Louis, USA	2006/1987–2005	NR	NR	Cis, 5FU, VCR	NR	Primary	Cad	For rec	DOD 1 year post LT	(44)
St. Louis, USA	2006/1987–2005	NR	NR	Cis, 5FU, VCR, ifos, doxo, CTX, VP16, carbo	NR	Rescue	Cad	NR	Alive	(44)
St. Louis, USA	2006/1987–2005	NR	NR	Cis, 5FU, VCR, ifos	NR	Primary	Living	NR	Alive	(44)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
St. Louis, USA	2006/1987–2005	NR	NR	Carbo, 5FU, VCR	NR	Primary	Cad	NR	Alive	(44)
St. Louis, USA	2006/1987–2005	NR	NR	Cis, 5FU, VCR	NR	Primary	Cad	NR	Alive	(44)
St. Louis, USA	2006/1987–2005	NR	NR	Cis, 5FU, VCR	NR	Primary	Living	NR	Alive	(44)
Delaware, USA	2007/2001–2005	NR	No	Cis, 5FU, VCR, irino	No	Rescue	Living	Yes	Alive NED 53 months	(45)
Delaware, USA	2007/2001–2005	NR	No	Cis, 5FU, VCR, carbo, doxo	No	Rescue	Living	Yes	DOD 8 months	(45)
Delaware, USA	2007/2001–2005	NR	No	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive NED 23 months	(45)
Delaware, USA	2007/2001–2005	NR	No	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive NED 23 months	(45)
Delaware, USA	2007/2001–2005	NR	No	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive NED 22 months	(45)
Delaware, USA	2007/2001–2005	NR	No	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive NED 8 months	(45)
Delaware, USA	2007/2001–2005	NR	Yes	Carbo, cis, VCR, CTX, doxo, topo	No (radio)	Primary	Living	Yes	Alive NED 48 months	(45)
Delaware, USA	2007/2001–2005	NR	Yes	Cis, 5FU, VCR, CTX, doxo, ifos, VP16	No (radio)	Primary	Living	Yes	DOD	(45)
London, UK	2008/1993–2007	III	NR	Cis, 5FU, VCR	No	NR	Cad	No	Alive	(46) [without pts reported in (39)]
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	III	NR	Cis, carbo, doxo	No	NR	Cad	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Living	Yes	Died	(46)
London, UK	2008/1993–2007	II	NR	Cis, carbo, doxo	No	NR	Living	Yes	Alive	(46)
London, UK	2008/1993–2007	IV	NR	Cis, carbo, doxo	No	NR	Living	Yes	Alive	(46)
Poland: 6 pts	2008/1990–2007	NR	NR	NR	NR	Primary (4 pts) Rescue [2]	NR	NR	DOD (2 pts, both post rescue LT), Alive post pulm rec (1 pt), Alive NED (3 pts)	(50,51)
Finland	2010/1990–2007	III	Yes	Cis, doxo, CTX, VCR, 5FU	No	Primary	Cad	No	Died 15.9 years, awaiting heart transplant for cardiomyopathy	(47)
Finland	2010/1990–2007	III	No	Cis, doxo	No	Primary	Cad	No	Alive 18.1 years	(47)
Finland	2010/1990–2007	III	No	Cis, doxo, carbo, CTX	No	Rescue	Cad	No	DOD	(47)
Finland	2010/1990–2007	IV	No	Cis, doxo, CTX, VP16, VCR	No	Primary	Cad	No	Alive 18.5 years	(47)
Finland	2010/1990–2007	III	No	Cis, doxo	No	Primary	Cad	No	Alive 14.5 years	(47)
Finland	2010/1990–2007	IV	Yes	Cis, doxo, carbo	No	Primary	Cad	No	Alive 2.3 years	(47)
SIOPEL-3HR: 31 pts	2010/1998–2004	PRE-TEXT IV in 26 pts	Yes (6 pts)	Cis, carbo, doxo	Yes (5 pts)	Primary	NR	Yes (23 pts)	8 of 31 pts DOD; 74% 3 yr EFS	(48)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	Yes	DOD, 1.9 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	Yes	DOD, 1.5 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	Yes	Alive, 2.5 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	No	Died cardiac failure, 1.4 years	(15)
France	2011/2001–2009	II	No	Yes	No	Primary	NR	Yes	Alive, 2.9 years	(15)
France	2011/2001–2009	IV	Yes	Yes	No	Primary	NR	Yes	Alive, 4.4 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	Yes	Alive, 4.6 years	(15)
France	2011/2001–2009	IV	Yes	Yes	No	Primary	NR	Yes	Alive, 4.8 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	No	Alive, 4.9 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	Yes	Alive, 4.6 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	No	Alive, 1 year	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	No	Alive, 1.5 years	(15)
France	2011/2001–2009	IV	No	Yes	No	Primary	NR	Yes	Alive, 3.7 years	(15)
Seoul, Korea	2011/1991–2009	III	NR	Cis/doxo	NR	NR	NR	NR	Alive NED	(49)
Seoul, Korea	2011/1991–2009	III	NR	Cis/doxo	NR	NR	NR	NR	Alive NED	(49)
Seoul, Korea	2011/1991–2009	IV	NR	Cis/doxo	NR	NR	NR	NR	Alive NED	(49)
Seoul, Korea	2011/1991–2009	IV	NR	Cis/doxo	NR	NR	NR	NR	Alive NED	(49)
Seoul, Korea	2011/1991–2009	IV	NR	Cis/doxo	NR	NR	NR	NR	Alive NED	(49)
Poland: 12 pts	2012/1990–2010	II (1 pt); III (6 pts); IV (5 pts);	Yes (2 pts)	Yes, at least cis/doxo	No	Primary (10 pts) rescue [2]	NR	NR	• 2 of 2 pts with rescue LT DOD 5 & 14 months post LT • 8 of 10 survived post primary LT	(50) [6 in (51)]
Stanford, USA	2015/1997–2014	IV	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	Died of sepsis	(10)
Stanford, USA	2015/1997–2014	IV	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	DOD	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	Yes	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Stanford, USA	2015/1997–2014	IV	Yes	Cis, 5FU, VCR	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	No	NR	No	Primary	Cad	NR	Alive	(10)
Stanford, USA	2015/1997–2014	IV	No	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	Yes	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	No	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, doxo	No	Rescue	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	Died of primary nonfunction	(10)
Stanford, USA	2015/1997–2014	III	No	NR	No	Primary	Cad	NR	Alive	(10)
Stanford, USA	2015/1997–2014	IV	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, doxo	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	Yes	Cis, 5FU, VCR	No	Primary	Cad	Yes	Died of sepsis	(10)
Stanford, USA	2015/1997–2014	III	No	SIOPEL 4	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	Yes	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	Cis, 5FU, VCR	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	SIOPEL 4	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	No	Cis, 5FU, VCR	No	Primary	Living	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	IV	Yes	COG AHEP0731	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	II	No	NR	No	Rescue	Living	NR	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	COG AHEP0731	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	No	COG AHEP0731	No	Primary	Cad	Yes	Alive	(10)

Table S1 *(continued)*

Table S1 *(continued)*

Source/location	Pub. date/era	PRE-TEXT	Mets at dx	Neoadj chemo	Mets prior to LT	LT-primary *vs*. rescue	LT source	Adjuvant chemo	Outcome	Ref
Stanford, USA	2015/1997–2014	III	No	COG AHEP0731	No	Primary	Cad	Yes	Alive	(10)
Stanford, USA	2015/1997–2014	III	Yes	COG AHEP0731	No	Primary	Cad	Yes	Alive	(10)

Pub., publication; mets, metastatic; dx, diagnosis; neoadj, neoadjuvant; chemo, chemotherapy; LT, liver transplantation; ref, reference; NR, not reported; VCR, vincristine; CTX, cyclophosphamide; doxo, doxorubicin; 5FU, 5-fluorouracil; bleo, bleomycin; cis, cisplatin; pulm, pulmonary; met, metastasis; NED, no evidence of disease; PCP, pneumocystis carinii pneumonia; hep, hepatic; art, artery; DOD, died of disease; rec, recurrence; carbo, carboplatin; VP16, etoposide; radio, radiologically; cad, cadaveric; FAP, familial adenomatous polyposis; AFP, alphafetoprotein; ifos, ifosfamide; MTX, methotrexate; irino, irinotecan; topo, topotecan; SIOPEL, International Childhood Liver Tumors Strategy Group; OS, overall survival; Mel, melphalan; mito, mitomycin.