Exploring new strategies in diagnosis and treatment of hilar cholangiocarcinoma
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 6

Vascular Complications after Orthotopic Liver Transplantation Following Neoadjuvant Therapy for Hilar Cholangiocarcinoma


ABSTRACT

Liver transplantation after neoadjuvant chemoradiotherapy has emerged as an effective treatment for patients with localized, node-negative, unresectable hilar cholangiocarcinoma (CCA) or CCA arising in the setting of primary sclerosing cholangitis (PSC). However, concern has arisen regarding the potential for vascular complications due to high-dose neoadjuvant therapy before transplantation. We reviewed our experience with specific aims to determine the incidences of arterial, portal, and hepatic venous complications in patients transplanted for CCA compared with patients who undergo transplantation for other indications, and to describe patient outcome as a result of these vascular complications.

We reviewed data for all patients who underwent liver transplantation for CCA between January 1993 and April 2006 and compared the incidences of vascular complications to whole organ and living donor recipient control groups.

Sixty-eight patients underwent neoadjuvant therapy and subsequent liver transplantation. Arterial complications arose in 21%; portal venous complications arose in 22%; and overall, 40% developed vascular complications. Late hepatic artery complications occurred more often in living donor recipients transplanted for CCA compared with the living donor control group (P=0.047). Late portal vein complications occurred more often in both whole organ and living donor recipients transplanted for CCA compared with the control groups (P=0.01 and P=0.009). Hepatic venous complications were rare. Patient and graft survival were not different between CCA and control patients.

Liver transplantation with neoadjuvant therapy is associated with far higher rates of late arterial and portal venous complications, but these complications do not adversely affect patient and graft survival.
INTRODUCTION

Cholangiocarcinoma (CCA) is a devastating disease. Resection is widely accepted as conventional treatment. Unfortunately, 5-year survival is only 20-40% for resectable CCA, and few tumors are amenable to resection. Liver transplantation alone is an equally poor treatment. Five-year survival was only 28% and recurrence was 51% in the large series reported by the Cincinnati Transplant Tumor Registry. Others have also reported disappointing results, even for incidentally detected CCA. In 1993, we developed a protocol combining the benefits of radiotherapy, chemosensitization, liver transplantation, and appropriate patient selection for patients with unresectable hilar CCA. Patient survival is high ~80% at 5 years after transplantation— and exceeds results with resection for patients with resectable disease. From the outset, we have been concerned about the adverse effect that neoadjuvant therapy might have on the transplantation procedure and patient outcome. Indeed, we encounter occasional difficulty oversewing the recipient hepatic artery because the vascular tissue may be friable. We also had several problems with hepatic artery thrombosis early in our experience and abandoned use of the native artery for reconstruction during deceased donor liver transplantation. Likewise, we often encounter difficulty with the portal vein dissection, especially separating it from the common bile duct. We have observed an unusually high incidence of late portal vein problems, which we attribute to the neoadjuvant therapy.

Liver transplantation after neoadjuvant therapy has emerged as effective therapy for patients with CCA. With wider spread application of this treatment strategy, recognition, and treatment of vascular complications will gain importance. We thus reviewed our experience to describe the incidence and treatment of vascular complications after neoadjuvant therapy and liver transplantation for CCA. Our specific aims were to determine the incidences of arterial, portal, and hepatic venous complications compared with patients who underwent liver transplantation for other indications, and to determine patient and graft outcome in patients who develop vascular complications.

MATERIALS AND METHODS

This retrospective study was conducted after review and approval by the Mayo Clinic Institutional Review Board. Data were abstracted from patient medical records and a database maintained on all patients treated for CCA in our transplant center. We reviewed data for all patients who underwent neo-adjuvant therapy and subsequent liver transplantation at Mayo
Clinic Rochester between January 1993 and April 2006. Follow-up was through May 2006.

The neoadjuvant protocol that patients completed before undergoing liver transplantation has been previously described in detail. In summary, patients received external-beam radiotherapy to a target dose of 4,500 cGy in 30 fractions. Concomitantly, intravenous fluorouracil was provided at 500 mg/m² as a daily bolus for the first 3 days of radiation.

Two or 3 weeks after completion of the external-beam radiotherapy, a transluminal boost of radiation was delivered by a transcatheter iridium-192 brachytherapy wire, with a target dose of 2,000-3,000 cGy. Thereafter, patients were treated with oral capecitabine at a dose of 2,000 mg/m² per day for 2 out of every 3 weeks, as tolerated until transplantation. A staging laparotomy was performed on completion of the brachytherapy. It consisted of complete abdominal exploration with biopsy of any abnormal lymph node or nodules suspicious for tumor, examination of the tumor, and routine biopsy of regional lymph nodes. Only patients with negative staging operations remained eligible for liver transplantation.

Transplantation was performed with deceased donor livers, living donor right livers, and a familial amyloid domino liver. The liver grafts were inspected before transplantation. In the case of aberrant arterial anatomy, a reconstruction was carried out on the back table. Between 1993 and 1997, transplantation was performed with excision of the retrohepatic vena cava followed by donor caval interposition using portovenous and venovenous bypass. After 1997, caval-sparing hepatectomy became the standard technique in our center and was also used to treat CCA patients, unless there was suspected caudate involvement. We avoided the hilus during dissection and divided the bile duct, hepatic artery, and portal vein as low as possible. Since 1999, frozen sections of bile duct margins are obtained and evaluated for involvement. If tumor was present at the margin, we proceeded with pancreateoduodenectomy in addition to hepatectomy and transplantation. To minimize the anticipated risk of radiation-induced vascular complications, arterial reconstruction was preferentially performed with a donor iliac artery interposition graft to the infrarenal aorta during deceased donor transplantation.

All living donor transplants were performed with a segment of deceased donor iliac vein as an interposition graft between the donor right portal vein and recipient portal vein. Biliary reconstruction was with a Roux-en-Y hepatico- or choledochojenunostomy, or with a standard pancreateoduodenectomy reconstruction.

Duplex Doppler ultrasonography for assessment of vascular patency was routinely performed on days 1, 7, and 21, at 4 months, and annually after transplantation for all deceased and
living donor liver recipients. Patients with CCA, hepatocellular carcinoma, or other liver malignancies also underwent annual computed tomographic (CT) scans of the abdomen and chest for the first 5 years after transplantation. Additional studies were obtained whenever clinically necessary. Abnormal findings were further evaluated with angiography, contrast CT scan, or reoperation. All vascular thrombosis and stenosis were confirmed by angiography, contrast CT scan, or reoperation.

To assess the effect of radiotherapy on the incidence of vascular complications after transplantation, we performed 2 comparative analyses with 2 separate control groups. In the first analysis, we compared vascular complication rates between CCA recipients of whole liver allografts to recipients of whole liver allografts transplanted for other indications between June 2000 and April 2006. All patients in this analysis had a deceased donor iliac artery interposition graft to the infrarenal aorta. In the second analysis, we compared vascular complication rates between CCA recipients of living donor livers to recipients of living donor livers who underwent transplantation for other indications. All patients in this analysis had arterial reconstruction to the recipient common hepatic artery or a distal branch (proper, left, or right hepatic artery) without an interposition graft and underwent transplantation between June 2000 and April 2006.

Statistical analyses were performed by JMP version 6.0 (SAS Institute, Cary, NC). Continuous variables were compared by the 2-tailed unpaired t-test, and the Pearson $\chi^2$ test was used for categorical variables. In the case of small numbers, we applied the Fisher exact test. $P < 0.05$ was considered significant.

**RESULTS**

Sixty-eight patients with CCA completed neoadjuvant therapy and underwent liver transplantation at Mayo Clinic Rochester between January 1993 and April 2006. There were 49 men and 19 women with a mean age at transplantation of 49 years (range, 22-66 years). Forty-two patients (62%) had underlying PSC. Liver allografts included 51 deceased donor whole livers (75%), 16 living donor right livers (23.5%), and 1 familial amyloid domino donor whole liver (1.5%). Eleven transplantations were performed with excision and 57 with sparing of the retrohepatic vena cava. Arterial reconstruction was accomplished with an iliac artery interposition graft to the infrarenal aorta for all but 7 recipients of whole organ grafts. Eleven donor livers had replaced right hepatic arteries that were sewn to the donor
gastroduodenal artery (n=6), splenic artery (n=4), or celiac trunk (n=1). Another donor liver had replaced right and left hepatic arteries that were sewn together before implantation. A small accessory right hepatic artery was encountered during procurement of a living donor right liver, and it was sewn to the cystic artery that arose from the main right hepatic artery. All 16 living donor recipients and 2 whole donor recipients had deceased donor iliac vein grafts either as an interposition graft between the donor and recipient portal veins or as a graft between the donor portal vein and the recipient superior or inferior mesenteric veins. Biliary reconstruction was with a Roux-en-Y choledochojejunostomy (whole organ grafts), Roux-en-Y hepaticojejunostomy (living donor grafts) or a choledochojejunostomy with standard pancreatectoduodenectomy reconstruction for those patients who underwent combined pancreatectoduodenectomy and liver transplantation.

**Vascular Complications**

We identified 35 vascular complications occurring in 27 (40%) of 68 patients. Eight patients developed both arterial and portal venous complications (n=4), arterial and hepatic vein/caval complications (n=2), and portal and hepatic vein/caval complications (n=2). Twenty of 27 patients with vascular complications were alive at last follow-up. Five patients underwent retransplantation for vascular (arterial) complications. Two deaths were attributable to vascular complications (whole donor patient 12 and living donor patient 1). Four deaths were due to recurrent CCA, and one death was due to sepsis from an uncontrollable retained Wall stent leak.

**Hepatic Artery Complications**

Fourteen patients (21%) developed hepatic artery complications, 7 within 30 days and 7 between 2 and 11 months after transplantation (Tables 1 and 2). Two deaths were attributable to hepatic artery complications. Hepatic artery complications developed in 7 (13%) of 52 whole organ recipients. One patient required retransplantation for arterial thrombosis at 1 month. This patient was early in our experience, before routine use of iliac artery grafts for reconstruction to avoid anastomoses to the irradiated recipient artery. Two additional arterial thromboses were treated with operative thrombectomy. Both required subsequent angioplasty procedures for stenosis, and one eventually developed thrombosis that required retransplantation. One patient with late thrombosis was successfully treated with
thrombolysis and angioplasty. Two patients developed arterial stenosis at the anastomosis between the donor common hepatic artery and the iliac artery graft (1 week and 11 months) and were successfully treated with angioplasty and angioplasty/stent placement. Another patient required emergency retransplantation for graft failure and developed hepatic artery thrombosis at 3 weeks. Operative intervention was unsuccessful, and he died during attempted retransplantation for cholangiopathy.

Hepatic artery complications developed in 7 (44%) of 16 living donor recipients, including 2 early and 5 late (2-11 months) complications. Two patients developed arterial thrombosis. One had a late thrombosis (living donor recipient 2, at 3 months) with spontaneous rearterialization but died from recurrent CCA at 24 months. Living donor recipient 6 had arterial thrombosis at 2 weeks and underwent operative thrombectomy and subsequent reoperation for a pseudoaneurysm. He is alive with a patent artery 16 months after transplantation. Five patients developed arterial stenosis. Four of the patients had stenoses at the donor-recipient arterial anastomoses. Two were successfully treated with angioplasty. One died from sepsis (unrelated to the stenosis) and another eventually developed thrombosis and died after retransplantation. Living donor recipient 4 developed an early stenosis due to a donor artery injury during procurement. An attempted angioplasty required stent placement for intimal dissection and led to thrombosis that required retransplantation.

**Portal Vein Complications**

Fifteen (22%) of 68 patients developed portal vein complications, including 5 thromboses and 10 stenoses. Three early portal complications were all thromboses. Twelve late complications included 10 stenoses and 2 thromboses. Portal vein stenoses involving the recipient portal vein and the anastomosis developed in 7 of the 52 whole organ recipients. Early in our experience, we observed progression of portal vein stenosis in several patients and 2 thromboses. Because of the progressive nature of late portal vein stenosis, we decided to intervene, regardless of symptoms, for all patients with portal stenosis. All were treated with percutaneous transhepatic portal angioplasty and stent placement (Figs. 1 and 2) with conscious sedation and local anesthesia. From the right midaxillary approach, a 22-gauge Chiba needle was advanced under fluoroscopic guidance into the liver, and small amounts of contrast were injected as the needle was withdrawn. When the needle tip was identified within a portal vein branch, a guidewire was advanced into the portal system, followed by a
### Table 1. Whole donor Liver Allograft Recipients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Iliac artery graft</th>
<th>Hepatic artery complication</th>
<th>Treatment and outcome</th>
<th>Portal vein complication</th>
<th>Treatment and outcome</th>
<th>Follow-up (months) and status</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>44</td>
<td>No</td>
<td>HAT (day 26)</td>
<td>Re-OLT</td>
<td>-</td>
<td>-</td>
<td>160, Alive</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>65</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVT (month 62) recurrent CCA</td>
<td>Anticoagulation</td>
<td>65, Dead (recurrent CCA)</td>
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<tr>
<td>3</td>
<td>M</td>
<td>22</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVS (month 41)</td>
<td>PTA + stent</td>
<td>85, Alive</td>
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<tr>
<td>4</td>
<td>M</td>
<td>43</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVS (month 11)</td>
<td>PTA + stent, repeat PTA and restenting for early PVT</td>
<td>84, Alive</td>
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<tr>
<td>5</td>
<td>M</td>
<td>42</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVS (month 7)</td>
<td>PTA, repeat PTA + stent for persistent PVS, failed repeat PTA for PVT</td>
<td>47, Dead (recurrent CCA)</td>
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<tr>
<td>6</td>
<td>F</td>
<td>33</td>
<td>Yes</td>
<td>HAT (day 1)</td>
<td>Operative embolectomy, PTA for HAS, Re-OLT for HAT, observation for HAS after re-OLT</td>
<td>-</td>
<td>-</td>
<td>34, Alive</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>59</td>
<td>Yes</td>
<td>HAS (day 6)</td>
<td>PTA</td>
<td>-</td>
<td>-</td>
<td>38, Alive</td>
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<td>8</td>
<td>F</td>
<td>52</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVT (day 1)</td>
<td>Operative thrombectomy</td>
<td>33, Alive</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>56</td>
<td>Yes</td>
<td>HAT (day 1)</td>
<td>Operative thrombectomy, PTA and stent for HAS, repeat PTA (x2)</td>
<td>-</td>
<td>-</td>
<td>27, Alive</td>
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<tr>
<td>10</td>
<td>M</td>
<td>47</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVS (month 9)</td>
<td>PTA + stent, no intervention for late recurrent PVS due to recurrent CCA</td>
<td>17, Dead (recurrent CCA)</td>
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<tr>
<td>11</td>
<td>M</td>
<td>50</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVT (day 15)</td>
<td>Operative revision, PTA + stent for late PVS</td>
<td>22, Alive</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>58</td>
<td>Yes</td>
<td>PGF (day 2) HAT (day 24 after re-OLT)</td>
<td>Re-OLT Unsuccessful operative thrombectomy and thrombolysis, Second re-OLT for HAT and cholangiopathy</td>
<td>-</td>
<td>-</td>
<td>5, Dead (intraoperative during attempted second re-OLT)</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>38</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVT (day 18)</td>
<td>Operative revision (2x), anticoagulation for early recurrent PVT</td>
<td>14, Alive</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>46</td>
<td>Yes</td>
<td>HAS (month 11)</td>
<td>PTA, repeat PTA and stent</td>
<td>-</td>
<td>-</td>
<td>13, Alive</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>36</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVS (month 9)</td>
<td>PTA + stent</td>
<td>9, Alive</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>66</td>
<td>Yes</td>
<td>HAT (month 5)</td>
<td>Angiographic thrombolysis + PTA</td>
<td>-</td>
<td>-</td>
<td>8, Alive</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>56</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>PVS (month 4)</td>
<td>PTA + stent</td>
<td>4, Alive</td>
</tr>
</tbody>
</table>

Table 2. Living Donor Liver Allograft Recipients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Iliac artery graft</th>
<th>Hepatic artery complication</th>
<th>Treatment and outcome</th>
<th>Portal vein complication</th>
<th>Treatment and outcome</th>
<th>Follow-up (months) and status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>59</td>
<td>Yes</td>
<td>HAS (month 2)</td>
<td>PTA, re-OLT for late HAT</td>
<td>-</td>
<td>-</td>
<td>4, Dead (sepsis after re-OLT)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>47</td>
<td>Yes</td>
<td>HAT (month 3)</td>
<td>Spontaneous revascularization prior to planned re-OLT</td>
<td>PVS (month 3)</td>
<td>PTA, repeat PTA for persistent PVS</td>
<td>24, Dead (recurrent CCA)</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>Yes</td>
<td>HAS (month 2)</td>
<td>No intervention</td>
<td>-</td>
<td>-</td>
<td>2, Dead (sepsis from retained Wall stent leak)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>42</td>
<td>Yes</td>
<td>HAS (day 7)</td>
<td>PTA, PTA + stent for persistent HAS, re-OLT for stent occlusion and HAT</td>
<td>-</td>
<td>-</td>
<td>37, Alive</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>43</td>
<td>No</td>
<td>-</td>
<td></td>
<td>PVT (month 13)</td>
<td>Asymptomatic, no intervention</td>
<td>23, Alive</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>33</td>
<td>No</td>
<td>HAT (day 17)</td>
<td>Operative revision, reoperation for mycotic pseudoaneurysm</td>
<td>-</td>
<td>-</td>
<td>16, Alive</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>No</td>
<td>HAS (month 6)</td>
<td>PTA, repeat PTA for persistent HAS</td>
<td>PVS (month 3)</td>
<td>Asymptomatic, no intervention</td>
<td>15, Alive</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>58</td>
<td>No</td>
<td>HAS (month 11)</td>
<td>PTA</td>
<td>PVS (month 11)</td>
<td>PTA</td>
<td>12, Alive</td>
</tr>
</tbody>
</table>

Figure 1. Portal vein stenosis – transhepatic angiography.

Figure 2. Portal vein stenosis – transhepatic angioplasty and stent placement.
5-F angiographic catheter. Portal venography was performed to characterize the stenosis. The lesions were predilated with standard angioplasty balloons, with selective stenting for cases that did not respond satisfactorily to the angioplasty alone. At the completion of the procedure, the transhepatic track was occluded with 3- or 5-mm embolic coils to prevent intraabdominal hemorrhage. Two patients with portal venous complications died from recurrent CCA, and another died during retransplantation for hepatic artery thrombosis and cholangiopathy (patient 12; Table 1). The other 4 patients are alive with patent portal veins 4-85 months after transplantation, 1-45 months after angioplasty and stent placement.

Four whole organ recipients developed portal vein thrombosis. Three patients with early thrombosis underwent operative thrombectomy. One required angioplasty and stent placement 1 year later for portal stenosis, and all are alive with patent portal veins 14, 22, and 33 months after transplantation. Another patient developed portal vein thrombosis 5 years after transplantation that was associated with locally recurrent CCA.

Portal vein stenoses developed in 3 of 16 living donor recipients at 3-11 months after transplantation. The stenoses appeared to involve the anastomoses between the deceased donor iliac vein grafts and the recipient portal veins. Two were successfully treated with percutaneous transhepatic portal angioplasty (no stents); one died from recurrent CCA, and the other is alive with a patent portal vein 12 months after transplantation and 1 month after angioplasty. Treatment was withheld for 1 asymptomatic patient with modest stenosis. The patient is alive with a patent portal vein 15 months after transplantation and 12 months after detection of stenosis.

One living donor recipient developed asymptomatic portal thrombosis 12 months after transplantation. He is alive and doing well 23 months after transplantation.

Hepatic Vein and Inferior Vena Cava Complications

Six (12%) of 52 whole organ recipients developed venous outflow obstruction. Two caval and 2 hepatic venous thrombotic complications occurred early after transplantation. Two patients developed late stenotic complications, one involving the donor suprahepatic cava anastomosis and the other involving the recipient vena cava. One of the 4 thrombotic complications was treated with percutaneous transvenous angioplasty. The other 3 patients had nonocclusive thromboses and were initially treated with anticoagulation. Two patients subsequently
required percutaneous transvenous angioplasty for residual stenoses. The 2 patients with stenotic complications underwent angioplasty with stent placement. One of the patients died 3 years later from recurrent CCA. No graft losses or deaths were attributable to venous complications.
Whole Donor Liver Recipient Comparison

We compared the incidences of vascular complications for patients who underwent whole organ liver transplantation from a deceased donor for CCA (DD-CCA) to patients who underwent whole organ liver transplantation for other indications (DD-control) between June 2000 and April 2006. We included only recipients of whole donor livers that had arterial reconstruction with deceased donor iliac grafts to the recipient infrarenal aorta in both the CCA and control groups. There were 45 patients in the DD-CCA group and 52 patients in the DD-control group (Table 3). There were more patients with underlying PSC in the DD-CCA group. Otherwise, gender and age distributions were similar. There were no statistically significant differences in early or late hepatic artery complications in the 2 groups. Early hepatic artery complications occurred in 3 patients (6.7%) in the DD-CCA group vs. 4 patients (7.7%) in the DD-control group (P=0.85). Late hepatic artery complications occurred in 2 patients (4.4%) in the DD-CCA group vs. 4 patients (7.7%) in the DD-control group (P=0.68).

Portal vein complications were far higher in the DD-CCA group. Early portal vein problems occurred in 3 patients (6.7%) in the DD-CCA group vs. 2 patients (3.8%) in the DD-control group (P=0.66). Late portal vein complications developed in 8 patients (17.8%) in the DD-CCA group vs. 1 patient (1.9%) in the DD-control group (P=0.01).

Hepatic venous outflow and caval complications were slightly higher in the DD-CCA group vs. the DD-control group. Four (8.9%) DD-CCA patients had early complications vs. 1 (1.9%) DD-control patient (P=0.18), and 2 (4%) DD-CCA patients had late complications vs. 1 (1.9%) DD-control patient (P=0.60).

Outcome was comparable for the 2 groups. Retransplantation was necessary for 3 patients (6.7%) in the DD-CCA group vs. 2 patients (3.8%) in the DD-control group (P=0.66). Similarly, 1 patient (2.2%) died in the DD-CCA group vs. 0 deaths in the DD-control group (P=0.46).

Living Donor Liver Recipient Comparison

We compared the incidences of vascular complications for patients who underwent living donor liver transplantation for CCA (LD-CCA) with patients who underwent living donor liver transplantation for other indications (LD-control) between June 2000 and April 2006. Because our initial experience with living donor liver transplantation for CCA using deceased donor iliac artery grafts was poor, we excluded patients with iliac artery grafts from both groups for comparison. There were 11 patients in the LD-CCA group and 38 in the LD-control group.
group. As expected, more patients in the LD-CCA group had PSC. Otherwise, gender and age distributions were similar for the 2 groups (Table 4). Arterial complications were slightly more common in the LD-CCA group than the LD-control group. Early hepatic artery complications occurred in 1 (9.1%) LD-CCA patient vs. 7 (18.4%) LD-control patients (P=0.66). Late hepatic artery complications occurred in 2 (18.2%) LD-CCA patients vs. none (0%) LD-control patients (P=0.047).

Portal vein complications were far more common in the LD-CCA group than the LD-control group. Early portal vein complications were unusual in both groups, 0 in the LD-CCA group and 1 (2.6%) in the LD-control group. Late portal vein complications were more frequent in the LD-CCA group. The LD-CCA group had 3 (27.3%) late portal complications vs. none in the LD-control group (P=0.009).

Hepatic venous and caval complications were uncommon in both groups; there was only one patient in the LD-control group that developed a late complication.

Outcome was comparable for the 2 groups. Retransplantation was necessary for 2 patients (18.2%) in the DD-CCA group vs. 1 patient (2.6%) in the DD-control group (P=0.12). Similarly, 1 patient (9.1%) died in the DD-CCA group vs. 1 death (2.6%) in the DD-control group (P=0.40).

DISCUSSION
Liver transplantation after neoadjuvant radiotherapy with chemosensitization has emerged as an effective treatment for patients with localized, node-negative, unresectable hilar CCA or CCA arising in the setting of PSC. Over 70 patients with CCA have undergone liver transplantation at our center since 1993, and 5-year patient survival is 80%. We noted an unusually high incidence of vascular complications in this group of patients and thus reviewed our experience with the specific aims of determining the incidences of arterial, portal, and hepatic venous complications in comparison to patients who undergo liver transplantation for other indications; and determining the effect of these vascular complications on patient outcome. We reviewed our experience with 68 patients who had undergone neoadjuvant therapy and subsequent liver transplantation between January 1993 and April 2006. Vascular complications developed in 40% of the patients, with arterial and portal venous complication rates of 21% and 22%. These complication rates were far higher than those for control groups of patients who underwent liver transplantation at our institution for other indications. Seven patients died during the study period, and 2 of these deaths were attributable to vascular
Vascular Complications after Orthotopic Liver Transplantation Following Neoadjuvant Therapy for Hilar Cholangiocarcinoma

(arterial) complications. Five patients required retransplantation for arterial complications. Portal venous complications were equally common but did not lead to graft loss or patient death.

From the outset, we have been concerned about the potential adverse effect that neoadjuvant therapy might have on patients undergoing liver transplantation. One of our patients required retransplantation for hepatic artery thrombosis early on in our experience. Since then, we have preferentially used donor iliac artery grafts between the donor hepatic artery and the recipient infrarenal abdominal aorta for all deceased donor recipients. This technique completely avoids the potential adverse effect of neoadjuvant therapy on arterial inflow to the donor liver, and our experience supports this approach. Indeed, we found no differences in early or late arterial complications between the CCA patients and a control group of recipients with iliac artery grafts.

We began living donor liver transplantation in June 2000 and used deceased donor iliac artery grafts for arterial reconstruction in our first 4 CCA patients. Our results with these 4 patients were poor (Table 2, patients 1-4), and we temporarily stopped performing living donor transplantation for patients with CCA while we accrued more experience with living donor liver transplantation for other indications. We attributed all but one of the arterial complications to technical problems related to iliac graft use. In 2004, we resumed living donor liver transplantation for CCA patients after changing the timing of the staging operation and our approach to arterial reconstruction. We decided to defer the staging operation to a few days before living donor transplantation in order to facilitate transplantation from a technical standpoint. We also changed to preferential use of the recipient common or proper hepatic artery for arterial reconstruction. Since then, we have only used a deceased donor iliac artery for one patient (no arterial complication).

We compared the CCA patients to a control group of patients who underwent living donor liver transplantation for other indications, including only those patients with direct donor-to-recipient arterial anastomoses. We found no difference in the early complication rates between the 2 groups. Although the patient numbers were small, there was a far higher rate of late arterial complications in the CCA group, presumably as a result of neoadjuvant therapy. It is noteworthy that routine use of deceased donor iliac artery grafts seems to be advantageous with deceased donor transplantation but detrimental with living donor transplantation. Use of iliac arterial grafts avoids late arterial complications attributable to neoadjuvant therapy,
but the higher risk of early arterial complications with living donor transplantation outweighs the late benefit. We are concerned that with longer follow-up, we will observe even more late arterial complications after living donor transplantation and use of the irradiated recipient artery. Thus, we follow all living donor recipients closely with Doppler ultrasonography for changes in arterial waveforms and flow over time. We now continue low-dose aspirin indefinitely after both living and deceased donor liver transplantation.

Late portal vein stenosis and thrombosis were common complications in our CCA patients who underwent liver transplantation after neoadjuvant therapy. Fifteen (22%) of 68 patients developed either portal thrombosis or stenosis. The portal complications were usually detected 3 to 12 months after transplantation. The late portal vein complication rates were far higher than those for deceased and living donor control groups. Despite the high portal complication rates, portal complications did not lead to graft loss or patient death. Nine patients have undergone percutaneous transhepatic portal venous angioplasty with stent placement. Two patients subsequently died, but both deaths were due to recurrent CCA.

Hepatic venous and caval complications occurred after liver transplantation for CCA, but the complication rates were similar to those observed after both deceased and living donor liver transplantation for recipients with other indications.

Our experience with liver transplantation after neoadjuvant therapy is unique. Few patients have undergone liver transplantation after radiotherapy, and the effect of radiotherapy on outcome was unknown when we started our treatment protocol in 1993. Both the recipient portal vein and hepatic artery are directly within the field of external beam radiotherapy, and the portal vein is also within the penetration field of intraluminal biliary brachytherapy. The adverse effect of radiotherapy on vascular tissue is well known. Vascular endothelial cells are quite radiosensitive, and smaller vessels are especially sensitive to radiation injury. Larger vessels are also susceptible to injury, especially late after therapy. Indeed, carotid and iliac artery injuries have been well described after radiotherapy for head and neck and pelvic malignancies. Veins seem to be more resistant to the injurious effects of ionizing radiation, but stenotic and thromboembolic complications have also been reported in the literature. Typically, radiation-induced damage to vascular structures is a late development, arising several months to many years after exposure. The time course that we observed for both arterial and portal complications in our CCA patients is consistent with the known adverse effect of radiotherapy on vascular tissue. Both arterial and portal complications typically arose
3-12 months after transplantation. We also observed progression of portal stenoses before intervention, which is also indicative of a late radiation effect. The CCA patients often required multiple interventional procedures for arterial and portal venous complications, whereas those with complications in our control groups usually required only one. This observation is consistent with the progressive nature of radiation induced vascular injury.

Clearly, the higher arterial and portal venous complication rates observed in our CCA patients are both attributable to neoadjuvant therapy. The complication rates are higher than our center’s experience overall,\textsuperscript{20,21} reports in the literature,\textsuperscript{22-27} and our deceased and living donor control groups.

The CCA vs. control group comparisons for both living and deceased donor transplantation had comparable gender and age distributions. However, underlying PSC was far more common in the CCA group for both comparisons. PSC has been associated with hypercoagulability\textsuperscript{28} and may be a risk factor for hepatic artery complications after transplantation.\textsuperscript{22} Nevertheless, we did not observe higher rates of early vascular complications in either CCA recipients of living or deceased donor livers.

In summary, liver transplantation with neoadjuvant radiotherapy and chemosensitization is associated with higher rates of late hepatic artery and portal venous complications than is liver transplantation without neoadjuvant therapy. Routine use of donor iliac artery grafts avoids arterial complications in deceased donor recipients but leads to more early technical complications in living donor recipients. We cautiously continue to use the recipient artery for living donor transplantation and follow all recipients closely for the development of late arterial complications. Late portal vein stenosis is common after both living and deceased donor transplantation. Transhepatic angioplasty with stent placement for both portal and hepatic arterial stenosis effectively maintains vascular patency for most patients.
REFERENCES


Vascular Complications after Orthotopic Liver Transplantation Following Neoadjuvant Therapy for Hilar Cholangiocarcinoma


