ORIGINAL ARTICLE

Neoadjuvant Stereotactic Body Radiation Therapy, Capecitabine, and Liver Transplantation for Unresectable Hilar Cholangiocarcinoma

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Hilar cholangiocarcinoma (CCA) is a difficult malignancy to treat surgically because of its anatomical location and its frequent association with primary sclerosing cholangitis. Neoadjuvant chemoradiotherapy followed by liver transplantation in lymph node–negative patients has been advanced by select liver transplant centers for the treatment of patients with unresectable disease. This approach has most commonly used external-beam radiotherapy in combination with biliary brachytherapy and 5-fluorouracil–based chemotherapy. Our center recently embarked on a protocol using stereotactic body radiation therapy (SBRT) followed by capecitabine in lymph node–negative patients until liver transplantation. We, therefore, retrospectively determined the tolerability and pathological response in this pilot study. During a 3-year period, 17 patients with unresectable hilar CCA were evaluated for treatment under this protocol. In all, 12 patients qualified for neoadjuvant therapy and were treated with SBRT (50-60 Gy in 3-5 fractions over the course of 2 weeks). After 1 week of rest, capecitabine was initiated at 1330 mg/m^2/day, and it was continued until liver transplantation. During neoadjuvant therapy, there were 35 adverse events in all, with cholangitis and palmar-plantar erythrodysesthesia being the most common. Capecitabine dose reductions were required on 5 occasions. Ultimately, 9 patients were listed for transplantation, and 6 patients received a liver transplant. The explant pathology of hilar tumors showed at least a partial treatment response in 5 patients, with extensive tumor necrosis and fibrosis noted. Additionally, high apoptotic indices and low proliferative indices were measured during histological examinations. Eleven transplant-related complications occurred, and the 1-year survival rate after transplantation was 83%. In this pilot study, neoadjuvant therapy with SBRT, capecitabine, and liver transplantation for unresectable CCA demonstrated acceptable tolerability. Further studies will determine the overall future efficacy of this therapy. ***Liver Transpl 20:81-88, 2014***. © **2013 AASLD.**

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The treatment of hilar cholangiocarcinoma (CCA) is most effective when hepatic resection is performed and negative surgical margins can be achieved. Unfortunately, only 35% to 40% of presenting patients

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Abbreviations: AI, apoptotic index; CCA, cholangiocarcinoma; CK7, cytokeratin 7; CT, computed tomography; EUS, endoscopic ultrasound; H&E, hematoxylin and eosin; MRI, magnetic resonance imaging; OLT, orthotopic liver transplantation; PI, proliferative index; PSC, primary sclerosing cholangitis; SAE, significant adverse event; SBRT, stereotactic body radiation therapy; TUNEL, terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling; PTC, percutaneous transhepatic cholangiography.

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are able to undergo resection because of bilateral vascular/biliary involvement, metastatic disease, or underlying hepatic disease, including primary sclerosing cholangitis (PSC).[1] Pioneering work by the Mayo Rochester group demonstrated the feasibility and efficacy of using neoadjuvant chemoradiotherapy, staging for negative hilar lymph nodes, and then orthotopic liver transplantation (OLT).[2,3] This therapeutic approach to hilar CCA has resulted in survival rates that are similar to the rates for patients undergoing OLT for other forms of liver disease.[4] Therefore, in 2008, the United Network for Organ Sharing began to accept the listing of patients with unresectable hilar CCA as long as the centers had an established protocol using neoadjuvant chemoradiotherapy along with a demonstration of a negative lymph node status for metastatic disease.

Recent neoadjuvant chemoradiotherapy protocols have primarily used a combination of external-beam radiotherapy (given over several weeks) and brachytherapy via biliary catheterization to a total dose of 45 to 55 Gy.[4] After radiation therapy, chemotherapy has traditionally been based on a 5-fluorouracil infusion followed by capecitabine. Our center has developed the novel use of stereotactic body radiation therapy (SBRT) in the treatment of hepatic malignancies.[5,6] Safety and efficacy have been demonstrated for these cancers often in many patients with underlying liver disease or cirrhosis.[5,7] SBRT has the advantage of delivering high doses of radiotherapy to confined areas while sparing surrounding structures or parenchyma from toxicity. SBRT, therefore, has the added advantage of allowing a shorter treatment course, often in 3 to 5 fractions in a 2-week period.

We therefore, decided to use our center's expertise in SBRT, a recently developed therapy for the treatment of hepatic malignancies, in our neoadjuvant chemoradiotherapy protocol (followed by OLT) for patients with unresectable CCA and lymph node–negative disease. The aims of this pilot study were to determine (1) the overall tolerability of this regimen with respect to side effects and adverse events and (2) the pathological response through histological evaluations of explanted transplant specimens. We also sought to examine tolerability as it was related to reaching successful transplantation and any influence on transplant related complications. Although significant adverse events (SAEs) occurred, these were often well tolerated as 9 patients were listed and 6 of these patients have undergone transplantation to date. Significant tumor responses were noted on suggesting that this regimen utilizing SBRT results in acceptable tumor control with tolerable side effects until definitive therapy with transplantation.

PATIENTS AND METHODS

Patient Selection

This retrospective study was approved by the University of Michigan institutional review board. Patients with hilar CCA were identified through a review by our multidisciplinary liver tumor clinic and board. Patients' diagnoses and treatments followed an existing transplant committee treatment protocol at the University of Michigan. The diagnosis and inclusion criteria were similar to those described by the Mayo Rochester group previously.[2,3] Patients were required to have a malignant-appearing hilar biliary stricture above the cystic duct and a carbohydrate antigen 19-9 level greater than 100 ng/mL, a transcatheter biopsy/brush cytology positive for adenocarcinoma, or an associated mass on cross-sectional imaging that was 3.0 cm or less in its maximal radial diameter. Patients whose tumors were determined to be unresectable on the basis of bilateral vascular or biliary involvement or underlying liver disease (PSC) were further evaluated by our multidisciplinary liver transplant committee. Staging included computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and CT of the chest. Positron emission tomography was used selectively for indeterminate lesions noted on initial cross-sectional imaging. Patients were excluded if they had any overt evidence of distant disease or regional lymph node metastasis. Patients were likewise excluded if there was any prior attempt at surgical resection or open or percutaneous biopsy or prior treatment. Finally, endoscopic ultrasound (EUS) with fine-needle aspiration of hilar lymph nodes was routinely performed, and if the results were positive, patients were excluded from entry into the protocol.[8]

Neoadjuvant Protocol and Transplantation

Patients who were found to be acceptable transplant candidates and met the inclusion criteria for the neoadjuvant protocol were treated with SBRT: the total dose of 50 to 60 Gy was divided into 3 to 5 fractions (10-20 Gy/fraction)[5,6] in accordance with our routine institutional practice. Briefly, patients underwent CT simulation with a customized vacuum body mold. Active breathing control was used to eliminate breathing-related tumor motion. Tumors were delineated on MRI, and these images were fused with CT images for planning. To account for setup variations, 5-mm radial margins and 8-mm superior and inferior margins were added to generate the planning target volume. SBRT was delivered with 8 to 16 nonopposed, noncoplanar, static 6- and 16-MV photon beams. The radiation dose was prescribed to the isodose surface covering 99.5% of the planning target volume (typically 75%-85% of the maximum dose). Daily cone-beam CT was used before each treatment for image guidance. SBRT was completed in 2 weeks, and after a 1-week rest, patients were initiated on capecitabine (1330 mg/m^2/day in 2 divided oral doses rounded to the nearest 500 mg). The staging operation was performed 4 to 6 weeks after the initiation of SBRT after a 3-day hold of capecitabine. The staging operation was performed in a completely laparoscopic or laparoscopy-assisted manner. An examination for extrahepatic disease was performed

along with hepatic ultrasound. Excisional biopsy of hilar lymph nodes was performed, and samples were subjected to permanent pathology. Patients were removed from the protocol for any evidence of peritoneal metastasis or lymph node metastasis. Capecitabine was reinitiated at discharge and continued until transplantation. Capecitabine was held for a 1-week rest every 6 weeks while patients were listed.

Once the final pathology was completed after the staging operation, patients were listed for liver transplantation. The regional review board was asked to grant a Model for End-Stage Liver Disease exception of 22 points[9] with an additional 3-point increment if the wait time went beyond 3 months. Staging CT scans were repeated every 3 months to evaluate patients for disease stability while they were on the wait list. The transplant procedure was performed as previously described, and care was taken to divide hilar structures as distally as possible and to remove any additional hilar lymph nodes.[2,3] Frozen sections were performed for the distal bile duct to determine whether pancreaticoduodenectomy would be necessary. A vena cava–sparing technique was used along with a donor iliac artery conduit for donor hepatic artery reconstruction to the recipient supraceliac aorta to prevent arterial complications.[10] Biliary reconstruction was performed via hepaticojejunostomy. Capecitabine was discontinued, and immunosuppression was initiated according to our center's standard protocol with a prednisone taper, mycophenolate mofetil, and tacrolimus. Hepatic duplex was performed on postoperative days 1, 7, and 21, and subsequently, contrast-enhanced CT or MRI was performed every 3 months after the operation for the first year and every 6 months thereafter.

Patient Monitoring

One week after SBRT, capecitabine was initiated, and patients were monitored weekly for signs of toxicity by laboratory and symptom assessment. For patients who experienced a clear treatment–related toxicity of grade 2 or greater, capecitabine was held until grade 1 or less was achieved. Capecitabine was then resumed with a daily dose reduction of 500 mg. All adverse events were defined as those occurring after the initiation of neoadjuvant therapy and were determined upon a retrospective review of the medical history, with SAEs defined as those that resulted in hospitalization, an escalated level of care, or a significant clinical intervention. An SAE related to cholangitis was treated with urgent antibiotics and biliary tube interrogation.

Tumor Histological Analysis

Tumor explants after transplantation were paraffin-embedded and sectioned for routine hematoxylin and eosin (H&E) staining, and they were reviewed by a gastrointestinal pathologist. Additional serial sections were deparaffinized in xylene and rehydrated in descending alcohol concentrations, and this was followed by heat-induced antigen retrieval via boiling in a citrate buffer. Antibodies for cytokeratin 7 (CK7; clone OV-TL 12/30, Dako, United States) and Ki-67 (clone MIB-1, Dako) were used for immunohistochemical staining after the blockade of endogenous peroxidase and protein according to the manufacturer's instructions.[11,12] Biotinylated Link and streptavidin/horseradish peroxidase (Dako) were subsequently incubated, and this was followed by 3,3′-diaminobenzidine chromogen incubation (Dako) for development. Terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling (TUNEL) staining was performed according to the manufacturer's procedure (ApopTag Plus peroxidase in situ apoptosis kit, #S7101, Millipore, United States). Slides from 2 to 3 representative areas in each tumor specimen were examined at a magnification of ×40, and Ki-67$^+$ and TUNEL$^+$ cells were determined for at least 200 CK7$^+$ tumor cells per patient. Proliferative indices (PIs) and apoptotic indices (AIs) were calculated as percentages of Ki-67$^+$ CK7 cells and TUNEL$^+$ CK7 cells, respectively.[13] Surgically resected tumors that had not been subjected to neoadjuvant therapy served as controls for this analysis.

RESULTS

Patient Presentation

Seventeen patients with unresectable hilar CCA were evaluated for the neoadjuvant chemoradiotherapy protocol and transplantation after a review by our multidisciplinary liver tumor and transplant programs. The baseline demographics (Table 1) showed that the majority of the patients were male; 24% of the patients had PSC as an underlying etiology, and 71% had a de novo or no predisposing etiology. One patient had an underlying type IV choledochal cyst. Ten patients (59%) had a measurable mass on cross-sectional imaging with an overall mean tumor

TABLE 1. Presentation of Patients With Unresectable Hilar CCA

Evaluated patients (n)	17
Mean age (years)	58
Males/females (n/n)	12/5
Etiology [n (%)]	
PSC	4 (24)
De novo	12 (71)
Other	1 (6)
Mean mass size (cm)*	1.42 (0-3.2)
Mean carbohydrate antigen 19-9 level (ng/mL)	429
Mass [n (%)]	10 (59)
Only brushing positive [n (%)]	5 (29)
PTC [n (%)]	13 (76)

*The range is shown in parentheses.

diameter of 1.42 cm. Five patients (29%) had brushings positive for adenocarcinoma on cholangiography along with a malignant-appearing stricture as their diagnostic criteria. Two patients had a malignant-appearing stricture along with an elevated carbohydrate antigen 19-9 level as their only presenting diagnostic criteria.

Ultimately, 12 patients (71%) were able to start neoadjuvant therapy (Table 2 and Supporting Fig. 1); 5 patients were excluded from entering neoadjuvant therapy because of positive findings on an EUS lymph node aspirate (1 patient), peritoneal metastasis on early diagnostic laparoscopy (3 patients), or newly symptomatic coronary artery disease (1 patient). Diagnostic laparoscopy was performed for these patients because of clinical concerns about a higher disease stage despite initial eligibility according to cross-sectional imaging and EUS screening.

Protocol Completion and Tolerability

Radiation therapy for a total dose of 50 to 60 Gy was achieved in all 12 patients, although 1 patient was treated with a non-SBRT protocol because of concern about longitudinal extension; ultimately, this patient had peritoneal metastases on later staging laparoscopy. The other 11 patients received SBRT in 3 to 5 fractions, and capecitabine was initiated as scheduled. During the neoadjuvant treatment, 35 adverse events occurred after the initiation of therapy, with 14 of these being significant enough to be classified as SAEs (Table 3). SAEs occurred in 6 patients (50% of treated patients), with cholangitis related to PTC tube dysfunction being the most significant and common etiology. Other SAEs were related to dehydration (3 episodes) and occurred in the same patients with cholangitis. The most common non-SAE adverse events were palmar-plantar erythrodysesthesia (6 patients), diarrhea (2 patients), and wound infections after the staging operation (2 patients). No other gastrointestinal toxicity such as gastritis or ulcer disease was noted. In all, there were 5 dose reductions of capecitabine among 4 patients. All 12 patients underwent staging laparoscopy or laparoscopy-assisted exploration and portal lymph node sampling 4 to 6 weeks after the completion of SBRT. One patient was found to have peritoneal disease, and 2 patients were found to have positive lymph nodes according to the final pathological examination (Supporting Fig. 1). Therefore, 9 patients were formally listed for transplantation with Model for End-Stage Liver Disease exception scores of 22 points. The need for elective and urgent biliary interventions was common: a mean of 7 such interventions were required per patient during the treatment and transplant wait time period. One patient was ultimately removed from the list because of concerns about decreasing performance status along with weight loss, and another was removed at the time of exploration with transplant intent when a peritoneal metastasis was identified. Therefore, the dropout rate after neoadjuvant therapy due to a positive staging operation (3 patients), disease progression (1 patient), or a lack of tolerability (1 patient) was 42%.

Transplantation and Tumor Responses

Ultimately, 6 patients underwent deceased donor OLT, with 1 patient actively listed at the time of this writing (Table 3). The mean and median wait times were 92 and 88 days, respectively (range = 29-201 days). The mean cold and warm ischemia times were 344 and 27 minutes, respectively. One patient required a concomitant pancreaticoduodenectomy secondary to an initially positive distal bile duct margin. All patients received a supraceliac aorta interposition graft to the hepatic artery with a donor iliac conduit. There were 11 transplant-related complications in all (Table 3). One patient was free of any complications. The 1-year survival rate was 83%, with 1 patient dying after discharge because of presumed cardiovascular collapse 21 days after transplantation. The median follow-up time was greater than 14 months to date. There were 2 re-explorations for bleeding secondary to a pancreatic leak; however, there were no vascular, biliary, or hepatic insufficiency complications to date. The median length of stay after OLT was 12.5 days.

TABLE 2. Neoadjuvant Chemoradiotherapy and Transplant Protocol Completion

Evaluated patients (n)	17
Ruled-out patients (n)	5
Positive EUS [n (%)]	1 (6)
Early progression: peritoneal disease [n (%)]	3 (18)
New comorbidity [n (%)]	1 (6)
Patients undergoing neoadjuvant therapy (n)	12
Patients with positive staging laparoscopy [n (%)]	3 (25)
Lymph node	2
Peritoneal metastasis	1
Patients listed for transplantation [n (%)]	9 (75)
Removed from list (n)	2
Received transplant (n)	6
Waiting (n)	1

TABLE 3. Tolerability of Neoadjuvant Therapy and Transplant Outcomes

Total adverse events (n)	35
Total SAEs (n)	14
SAEs per patient (n)*	1 (0-6)
Total other adverse events (n)	21
Adverse events per patient (n)*	2 (0-8)
Most frequent adverse events [n/N (%) of treated patients]	
Cholangitis	6/12 (50)
Palmar-plantar erythrodysesthesia	6/12 (50)
Diarrhea	2/12 (17)
Wound infection (after staging procedure)	2/12 (17)
Dose reductions (n)	5
Mean biliary interventions (n)	7
Total transplants (n)	6
Mean waiting time (days)	92
Mean cold ischemia time (minutes)	344
Mean warm ischemia time (minutes)	27
Median length of stay (days)	12.5
Posttransplant complications (n)	11
1-year survival (%)	83
Tumor explant pathology	
Mean tumor size (cm)	1.95
Neurovascular invasion (n)	3
Positive lymph node (n)	1
Response [n/N (%)]	
Complete response	1/6 (17)
Partial response	4/6 (67)
No response	1/6 (17)

*The range is shown in parentheses.

Routine clinical pathological reviews of tumor explants showed at least a partial response for 5 of the 6 patients, with 1 patient histologically demonstrating a complete response. One patient was a nonresponder. The responding patients showed evidence of significant necrosis and fibrosis on routine histological examinations (Fig. 1). Patients with a partial response had only minute foci (<0.2 cm) of viable tumor cells remaining. We, therefore, performed further examinations with immunohistochemical staining, and we showed that in contrast to patients who had undergone surgical resection without neoadjuvant therapy (controls), all patients who had been treated neoadjuvantly and then had undergone transplantation had a low PI (Ki-67$^+$) among CK7$^+$ tumor cells (Figs. 2 and 3 and Supporting Fig. 2; range = 0%-17%). Additionally, a high AI (TUNEL$^+$/CK7$^+$) was noted among remaining tumor cells (range = 2%-51%) in comparison with untreated (control) patients. The 1 patient with a complete response according to the clinical histological examination had an undetectable PI but the highest AI among CK7$^+$ tumor cells at 51% (Supporting Fig. 2). The mean gross tumor size at explant was 1.95 cm. Three patients had evidence of neurovascular invasion: one of these patients had a positive lymph node, and another patient had a subsequent peritoneal implant noted on the final pathology report. Both of these patients ultimately suffered from recurrence and succumbed to disease after systemic therapy 16 and 30 months after transplantation. Four of the 6 explants (67%) were noted to have perihilar cirrhosis or fibrosis in the liver parenchyma not involved by tumor. Two of these patients did not have a diagnosis of PSC and had de novo hilar CCA.

DISCUSSION

Hilar CCA continues to be a challenging treatment problem because of the often distant and local extent of the disease. It has been estimated that 30% of these patients present with advanced disease, and as few as 50% of those with disease confined to the liver hilum will undergo R0 (negative margin) resection because of bilateral biliary and vascular invasion.[1] Additionally, many patients have underlying PSC, which further limits safe resection. Although early experiences involved the exploration of whether liver transplantation might be a therapeutic option for patients with unresectable disease,[14] the Mayo Rochester group pioneered the use of neoadjuvant chemoradiotherapy in addition to rigorous surgical staging before transplantation, and the overall results have been similar to those for transplantation for other disease etiologies.[2,3] The ability to achieve R0 resection and the presence of negative lymph nodes are the most significant positive prognostic factors for the surgical therapy of hilar CCA.[1,15,16] Consequently, an evaluation of lymph nodes using a combination of EUS-guided biopsy and surgical

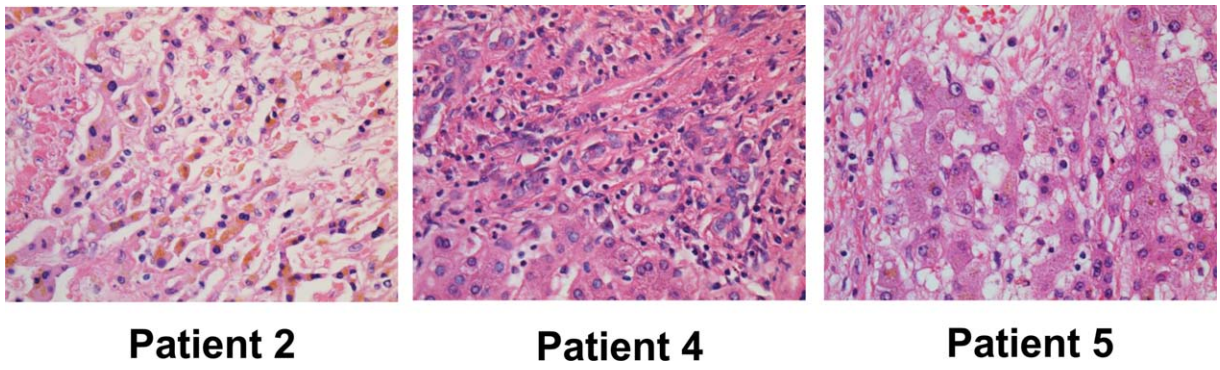

Figure 1. Histology of hilar CCAs after neoadjuvant therapy. Representative hilar tumors from patients with partial clinical pathological responses after transplantation (n = 3) were stained with H&E (magnification ×40).

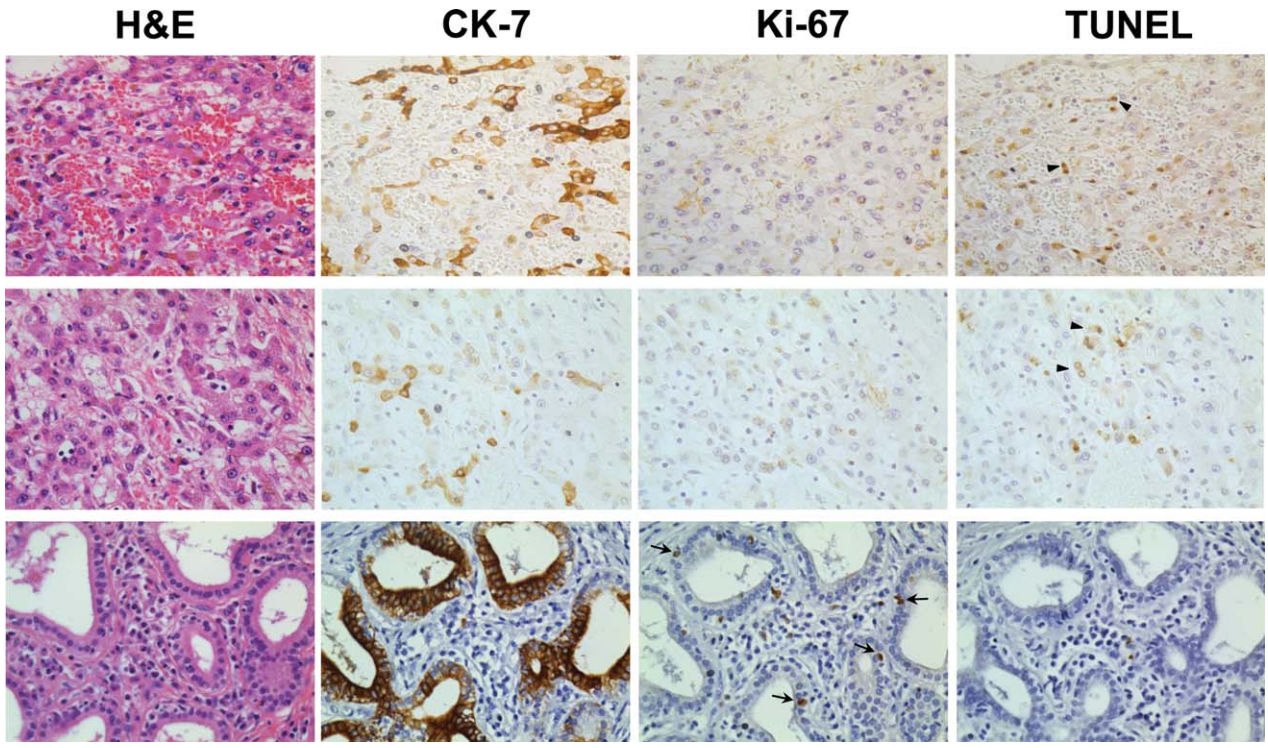

Figure 2. Immunohistochemistry for proliferating and apoptotic CCA cells. Images from 2 representative patients with partial pathological responses are shown (top row, patient 2; middle row, patient 5). An untreated, surgically resected CCA is shown for comparison (bottom row). Serial sections for H&E staining, CK7 staining for CCA cells, Ki-67 staining for proliferation, and TUNEL staining for apoptosis are indicated, and the staining was performed as described in the Patients and Methods section. Arrows indicate dual-positive $TUNEL^+/CK7^+$ cells (magnification ×40).

staging is critically important in selecting patients for this transplant therapy.[8]

The experience with neoadjuvant chemoradiotherapy using external-beam radiation therapy, brachytherapy, and 5-fluorouracil–based chemotherapy has shown significant tumor responses to date, but a significant number of therapeutic sessions are required to deliver this therapy. SBRT has the ability to concentrate the radiation dose to a confined anatomical area over a shorter number of fractions and to minimize adjacent toxicities. Our center has been a forerunner in the use of SBRT for a variety of hepatic malignancies, and it has been shown to be safe and effective, even in the presence of underlying liver disease.[5,6] Therefore, we sought to build on this experience by using a combination of SBRT (in 5 fractions or fewer) and subsequent oral capecitabine for the neoadjuvant treatment of patients with unresectable hilar CCA before transplantation. Our total dose of 50 to 60 Gy in 3 to 5 twice weekly treatments is, therefore, similar or more biologically intense than the originally described protocol of an external beam given in 30 fractions along with supplemental brachytherapy.[3,10]

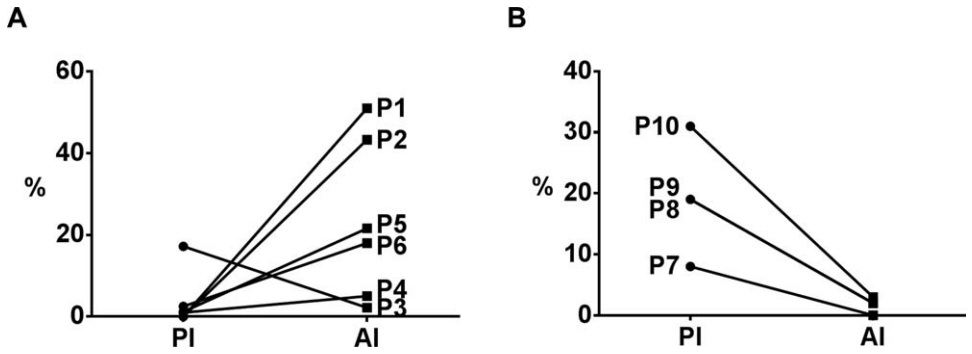

Figure 3. PIs and AIs of hilar CCAs after neoadjuvant therapy. (A) After patients underwent neoadjuvant therapy and transplantation (P1-P6), hilar CCAs were subjected to immunohistochemistry for CK7, Ki-67, and TUNEL staining, as shown in Fig. 2 and as described in the Patients and Methods section. PIs and AIs were calculated as the percentages of Ki-67$^+$ CK7 cells and TUNEL$^+$ CK7 cells, respectively. (B) Results for patients who underwent only resection (no neoadjuvant therapy; P7-P10) are shown for comparison.

The present analysis represents a pilot study designed to examine our initial experience with this algorithm and to determine overall tolerability. We also sought to examine tumor responses histologically in explants after transplantation. Overall, other than the expected adverse events related to cholangitis and the need for continuous biliary decompression, our protocol was well tolerated. Over the course of our experience, episodes of cholangitis requiring admission and urgent biliary interventions appeared to dissipate, with the majority of episodes occurring in our earlier patients and with 50% of our patients being completely free of such episodes. It is possible that the increasing coordination of our multidisciplinary care during the course of our protocol accounted for a gradual reduction in cholangitis-related events, although it is difficult to generalize with a cohort of this size. Palmar-plantar erythrodysesthesia was the next most common adverse event associated with capecitabine therapy; however, only 5 dose reductions were necessary. One patient required removal from the list because of a declining performance status after a significant waiting time. No patients experienced decompensation of liver disease after neoadjuvant therapy. Therefore, the overall dropout rate due to disease progression or a lack of tolerability was somewhat comparable to the rate of previous experiences: we experienced a dropout rate of 42%, whereas other groups have experienced a 31% dropout rate.[17] Care must be taken when comparisons are made between this pilot study and other experiences such as those at the Mayo Clinic in Rochester. Indeed, in our cohort, only 24% of the patients had PSC as a predisposing etiology, whereas the rate experienced elsewhere has been approximately 70%. These differences are difficult to explain but may be due to referral biases, the differential use of fluorescent in situ hybridization analysis for diagnosis, or our small size cohort.

Transplant-related complications did not appear to be particularly increased, although 1 early death was noted after an initially uncomplicated course because of presumed cardiovascular collapse of an unknown cause. The length of stay after transplantation was otherwise acceptable (median = 12.5 days), and no patients experienced biliary, vascular, or hepatic insufficiency complications. This compares favorably with other experiences, which have documented arterial complications in as many as 21% of patients and portal venous complications in as many as 22% of patients[10] and, as a result, have used donor iliac artery conduits to the recipient aorta[10] (which was also performed in our protocol).

Tumor responses to neoadjuvant therapy were demonstrated on the basis of an explant analysis, which showed extensive necrosis of hilar tumors, with 4 of 6 patients demonstrating <0.2-cm foci of residual carcinomas and 1 patient having no viable tumor remaining. However, a more detailed analysis using CK7 immunohistochemical analysis showed that this patient had minute evidence of residual tumor cells. Although small foci of tumor cells remained, low PIs and high AIs were noted among the remaining CK7$^+$ cells, and they could reflect even greater tumor control than indicated by routine histological analysis.[12] Other experiences have indicated perhaps a greater tumor eradication rate[17]; however, direct comparisons are difficult because of perhaps varying disease burdens at entry and the nonprospective nature of the pathological evaluation in the current study as well as previously reported experiences. Nonetheless, it is hoped that further analysis of tumor explants will allow us to continue to improve neoadjuvant therapy while minimizing its toxicity on the basis of this pilot experience. Unfortunately, our protocol failed to identify 2 patients with more advanced disease: one with a positive lymph node and another with a peritoneal metastasis at the time of transplantation. The isolated peritoneal implant is difficult to explain, but it may have been related to unrecognized perforation due to the numerous complicated biliary interventions required for this patient. Percutaneous biliary decompression by itself has not been previously shown to be a risk factor for tumor recurrence after transplantation.[3] Patients with previously known percutaneous, transduodenal, or operative biopsies of the primary

mass were otherwise excluded from this protocol as well as other reported protocols because of the risk of tumor seeding.

It must be emphasized that the present study was a pilot study designed primarily to examine the overall tolerability and feasibility of using SBRT, capecitabine, and transplantation for unresectable hilar CCA. Although this regimen appears to have acceptable tolerability, more patients and a longer follow-up will be necessary to measure the overall long-term oncological benefits of this treatment regimen and to allow additional comparisons to other currently used regimens. An explant analysis demonstrated evidence of a pathological response, in that a partial to complete response was achieved in almost all patients. The treatment in this pilot study using SBRT allowed a short radiation treatment interval and led to acceptable rates of protocol completion and listing for transplantation. This regimen, therefore, appears to be a reasonable multimodality therapy worthy of additional study as a treatment for unresectable hilar CCA.

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