

Neoadjuvant chemoradiotherapy followed by liver transplantation for perihilar cholangiocarcinoma

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Background

Due to high rate of recurrence, liver transplantation alone has long been considered contraindicated for patients with hilar cholangiocarcinoma. However, beginning in 1993, we initiated a protocol utilizing neoadjuvant chemoradiotherapy followed by liver transplantation for selected patients with early stage hilar cholangiocarcinoma. In addition to determining outcomes for this rigorous protocol, we sought to identify predictors of dropout before transplantation and predictors of cancer recurrence after transplantation. In addition, we analyzed a multicenter experience to ascertain the overall effectiveness of this treatment across multiple U.S. centers.

Methods

We reviewed all patients with unresectable perihilar CCA treated at our center with neoadjuvant chemoradiation in anticipation for transplantation between 1993 and 2010. Predictors of dropout or recurrence were identified by uni- and multivariable Cox regression analysis of clinical variables.

Results

At our center, a total 199 patients were enrolled, of whom 62 dropped out and 131 underwent transplantation at our institution, with 6 undergoing transplantation elsewhere (Figure 1). Predictors of dropout were CA 19-9 ≥ 500 U/ml (HR 2.3; $P=.04$), mass > 3 cm (HR 2.1; $P=.05$), malignant brushing or biopsy (HR 3.6; $P=.001$) and MELD score ≥ 20 (HR 3.5; $P=.02$). Post-transplant, recurrence-free 5-year survival was 68% (Figure 2). Predictors of recurrence were elevated CA 19-9 (HR 1.8; $P=.01$), portal vein encasement (HR 3.3; $P=.007$) and residual tumor on ex-

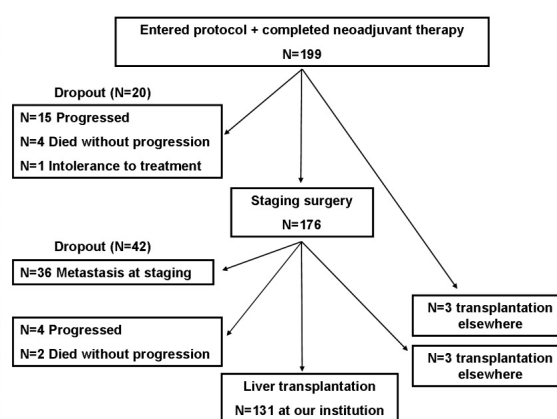


Figure 1. Patients treated with neoadjuvant chemoradiotherapy followed by LT at Mayo Clinic in Rochester, MN, USA.

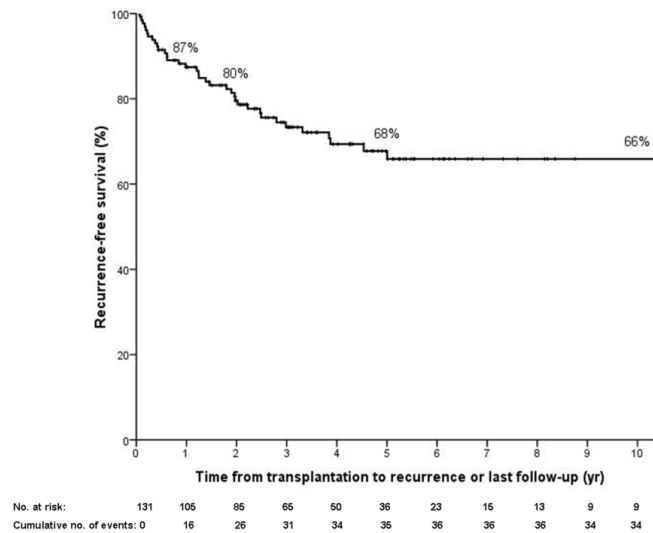


Figure 2. Outcomes of neoadjuvant chemoradiotherapy followed by liver transplantation for 131 patients treated at Mayo Clinic, Rochester MN, USA.

plant (HR 9.8; $P < .001$). PSC, age, history of cholecystectomy and waiting time were not independent predictors.

Of all large-volume U.S. transplant centers invited to participate, 12 were identified who transplanted three or more patients with perihilar cholangiocarcinoma using neoadjuvant therapy from 1993-2010. They contributed 287 eligible patients. Center-specific protocols and medical charts were reviewed on-site. Patients completed external radiation (99%), brachytherapy (75%), radio-sensitizing (98%) and/or maintenance chemotherapy (65%). In total, 71 patients dropped out before LT at a rate of 11.5% per 3 months. Intent-to-treat survival was 68% and 53% at 2- and 5 years. Post-transplantation, recurrence-free survival was 78% and 65%, respectively. Patients outside UNOS criteria (i.e. mass > 3 cm, tumor biopsy or metastatic disease) or with prior malignancy had significantly worse survival ($P < .001$). There were no differences in outcome based on variation in operative staging or brachytherapy. Although one center contributed a majority of patients (N=193), survival was equally excellent in the other 11 centers.

Conclusion

Five-year disease free survival following neoadjuvant chemoradiation and liver transplantation for perihilar CCA is 68%. Similar results were demonstrated in a multi-center analysis of outcomes among 12 U.S. transplant centers. Risk of dropout is related to patient and tumor characteristics and this can be used to guide patient counseling prior to enrolment. Recurrence risk is mostly associated with presence of residual cancer on explant. The 11.5% 3-month dropout rate confirms the appropriateness of the MELD exception. Rigorous selection is of paramount importance for continuing the success of this treatment.