Hilar Cholangiocarcinoma: No Longer Hopeless

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Cholangiocarcinoma affecting the bifurcation of the common hepatic duct is a devastating disease. Surgical resection is standard therapy, but tumor involvement of vascular and biliary structures in the hilus of the liver often preclude a margin-free resection with preservation of viable liver. During the 1980s, it was thought that liver transplantation would overcome the aforementioned barriers to resection and achieve success in the treatment of unresectable hilar cholangiocarcinoma. The entire tumor can be removed with the liver, including involved vascular and biliary structures, which are simply replaced by implantation of a donor liver.

Unfortunately, liver transplantation did not achieve results good enough to justify use of scarce donor livers [1], and hilar cholangiocarcinoma became recognized as a contraindication for liver transplantation. The University of Nebraska attempted to overcome the limitations of transplantation by treating patients with high dose brachytherapy prior to transplantation [2]. Complications from the brachytherapy were prohibitive, but there was an excellent tumor response. Our team at Mayo Clinic Rochester refined this approach and cautiously moved forward with a neoadjuvant therapy protocol that included high-dose external beam therapy, lower dose brachytherapy, and chemosensitization with 5-FU. We proposed that liver transplantation—after careful selection of patients with early stage disease, neoadjuvant therapy, and operative staging—could achieve reasonable survival. We reported our initial results with treatment of 19 patients between 1993 and 2000 [3].

Twelve underwent transplantation with 100 % survival at a median follow-up of 44 months.

Since that time, other centers have implemented identical or similar protocols and achieved comparable success. The United Network for Organ Sharing (UNOS) adopted the Mayo Clinic approach, including diagnostic and selection criteria, for MELD (Model for End-stage Liver Disease) exception guidelines [4] and policies. Most commercial insurance plans will cover this treatment, and the CMS (Center for Medicare Services) recently agreed to provide reimbursement as well.

In this issue of *Digestive Diseases and Sciences*, Salgia et al. [5] from the University of Michigan report their findings from a study of the US experience with liver transplantation for cholangiocarcinoma using the US Scientific Registry of Transplant Recipients (SRTR) database. They associate an improvement in patient survival after transplantation with publication of the initial results from Mayo Clinic Rochester in 2000. Their key findings are: (1) national results with liver transplantation for cholangiocarcinoma showed significant improvement after 2000; (2) there were no differences in survival between UNOS regions; (3) the number of transplants for cholangiocarcinoma increased after 2000. They also report that survival was favorably associated with acute cellular rejection. These findings validate the Mayo Clinic protocol, highlight the value of a national registry study, and also demonstrate the limitations of a registry study.

Does this report validate the Mayo Clinic protocol? The authors report a significant improvement in survival after 2000 (Figure 4), the time of publication of our initial results. Their study included 595 patients registered for transplantation and 359 transplanted with a diagnosis of cholangiocarcinoma between October 1987 and May 2008. During that time, Mayo Clinic Rochester registered 163

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patients and transplanted 105 patients (unpublished data), 27 and 29 % of those groups. Mayo Clinic Rochester thus accounted for nearly a third of the national experience. Despite this bias, the authors report no differences in patient survival between UNOS regions. Improvements in survival were seen in other centers that presumably adopted the Mayo Clinic protocol, either completely or with modification. The finding that MELD exception was associated with improved survival lends support to this view, since most regional review boards would have required some type of plan for neoadjuvant therapy and selection criteria.

This study is limited by incomplete data. The SRTR data do not include tumor characteristics, selection criteria, or use of neoadjuvant therapy. Thus, the conclusion is based purely on circumstantial evidence. Since there are no other explanations for the improvement in survival, it seems reasonable to attribute the improvement to wide spread application of neoadjuvant therapy and careful patient selection per the Mayo Clinic protocol.

Was there an increase in transplantation for cholangiocarcinoma? The answer to this question is an unequivocal yes. Figure 2 shows a decrease in transplantation for cholangiocarcinoma during the 1990s due to the realization that survival with transplantation alone was too low to justify use of a donor liver. There is a clear increase in transplantation for cholangiocarcinoma during the years following publication of initial and subsequent results from Mayo Clinic.

The authors' attempt to identify prognostic factors (Table 2) reveals additional limitations of an SRTR-based study. Their finding that incidental tumor detection did not affect survival is contrary to several other studies [6, 7], all of which show a deleterious effect of an incidentally detected cholangiocarcinoma in an explanted liver. This discrepancy might have arisen from inaccurate or incomplete data. The natural history and response to treatment are different for all combinations of location (intrahepatic, hilar, extrahepatic) and growth patterns (mass forming, sclerosing, polypoid) and none of this information is available in the SRTR data.

Incidental tumors reported to the SRTR could, and probably do, include intrahepatic mass-forming cholangiocarcinoma misdiagnosed as hepatocellular carcinoma and missed hilar cholangiocarcinoma arising in the setting of primary sclerosing cholangitis (PSC). Both situations could be either advanced or early stage disease and have highly variable effects on survival. Thus, it is not surprising that the authors were unable to corroborate single and multicenter studies that have demonstrated the adverse prognostic effect of incidental cholangiocarcinoma.

Incomplete and inaccurate data are inherent weaknesses of most registry studies. The authors identified history of

acute rejection as a significant prognostic factor by univariate and multivariate analyses. Table 1 shows that none of the 150 patients transplanted between 1987 and 2000 had rejection and that only 9 of 209 patients (4.3 %) transplanted between 2000 and 2008 had rejection. These numbers are simply too low. The conclusion that rejection affects survival should be considered invalid because of incomplete and/or inaccurate data.

The national results reported by this study are considerably lower than the survival rates reported by Mayo Clinic. Potential explanations include differences in patient selection, operative staging, neoadjuvant therapy administration, and specific patient and tumor characteristics. This SRTR study, by its very nature, cannot provide the answers. However, it is noteworthy that the proportion of patients with underlying PSC is much less for the national experience than for Mayo Clinic, 23 versus 66 % [8]. The most recent publication from Mayo Clinic demonstrates significantly better survival for patients with cholangiocarcinoma arising in the setting of PSC than for patients with de novo cholangiocarcinoma [9].

This SRTR study corroborates findings from a multicenter study that demonstrated results comparable to those reported by Mayo Clinic achieved by other centers that have adopted patient selection criteria, neoadjuvant therapy, and operative staging prior to liver transplantation for hilar cholangiocarcinoma [10]. The study by Salgia et al. is important because it includes all patients transplanted for cholangiocarcinoma in the US, a number much larger than those reported in the multicenter study.

This paper validates single and multicenter reports of the efficacy of neoadjuvant therapy and liver transplantation. It has the usual limitations of a registry study, but an important message: neoadjuvant therapy and liver transplantation has emerged as an effective treatment for patients with unresectable hilar cholangiocarcinoma and hilar cholangiocarcinoma arising in the setting of PSC.

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