



## The High Risk Recipient

### Honey, You Shrunk My Tumor: Downstaging for HCC

Francis Y. Yao, MD

University of California San Francisco

The concept of using loco-regional therapy such as trans-arterial chemoembolization (TACE) to reduce the size of hepatocellular carcinoma (HCC), thereby facilitating resection or orthotopic liver transplantation (OLT), was first tested by Majno et al. from Hospital Paul Brousse, France (1). Successful down-staging in their study was defined as a 50% reduction of the product of perpendicular diameters of the largest lesion. In a subgroup of 57 patients with 1 or more tumors greater than 3 cm, 19 patients with tumors successfully down-staged had a 5-year disease-free survival of 71% versus 49% for 22 patients without TACE ( $p=0.09$ ) and 29% for the 16 patients who did not respond to TACE ( $p=0.01$ ).

In the past 10 years, the Milan criteria (single lesion up to 5 cm, or 2-3 lesions up to 3 cm in diameter) have remained the paradigm for the selection of the best candidates with HCC for OLT (2). However, it is also accepted that a subgroup of patients with HCC beyond Milan criteria have acceptable outcome after OLT (3-6). We have previously reported the results of down-staging of HCC to meet conventional UNOS T2 criteria (single lesion 2-5 cm, or 2-3 lesions up to 3 cm) as a test of concept (7). We have now enrolled 61 patients in our down-staging protocol between June 2002 and January 2007 with long-term follow-up. Eligibility criteria for down-staging included 1 lesion > 5 cm but within 8 cm, 2 to 3 lesions at least one > 3 cm but none exceeding 5 cm with total tumor diameter up to 8 cm, or 4 to 5 nodules none greater than 3 cm, with total tumor diameter within 8 cm. A minimum observation period of 3 months after down-staging was required before OLT. Criteria for successful down-staging included tumor size meeting T2 criteria or complete tumor necrosis, equivalent to obliteration of the tumor. Tumor down-staging was successful in 43 patients (70.5%). Thirty-five patients (57.4%) had received OLT, including 2 who had live-donor liver transplantation. Treatment failure, defined as dropout from the waiting list or death without OLT, was observed in 18 patients (29.5%), primarily due to tumor progression. In the explant of 35 patients who underwent OLT, 13 had complete tumor necrosis, 17 met T2 criteria, and 5 exceeded T2 criteria. The Kaplan-Meier intention-to-treat survival at 1 and 4 years after down-staging were 87.5% and 69.3%, respectively. The 1- and 4-year post-transplant survival rates were 96.2% and 92.1%, respectively. None had HCC recurrence after a median post-transplant follow-up of 25 months. The only factor predicting treatment failure was pre-treatment alpha-fetoprotein > 1000 ng/mL.

These results suggest that successful down-staging of HCC can be achieved in the majority of carefully selected patients, and is associated with excellent post-transplant outcome. Down-staging put selection pressure against aggressive tumors that are likely to progress despite treatment, whereas tumors with more favorable histology are more likely to respond to treatment and do well after OLT. Balancing the risk of dropout due to long wait-list time and the selection of candidates with more favorable tumor biology remains a challenge. There is still a need for refinement of the down-staging treatment strategies to further improve the intention-to-treat outcome.

#### REFERENCE

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