Liver and Biliary Injuries Following Transarterial Chemoembolization of Endocrine Tumors and Hepatocellular Carcinoma: Lipiodol versus Drug-Eluting Beads

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Background:
TACE (transarterial chemoembolization) is the mainstay of the treatment of patients with intermediate-stage HCC (hepatocellular carcinoma) and is effective in achieving both control hormone-related symptoms and reduction of tumor growth in NETs (endocrine tumors). Despite undeniable pharmacological advantages, TACE using drug-eluting beads (DEB-TACE) has not demonstrated its superiority to conventional-TACE (using lipiodol) regarding tumor response. Though a lower systemic toxicity of DEB-TACE compared with conventional TACE has been reported in HCC, very few data are available regarding liver/biliary toxicity. The aim of this study was to describe and compare the liver/biliary injuries encountered with DEB-TACE and conventional-TACE in liver metastatic NETs and in HCC with underlying cirrhosis.

Methods:
Two hundred and eight consecutive patients referred to Gustave Roussy Institute between January 2003 and June 2010 for TACE of a well-differentiated metastatic NET (n=120) or a HCC (n=88) with underlying cirrhosis were included in this retrospective study, approved by our institutional review board.
Liver imaging was performed by either CT or MRI. Baseline imaging was performed <1 month before each TACE session, and follow-up imaging was performed 1-3 months after each session using the same imaging modality. For each patient, successive liver imaging follow-up exams were reviewed and compared at consensus by two experienced radiologists blinded to information regarding the patient and the TACE sessions. A total of 638 CT- and 46 MR-scans were examined. According to previously published papers, liver and biliary injuries were classified as follows: dilated bile duct, portal vein narrowing, portal venous thrombosis and biloma/parenchymal infarct
Univariate and multivariate logistic regression was used to compute odds ratios (with 95% confidence interval [95%CI]) for liver/biliary injury or biloma/parenchymal infarct. We performed repeated measures logistic regressions by using a generalized estimating equation (GEE) logistic regression model to take into account repeated TACE sessions for each patient. The multivariate models were internally validated using bootstrapping (200 replications).

Results:
In NET-group, 65 patients were treated by lipiodol-TACE (152 sessions) while 55 were treated by DEB-TACE (126 sessions). In HCC-group, 59 patients and 29 patients were treated by lipiodol-TACE (142 sessions) and DEB-TACE (56 sessions) respectively. In each group, there was no difference in the two subgroups (lipiodol and DEB-TACE) for the main characteristics including: age, sex, BMI, performance status, liver involvement and baseline liver enzymes.
The occurrence of a liver/biliary injury was strongly associated with DEB-TACE (OR:6.62, p<.001; bootstrapping 95%CI:[3.77-11.63]) irrespectively of the type of tumor. Biloma/parenchymal infarct was strongly associated with both DEB-TACE (OR:9.78, p=.002; bootstrapping 95%CI:[3.32-28.77]) and NETs (OR:8.12, p=0.04; bootstrapping 95%CI:[4.13-15.97]). Biloma/parenchymal infarct was significantly associated with the serum level of alkaline phosphatase (p=0.012). Among patients
treated by DEB-TACE, the amount of treated liver, DEB type, DEB size, and volume of anticancer agent were not associated with liver/biliary injury or biloma/parenchymal necrosis.

**Conclusion:**
The use of DEB-TACE is associated with liver/biliary injuries and especially biloma/parenchymal infarct when TACE is performed for NETs. The absence of such association in TACE of HCC may be explained by the hypertrophied peribiliary plexus observed in cirrhosis, acting as a protection against biloma/parenchymal necrosis. We suggest caution when using doxorubicin-loaded beads in TACE for NETs.