

The puzzle and challenge in the treatment of an intraoperative margin-positive proximal bile duct in hilar cholangiocarcinoma

Fei Liu*, Wen-Jie Ma*, Hai-Jie Hu, Parbatraj Regmi, Jun-Ke Wang, Fu-Yu Li

Department of Biliary Surgery, West China Hospital of Sichuan University, Chengdu 610041, China

*These authors contributed equally to this work and were the co-first authors.

Correspondence to: Fu-Yu Li, MD, PhD. Department of Biliary Surgery, West China Hospital of Sichuan University, Chengdu 610041, China.

Email: lfy_74@hotmail.com.

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Hilar cholangiocarcinoma (HCCA) is an uncommon neoplasm involving confluence of the hepatic ducts. Complete surgical resection (R0) is the only treatment with the potential for cure for HCCA (1). Over the past decades, the operative approach of HCCA has rapidly evolved, but in some cases, its anatomic location and longitudinal extent along the bile duct have made curative resection difficult. It remains controversial whether additional resection of the remaining proximal bile duct to obtain a negative resection margin when the frozen section (FS) examination of the proximal bile duct is positive. There is a consensus that cancer in situ (CIS) without invasive carcinoma at the duct margin is not related to poorer survival than a negative margin (2-5).

Shingu *et al.* (3) analyzed 303 patients, of which 12 patients underwent additional resection; as a result, 8 patients achieved a negative margin. The 3- and 5-year survival rate of the secondary R0 group (n=8) was 0% and 0% respectively, while the 3- and 5-year survival rate of the primary R0 group and patients who possessed a positive margin with CIS (n=275) was 53% and 37% respectively, which showed statistical difference (P=0.022), in addition, the 3- and 5-year survival rate of patients (n=20) with a positive margin diagnosed in permanent histopathology was 36% and 16% respectively, and compared with the secondary R0 group there was no statistical difference (P=0.294). Visibly, their results demonstrated that when the FS examination of the proximal bile duct was positive, due to the specific location of the proximal bile duct, an additional resection of the remaining proximal bile

duct to obtain a negative resection margin duct did not increase the long-term survival outcome (3). The similar results were also reported by Oguro *et al.* (4) and Endo *et al.* (5). In the study conducted by Oguro *et al.* (4), 224 patients underwent curative surgery, of which 52 patients underwent additional resection because the FS examination of the proximal bile duct was positive, and 43 patients achieved negative margins. The median survival of the 43 patients (29.4 months) was significantly worse than those 149 patients with a negative margin achieved at the time of the first resection or a positive margin with CIS (56.6 months, P=0.031), and the median survival of the 43 patients was just similar to those of the patients (n=32) with positive margins at the final pathological diagnosis (21.5 months, P=0.215). Endo *et al.* (5) reported the median survival in the secondary R0 group (n=28) was 38 months, which was comparable to 32 months of those 19 patients with R1 resection margins diagnosed in permanent histopathology; while, this was lower than those in primary R0 group (n=54) whose median survival time was 56 months (P=0.010).

However, it has been reported that an additional resection of the intraoperative margin-positive proximal bile duct can prolong the survival time of patients with HCCA. Ribero *et al.* (6) reported the median survival of patients (n=13) with secondary R0 resection was 30.6 months, the 1-, 3-, and 5-year survival rate was 88.8%, 50.0%, and 50.0% respectively, which was significantly better than the median survival time of 4.9 months of those 8 patients with positive margins in permanent histopathology (P=0.026), whose 1-, 3-, and 5-year survival rate was 65.2%, 12.5%,

and 0% respectively; The survival outcome of patients with secondary R0 resection was similar to those with primary negative margins (n=54) who had a median survival time of 29.2 months and 1-, 3-, and 5-year survival rate of 75.8%, 45.0%, and 30.8%, respectively. Although additional resection could improve the survival of the patient who possesses a positive intraoperative margin status of the proximal bile duct, it significantly increased the incidence of biliary fistula (44.4% vs. 17.5%; P=0.02) (6).

From the above studies, we can conclude that whether additional resection can improve the survival rate of patients with an intraoperative margin-positive proximal bile duct in HCCA is highly disputable. Negative resection margin is an important prognostic factor in patients with HCCA, but the long-term survival of HCCA with different pathological types is completely different. Sakamoto *et al.* (7) pointed out the submucosal extension was predominant in infiltrating type, and the length ranged from 0.6 to 18.8 (mean, 6.0 mm) and was less than 10 mm in 25 patients (83%). The superficial spread was predominant in papillary and nodular types, and the mean length was 11.5 mm. Ebata *et al.* (8) observed intramural spread in proximal direction within 10 mm in all the cases, and superficial extent in proximal direction within 19.5 mm in 75% of the cases. Additionally, Seyama *et al.* (9) pointed out a macroscopic surgical margin over 10 mm is preferable in the invasive type and over 20 mm in the papillary and nodular types. Whether to additional resection, we should be based on the different cases and the possible pathological types. The 2017 National Comprehensive Cancer Network guidelines indicated that for those with resectable proximal and distal bile duct margins, intraoperative FS assessment was recommended. It is important to note that the sensitivity and specificity of intraoperative FS was 68% and 97% respectively, but the false negative rate was as high as 16% (10). Intraoperative FS assessment must be routine, but for the particular pathological type, we should pay more attention to the accuracy of intraoperative FS assessment.

Currently, the most of existing literature does not support additional resection can increase long-term survival. The ductal margin status is an important prognostic factor in patients with HCCA. Therefore, we believe that additional resection should be attempted whenever possible to reach R0 on the premise of ensuring patient safety. We should take individualized programs for patients with an intraoperative margin-positive proximal bile duct. The

final guidelines need to be developed through randomized controlled trials and multicenter studies. We need the internationally recognized guidelines to guide clinical surgery programs.

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Footnote

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