



Endoscopic Management of Cholangiocarcinoma: Putting in Your Two Stents' Worth

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Published online: 17 October 2018
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Cholangiocarcinoma (CCA) is an uncommon and locally aggressive malignancy of the biliary epithelium, which presents significant challenges to patients and physicians. Without treatment, most patients with CCA follow a dismal and progressive disease course eventuating in loss of life as a result of cholestatic liver failure, biliary infection, or bleeding [1]. In particular, hilar CCA represents an especially challenging entity with respect to relieving obstructive jaundice due to the intense desmoplastic reaction and local tumor extension into biliary radicals that may separately occlude more than one hepatic lobe, sector, or segment [1]. Due to this infiltrative and sometimes piecemeal pattern of obstruction, achieving meaningful drainage can require technically complex or multiple intervention(s).

Reliably studying outcomes in CCA can be as daunting a task as is caring for patients. Up-front management is often biased by the need to provide palliation prior to affirmative diagnosis, retrospective data are easily tainted by unaccounted for patient-centric variables, and the disease is rare. Currently, prospective data are generally lacking due to logistical difficulties and the risk of long-running enrollment. In this context, it is no surprise that the optimal strategy to manage biliary obstruction in hilar CCA remains a minefield of controversy. Numerous questions remain unanswered: What is the preferred route of biliary access for decompression (endoscopic versus percutaneous)? What is the preferred method of decompression (plastic or self-expanding metal stents [SEMS])? Should stenting and drainage be unilateral, bilateral, or multi-sectoral within a particular lobe? How should the selection of a particular method be influenced by the plan for operative or nonsurgical treatment, including endobiliary local therapies? How do

these choices ultimately influence pivotal patient outcomes such as relief of jaundice, durable decompression, infection risk, and overall survival?

In this issue of *Digestive Diseases and Sciences*, Cassani and colleagues [2] compared the overall survival of patients with CCA based upon the clinical success of biliary decompression. Moreover, various secondary outcomes of endoscopic retrograde cholangiopancreatography (ERCP)-directed biliary drainage are also presented in this large, retrospective experience from a referral cancer center. Cassani *et al.* included 199 subjects with obstructing CCA referred for ERCP over an extensive 17-year timeframe. This cohort underwent 504 ERCP procedures, conducted with methodology typical for an academic interventional endoscopy center. At baseline, patients included are characteristic of CCA, with a predominance of hilar tumors (85%). Most patients had previously undergone ERCP with plastic stent placement at a referring institution (52.8%); the technical success rate of the procedures was comparable with that of an expert center (98.2%).

The most striking observation made by Cassani *et al.* is that patients who underwent clinically successful biliary decompression had substantially prolonged overall survival (OS) compared with those in which decompression was not achievable (15.2 vs. 4.8 months). Although this is superficially unsurprising, there is little contemporary literature that clearly delineates this salient point. Though this distinction may reflect a fundamental difference in disease prognosis between groups irrespective of the intervention, it nonetheless underscores the potential importance of providing adequate relief of jaundice whenever possible. Resolution of jaundice was also observed more frequently in patients who underwent successful bilateral biliary stent placement than in those who underwent unilateral intervention. This finding, in keeping with published data [3, 4], supports the concept that there is likely benefit in maximizing preserved liver volume via providing adequate drainage. One potential major risk of intended bilateral drainage appears to be an

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increased risk of subsequent cholangitis and the need for percutaneous trans-hepatic biliary drainage (PTBD) as rescue therapy, as previously reported in the trial by De Palma et al. [5], was not obvious here. The only subset of cases where a nonsignificant additive risk of cholangitis was present were instances where unilateral drainage was achieved, despite bilateral contrast opacification, mirroring the intention-to-treat analysis of *De Palma et al.* and also violating a universal and cardinal rule of ERCP: “do not inject what you do not drain.” This association has less to do with the principle of bilateral drainage than with ensuring successful execution. I interpret this finding as a reminder to maintain a high degree of vigilance for subsequent infection when it is technically impossible to achieve drainage of an injected segment, rather than as a deterrent against carefully pursuing bilateral or multi-sectoral decompression.

The debate over stent choice appears inconclusive in the data presented by *Cassani et al.* While there may be a trend toward improved clinical success with SEMs vs. plastic stents, this finding was nonsignificant and should be cautiously interpreted. Most centers, including that of the authors of the present manuscript, generally reserve placement of a SEMs for what is intended to be a terminal endoscopic procedure (Table 2: supplement). This choice is highly individualized in the absence of discrete clinical trial data and is subject to significant unmeasured bias. Furthermore, since placement of a SEMs across the hepatic hilum is irreversible, its use must be thoughtfully considered. Remediation of one or more occluded hilar SEMs can represent a highly unsatisfying endoscopic dilemma, frequently requiring percutaneous hepatic biliary drainage (PTBD). Analyses which strongly favor SEMs use [6] usually rely on designs formulated to measure the number rather than the complexity of re-interventions, and may not capture the totality of interventions such as unwanted external drainage that often negatively impacts the quality of life in patients with terminal cancer.

The optimal management strategy for malignant biliary obstruction secondary to cholangiocarcinoma remains a subject of vigorous debate. Although the experience presented here by *Cassani et al.* is limited by its retrospective design, the data presented underscore several fundamental principles that are important to endoscopists caring for patients with this difficult disease. In the palliative setting, the impact of successful biliary decompression cannot be overstated. Relief of jaundice is of major significance to patients, as well

as to medical and radiation oncologists, whose subsequent care may be markedly hampered by a failure to normalize serum bilirubin. Furthermore, maximizing the volume of successfully decompressed liver may have a meaningful impact on overall survival, independent of how that goal is achieved. Segments that remain undrained following ERCP likely increase the risk of cholangitis if injected, and should be avoided when possible.

Despite considerable interest, the optimal timing and precise contributions of plastic stents, PTBD, SEMs, and their interaction with emergent endoscopic local therapies for CCA, including radiofrequency ablation and photodynamic therapy, remain unsettled. Further randomized controlled data investigating each of these questions are sorely needed, but with rare exceptions [7], are unlikely to be forthcoming.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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