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An Unsuccessful Randomized Trial of Percutaneous vs Endoscopic Drainage of Suspected Malignant Hilar Obstruction

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Supplementary Material

Note: to access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org/, and at https://doi.org/10.1016/j.cgh.2020.05.035.

Conflicts of interest

The authors disclose no conflicts.

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Percutaneous transhepatic biliary drainage (PTBD) and endoscopic retrograde cholangiopancreatography (ERCP) are widely accepted but competing approaches for the management of malignant obstruction at the hilum of the liver. ERCP is favored in the United States on the basis of high success rates for non-hilar indications, the perceived safety and superior tissue sampling capability of ERCP relative to PTBD, and the avoidance of external drains that are undesirable to patients. A recent randomized controlled trial (RCT) comparing the 2 modalities in patients with resectable hilar cholangiocarcinoma was terminated prematurely because of higher mortality in the PTBD group.[1] In contrast, most observational data suggest that PTBD is superior for achieving complete drainage.[2–6] Because the preferred procedure remains uncertain, we aimed to compare PTBD and ERCP as the primary intervention in patients with cholestasis due to malignant hilar obstruction (MHO).

Methods

The eligibility criteria and study protocol were published previously[7] and are provided in Supplementary Appendix A. In brief, patients ≥40 years old with cholestasis and radiographic evidence of obstruction at the liver hilum were considered eligible. Patients were excluded if there was suspicion of a benign stricture or if they had relative contraindications to either PTBD or ERCP.

Eligible patients were randomly assigned to PTBD or ERCP as their first intervention. The technical approach to the procedure and all subsequent clinical interventions were dictated by treating physicians per usual clinical care. The primary endpoint was successful biliary drainage, which was defined as 50% reduction in the bilirubin level within 3 weeks of the study intervention without additional ERCP or PTBD. Patients were followed for 3 months.

Because of the avoidance of extracorporeal tubes and the other perceived advantages of ERCP, we estimated that PTBD would have to be at least 20% more effective to impact clinical practice. Assuming a response of 90% in the PTBD group,[2] we estimated that 160 patients would provide a power of at least 85% to detect a 20% absolute difference between study groups, with a two-sided significance level of .05. To address attrition, the sample size was inflated by 15% to 184.

There was no extramural grant support. All authors approved the final manuscript.

Results

From October 2017 through March 2019, 51 patients were screened, and 13 were randomized across 16 referral centers in the United States. In April 2019, the data and safety monitoring board recommended study termination because of prohibitively slow subject accrual.

Baseline characteristics and outcomes according to study group are presented in Table 1. There were no major differences between groups. Less than 50% of patients achieved the primary endpoint. Ten patients experienced adverse events requiring hospitalization, and 8 died during follow-up.

Discussion

This trial was intended to determine whether PTBD or ERCP is the preferred initial intervention for patients with suspected MHO. We used a pragmatic study design that included only one protocol-driven intervention (randomization) because the varying approaches to this highly complex disease process between patients and across practice settings constrain protocol standardization and threaten the generalizability of a more traditional study design. Despite this, the study did not meet enrollment targets because of several possible factors including lack of funding, provider/institutional bias in favor of one procedure, and logistical challenges associated with randomization, which are outlined in Supplementary Appendix B.

Whether to recommend PTBD or ERCP as the first intervention for suspected MHO remains a fundamental question in clinical practice that can be answered by high-quality observational data and a randomized trial. Toward the goals of improved patient care and clinical trial readiness, prospective cohort studies should aim to elucidate the following:

1. A precise estimate of the fraction of PTBD and ERCP patients who experience a bilirubin reduction to the level at which chemotherapy is tolerated. The sample size of this trial was based on achieving a 50% reduction in bilirubin because this was the only endpoint for which data are published; however, it is unlikely to represent the most meaningful biochemical endpoint.
2. Non-laboratory outcome measures that are of importance to patients and their caregivers. Because of the high death rate despite chemotherapy and considering that MHO patients are often excluded from decisions about drainage, a focus on patient-centered outcomes in future RCTs is critical.
3. Patient and stricture characteristics that predict response to PTBD or ERCP. These might inform clinical decision making and randomization strata in future RCTs.
4. The barriers to successful execution of a large-scale trial. Future studies should explore patient, caregiver, and physician perspectives on clinical trial

participation as well as institutional and systems-level factors that might impact accrual and influence trial design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations used in this paper:

ERCP	endoscopic retrograde cholangiopancreatography
MHO	malignant hilar obstruction
PTBD	percutaneous transhepatic biliary drainage
RCT	randomized controlled trial

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Table 1.

Baseline Characteristics and Outcomes by Study Group

Characteristic	PTBD (N = 5)	ERCP (N = 8)
Age, *y* (SD)	69.6 (6.2)	63.9 (14.2)
Male sex, n (%)	3 (60)	5 (62.5)
White race, n (%)	5 (100)	7 (87.5)
Charlson score, mean (SD)	3 (2.5)	3.75 (4.2)
Serum bilirubin, *mg/dL*, mean (SD)	15.9 (7.8)	13.7 (6.8)
Bismuth class 3 or 4 stricture, n (%)	3 (60)	5 (62.5)
Outcome		
Successful biliary drainage, n (%)	2 (40)	4 (50)
Bilirubin drop to ≤2.5 mg/dL, n (%)	1 (20)	2 (25)
Adverse event related to randomization procedure resulting in hospitalization, n (%)	4 (80)	6 (75)
Cancer confirmed by randomization procedure, n (%)	1 (20)	3 (37.5)
Mean no. of procedures/patient	2.6	2.3
Mean no. of hospital days/patient during follow-up (SD)	10.2 (10.4)	15.1 (17.7)
Death within 3 months, n (%)	4 (80)	4 (50)