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ORIGINAL ARTICLE

Meta-analysis of Duct-to-duct versus Roux-en-Y biliary reconstruction following liver transplantation for primary sclerosing cholangitis

Sanjay Pandanaboyana,[1] Richard Bell,[1] Adam J. Bartlett,[2] John McCall[2] and Ernest Hidalgo[1]

1 Department of HPB Surgery and Transplant, St James University Hospital, Leeds, UK
2 Department of HPB and Transplant, Auckland City Hospital, Auckland, New Zealand

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Correspondence
Sanjay Pandanaboyana MS, FRCS, MPhil, Fellow in HPB and Transplant Surgery, St James University Hospital, Beckett Street, Leeds, UK.
Tel.: +44 113 2068378;
fax: +44 113 2448182;
e-mail: sanjay.pandanaboyana@gmail.com

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Summary

This meta-analysis aimed to compare outcomes following bile duct reconstruction in patients with primary sclerosing cholangitis (PSC) undergoing liver transplantation depending on whether duct-to-duct or Roux-en-Y anastomosis was utilized. An electronic search was performed of the MEDLINE, EMBASE, PubMed databases using both subject headings (MeSH) and truncated word searches. Pooled risk ratios and mean difference were calculated using the fixed-effects and random-effects models for meta-analysis. Ten studies including 910 patients met the inclusion criteria. There was no difference in the overall incidence of biliary strictures between the two groups [odds ratio (OR) 1.06 (0.68, 1.66); ($P = 0.80$)]. The anastomotic stricture rate was similar, [OR 1.18 (0.56, 2.50); ($P = 0.67$)]. Ascending cholangitis was higher in the Roux–en-Y group [OR 2.91 (1.17, 7.23); ($P = 0.02$)]. Anastomotic bile leak rates, graft survival, PSC recurrence and number of patients diagnosed with cholangiocarcinoma following transplantation were comparable between both groups. Duct-to-duct and Roux-en-Y reconstruction had comparable outcomes. Both techniques are associated with similar incidence of biliary stricture. The bilioenteric reconstruction was associated with a higher risk of cholangitis. The incidence of de novo cholangiocarcinoma was similar in both groups. Duct-to-duct reconstruction should be considered when feasible in patients with PSC.

Introduction

Liver transplantation (LT) is the treatment of choice for advanced primary sclerosing cholangitis (PSC) [1,2]. However, controversy still exists regarding the type of biliary reconstruction, with Roux–en-Y hepaticojejunostomy (RY) and a duct-to-duct (DD) anastomosis commonly being used. RY reconstruction is often the preferred technique in most centres as some studies have suggested reduced rates of stricture formation and improved patient and graft survival [3]. In addition, the RY reconstruction allows a more extensive resection of the native bile duct reducing the theoretical risk of recurrent PSC and/or de novo cholangiocarcinoma [4]. Conversely, a duct-to-duct anastomosis provides a more physiological reconstruction of the biliary system, a shorter operating time [5–7] in addition to facilitating easier postoperative instrumentation of the biliary tree [8]. Several studies have been published recently with conflicting results, some favouring a RY reconstruction, while others showed comparable results. In this context, this systematic review and meta-analysis compared DD and RY biliary reconstruction following LT for PSC, focussing on perioperative and long-term outcomes.

Methods

A search for all randomized (RCT) and case-controlled studies, irrespective of language, country of origin, hospital,

blinding, sample size or publication status, comparing duct-to-duct and RY biliary reconstruction following liver transplantation for PSC was included in this review. The Cochrane Colorectal Cancer Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE, Embase and Science Citation Index Expanded were searched for articles published up to April 2014 using the medical subject headings (MeSH) terms 'duct to duct, Roux en Y, biliary reconstruction, hepaticojejunostomy, PSC, primary sclerosing cholangitis, liver transplantation'. Equivalent free-text search terms, such as 'duct to duct and Roux en Y, were used in combination with 'liver transplantation'. The references from the included studies were searched to identify additional studies comparing the two techniques. All patients who underwent liver transplantation for PSC were included. Inclusion criteria were as follows: studies evaluating the use of use of duct-to-duct biliary reconstruction and Roux-en-Y biliary reconstruction following liver transplantation for PSC. Our search strategy is summarized in Fig. 1.

Types of outcome measures

The primary outcome measures were the incidence of postoperative biliary stricture formation and anastomotic biliary leaks. The overall incidence of strictures (including anastomotic and nonanastomotic) was analysed separately from anastomotic strictures. Secondary outcome measures were episodes of cholangitis, morbidity, 1-year graft survival and the development of cholangiocarcinoma during follow-up.

Definitions

Unfortunately, no routine definition or classification of type (i.e. intrahepatic or diffuse) PSC was given.

Biliary stricture was defined as a narrowing in the biliary tree, evident on radiological investigations and associated with biochemical abnormalities requiring intervention.

Nonanastomotic stricture was defined as any stricture, dilatation or irregularity of the intra- or extrahepatic bile duct, located at a site other than the anastomosis.

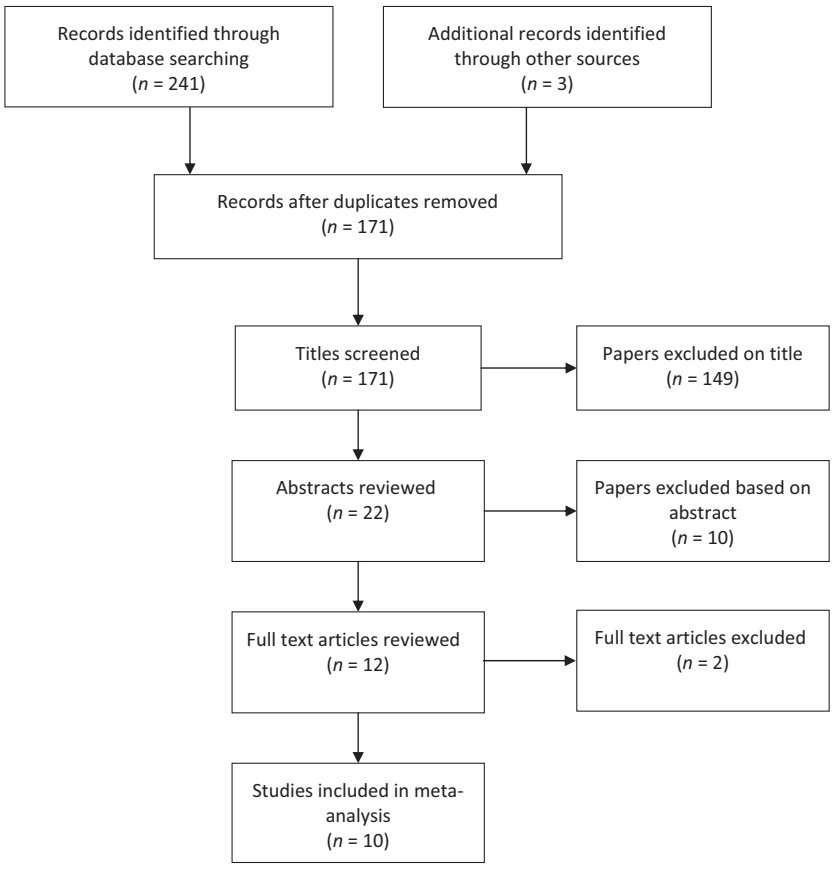

Figure 1 PRISMA flow diagram.

Biliary leak was diagnosed when clinically or radiologically evident persistent drainage of bile was reported requiring intervention.

Recurrent PSC was diagnosed based on liver biopsy and/or radiological assessment in the absence of a dominant anastomotic stricture.

Morbidity was defined as any complication within 30 days from the operation that required hospitalization, surgical/radiological or endoscopic intervention. Unfortunately, no classification, for example Clavien-Dindo, was used to allow stratification.

Ascending cholangitis was diagnosed based on clinical signs of biliary infection supported by laboratory blood tests with or without imaging.

Data extraction and quality assessment

Studies were identified and data were extracted by two authors independently (RB, SP). To our knowledge, and not unsurprisingly, no RCT has been published comparing the two techniques. The accuracy of the extracted data was further adjudicated by a third author (EH). The quality assessment of included studies was based on the Newcastle–Ottawa score.

Statistical analysis

Statistical analysis was performed using Review Manager version 5.2 software (Cochrane Collaboration, Copenhagen, Denmark). The risk ratio (RR) with 95% confidence interval (CI) was calculated for binary data, and the mean difference with 95% CI was calculated for continuous variables. When median and range were reported instead of mean and variance, their mean and variance were calculated based on the methods described by Hozo and colleagues [9]. Random and fixed-effects models were used to calculate the combined outcomes of both binary and continuous data [10,11]. In cases of heterogeneity, only the results of the random-effects model were reported. Heterogeneity was explored using the χ^2 test, with significance set at $P < 0.05$. Low heterogeneity was defined as an I^2 value of 33% or less [12]. If the standard deviation was not available, it was calculated according to the method described in the Cochrane Handbook [13]. This process involved assumptions that both groups had the same variance, which may not have been true, and variance was estimated either from the range or from the P value. Forest plots were used for graphical display of the results.

Results

Ten studies fully met the inclusion criteria and formed the basis of this meta-analysis [3–7,14–18] (Fig. 1). All studies were retrospective in nature. In total, 910 patients were included of which 572 patients were in the RY group and 338 patients in the duct-to-duct group. The characteristics and quality of the studies are included in Table 1. Pooled data were analysed by combining the results of the 10 studies.

Primary outcome measures

Biliary stricture (anastomotic and nonanastomotic)

Nine studies including 850 patients were analysed with 123 events. There was no heterogeneity amongst the included studies ($\chi^2 = 10.72$, d.f. = 8 ($P = 0.22$); $I^2 = 25\%$. In a random-effects model, there was no significant difference in the incidence of biliary stricture between RY (13%) and DD (16%) reconstruction with an OR 1.06 [0.68, 1.66] $Z = 0.26$ ($P = 0.80$) Fig. 2.

Table 1. Characteristics of included studies.

Author	Country	Year	Patients per group		Biliary stricture (%)		Biliary leak (%)		Newcastle Ottawa score
			DD	RY	DD	RY	DD	RY	
Aljudaibi *et al.*	Canada	2012	15	58	7	9	7	0	6
Damrah *et al.*	UK	2011	63	28	10	7	8	14	7
Distante *et al.*	UK	1996	16	10	19	10	6	20	7
Esfeh *et al.*	USA	2011	18	28	11	11	0	0	7
Feith *et al.*	The Netherlands	1997	13	21	15	5	15	14	7
Heffron *et al.*	USA	2003	22	38	NS	NS	9	5	7
Hoekstra *et al.*	The Netherlands	2009	34	60	26	30	NS	NS	6
Schmitz *et al.*	Germany	2006	6	20	0	10	0	0	8
Sutton *et al.*	The Netherlands	2014	45	53	44	66	6	4	8
Welsh *et al.*	UK	2003	98	264	7	2	7	4	7
Total or mean (SD)			338	572	15 (13)	17 (20)	6 (5)	7 (7)	

Anastomotic biliary stricture

Four studies were included in the analysis with 261 patients and 32 events. There was no heterogeneity amongst the included studies (χ^2 = 1.68, d.f. = 3 (P = 0.64); I^2 = 0%. In a fixed-effects model, there was no significant difference in the incidence of anastomotic stricture between RY (13%) and DD (11%) reconstruction, OR 1.18 [0.56, 2.50] Z = 0.43 (P = 0.67).

Anastomotic biliary leakage

Nine studies were included in the analysis with 816 patients. Forty-four events were observed. There was no heterogeneity amongst the included studies (χ^2 = 5.73, d.f. = 6 P = 0.45); I^2 = 0%. In a fixed-effects model, there was no significant difference in the incidence of biliary leakage between RY (4%) and DD (7%) reconstruction, OR 0.80 [0.43, 1.47] Z = 0.73 (P = 0.47) Fig. 3.

Secondary outcome measures

Ascending cholangitis

Three studies were included in the analysis. One hundred and fifty-eight patients and 35 events were encountered. There was no heterogeneity amongst the included studies (χ^2 = 2.05, d.f. = 2 (P = 0.36); I^2 = 2%. In a fixed-effects model, there was a significant difference in the incidence of cholangitis between RY (30%) and DD (10%) reconstruction with an OR 2.91 [1.17, 7.23] Z = 2.30 (P = 0.02) Fig. 4.

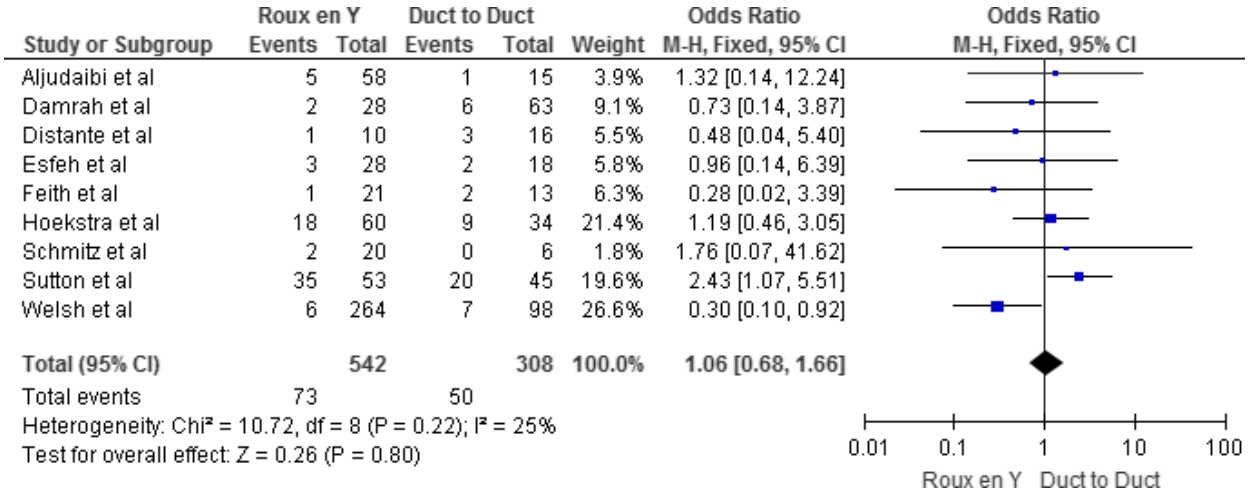

Figure 2 Forest plot comparing duct-to-duct versus Roux-en-Y reconstruction with regard to biliary stricture.

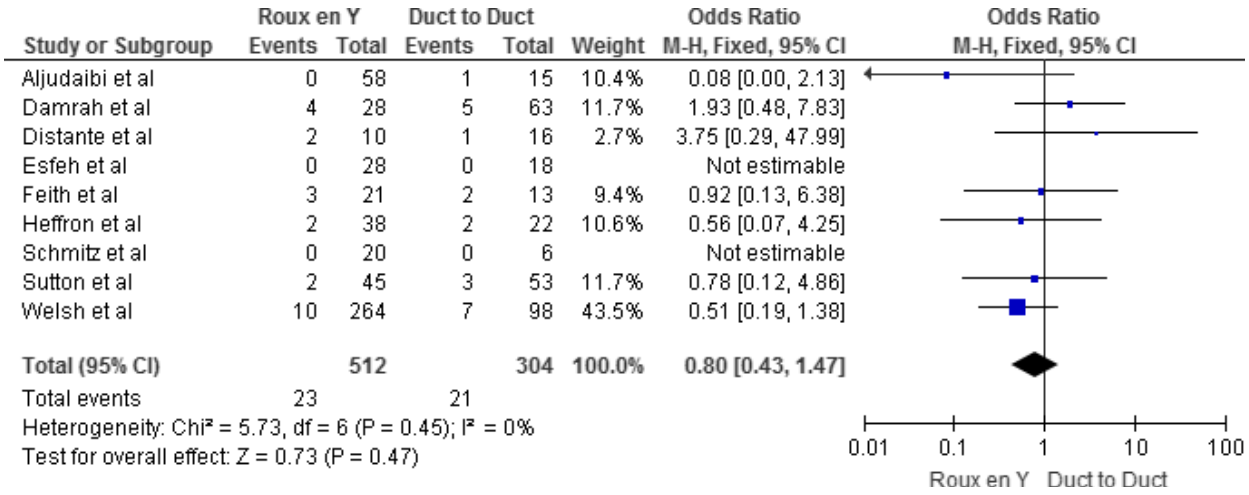

Figure 3 Forest plot comparing duct-to-duct versus Roux-en-Y reconstruction with regard to biliary leakage.

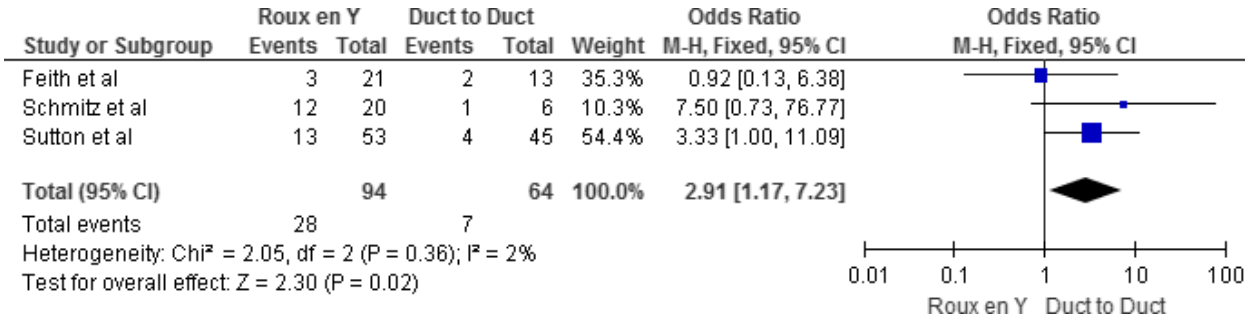

Figure 4 Forest plot comparing duct-to-duct versus Roux-en-Y reconstruction with regard to episodes of cholangitis.

Morbidity

Two studies were included in the analysis. There was no heterogeneity amongst the included studies ($\chi^2 = 0.12$, d.f. = 1 ($P = 0.73$); $I^2 = 0\%$. In a fixed-effects model, there was no significant difference in the postoperative morbidity between RY and DD reconstruction, OR 0.87 [0.32, 2.33] $Z = 0.28$ ($P = 0.78$).

One-year graft survival

Four studies were included in the analysis with 597 patients. Graft survival at one year was 77% in the Roux-en-Y group and 83% in the duct-to-duct group. There was no heterogeneity amongst the included studies ($\chi^2 = 0.45$, d.f. = 3 ($P = 0.93$); $I^2 = 0\%$. In a fixed-effects model, there was no significant difference in the one-year graft survival between RY and DD reconstruction, OR 0.89 [0.57, 1.41] Z = 0.48 ($P = 0.63$).

Cholangiocarcinoma

Four studies were included in the analysis with 597 patients and 9 events; those were patients diagnosed with cholangiocarcinoma during their follow-up. There was heterogeneity amongst the included studies ($\tau^2 = 1.51$, $\chi^2 = 3.98$, d.f. = 2 ($P = 0.14$); $I^2 = 50\%$. In a random-effects model, there was no significant difference in the incidence of cholangiocarcinoma between RY (1%) and DD (2%) reconstruction OR 0.67 [0.09, 4.81] $Z = 0.40$ ($P = 0.69$). Three of the five cases reported by Welsh in the DD group died within 3 month suggesting recurrence rather than de novo tumour.

Recurrent PSC

Three studies were included in the analysis representing 197 patients with 12 events. There was no heterogeneity amongst the included studies ($\chi^2 = 0.67$, d.f. = 2 ($P = 0.71$); $I^2 = 0\%$. In a fixed-effects model, there was no significant difference in the incidence of recurrent PSC between RY (7%) and DD (5%) reconstruction, OR 1.56 [0.49, 5.02], $Z = 0.75$ (P = 0.45).

Discussion

This present meta-analysis includes 10 studies with 910 patients, comparing duct-to-duct (338) versus Roux-en-Y (572) reconstruction in PSC during liver transplantation. No differences were observed between both techniques when the incidence of biliary stricture and anastomotic bile leak was compared. In addition, it would appear that postoperative morbidity (defined by the authors as 'complications') was not different. However, RY reconstruction was associated with higher rates of cholangitis. As far as potential longer-term complications are concerned, 1-year graft survival, recurrence of PSC and development of cholangiocarcinoma were comparable between the two techniques.

This study has a significant number of limitations due to the nature of the primary studies included in the meta-analysis. The studies were retrospective, and some of them were single centre audits (Table 1). The definitions of some outcomes were not consistently reported hence the number of papers and abstracts that were excluded. Unfortunately, preoperative liver function was not documented and the disease type ratio (mainly intra- versus diffuse PSC) was not described in the included studies. However, the decision to perform either a DD or RY biliary reconstruction was based on the following factors in the majority of studies: (i) normal appearances of the common bile duct on preoperative cholangiography, (ii) nonmalignant brushings or cytology when available, (iii) normal appearing distal bile on intraoperative assessment and (iv) normal histology on frozen section when appropriate. It is therefore likely that there is a selection bias with more extensive cases of PSC receiving a RY reconstruction, although interestingly this did not translate to increased disease recurrence and cholangiocarcinoma in the RY group. Finally, the length of the follow-up might not be enough to detect long-term relevant differences, such as the rate of recurrent PSC or cholangiocarcinoma. A similar meta-analysis was published recently by Wells *et al.* [19]. The authors analysed a smaller cohort of patients, reporting fewer outcome measurements

and reached comparable conclusions to the present study. Notwithstanding the paucity and quality of data available in the literature comparing the two techniques, this present study amounts for a substantial collective experience and is likely to be more useful than any pre-existing dogmatic view.

The overall incidence of biliary complications following duct-to-duct anastomosis in LT ranges between 5% and 30%, with biliary stricture being the most frequently encountered [20,21]. Both, anastomotic and nonanastomotic strictures are reported in the literature with an incidence between 4–9% and 10–25%, respectively, with some series showing a higher rate of stricturing formation after hepaticojejunostomy [22–24]. The very nature of the PSC poses a theoretical risk of increased anastomotic stricture rate in those patients with extensive extrahepatic bile duct disease. A relatively large multicentric and retrospective database analysis published by Welsh *et al.* [3] in 2004 found that RY reconstruction was associated with lower stricture formation and better graft and recipient survival compared with duct-to-duct anastomosis reconstruction. The biliary leak incidence was not different amongst these two groups. In that study, seven patients of 98 developed anastomotic stricture when DD anastomosis was used vs. 6 of 264 in RY. The data were collected from 1994 until 2003 although the majority of DD anastomoses collected for this comparison were performed from 1994 to 1995. It is conceivable therefore that there is an historical bias as well as a centre-specific influence. Nevertheless, the potential concern exists, and it is probably related to the fact that if the extrahepatic bile duct in patients with PSC is abnormal, then there is an increased risk of biliary complications. The alleged increased risk to graft and patient survival is more complex to analyse as the majority of losses were due to sepsis/multiorgan failure, and is not clear whether were related to the type of biliary reconstruction. In addition, beyond a year, both curves were similar. More recent publications have continued to question the need for systematically performing a RY anastomosis, with series of DD anastomosis in patients with PSC showing similar results. Some studies favour a DD reconstruction [17], while others show comparable results [4,7,14]. In this meta-analysis, pooled data from 10 studies including 910 patients did not show any difference with respect to biliary complications, other than cholangitis, or graft survival when both techniques were compared. The overall incidence of biliary strictures and anastomotic leaks in DD reconstruction was 15% and 6%, respectively. This is similar to the overall population of patients having LT and not different from the RY subset in PSC [25]. Some authors have even suggested that the incidence of late nonanastomotic stricture (NAS) after RY reconstruction continued to rise more than 5 years after transplantation [17]. This increase in the cumulative incidence of NAS was not observed after duct-to-duct anastomosis, and the authors speculate that it might be secondary to recurrent episodes of ascending cholangitis associated with a RY reconstruction shown by this meta-analysis. There was no comparable long-term data available in the included studies to assess NAS formation.

Another significant concern when choosing DD anastomosis is the risk of developing de novo cholangiocarcinoma in the remnant native common bile duct, probably related to dysplasia of bile duct epithelium from PSC. It is, however, unclear the mechanism of carcinogenesis and even whether the removal of the majority of the recipient's bile duct reduces the risk of de novo cholangiocarcinoma after transplantation. On the other hand, unless liver transplantation is routinely combined with pancreaticoduodenectomy, a portion of the native bile duct will always be left even with RY reconstruction. In this meta-analysis, only 4 papers included data on cholangiocarcinoma. A total of nine cholangiocarcinomas were diagnosed during follow-up. Of note, Welsh *et al.* identified three patients in DD group (3%) who died within 3 months after LT because of cholangiocarcinoma, and these may have been due to recurrent rather than de novo cholangiocarcinoma. The review was able to identify only two true de novo cholangiocarcinomas developing in 224 patients with PSC who had DD anastomosis. This suggests that the risk of de novo cholangiocarcinoma in the recipient bile duct remnant is very low irrespective of the type of reconstruction. This is clearly lower than the annual incidence (1.5%) estimated for patients with PSC after diagnosis [26].

Despite the limitations inherent to this meta-analysis, we believe it might help clinicians to expand their options in selected patients. We did not document any disadvantage when duct-to-duct anastomosis was performed in patients with PSC undergoing LT. It is evident that there is selection bias when it comes to decide which patients can have a DD reconstruction. Cholangiography is routinely included in the assessment of candidates for LT with PSC. If the extrahepatic bile duct appears normal and the intraoperative findings support it, it is a reasonable alternative to perform a DD anastomosis. In addition, there might be some postoperative advantages, including easier endoscopic access to the biliary tree and a possibly lower risk of cholangitis.

Authorship

SP and RB: wrote the paper. EH: conceived the idea and critically appraised the manuscript. AB and JM: critically appraised the manuscript.

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