Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma

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Objective: To systematically review studies reporting survival data following neoadjuvant chemoradiation and orthotopic liver transplantation (NCR-OLT) for unresectable perihilar cholangiocarcinoma (*p*CC).

Background: Despite survival improvements for other cancers, the prognosis of *p*CC remains dismal. Since publication of the Mayo protocol in 2000, increasing numbers of series globally are reporting outcomes after NCR-OLT.

Methods: MEDLINE, EMBASE, Scopus, and Web of Science databases were searched from January 2000 to February 2019. A meta-analysis of proportions was conducted, pooling 1, 3-, and 5-year overall survival and recurrence rates following NCR-OLT across centers. Per protocol and intention to treat data were interrogated. Meta-regression was used to evaluate PSC as a confounder affecting survival.

Results: Twenty studies comprising 428 patients were eligible for analysis. No RCTs were retrieved; the majority of studies were noncomparative cohort studies. The pooled 1, 3-, and 5-year overall survival rates following OLT without neoadjuvant therapy were 71.2% (95% CI 62.2%–79.4%), 48.0% (95% CI 35.0%–60.9%), and 31.6% (95% CI 23.1%–40.7%). These improved to 82.8% (95% CI 73.0%–90.8%), 65.5% (95% CI 48.7%–80.5%), and 65.1% (95% CI 55.1%–74.5%) if neoadjuvant chemoradiation was completed. Pooled recurrence after 3 years was 24.1% (95% CI 17.9%–30.9%) with neoadjuvant chemoradiation, 51.7% (95% CI 33.8%–69.4%) without.

Conclusions: In unresectable *p*CC, NCR-OLT confers long-term survival in highly selected patients able to complete neoadjuvant chemoradiation followed by transplantation. PSC patients appear to have the most favorable outcomes. A high recurrence rate is of concern when considering extending national graft selection policy to *p*CC.

Keywords: cholangiocarcinoma, neoadjuvant chemoradiation, perihilar, transplantation

(*Ann Surg* 2021;273:240–250)

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The unanimity of the HPB/transplant community in seeking substantial progress toward reversing the dire outcomes of patients with *p*CC led to experimentation of transplantation as a treatment 30 years ago. It was anticipated that transplant would prove an ideal therapy for unresectable *p*CC; offering both removal of the tumor and cure from background parenchymal damage.[1] Early experiences however reported dismal survival rates due to aggressive early recurrence and the practice was soon abandoned to conserve grafts for patients with better potential long-term outcomes.[2,3] The publication of the impressive outcomes by the Nebraska group[4] and the Mayo clinic in 2000[5] and beyond has prompted units around the world to re-evaluate *p*CC as an indication for liver transplantation[6] and centers have developed protocols to refine patient selection and introduce neoadjuvant chemoradiation regimes prior to transplant. These institutional protocol-based experiences have reported recurrence-free survival rates that appear comparable or even superior to resection or transplantation for chronic liver disease or early hepatocellular carcinoma.[5,7,8] Today in several centers in the United States (US) neoadjuvant chemoradiation and liver transplantation (NCR-OLT) is no longer considered experimental for unresectable disease but as standard of care[9,10] and with an increasing number of centers in the US and Europe adopting similar protocols and reporting favorable outcomes in expanding patient cohorts, evermore discussion is ensuing globally as regards the safety and utility of liver transplantation in *p*CC. The question therefore arises whether national criteria should be expanded to permit provision of graft livers to a select group of patients with inoperable *p*CC. A Model for End-Stage Liver Disease (MELD) exception for *p*CC was introduced in the US in 2009 by the United Network for Organ Sharing/Organ Procurement and Transplantation Network [9] and in 2006 in the Eurotransplant MELD countries: Germany, Belgium, and the Netherlands.[11] The rigorous patient selection and arduous neoadjuvant chemoradiotherapy means that only the fittest patients with sufficiently favorable disease are suitable for transplantation. However, variations in selection criteria and neoadjuvant protocols are likely reflected in the wide range in reported survival rates.[7,12,13] Favorable reported survival in intention to treat comparisons has prompted critics to call for further analysis of the certainty of the initial diagnosis of *p*CC in these studies, especially in the context of patients with dominant PSC strictures. With an established diagnosis of unresectable *p*CC, one would expect extremely poor outcomes in patients not ultimately proceeding to transplantation; however, this has not always been reflected in survival rates.

Heterogeneity in published reports has made the direct interpretation of clinical outcomes following OLT in *p*CC highly challenging. Studies combine data from PSC and non-PSC patients, perihilar and intrahepatic CC, varying neoadjuvant regimes (doses and types of chemotherapy, use of radiotherapy) and some include patients undergoing other major resections such as partial pancreatoduodenectomy (PPD). Primary endpoints and lengths of follow-up differ between studies. Moreover, there continues to be much debate as to the true correct denominator for comparison in assessing survival outcomes. Studies have used various groups for comparison, including those undergoing surgical resection (± adjuvant chemotherapy), those undergoing transplantation for hepatocellular carcinoma (HCC) or chronic liver disease or even palliative

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This work received no specific source of funding. RVG is currently receiving funding from the Academy of Medical Sciences (UK) and PSC Support (UK).

The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

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ISSN: 0003-4932/20/27302-0240

DOI: 10.1097/SLA.0000000000003801

chemotherapy. Indeed, palliative chemotherapy remains the most frequently adopted alternative therapeutic option in patients who cannot proceed to transplant.

Thus, this systematic review and meta-analysis aims to systematically evaluate directly comparable survival and oncological outcome data in patients with unresectable perihilar CC undergoing OLT in this new era of patient selection and neoadjuvant work-up and assess whether transplantation represents a safe and effective strategy in these patients.

METHODS

The protocol for this systematic review was prospectively registered with the International Prospective Register of Systematic reviews, PROSPERO (CRD42019127662) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) standards (Suppl. Table S1, http://links.lww.com/SLA/C4).[14,15]

Study Identification

In collaboration with a senior information specialist, a maximally sensitive search strategy was developed. A comprehensive search was conducted of the EMBASE (Ovid), MEDLINE (Ovid), Scopus, and Web of Science: Core Collection electronic databases from January 2000 (the year the Mayo Clinic, Rochester, MN published their first report of a neoadjuvant/OLT protocol) until February 2019. The following search terms were used: cholangiocarcinoma, Klatskin tumor, bile duct cancer AND liver transplantation, liver graft AND survival rate. The reference lists of identified articles were then manually searched to identify potentially relevant omitted citations and Google Scholar's ''Cited By'' tool was used to identify other potentially relevant articles that had cited studies already identified for data extraction. Articles that were not published in the English language were not included in this study.

Eligibility/Study Selection

Study selection was performed in 3 stages according to PRISMA recommendations with 2 reviewers (W.A.C., C.F.) independently assessing citations for eligibility. Duplications were excluded, as were letters, reviews, editorials, supplements, comments, case reports, and case series of fewer than 5 patients. Studies were excluded if they reported only patients with mixed hepatocellular-cholangiocarcinoma or did not report the primary endpoints of 1, 3-, or 5-year survival rates following OLT. If studies originated from the same center or included data from the same database, only the most recent publication or the largest cohort was included in data synthesis. Database studies incorporating data across centers that were already primarily reported elsewhere were also excluded. To reduce the exclusion of gray literature, conference abstracts identified through the search which met inclusion criteria were included in the synthesis. Two reviewers selected full-text studies for inclusion in the review against exclusion and inclusion criteria.

Quality Assessment/Risk of Bias

Three researchers (W.A.C., C.F., R.V.G.) critically appraised the quality of each study independently using the Newcastle-Ottawa scale for nonrandomized studies.[16] Funnel plots were constructed to assess publication bias for outcomes reported by a minimum of 8 studies.[17]

Data Extraction and Outcome Measures

Data were extracted by 1 reviewer (W.A.C.) from each included study using a data extraction form developed a priori. Data extracted were study center location, study inclusion period, patient number and characteristics, comorbidities, etiology of liver disease (including PSC), anatomical classification of CC, intervention details in particular type of surgery (OLT or resection), cointerventions (neoadjuvant protocol and/or adjuvant treatment details), preoperative assessment of resectability, histological confirmation of CC on explant, postoperative complications, and length of follow-up. Primary outcomes were 1, 3-, and 5-year overall survival and the secondary outcome was recurrence rate at 3 years. Study authors were approached via email to provide missing data; otherwise these were treated as ''not reported.''

Synthesis and Statistical Analysis

A descriptive synthesis was used to summarize study characteristics, patient demographics, and intervention details. The majority of cohort studies did not report outcome data for a control group (eg, resection or palliative chemotherapy) and so consequently meta-analyses of proportions were conducted for data using a random effects model to calculate pooled 1, 3-, and 5-year overall survival rates and their confidence intervals using per protocol and intention to treat data when available.[18] Statistical heterogeneity was assessed using χ^2 and I^2 analyses, with the threshold for heterogeneity considered present if the P value was ≤ 0.05 or I^2 was greater than 50%. Subgroup analyses were completed for patients who underwent neoadjuvant therapy and patients who underwent adjuvant therapy or no therapy. To better understand potential sources of heterogeneity, random effects meta-regressions were performed for studies reporting the proportion of patients with PSC. A prespecified publication bias assessment was performed by means of a funnel plot. All statistical analyses were performed using MedCalc for Windows, version 19.0 (MedCalc Software).

RESULTS

Systematic Review

Following the literature search 1717 studies were identified through the EMBASE, Medline, Scopus, and Web of Science: core collection databases. Twenty-seven studies were identified from other sources, namely, through searching the bibliographies of studies identified for data extraction, and through using Google Scholar's ''Cited By'' tool to identify relevant articles that had cited studies identified for data extraction. After removal of duplicates, the titles and abstracts of 1385 studies were screened for inclusion. Of these 1128 were excluded as not relevant and the full texts of 257 studies were retrieved. Of these 237 did not meet inclusion criteria (Fig. 1), including 10 studies reporting data from 5 national or international databases, which included patients already reported primarily by other studies (Suppl. Table S2, http://links.lww.com/SLA/C4). This left 20 studies to be included in the quantitative synthesis that either included or were comprised exclusively of patients transplanted for unresectable perihilar cholangiocarcinoma (studies comprised of patients with PSC-related tumors were considered to be unresectable). The characteristics of these studies are shown in Table 1. The range of median follow-up was 14 to 89.5 months.

Study Characteristics

No RCTs were retrieved; all studies were observational cohort studies, case-control studies, or noncomparative series. Study quality as assessed by the Newcastle Ottawa scale was found to range from poor to good (range 1–7) (Suppl. Table S3, http://links.lww.com/SLA/C4). The distributions of effects estimate (survival rates at 1, 3, and 5 yrs and recurrence rate) plotted against the precision of the study (standard error) were symmetrical and overall publication bias was acceptable. Visual interpretation of the funnel plots suggested

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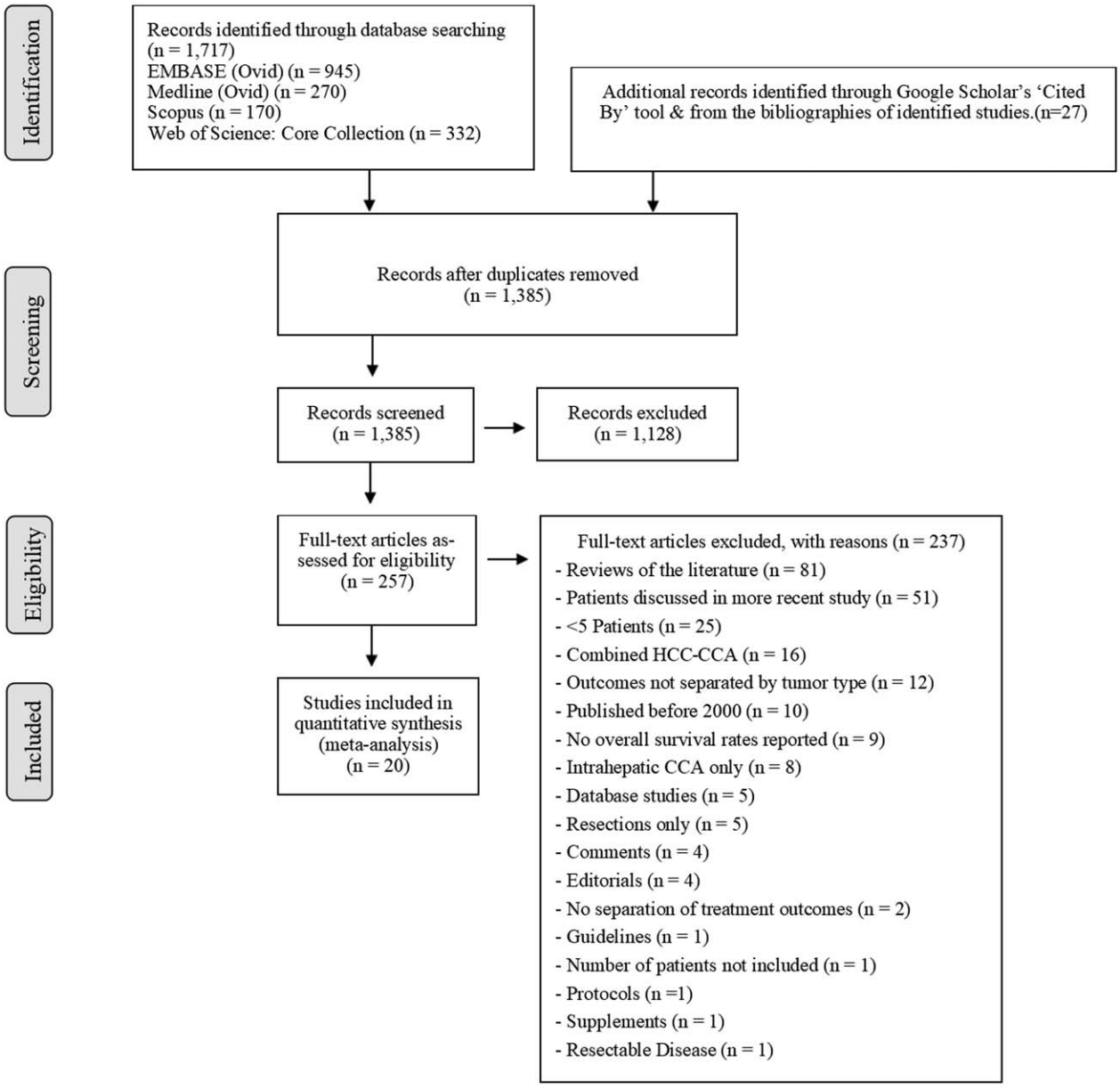

FIGURE 1. PRISMA flow diagram of search strategy and study selection (PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analysis).

the presence of missing studies reporting enhanced survival rates at 5 years and smaller studies reporting poorer survival outcomes at 3 years (Suppl. Figure S1, http://links.lww.com/SLA/C4).

Patient Population Characteristics

A total of 428 patients from 20 studies were included in the final meta-analysis with a median age range from 37 to 54 years (Table 1). By far the largest series was that published by the Mayo group, comprising 152 patients.[19] Thirteen studies declared the sex distribution of their study population, and of these patients 71% were male.[19–31] Figure 2 shows the geographical distribution of centers reporting OLT-CR for *p*CC; 11 studies originated from Europe (Spain, Germany, Republic of Ireland, UK, Switzerland, Norway), 7 from the United States, 1 from Canada, and 1 from China. There was variation between studies in terms of inclusion criteria as shown in Table 1.

Neoadjuvant Protocols

Eleven studies[4,19–23,25,30,32–34] reporting 272 patients (63.6%) underwent a neoadjuvant chemoradiation protocol in >80% of patients prior to proceeding to transplantation. Two studies reported data with <20% of the cohort undergoing neoadjuvant treatment and were therefore not included in this subgroup.[27,28] All such studies used strict patient selection criteria although the full details of these criteria were not available in the case of Deoliveira et al[21] or Solheim et al[33] where only abstracts were available. The most frequent inclusion criteria were a tumor size of ≤3 cm, irresectability due to bilobar involvement, involvement of major hilar structures or the

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TABLE 1. Characteristics of Studies Included in Final Quantitative Synthesis.

Study Publication	Study Center	Inclusion Period	No. Patients	Median Age (yrs)	Male (%)	PSC (%)	Tumor Type	Unresectable (%)	NCR n (%)	OLT-PPD n (%)	LDLT (%)	Median Follow-up (mo)
Axelrod et al 2005	Northwestern University, USA	1997–2004	5	48	80%	100%	100% PSC-pCC	100%	4 (80%)	0	100	6
DeOliveira et al 2012	University Hospital Zurich, Switzerland	2001–2012	11	48	73%	–	100% pCC*	100%	11 (100%)	0	63.6	–
Duignan et al 2014	St Vincent's University Hospital, Ireland	2004–2011	20	–	95%	80%	80% PSC-CC 20% pCC	100%	20 (100%)	30	0	–
Ethun et al 2018	10 USA Transplant Centers	2000–2016	41	54	71%	61%	61% PSC-CC 39% pCC	100%	39 (95%)	0	0	58
Figueras et al 2000	Bellvitge University Hospital, Spain	1989–1999	8	Mean 64	–	13%	100% pCC	88%	0	0	0	–
Hidalgo et al 2008	St James's University Hospital, UK	1993–2003	12	48	67%	33%	100% pCC	100%	0	0	0	–
Jonas et al 2005	Charité-University Medical Center Berlin, Germany	1999–2004	5	–	–	60%	100% pCC	100%	0	20	100	–
Kaiser et al 2008	11 German Transplant Centers	32 Before 1998 15 Since 1998	47	–	–	16%	100% PSC-pCC	100%	0	0	0	–
Lehrke et al 2016	Mayo Clinic, Rochester, USA	1993–2013	152	Mean 51	72%	64%	36% pCC 64% PSC-CC	100%	152 (100%)	0	–	61
Loveday et al 2018	University of Toronto, Canada	2009–2015	6	53.9 (overall)	–	–	100% pCC	100%	6 (100%)	0	50	13
Marchan et al 2016	Emory University School of Medicine, USA	2008–2011	8	Mean 58	50%	–	100% pCC	100%	8 (100%)	0	–	27
Robles et al 2004	19 Spanish Transplant Centers	1988–2001	36	Mean 44	72%	–	100% pCC	61%	0	5.6	0	–
Robles et al 2010	University Hospital Virgen Arrixaca, Spain	1988–2008	11	51	91%	–	100% pCC	100%	2 (18.2%)	0	0	45
Schule et al 2013	University of Jena, Germany	1997–2010	16	54	75%	6%	94% pCC 6% PSC-pCC	100%	1 (6.3%)	0	43.8	31
Seehofer et al 2009	Charité Campus Berlin, Germany	1992–1998	16	50	56%	0%	100% pCC	100%	0	100	0	67
Solheim et al 2014	Oslo University Hospital, Norway	2009 Onwards	6	–	–	–	100% pCC	100%	6 (100%)	0	0	–
Sudan et al 2002	University of Nebraska Medical Center, USA	1987–2000	11	46	–	64%	64% PSC-pCC 39% pCC	100%	11 (100%)	0	0	51
Welling et al 2014	University of Michigan Medical School, USA	–	6	Mean 58 (overall)	–	67%	100% pCC	100%	6 (100%)	16.7	0	14
Wu et al 2008	University of Iowa, USA	1988–2001	6	37	83%	100%	100% PSC-pCC	100%†	6 (100%)	100	0	90
Zheng et al 2005	Zhejiang University School of Medicine, China	1992–2003	5	52	60%	0%	100% pCC	100%	0	0	0	–

*De novo perihilar cholangiocarcinoma without PSC.
†Irresectability due to underlying PSC (Overall: age provided for entire cohort rather than patients undergoing NCR-OLT).
PSC indicates primary sclerosing cholangitis; PSC-CC, primary sclerosing cholangitis associated cholangiocarcinoma.

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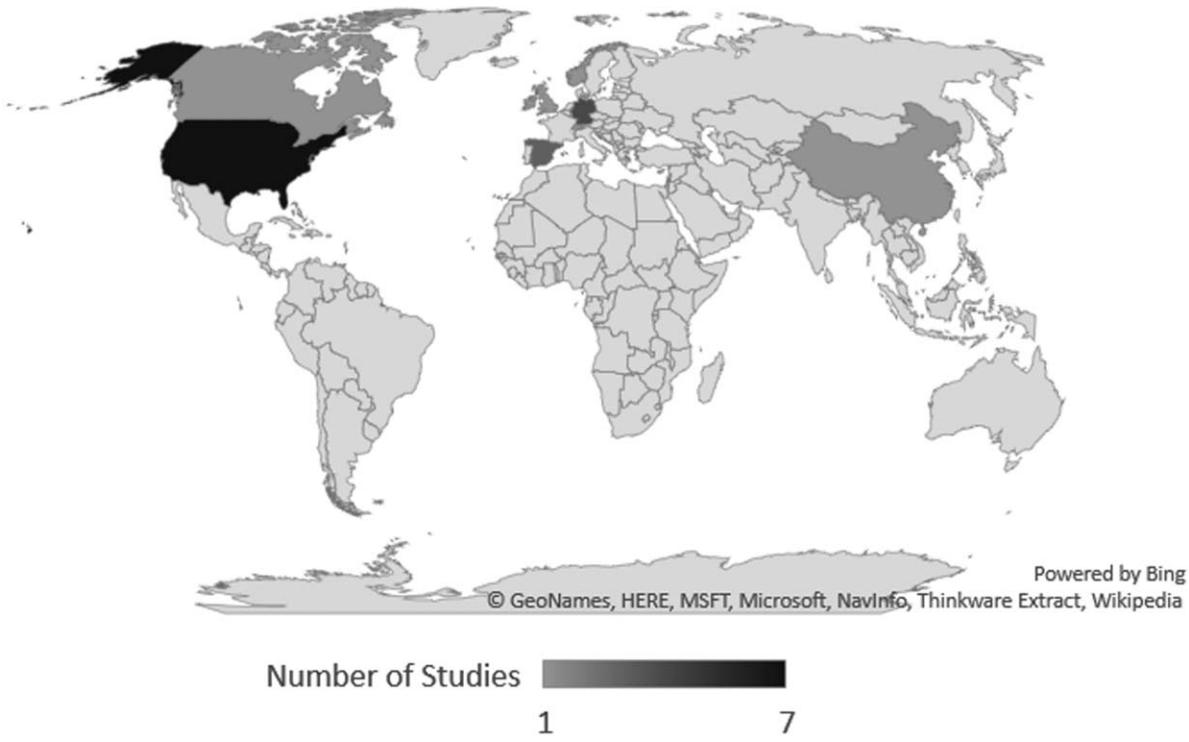

FIGURE 2. Geographical distribution of studies included in quantitative synthesis.

presence of parenchymal disease secondary to PSC. All studies with the exception of Duignan et al[22] considered locoregional nodal involvement to be an exclusion criterion. Six of the 11 studies included patients with PSC who exhibited a serum CA19−9 of $\geq$100 U/mL in the presence of a radiologically malignant stricture but who did not have positive cytology.[4,19,23,25,33,34] Fluorescent in situ hybridization to detect polysomy on biliary brushings was used in 1 study.[19] Exclusion criteria common to the majority of studies were resectable disease (except in the context of PSC), any previous resection attempt, a history of radiotherapy, previous open or transperitoneal biopsy and malignancy in the preceding 5 years (except squamous cell carcinoma or cervical carcinoma). Three studies excluded patients with tumor extending beyond the origin of the cystic duct.[25,32,34]

The most frequently utilized neoadjuvant regime was that referred to as the "Mayo Protocol;" [35] which was closely adhered to in 3 studies reporting 203 patients.[19,23,25] The remaining studies employed a range of variations of this protocol, as detailed in Figure 3. Following patient selection, the Mayo protocol begins with a course of External Beam Radiotherapy (EBRT) of 40to 55 Gy given in 30 fractions over 3 to 5 weeks alongside continuous 5-FU infusion. Departures from this regime included the substitution of 5-FU for oral capecitabine,[32] the use of EBRT without concomitant chemotherapy,[30] the use of Stereotactic Body Radiotherapy (without chemotherapy),[34] or no EBRT at all.[4] No studies of these 11 presented data using neoadjuvant chemotherapy alone without radiation.

Patients would then go on to receive brachytherapy delivered via percutaneously or endoscopically placed wires delivering 8 to 60 Gy Iridium-192 with or without concomitant 5-FU or capecitabine,[4,19,23,25,33] with or without an external boost of radiotherapy,[25] brachytherapy without chemotherapy[4,28,30] or no brachytherapy at all.[21,32,34] In 1 study brachytherapy was used prior to EBRT.[22] Patients then underwent staging laparoscopy or laparotomy. This was performed on completion of the neoadjuvant regime in 1 center[22] but more commonly at the time of deceased donor transplant or the day prior to living donor transplantation. There was variation in practice in terms of nodal sampling, with 5 of the 11 neoadjuvant studies sampling hepatoduodenal and hepatic artery lymph nodes at laparoscopy.[4,19,22,23,32] Almost all studies continued chemotherapy (either 5-FU or capecitabine) until the time of transplant (held perioperatively).[4,19,22,23,25,30,34] The protocol published by Loveday et al[32] substituted 5-FU/capecitabine for gemcitabine and cisplatin.

Intraoperative Practices

The consistency between studies in the reporting of intraoperative practices was poor. There was variation in surgical technique and use of adjunctive procedures. Two studies exclusively reported data on patients undergoing OLT after living donation[20,36] and 5 studies included patients transplanted after either living or cadaveric donation.[19,21,25,28,32] In 4 of these 5 studies patients underwent treatment with a neoadjuvant protocol prior to living donor transplantation.[19,21,25,32] Six studies included patients undergoing concurrent partial PPD[22,26,29,34,36] and 2 of these studies were comprised exclusively of patients undergoing OLT-PPD from the outset.[29,30] The use of extended bile duct resection/en-bloc resection of the hepatoduodenal ligament and reconstruction with roux-en-Y hepaticojejunostomy was widespread but many studies did not declare their operative technique. Regional lymphadenectomy was specifically cited as a routine procedure in 4 studies.[4,26,29,34]

Primary Outcomes: 1, 3, 5-year Survival

Survival for all patients after OLT for *p*CC at 1-year was reported by 18 out of 20 studies (265 patients),[20,22−34,36−39] 3-year survival by 13 studies (240 patients),[4,22−31,36−39] and 5-year survival by 10 studies (309 patients).[4,19,23,24,26−30,38] Meta-analysis showed that pooled survival was 76.9% at 1 year (95% CI = 69.5%−83.5%;

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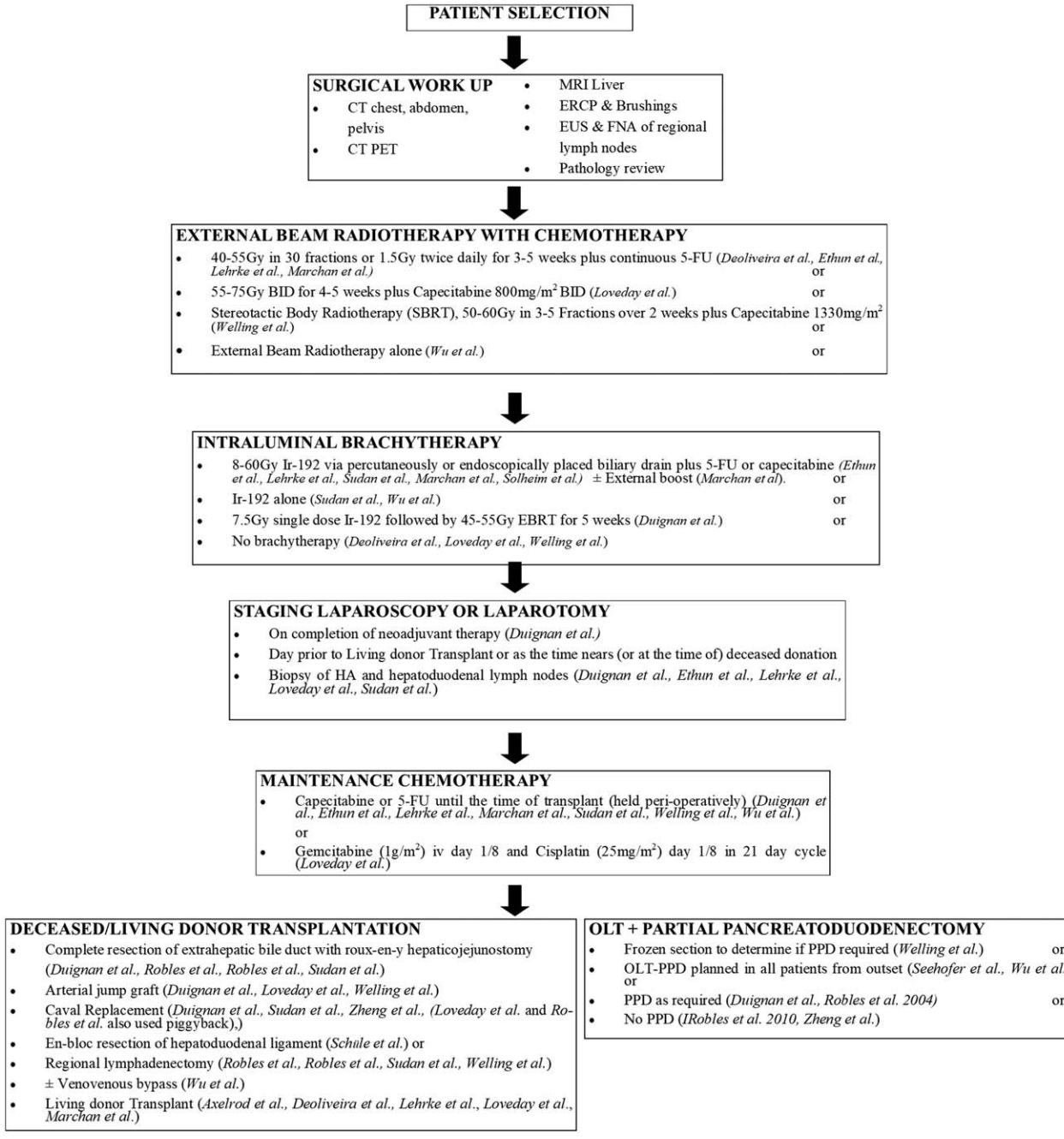

FIGURE 3. Patient workup and neoadjuvant protocols reported in the final 20 studies included in the meta-analysis.

I^2 43.9%), 55.3% at 3 years (95% CI = 43.7%–66.5%; $I^2$68.4%), and 44.9% at 5 years (95% CI = 31.4%–58.8%; I^2 78.6%). In patients who underwent a neoadjuvant protocol (NCR-OLT) for *p*CC across 11 studies (272 patients), survival at 1 year was reported by 9 studies (109 patients),[4,20,22,23,25,30,32–34] survival at 3 years by 5 studies (89 patients),[4,21,23,25,30] and at 5 years by 4 studies (210 patients).[4,19,23,30] Meta-analysis of these data showed that pooled survival at 1 year was 82.8% (95% CI = 73.0% –90.8%; I^2 33.0%), 65.5% at 3 years (95% CI = 48.7%–80.5%; I^2 58.7%), and 65.1% at 5 years (95% CI = 55.1% –74.5%; I^2 31.2%) (Fig. 4A).

As a large proportion of the survival outcomes were made up of patients reported by the Mayo Clinic (152 out of 210 patients), 5-year survival of patients from the Mayo Clinic was compared to pooled survival from other, non-Mayo centres (Supplementary Figure S2A, http://links.lww.com/SLA/C4).[4,23,30] The 5-year survival of patients undergoing a neoadjuvant protocol followed by transplantation (NCR-OLT) at the Mayo Clinic was not significantly different to that of patients at non-Mayo centres (Mayo Clinic 69.0%, 95% CI 61.0%–76.2% vs non-Mayo 60.6%, 95% CI 42.3%–77.4%, $\chi^2 = 1.2$; $P = 0.27$).

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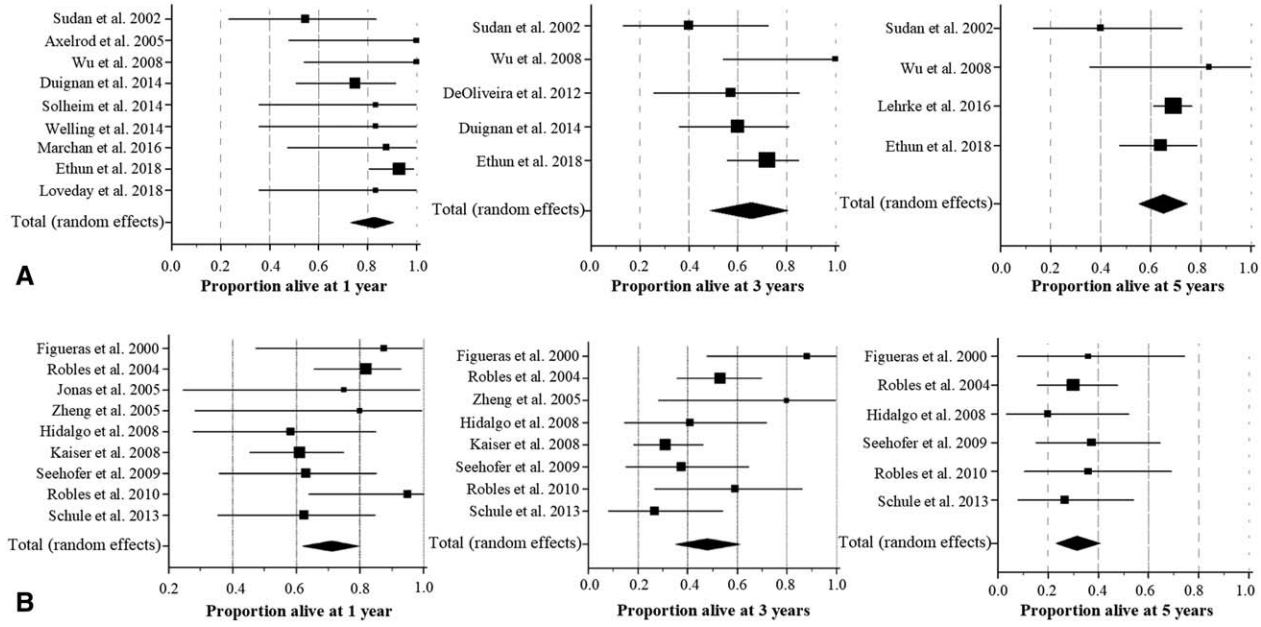

FIGURE 4. Forest plots of 20 cohort studies reporting survival outcomes following NCR-OLT for *p*CC with (A) and without neoadjuvant chemoradiation (B). Random effects modeling of pooled survival rates at 1, 3, and 5-yrs was used for the meta-analysis of proportions with 95% confidence intervals.

In patients who did not undergo neoadjuvant protocol (9 studies; 156 patients), survival at 1 year was reported by 9 studies (156 patients),[24,26–29,31,36–39] at 3 years by 8 studies (151 patients),[24,26–29,31,37,38] and at 5 years by 6 studies (99 patients).[24,26,27,29,38] Meta-analysis showed that pooled survival at 1 year without neoadjuvant therapy was 71.2% (95% CI 62.2% – 79.4%; I^2 28.5%), 48.0% at 3 years (95% CI 35.0%–60.9%; $I^2$58.9%), and 31.6% at 5 years (95% CI = 23.1% –40.7%; I^2 0.0%) (Fig. 4B).

Secondary Outcomes: Recurrence Rate

Disease recurrence was analyzed in studies which followed patients for ≥36 months (8 studies; 262 patients).[4,19,20,22,23,27,29,30] Meta-analysis showed that the pooled recurrence rate overall at 3 years was 29.4% (95% CI = 20.1%–39.7%). In patients who underwent neoadjuvant therapy (NCR-OLT) the recurrence rate was 24.1% (95% CI = 17.9% –30.9%; I^2 11.1%) (6 studies and 235 patients).[4,19,20,22,23,30] In patients who did not undergo neoadjuvant therapy the recurrence rate was 51.7% (95% CI = 33.8% –69.4%; I^2 0.0%) (2 studies; 27 patients)[27,29] (Fig. 5).

To assess any potential difference in recurrence rates between Mayo and non-Mayo centers, recurrence at 3 years was compared between those reported by Lehrke et al (152 patients) and pooled recurrence from non-Mayo centers (83 patients) (Supplementary Figure S2B, http://links.lww.com/SLA/C4).[4,20,22,23,30] No significant difference was observed in recurrence at 3 years between the Mayo

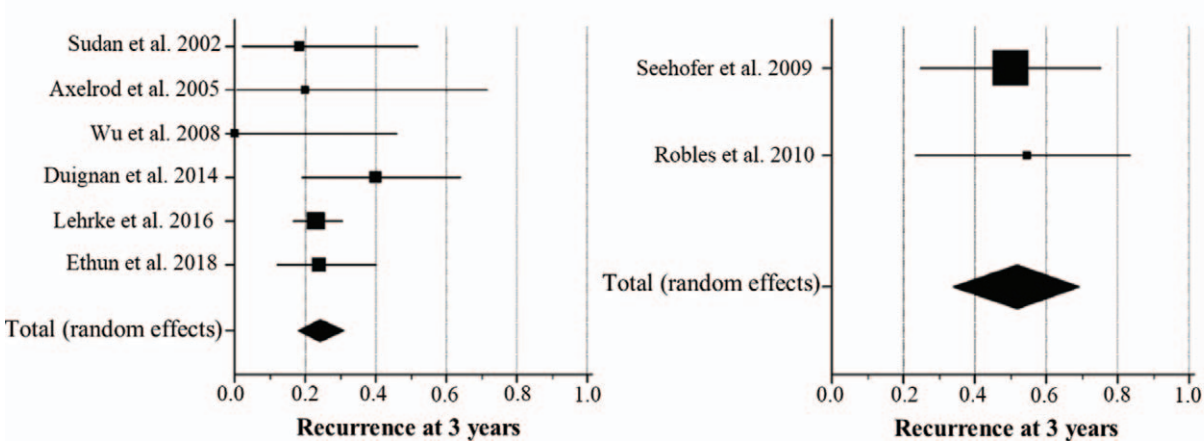

FIGURE 5. Forest plots of recurrence rates at 36 mo of follow-up with (*left*) and without (*right*) neoadjuvant treatment and OLT for unresectable *p*CC. Random effects modeling of pooled recurrence rates with 95% confidence intervals was used for the meta-analysis of proportions.

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Clinic (23.0%, 95% CI 16.6%–30.5%) and non-Mayo centers (24.6%, 95% CI 14.2%–36.7%) $\chi^2 = 0.03$; $P = 0.85$.

Preoperative Diagnosis and Complete Pathological Response Rate

Just 4 out of 20 studies reported the number of patients who had a pathological diagnosis of cholangiocarcinoma confirmed histologically prior to transplantation (confirmed in 40 out of 42 patients; 9% of all patients included in this analysis).[4,20,22,30] This was defined by these studies as either proven adenocarcinoma on biopsy or malignant or suspicious brushings. Other studies including the Mayo series included patients with a clinical diagnosis including those with a radiologically malignant stricture and a CA19–9 of >100U/mL.[19,23,25,32]

Of the 9 studies that did not use a neoadjuvant protocol prior to transplant, all 9 reported the proportion of patients with a pathologically confirmed diagnosis of *p*CC (histological examination of the explanted liver) and this was confirmed in 142 out of 145 explants (98%). Of the 11 studies presenting neoadjuvant transplant programs, 9 studies (256 patients) presented data on pathological diagnosis in the explanted liver.[4,19,20,22,23,25,30,32,34] Of these 255 patients undergoing neoadjuvant protocols (1 patient in the study from Axelrod et al did not undergo neoadjuvant treatment), 126 (49.6%) had no evidence of adenocarcinoma on histopathological examination. This does not include the 5 transplanted patients in the study by Ethun et al[23] which incorporated data from 10 US institutions, who were given a diagnosis other than *p*CC after pathological examination of the explanted liver and who were excluded from the paper's final survival analysis.

Intention to Treat Versus Per Protocol Survival

One aim of this study was to analyze per protocol and intention to treat data to differentiate survival rates between patients initially assessed compared with those who completed the NCR-OLT regime. Ultimately this was not possible as only 3 studies presented survival data for both groups of patients.[20,32,34] Furthermore, the definition of the patient groups undergoing initial assessment varied between studies, for example some studies included patients with resectable disease, some included patients with cholangiocarcinoma not located at the hilum etc. Evaluation of the drop-out rate between the time of patient assessment to administration of neoadjuvant chemoradiation and OLT was hampered by incomplete data and heterogeneous data presentation between studies. Of the 11 studies reporting outcomes of patients receiving NCR-OLT, only 5 studies presented the numbers of patients initially assessed alongside the number of patients successfully transplanted.[22,23,30,32,34] One of these studies was comprised of patients with asymptomatic PSC undergoing endoscopic surveillance and therefore was excluded.[30] Of the remaining 4 studies, the drop-out rate ranged from 25.9% to 86.1%. Six studies presented data comparing the number of patients commencing the neoadjuvant protocol to those successfully transplanted.[4,23,25,30,32,34] Here, the drop-out rate ranged from 0.0% to 66.7%. The most frequently cited indications for drop out were disease progression (n = 32, 41%), diagnosis of extrahepatic disease (n = 19, 24%) (including 5 patients (6.7%) with positive surgical staging laparoscopy and 2 patients with involved lymph nodes at EUS (2.7%)), death prior to transplantation (n = 8, 10.7%), patient refusal (n = 3, 4%), diagnosis of metastatic disease (n = 1, 1.3%), and alteration of the surgical plan to resection (n = 1, 1.3%).

Morbidity

Morbidity was variably reported by studies. Adequate reporting of morbidity was predefined as inclusion of the incidence of severe complications (Clavien-Dindo Grades III and IV) and the rate of retransplantation. This standard was met by 3 out of 20 studies which reported morbidity rates of 44% to 100%.[4,28,31] Several studies listed adverse events without stating the number of patients to whom these occurred. Only 1 study differentiated between morbidities arising pretransplant as a result of the neoadjuvant regime versus post-OLT complications.[4] Eight studies (105 patients) reported a retransplantation rate and this ranged from 0% to 40%.[4,20,22,26,28,30,31,34]

Primary Sclerosing Cholangitis

Thirteen of the 20 studies reported the proportion of patients with PSC undergoing transplantation.[19,20,23,24,26,28–31,33,36–38] Of these 365 patients, 180 (49.3%) had a background of PSC. Survival outcomes were not reported for patients with PSC as a specific subgroup by almost any study and therefore univariate meta-regressions were undertaken to explore potential heterogeneity between studies arising due to PSC as a potential confounder and assess whether the proportion of PSC patients per study affected survival in studies where 3 and 5-year survival outcomes had been declared (Fig. 6). Ten studies reporting 3-year survival data[4,22–24,28–31,37,38]

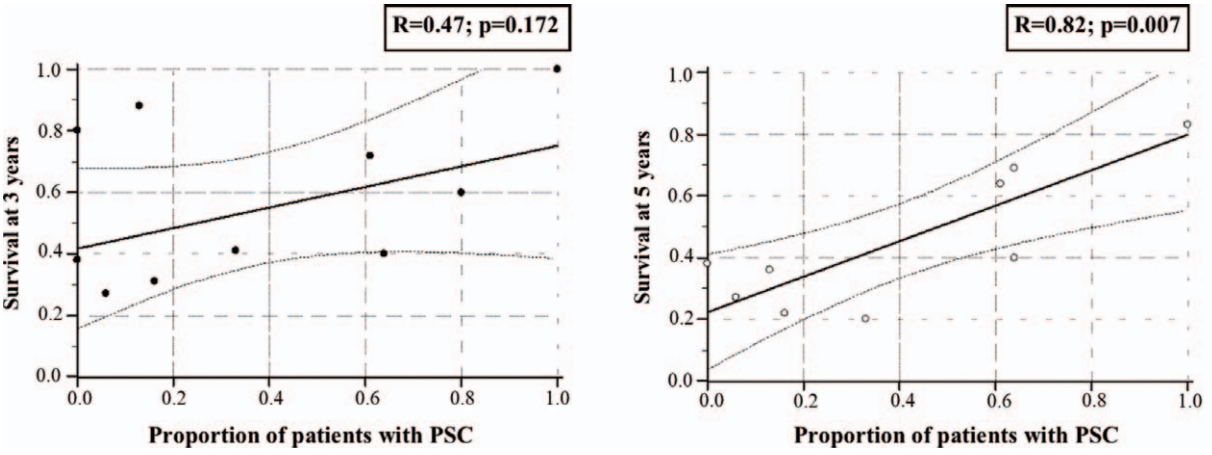

FIGURE 6. Random effects univariate meta-regression of survival at 3 yrs following transplantation for *p*CC (with and without neoadjuvant chemoradiation) versus the proportion of patients with PSC in each study (*left graph*) and at 5 yrs after transplantation for *p*CC (with and without neoadjuvant chemoradiation) (*right graph*) (scatter diagrams are log weighed). Each dot represents an individual study, the solid line represents the regression prediction, and the dotted lines the 95% confidence intervals.

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and 9 studies reporting 5-year survival data[9,19,23,24,28–30,37,38] declared the number of patients with PSC within the cohort. The association between number of patients with PSC and survival was not statistically significant for 3-year survival (adjusted $R^2 = 0.48$, $P = 0.172$); however at 5 years there was a positive correlation between the proportion of patients with PSC in the study and survival (adjusted $R^2 = 0.82$, $P = 0.007$). Insufficient studies were available ($n = 5$) to assess whether the proportion of patients with PSC affected disease recurrence post OLT/NCR-OLT for *p*CC.

Other Factors

Seven out of 20 studies included patients undergoing living donation liver transplantation (LDLT)[19–21,25,28,32,36] including 2 studies comprised solely of patients receiving grafts from living donors.[20,36] The rate of living donation ranged from 43.8% to 100% (comprising a total of 27 patients; 6.3% of all patients). Two studies did not report the number of patients undergoing living donor liver transplant[19,25] and 5 studies did not distinguish outcomes between living and deceased donations, leaving reported outcomes for just 12 patients (2.8% of the overall pooled cohort). Five of the 7 studies employed neoadjuvant protocols[19–21,25,32] and donor hepatectomy was timed to immediately follow recipient exploration to exclude extrahepatic disease.

Six out of 20 studies included patients who underwent partial pancreatoduodenectomy alongside liver transplant (PPD-OLT).[22,26,29,30,34,36] The rate of PPD-OLT ranged from 5.6% to 100% in these studies, comprising a total of 32 patients (7.5% of all patients). In some cases, PPD-OLT was planned from the outset of surgery, in others an intraoperative decision was taken to proceed to PPD-OLT due to positive frozen sections at the specimen margin.

DISCUSSION

This meta-analysis has shown that the pooled 5-year survival for patients undergoing liver transplant for unresectable *p*CC exceeds the 50% 5-year survival threshold broadly accepted by many liver transplant units if a neoadjuvant regime is completed (65.1%, 95% CI 55.1% –74.5%) but does not meet this standard if the patient proceeds directly to transplantation (31.6%, 95% CI 23.1%–40.7%). These pooled survival data for NCR-OLT certainly compare favorably to the outcomes of patients undergoing resection, where 5-survival rates of 35% to 45% are widely cited.[40–42] A previous meta-analysis of 5 studies comparing OLT to resection in operable *p*CC has demonstrated a trend toward improved survival for OLT at 1, 3, and 5 years (78% vs 72.5%, 55.5% vs 44%, and 46% vs 31%), although this did not achieve statistical significance (mortality odds ratio of 0.72 [0.30–1.69] in favor of OLT at 5 yrs).[43] This was echoed by a further meta-analysis of patients with nondisseminated nonresectable tumors undergoing NCR-OLT or resection, where noninferior survival was observed in the NCR-OLT group, although it must be noted that very few patients undergoing resection underwent any sort of neoadjuvant therapy.[44] A well-powered randomized controlled trial is required for the specific context of non-PSC related perihilar CC where there exists the alternative surgical option of resection, and the TRANSPHIL trial (NCT02232932) which has a planned completion date of 2021, aims to address this question.[45] Currently, the evidence supporting transplantation in this situation remains uncertain, especially as the rate of positive margins or inoperability at exploration is high in these patients.

In terms of tumor recurrence our analysis demonstrates that the use of neoadjuvant chemoradiation halves the risk of recurrence at 3 years (51.7% vs 24.1%). As it is established that recurrence is responsible for the majority of deaths following transplantation for cholangiocarcinoma[19,26] these data in their current form would support the case made most strongly by US centers that the use of transplantation for *p*CC without neoadjuvant chemoradiation should no longer be supported. Currently, Eurotransplant does not consider neoadjuvant therapy a prerequisite for graft allocation in cholangiocarcinoma,[46] and further data on recurrence in the absence of neoadjuvant therapy are required to make a decisive conclusion as regards this question.

In a field where the risks of surgery are high and prognosis poor, it was feared that significant publication bias might be encountered in favor of studies with positive outcomes; however, our analysis suggests that this is not true in terms of survival reporting. Insufficient studies reported data on disease recurrence to make a valid assessment for this secondary outcome. It has not been possible to accurately evaluate the role of selection bias on survival outcomes after NCR-OLT in this analysis as true intention to treat data was rarely available. Insufficient studies reported the number of patients initially assessed and it was frequently difficult to ascertain the nature of the group. In some publications this cohort included patients with hilar and intrahepatic cholangiocarcinoma, those with both unresectable and resectable disease, patients unfit for surgery, patients with extrahepatic spread, patients whose disease progressed etc. Furthermore, the outcomes of patients not enrolled on the NCR-OLT protocol and what treatment they subsequently received were incompletely reported. In a previous single-institution observational study, 1, 3, and 5-year survival rates of 92%, 82%, and 82% for 38 patients undergoing transplantation were reported compared with rates of 79%, 61%, and 58% for all 71 patients initially enrolled in the protocol.[7] This drop-out rate of 46% contrasts with a rate of 25% reported in a study of 12 US centers, where drop-out was defined as positive staging, tumor metastases, death, or withdrawal at any time before transplantation.[47] The analysis of such variance in patient selection is critical to understanding the reasons that non-Mayo centers frequently report inferior outcomes due to higher in-hospital mortality and needs to be characterized in greater detail before widespread protocol adoption can occur. In this relatively rare disease such heterogeneity has hampered the interpretation of outcomes and has arguably impeded progress toward clear identification of the group of patients who may significantly benefit from the NCR-OLT regime and global adoption of the protocol. To this end, consensus should be sought toward agreeing a standardized, minimum dataset for all patients evaluated and enrolled on NCR-OLT programs. Herein, we suggest a proposed collection form for such a dataset, based on parameters that were required in the preparation and analysis of this study, sufficient for intention-to-treat evaluation of the effects of patient selection and neoadjuvant protocols on outcomes (Supplementary Table S4, http://links.lww.com/SLA/C4).

The cumulative publication of results by the Mayo Clinic meant that for this meta-analysis the most recent and largest of their series citing the primary outcome of this review was selected for inclusion.[19] Individual studies have themselves highlighted how variability in surgical work-up and the NCR-OLT protocol is likely to affect survival; positive lymph nodes identified at EUS, the R_0 rate, and the presence of residual tumor in the explanted liver have been previously identified as the factors most predictive for disease recurrence.[19,34] This review identified wide variation in the diagnostic and neoadjuvant pathways of these patients and as the use of chemoradiation appears critical for achieving the broadly accepted 50% 5-year survival threshold for transplantation, improved consensus and uniformity across centers is again required. Most crucially in our view, agreement as to the necessity of histopathological diagnosis prior to NCR-OLT should be sought. Mayo studies and others include patients onto NCR-OLT protocols with a cancer antigen 19–9 level of >100 U/mL in the context of a radiologically malignant stricture.[8,48] Whilst this may represent a clinical scenario that might

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frequently win clinical consensus to the individual's requirement for transplantation, it must be conceded that this is unlikely to yield a 100% pathological diagnosis of *p*CC and might confuse subsequent comparison in oncological outcomes to studies not including such patients.[35,48] Indeed, some argue that in the absence of histological diagnosis prior to NCR-OLT, the true complete pathological response rate can never be determined. A previous study has shown that 5-year survival is significantly inferior for patients with PSC who have a confirmed pathological diagnosis of cholangiocarcinoma prior to transplant[49] and although there was no statistical difference found between the rate of confirmed *p*CC in explants or recurrent cancer in patients with or without a confirmed pathological diagnosis, the number of patients with recurrent cancer was relatively small. The outcomes of such patients therefore need to be examined and analyzed separately across centers to establish the true benefit conferred by neoadjuvant chemoradiation which may indeed even be under-represented in our study where only 9% of all patients had a histologically proven diagnosis. It should be noted that this is significantly less than other previously published single-institution studies[49] and is likely a result of histological diagnosis not being the primary end-point of the systematic search criteria used here. This serves to further compound the need for a consensus minimum reporting standard for data in this field.

In our review the correlation between a diagnosis of PSC and enhanced survival was not statistically significant at 3 years but exceeded this threshold at 5 years (adjusted $R^2 = 0.82$, $P = 0.007$). As there were insufficient studies to separate patients undergoing neoadjuvant therapy or proceeding directly to transplantation with and without PSC, it remains unknown whether there were proportionally more patients with PSC undergoing NCR-OLT regimes in this pooled cohort. It is therefore plausible that this might confound this observation of enhanced survival although it should be noted that the proportion of patients in this PSC subgroup (49.3%) was significantly less than that reported by other multicenter analyses.[23,47]

Proponents of LDLT for *p*CC hypothesize that reduced waiting list time will result in reduced disease progression and better outcomes.[28] The number of patients in this pooled cohort with reported outcomes for LDLT was too small to assess whether LDLT in the context of *p*CC may offer survival benefit over cadaveric donation. As for HCC, MELD exception points are currently allocated to patients in Europe meeting selection criteria on the waiting list for *p*CC. European studies have shown therefore that few patients with *p*CC proceed to transplantation.[28,37]

Similarly, the number of patients undergoing PPD-OLT represented a small proportion of the entire cohort and therefore conclusions on the role of extended bile duct resection and partial pancreatoduodenectomy cannot be drawn. The largest series of PPD-OLT in this review reported 1, 3, and 5-year survival rates of 63%, 38%, and 38%. Despite no neoadjuvant regime used in this study, a 94% morbidity rate was reported (15 out of 16 patients), with 2 patients requiring total pancreatectomy soon after transplantation for pancreatic leakage. The oncological benefits of PPD-OLT, particularly following neoadjuvant therapy, remain unresolved.

CONCLUSIONS

This systematic review and meta-analysis conclude that long-term survival is possible in patients undergoing NCR-OLT for unresectable *p*CC with the best prognosis observed in patients with PSC. Acceptable survival rates are not achieved if a neoadjuvant regime is not completed. The quality of data reporting in this field is poor and is hampering interpretation of outcomes. A minimum expected dataset should be established for all future studies examining the use of transplantation in cholangiocarcinoma.

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