Confounding by Indication Is a Major Issue in the Available Evidence on Role of Portal Vein Resection in Patients Undergoing Curative Surgery for Klatskin Tumour

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Dear Editor,

Visceral Medicine has recently published interesting articles on treatment strategies for improving outcomes in patients with Klatskin tumour [1–4]. We have a particular interest in these articles as we have systematically been reviewing the literature on outcomes of portal vein resection (PVR) in patients with Klatskin tumour undergoing curative surgical resection. Considering that Klatskin tumour has been the focus of recently published articles in *Visceral Medicine*, we recognized this as a great opportunity to discuss our findings.

Klatskin tumour is a rare tumour with an annual incidence of 1 in 100,000 [5]. It accounts for up to 60% of cholangiocarcinomas [6]. Complete surgical resection with achievement of negative resection margins remains the only curative treatment [1]. However, longitudinal intraductal tumour extension and the risk of vascular encasement associated with Klatskin tumour would make achievement of negative resection margins challenging. Consequently, there have been ongoing efforts to identify appropriate surgical strategies targeting achievement of negative resection margins in cases with Klatskin tumour.

Considering that the portal vein is involved (microscopically and macroscopically) in a conspicuous proportion of patients with Klatskin tumour [7], routine PVR during surgical resection of Klatskin tumour has been recommended by some authors for achievement of negative resection margins [8–10]. Nevertheless, because PVR

is technically challenging and may be associated with significant morbidity and mortality, its routine use has been controversial.

Two meta-analyses have previously compared outcomes of PVR and no PVR in patients with Klatskin tumour [11, 12]. However, most of the included studies in previous meta-analyses did not provide data on baseline characteristics of their included population. Knowledge about the baseline characteristics of patients undergoing curative surgery with PVR in comparison with those undergoing curative surgery without PVR is crucial to make meaningful conclusions.

Table 1. Baseline characteristics of the included population

Characteristic	PVR versus no PVR	
	summary measure (95% CI)	p value
Age	MD: –1.18 (–2.83 to –0.47)	0.16
Male gender	RD: –0.09 (–0.31 to –0.12)	0.38
AJCC T3/T4 disease stages	RD: 0.27 (–0.14 to –0.67)	0.19
Lymph node metastases	RD: 0.01 (–0.08 to –0.10)	0.84
Perineural invasion	RD: 0.13 (–0.03 to –0.29)	0.11
Portal vein invasion	RD: 0.26 (0.08 to –0.45)	0.005
R1 resection	RD: 0.09 (0.02 to –0.17)	0.01

PVR, portal vein resection; MD, mean difference; RD, risk difference; CI, confidence interval; AJCC, American Joint Committee on Cancer.

Fig. 1. Forest plots of the comparison between the PVR and no PVR groups: severe postoperative complications (a); postoperative mortality (b); liver failure (c); bile leak (d); intraoperative bleeding (e); postoperative bleeding (f); operative time (g); 5-year overall survival (h). (Figure continued on next page.)

In order to assess the level and limitations of available evidence on outcomes of PVR in patients with Klatskin tumour, we performed a systematic review and meta-analysis in compliance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement standards. In terms of eligibility criteria, we included all comparative studies comparing PVR with no PVR in patients undergoing curative surgical resection for Klatskin tumour. Studies that did not provide information on baseline characteristics of their included population were excluded.

The search of electronic databases identified 16 observational studies comparing PVR with no PVR in patients with Klatskin tumour. However, 10 studies (included in previous meta-analyses) had to be excluded due to lack of data on baseline characteristics of their included population. Therefore, 6 retrospective cohort studies including a total of 572 patients (PVR group: 174; no PVR group: 398) were included.

Analyses of baseline characteristics showed no difference between the 2 groups in terms of age (MD: -1.18 , 95% CI -2.83 to -0.47 , $p = 0.16$), gender (RD: -0.09 , 95%

CI -0.31 to -0.12, $p = 0.38$), AJCC T3/T4 disease stages (RD: 0.27, 95% CI -0.14 to -0.67, $p = 0.19$), lymph node metastases (RD: 0.01, 95% CI -0.08 to -0.10, $p = 0.84$), and perineural invasion (RD: 0.13, 95% CI -0.03 to -0.29, $p = 0.11$). However, portal vein invasion at baseline (RD: 0.26, 95% CI 0.08–0.45, $p = 0.005$) and R1 resection after surgery (RD: 0.09, 95% CI 0.02–0.17, $p = 0.01$) were significantly more frequent in patients who underwent PVR (shown in Table 1).

Analyses of outcomes showed no difference between the PVR and no PVR groups in terms of intraoperative blood loss (MD: 216.66, 95% CI 92.90–526.22, $p = 0.17$), severe postoperative complications (OR: 1.76, 95% CI 0.43–7.16, $p = 0.43$), postoperative mortality (OR: 1.29, 95% CI 0.61–2.74, $p = 0.51$), liver failure (OR: 1.54, 95% CI 0.70–3.40, $p = 0.28$), bile leak (OR: 0.70, 95% CI 0.30–1.65, $p = 0.42$), postoperative bleeding (OR: 1.13, 95% CI 0.51–2.54, $p = 0.76$), and 5-year overall survival (OR: 0.56, 95% CI 0.29–1.09, $p = 0.09$). The operative time was

shorter in the no PVR group (MD: 45.15, 95% CI 11.17–79.12, $p = 0.009$) (shown in Fig. 1).

The presence of more portal vein invasions at baseline in the PVR group suggests that the available evidence on comparison of PVR versus no PVR in patients undergoing curative resection for Klatskin tumour is subject to significant confounding by indication. This would mean that patients who underwent PVR had more advanced disease at baseline due to portal vein invasion; consequently, they were intentionally selected for PVR due to more advanced disease. This would also explain the lower rate of R0 resection in patients who underwent PVR. Therefore, due to the aforementioned confounding by indication that cannot be controlled due to the retrospective nature of the available studies, the potential benefits of PVR cannot be evaluated robustly based on the available evidence.

In summary, it is crucial to recognize that the role of PVR in patients undergoing curative surgical resection

for Klatskin tumour remains poorly understood. Any recommendations based on the available evidence could be misleading due to significant risk of confounding by indication associated with the results of currently available retrospective observational studies. A well-conducted randomized controlled trial with adequate statistical power could resolve the existing uncertainty.

Conflict of Interest Statement

Shahab Hajibandeh declares no conflict of interest; Shahin Hajibandeh declares no conflict of interest; Karim Hassan declares no conflict of interest; Sumera Baloch declares no conflict of interest; Thomas Satyadas declares no conflict of interest.

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Shahab Hajibandeh: conception and design, data collection, analysis and interpretation, writing the manuscript, critical revision of the manuscript, and final approval of the manuscript. Shahin Hajibandeh: data collection, analysis and interpretation, writing the manuscript, critical revision of the manuscript, and final approval of the manuscript. Karim Hassan: data collection, writing the manuscript, critical revision of the manuscript, and final approval of the manuscript. Sumera Baloch: data collection, writing the manuscript, critical revision of the manuscript, and final approval of the manuscript. Thomas Satyadas: conception and design, analysis and interpretation, writing the manuscript, critical revision of the manuscript, and final approval of the manuscript.