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REVIEW ARTICLE

Updates and Critical Insights on Glissonian Approach in Liver Surgery

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Abstract Recent advances in surgical techniques have broadened the indications of surgical management of liver malignancies. Intraoperative bleeding is one of the known predictors of postoperative outcomes following liver surgery, signifying the importance of vascular control during liver resection. Furthermore, preservation of future liver remnant plays a critical role in prevention of post-hepatectomy liver failure as one of the main causes of postoperative morbidity and mortality. Glissonian approach liver resection offers an effective method for vascular inflow control while protecting future liver remnant from ischemia-reperfusion injury. Several studies have demonstrated the feasibility of Glisson's pedicle resection technique in modern liver surgery with an acceptable safety profile. Moreover, with increasing popularity of minimally invasive surgery, laparoscopic liver resection via Glissonian approach has been shown to be superior to standard laparoscopic hepatectomy. Herein, we systematically review the role of Glissonian approach hepatectomy in current practice of liver surgery, highlighting its advantages and disadvantaged over other methods of vascular control.

Keywords Glissonian approach · Glisson's pedicle · Hepatectomy · Liver cancer · Liver resection · Liver malignancy

Introduction

Hepatic resection remains the cornerstone of treatment for liver malignancies.[1,2] With recent advances in surgical technique, the indications for surgical treatment of hepatic malignancies has expanded with more strategies to resect tumors that traditionally have been considered unresectable.[3–5] Intraoperative bleeding is a known predictor of postoperative morbidity and mortality following liver surgery, especially in cirrhotic patients.[6,7] Several vascular clamping techniques ranging from full hilar to more selective segmental pedicle clamping have been described to prevent or control intraoperative hemorrhage.[8] In general, the liver parenchyma is more tolerant to intermittent versus continuous pedicle clamping. In addition, extensive ischemia-reperfusion injury caused by hilar pedicle clamping may impair future liver remnant (FLR) function.[9] The extrahepatic control of Glisson's pedicle, known as the Glissonian approach, was first introduced by Lortat-Jacob et al. in 1952 as an alternative method to full hilar vascular clamping.[10] The transhepatic approach was described by others later in 1965.[11] Recently, the Glissonian approach has been increasingly proposed as a safe and efficient method for both open and laparoscopic liver surgery.[12–16] The objective of the current study was to review systematically the data on the Glissonian approach in the practice of liver surgery. Specifically, we sought to highlight the potential advantages and disadvantages of the Glissonian approach.

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Materials and Methods

The review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[17] Specifically, a systematic review of the English literature was performed utilizing MEDLINE/PubMed and Web of Science databases with an end date of May 31, 2017 (Fig. 1). The MESH terms "Glissonian approach," "Glissonean approach," "liver surgery," "liver resection," "hepatectomy," "laparoscopic liver resection," and "laparoscopic hepatectomy" in combination with "liver cancer," "hepatic malignancy," and "liver malignancy" were searched in the title and/or abstract. The references of relevant articles were reviewed to identify additional eligible publications ("snow-balling" technique). Reference lists of the eligible studies, as well as meta-analyses and reviews pertinent to the topic, were manually assessed to identify any additional potentially eligible articles. Two authors (INS, DIT) independently performed extraction and cross-checking of the data. Any discrepancies were resolved by team consensus. Data were extracted (e.g., year of publication, size of patient population, type of vascular control, perioperative outcomes, morbidity, mortality) and then tabulated and cumulative analysis was performed when possible.

Results and Discussion

Glissonian Versus Traditional Hilar Approach

Structures in the hepatoduodenal ligament are dissected to expose the portal vein, hepatic artery, and bile duct when performing a standard "conventional" hepatectomy.[18] After dissecting out these structures, an extrahepatic transection of the ipsilateral portal vein and hepatic artery can be performed to facilitate demarcation of the liver for the anticipated parenchymal transection. Depending on the location of the lesion, at other times, occlusion of the entire hepatoduodenal ligament (Pringle maneuver) may be preferred. Clamping of the portal triad at hepatic hilum (Pringle maneuver) controls vascular inflow and reduces blood loss during transection of the hepatic parenchyma.[19] The Pringle maneuver may have limitations, however, as it has been associated with total liver ischemia, as well as possible adverse oncological outcomes.[14,20]

In an attempt to reduce blood loss, avoid hilar dissection, and decrease operative time, the Glissonian approach was proposed.[12,21] According to ramification of the Glisson's pedicle tree, the liver is divided into three sections (left, middle, right) allowing highly selective control of these pedicles without the need for ultrasonographic or cholangiographic guidance (Fig. 2).[18] Although ultrasound assistance is frequently not necessary, ultrasound can assist in the intraoperative identification of liver vascular structures.[22–25] Moreover, ultrasound may help reduce blood loss during resection due to intraoperative identification of the vascular anatomy and the control of the segmental arteries and veins in liver surgery. In the extrahepatic Glissonian approach, the bifurcation of the pedicle tree is accessed through dissection of the hilar plate. Subsequently, the entire left or right pedicle is ligated and transected prior to hepatic resection (Figs. 3, 4, and 5). Compared with full hilar pedicle clamping (the Pringle maneuver), the Glissonian approach can help avoid ischemia-reperfusion injury to the FLR, as well as mitigate any adverse general and cancer-specific outcomes.[14]

In particular, the Glissonian approach has gained popularity over the last decade due to its ease of approach and lack of technical complexity.[18,21] Early reports that compared Glisson's pedicle transection with conventional hepatectomy demonstrated the feasibility and efficacy of the approach. For example, in a study of 90 patients who underwent major hepatectomy, Nakai et al. reported no difference in the amount of blood loss, operative duration, or postoperative complications comparing standard hilar dissection with the Glissonian approach.[26] There was, however, a higher incidence of bile leak with the Glissonian approach, mainly in patients who underwent a left hemi-hepatectomy (conventional hepatectomy 7% vs. Glissonian approach 23.4%; $p = 0.031$) (Table 1).[26] Of note, bile leak following the Glissonian approach hepatectomy persisted in less than 5% of patients and typically was small and self-limiting.[30] In a separate retrospective study, Giordano et al. study reported similar operative time, blood loss, postoperative morbidity, and mortality among patients who underwent extrahepatic Glissonian transection compared with hilar dissection.[16]

Mongolia et al. reported that the Glissonian pedicle approach had comparable surgical and long-term survival outcomes versus conventional liver resection.[27] Similarly, in a prospective randomized trial, Figueras et al. compared hilar dissection versus the Glissonian approach among patients undergoing a major hepatectomy.[15] Although en bloc transection of the Glisson's pedicle was faster than isolated ligation of each element in the hilar pedicle, the duration of pedicle clamping was shorter with hilar dissection, probably due to an initial period of Pringle maneuver applied for introduction of the stapler with the Glissonian approach.[15] There were no differences between the two techniques in terms of perioperative and long-term outcomes.[15] Ischemic injury to the FLR was, however, lower among patients who underwent a hepatectomy using the Glissonian approach, especially for patients with cirrhosis (Table 2).[14] Therefore, minimizing the clamping time or the extent of ischemic zones with the Glissonian approach may provide an advantage especially among patients with underlying liver disease.

Other reports have noted a superiority of the Glissonian approach versus hilar dissection. For example, in a study by Ji et al. of patients with large (> 5 cm) nodular HCC, the

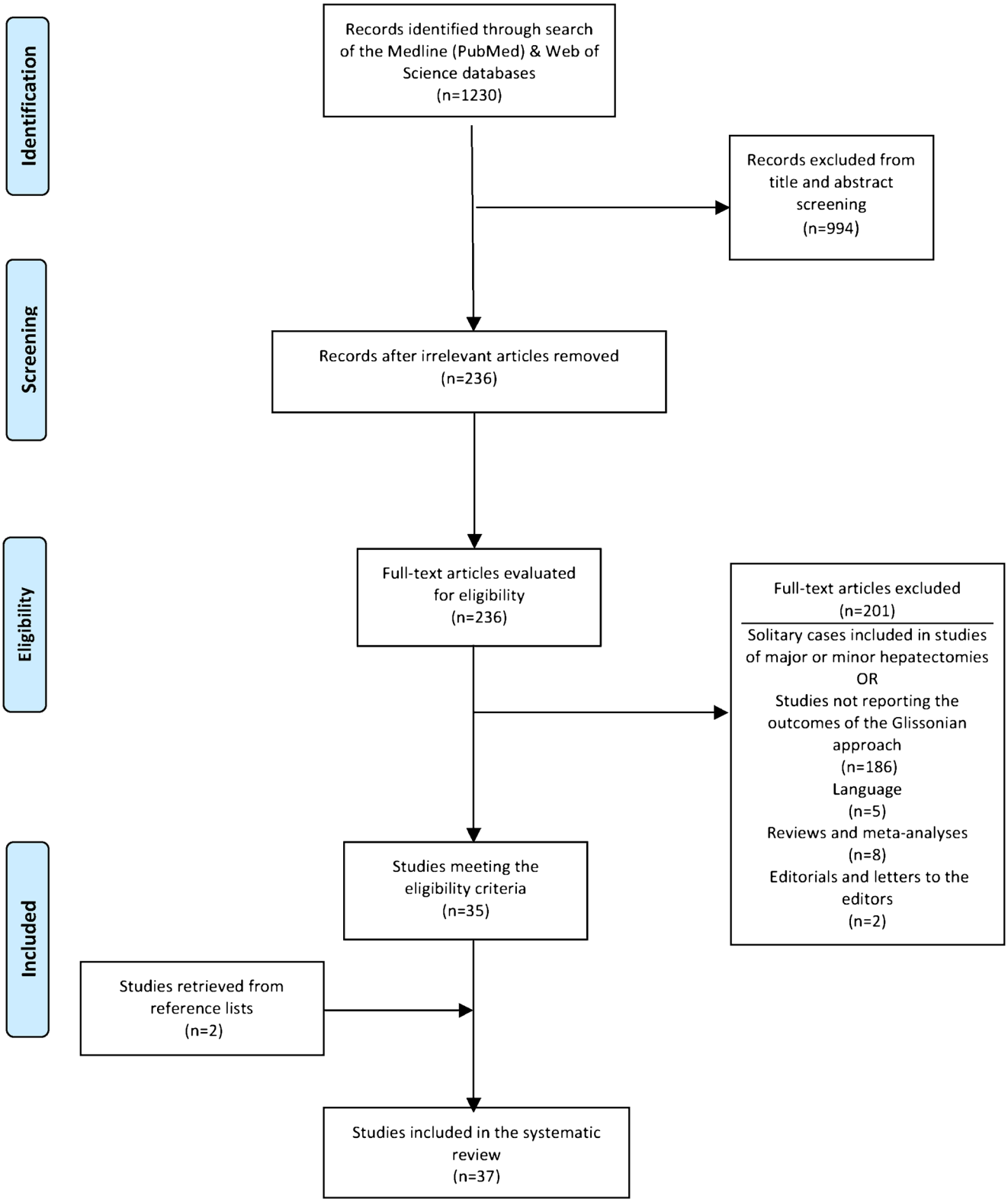

Fig. 1 Schematic diagram depicting how articles were selected for the systematic review

Glissonian approach was associated with shorter inflow interruption, lower amounts of blood loss and transfusion, and more rapid resolution of ascites (all $p < 0.001$).[31] Postoperative liver function tests, as well as 1- and 3-year survival, were comparable, however, among patients undergoing hepatic resection with the Glissonian versus traditional approach.[31] Other studies have suggested a possible survival benefit with the Glissonian approach. Specifically, Tsuruta

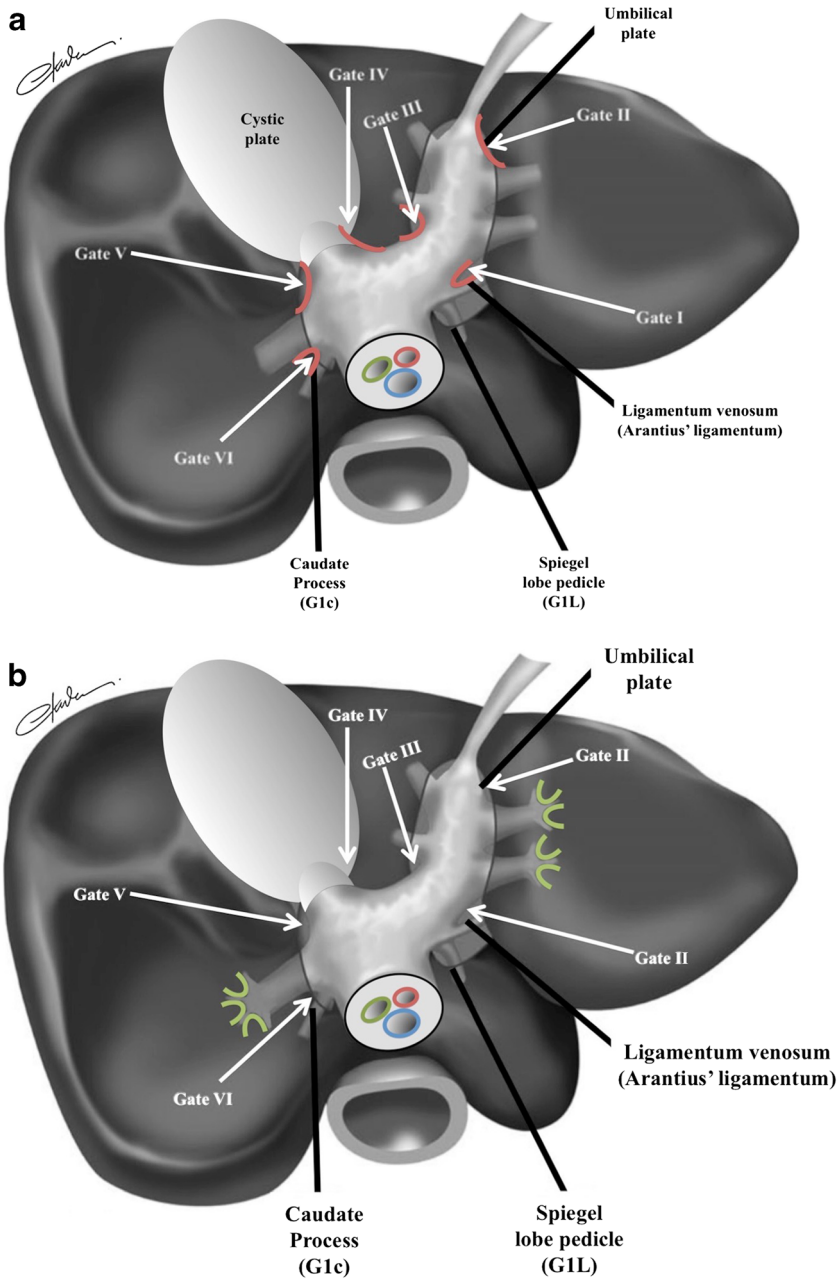

Fig. 2 **a** The four anatomical landmarks and six gates in the caudal view. The schema shows the relationship between the six gates and Laennec's capsule. The gaps between Laennec's capsule and the Glissonean pedicle could be entered only at these six gates (red curved lines). Gate I: the caudal end of the Arantius' ligamentum, Gate II: the junction between the round ligament and the umbilical plate, Gate III: the right edge of the Glissonean pedicle root of the umbilical portion (Gup: G2 + 3 + 4), Gate IV: the left edge of the posterior extremity of the cystic plate or the anterior Glissonean pedicle, Gate V: the bifurcation of the right main Glissonean pedicle, Gate VI: the space between the posterior Glissonean pedicle and the G1c. **b** Intrahepatic Glissonian approach. This approach can provide access to secondary or even tertiary pedicles though small incisions at anatomic landmarks in the supra-hilar area (green curved lines). (Used with permission)

et al. reported that the Glissonian approach was associated with improved 5-year survival (Pringle maneuver 36.4% vs. Glissonian approach 64.7%; $p < 0.0001$).[32] Furthermore, the incidence of diffuse intrahepatic recurrence was lower among patients who underwent hepatectomy with the Glissonian approach ($p = 0.0013$). Some investigators have suggested that transection of the pedicles above the level of the bifurcation may prevent the intraoperative spread of neoplastic cells.[32] To this end, Yamamoto et al. compared the effectiveness of "systematized hepatectomy" (Glissonian approach) with a partial hepatic resection among patients with small (< 5 cm) nodular hepatocellular carcinoma.[28] Although survival was similar among patients without extranodular tumor growth, patients with extranodular tumor invasion who underwent a Glissonian approach had a better higher 5-year survival (traditional 21% vs. Glissonian approach 67%; $p < 0.001$) and a lower incidence of recurrence-related death (traditional 39.4% vs. Glissonian approach 11.4%; $p = 0.011$).[28] These authors also postulated that the improved outcomes attributed to the Glissonian approach were related to the fact that HCC often invades central vascular structures and, therefore, ligation of a Glisson's pedicle may more effectively evade tumor spread. In a separate case-control study, the Glissonian approach was associated with a shorter operative duration, parenchymal

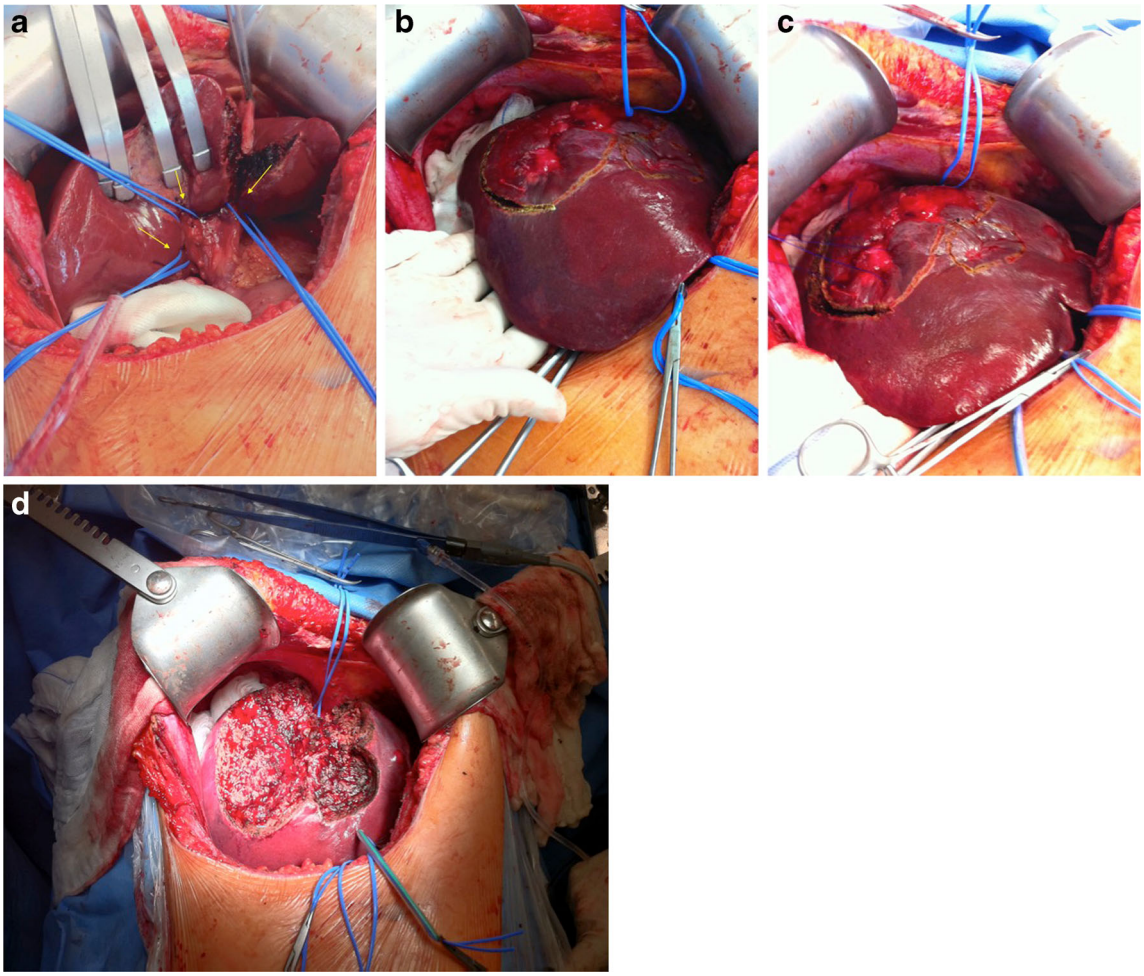

Fig. 3 Example of a patient undergoing several deep atypical parenchymal resections. **a** The right posterior pedicle (or right pedicle according to Takasaki), the right anterior pedicle (or median pedicle according to Takasaki), and the left pedicles were controlled separately. Depending on the specific area of parenchymal resection, the right posterior (**b**) or right anterior (**c**) was clamped separately to avoid prolonged or repetitive pedicular clamping. **d** Demonstration of the liver following resection

transection time, ischemia time, as well as lower blood loss, and amount of blood transfusion compared with hilar dissection among patients undergoing major hepatectomy (all $p < 0.05$).[29]

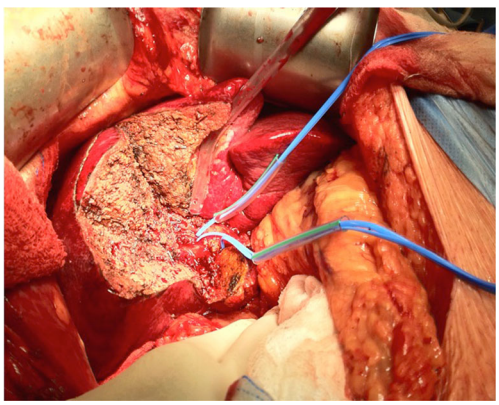

Fig. 4 A segmentectomy of segment 6 was performed for a hepatocellular carcinoma in a cirrhotic patient. The right anterior and posterior pedicles that had been previously controlled prior to resection can be seen (arrows)

Intrahepatic Glissonian Approach

Over the last decade, there has been an increasing emphasis on parenchymal-sparing liver surgery.[33] Parenchymal-sparing hepatectomy typically involves removing the tumor/diseased portion of the liver while preserving as much of the normal, non-tumorous liver parenchyma as possible. The benefits of a parenchymal-sparing approach to liver surgery can be multi-fold including a decreased risk of post-hepatectomy liver insufficiency, as well as an increased opportunity for repeat hepatic resections if needed.[34,35] To this end, an intrahepatic Glissonian approach facilitates a parenchymal-sparing approach to hepatic parenchymal transection. Specifically, an intrahepatic Glissonian approach provides access to secondary or even tertiary pedicles through small incisions at anatomic landmarks in the supra-hilar area (Fig. 3).[36,37] An intrahepatic

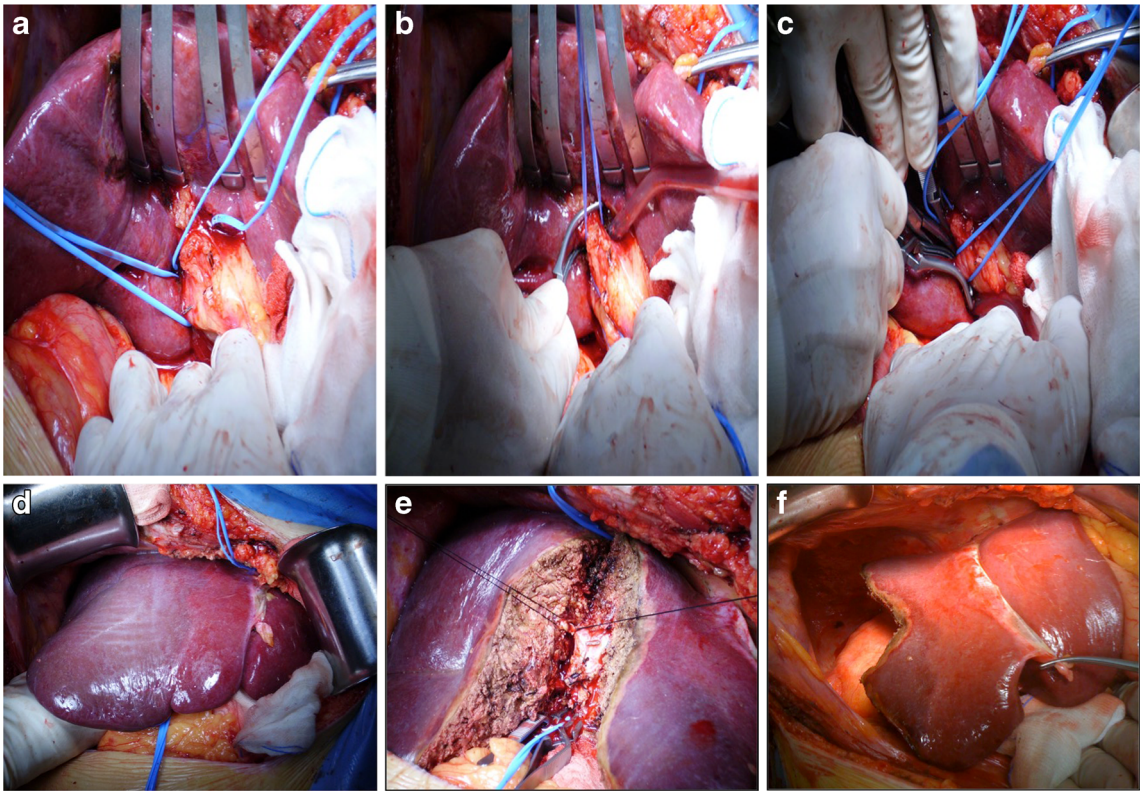

Fig. 5 An extended right posterior sectionectomy was performed in a patient with liver metastasis. After controlling the right anterior and right posterior pedicles (**a**) and subsequent clamping (**b**, **c**), right hemi-exclusion was performed (**d**). The parenchymal section line proceeded along the right anterior sector in a non-anatomic manner (**e**) allowing preservation of portions of segments 5/8 (**f**)

Glissonian approach may be particularly helpful for tumors confined to a single segment of the liver. Accurate delineation and occlusion of the vasculature feeding the tumor-bearing anatomic zone facilitates more limited hepatectomies with preserving FLR.[38] In fact, several studies have reported excellent outcomes using the Glissonian approach for single-segment resections.[38,39] In some instances, dissection of the hepatic pedicle bifurcation can be difficult, especially in the setting of repeat liver resection, which makes intrahepatic approach the preferred method over the extrahepatic method and classic hilar dissection in this clinical setting.[36,37]

In a study of 630 patients who underwent either a left hepatectomy or left lateral lobectomy, Chen et al. reported that the operative time was shorter (77 ± 35 min) and intraoperative blood loss was lower (110 ± 250 mL) using an intrahepatic Glissonian approach.[36] In addition, there were no 30-day postoperative deaths.[36] In a separate study of 182 patients who underwent either a right or left partial hepatectomy, Xia et al. similarly noted that intraoperative blood loss was much lower and there were no procedure-related morbidity or mortality associated with the Glissonian approach.[37] The intrahepatic Glissonian approach has also been reported to be feasible for central hepatectomy (segments 4, 5, and 8), right anterior sectionectomy (segments 5 and 8), and right posterior sectionectomy (segments 6 and 7).[40,41]

Glissonian Approach and Laparoscopic Liver Surgery

There has been a growing adoption of minimally invasive surgical (MIS) approaches to liver resection.[42,43] Of note, several reports have demonstrated the feasibility and safety of MIS right or left hepatectomy via Glissonian.[44–53] The Glissonian approach can even be applied to other types of MIS hepatic resections including single-segment resection of S2, S5, and S6, as well as mesohepatectomy (segments 4, 5, and 8) with no procedure-related complications.[45–47,54,55] Notably, Machado et al. has reported on almost every type of MIS liver resection using an intrahepatic Glissonian approach including left single segmentectomies (S1, S2, S3, S4), left bi-segmentectomies (S2-S3), right bi-segmentectomies (S5-S8, S6-S7, S7-S8), left and right hemihepatectomies, right tri-sectionectomies, and mesohepatectomies.[48–53] Machado and colleagues have also demonstrated the feasibility and safety of single-port MIS left lateral sectionectomy without any postoperative morbidity or mortality.[56] In a 7-year observational study, MIS intrahepatic Glissonian approach was noted to have several advantages over standard MIS resection including shorter operative time, lower transfusion rates, fewer patients with a postoperative positive margin, as well as less morbidity and a shorter duration of hospital stay.[44]

Table 1 Studies comparing the Glissonian approach with the conventional liver resection (hilar dissection)

Study ID	Years of enrollment	Study groups	Patients, *n*	Outcomes	Groups		*p* value
					Hilar dissection	Glissonian approach	
Nakai (1999)[26]	1988–1997	Group 1: hilar dissection	43	Operative time (min)	284.1 ± 79.7	285.3 ± 74.2	$p > 0.05$
		Group 2: Glissonian approach	47	Intraoperative bleeding (mL)	2100 ± 1119.2	2020.3 ± 1215.5	$p > 0.05$
				Complications	13 (30.2%)	20 (42.6%)	$p > 0.05$
				Bile leakage	3 (7%)	11 (23.4%)	*$p = 0.031$*
				Hospital mortality	3 (6.9%)	2 (4.2%)	$p > 0.05$
Figueras (2003)[15]	1998–2001	Group 1: hilar dissection	40	Operative time (min)	247 ± 54	236 ± 43	$p = 0.4$
		Group 2: Glissonian approach	40	Hilar dissection (min)	70 ± 26	50 ± 17	*$p < 0.001$*
				Pedicular clamping (min)	43 ± 15	51 ± 15	*$p = 0.015$*
				Intraoperative bleeding (mL)	887 ± 510	937 ± 636	$p = 0.7$
				Morbidity rates	23%	33%	$p = 0.3$
				LOS (days)	8	9	$p = 0.6$
Chinburen (2015)[27]	2003–2012	Group 1: hilar dissection	24	Operative time (min)	223.5 ± 59.3	269.16 ± 93.9	*$p = 0.022$*
		Group 2: Glissonian approach	45	Intraoperative bleeding (mL)	522.2 ± 528.7	447.8 ± 377.6	$p = 0.953$
				Complications	13 (54.2%)	15 (33.3%)	$p = 0.093$
				Postoperative mortality	3 (12.5%)	4 (8.9%)	$p = 0.636$
				LOS (days)	21.3 ± 9.6	14.9 ± 5.1	*$p = 0.004$*
				Overall survival (OS)			$p = 0.664$ (refers to the overall cumulative survival)
				1-year OS	74%	86%	
				3-year OS	64%	61%	
				5-year OS	55%		
Yamamoto (2001)[28]	1990–1994	G1: partial hepatic resection	114	5-year OS-single nodular HCC without EG	67%	70%	$p = 0.61$
		G2: Glissonian approach	90	5-year OS-single nodular HCC with EG	21%	67%	*$p < 0.001$*
				Recurrence-related mortality-single nodular HCC with EG	39.4%	11.4%	*$p = 0.011$*
Karamarkovic (2012)[29]	2009–2012	G1: hilar dissection	34	Operative time (min)	246.62 ± 56.55	191.18 ± 41.10	*$p < 0.001$*
		G2: Glissonian approach	34	Transection time (min)	56.32 ± 19.40	38.94 ± 14.56	*$p < 0.001$*
				Ischemic duration (min)	41.18 ± 12.80	26.03 ± 11.27	*$p < 0.001$*
				Intraoperative bleeding (mL)	344.71 ± 166.25	245.59 ± 169.39	*$p = 0.018$*
				Blood transfusion (mL)	414.76 ± 135.48	322.86 ± 102.07	*$p = 0.038$*

Statistically significant for $p < 0.05$

LOS length of stay, *EG* extranodular growth, *HCC* hepatocellular carcinoma, *OS* overall survival

Feasibility and Limitations

While generally associated with low perioperative morbidity and mortality (< 1%), application of the Glissonian method can be technically challenging in certain cases.[36,41,44] For example, Mouly et al. reported a feasibility rate of only 75% (24/32) for right hepatectomy, with incomplete clamping ($n = 2$) and clamping of the left portal pedicle due to aberrant portal vein anatomy ($n = 6$) as common reasons for technical failure.[57] As such, when considering the Glissonian approach, the presence of portal vein anatomic variations should always be considered. Timely recognition of these alterations before or during the operation is of paramount importance. In addition, aberrant bile duct anatomy needs to be considered and detailed preoperative imaging should be performed to assess for this possibility; if biliary anatomy is unclear at the time of surgery, cholangiography should be considered to identify and help plan repair of any possible bile duct injury.[44]

When performing the Glissonian approach, gentle handling of anatomic structures is extremely important. While

Table 2 Studies comparing the Glissonian approach with the Pringle maneuver

Study ID	Years of enrollment	Study groups	Patients, *n*	Outcomes	Groups		*p* value
					Pringle maneuver	Glissonian approach	
Figueras (2005)[14]	1999–2003	Group 1: Pringle maneuver	39	Operative time (min)	207 ± 48	219 ± 45	$p = 0.24$
		Group 2: Glissonian approach	41	Intraoperative bleeding (mL)	671 ± 533	735 ± 397	$p = 0.54$
				Ischemic duration (min)	41 ± 14	47 ± 18	$p = 0.07$
				Transfusion, *n*	4 (10%)	6 (15)	$p = 0.54$
				Complications	15 (38%)	12 (29%)	$p = 0.38$
				LOS (days)	9.38 ± 4.9	8.15 ± 3.8	$p = 0.21$
				In-hospital mortality	0	1 (2.4%)	$p = 0.33$
Ji (2012)[31]	2008–2011	Group 1: Pringle maneuver	25	Operative time (min)	100.0 ± 35.0	80.0 ± 25.0	*p = 0.022*
		Group 2: Glissonian approach	25	Inflow occlusion (min)	45.0 ± 13.0	30.0 ± 12.0	*p < 0.001*
				Intraoperative bleeding (mL)	298.0 ± 109.0	145.0 ± 20.0	*p < 0.001*
				LOS (days)	14.0 ± 2.1	12.0 ± 1.5	*p < 0.001*
Tsuruta (2002)[32]	N/R	Group 1: Pringle maneuver	159	5-year survival	36.4%	64.7%	*p < 0.0001*
		Group 2: Glissonian approach	100	Diffuse type intrahepatic recurrence (> 4 lesions)	Significantly reduced in G2 compared to G1 (*p = 0.0013*)		

Statistically significant for $p < 0.05$

N/R not reported, *LOS* length of stay

encircling the Glisson's pedicles, forceful maneuvers to the surrounding parenchyma can sometimes result in excessive bleeding with resultant perioperative morbidity and mortality. In fact, difficulty in encircling the pedicles or parenchymal bleeding during liver dissection at the supra-hilar area are the two most common causes of technical failure.[41] Such bleeding is more common in cirrhotic patients and patients with underlying portal hypertension. In addition, the inexperienced surgeon can induce parenchymal bleeding, as well as even injury to the pedicles. Finally, tumors located immediately adjacent to the hepatic hilum require special attention. Because ligation or transection of Glisson's pedicles that may harbor malignant cells can result in intraoperative tumor spread and recurrence, the Glissonian approach may not be the best approach for tumors immediately adjacent to the hilum.

It is also important to note that other limitations of the Glissonian approach may be under-reported. Specifically, the lack of data on potential negative consequences/outcomes associated with the Glissonian approach may be due to publication bias. In addition, given that most studies were retrospective in nature, selection bias may also have impacted the results. The majority of the studies also included heterogenous patient populations in terms of diagnosis, concomitant liver status (e.g., steatosis, cirrhosis), as well as technical modifications (e.g., combining Pringle maneuver or partial IVC interruption). The ongoing Classical Procedure Versus Intrahepatic Glisson's Approach (LAHIGA) trial is designed to compare the classical resection versus intrahepatic Glisson's approach for laparoscopic anatomical hepatectomy. The objective of this trial is to evaluate the feasibility, safety, and limitations of the Glissonian approach, as well as assess outcomes among patients with malignant and benign liver diseases (ClinicalTrials.gov Identifier: NCT01567631).

Conclusion

The Glissonian approach, either extrahepatic or intrahepatic has been demonstrated to be a safe and feasible method in liver surgery. In fact, the Glissonian approach may be preferred in many clinically settings as it is associated with shorter operative times, lower blood loss, and low morbidity. In addition, the Glissonian approach can be utilized for MIS resections and may be superior to standard MIS hepatectomy. While the Glissonian approach has many potential benefits, appropriate application of this technique requires accurate preoperative tumor localization, identification of potential anatomic pedicle variations, as well as expertise on the part of the surgeon to be successful.

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