Surgical Resection
Old Dog, Any New Tricks?

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KEYWORDS

• Hepatocellular carcinoma • Surgery • Liver resection • Laparoscopic liver resection • Future liver remnant • Portal vein embolization • Major resection • Immunotherapy

KEY POINTS

- Treatment guidelines of hepatocellular carcinoma (HCC) vary between Western and Eastern countries, taking into account local factors (eg, the availability of donors for liver transplant).
- The minimal requirement of future liver remnant/standardized liver volume is 40% in patients with cirrhosis, whereas it is 20% to 25% for patients with normal liver.
- A new 3-level complexity classification effectively stratifies 11 common liver resection procedures with respect to surgical and postoperative outcomes and may be useful as a training pathway.
- For patients with small HCCs (ie, <3 cm), both resection and ablation can be recommended from the results of 5 randomized controlled trials.
- New medical therapies, including multikinase inhibitors and immunotherapies, are promising, and perioperative use of these therapies may further improve outcomes in patients undergoing HCC resection.

INTRODUCTION

Liver cancer is the sixth most common cancer and, in 2018, was the fourth leading cause of cancer-related death worldwide.[1] The rates of incidence and mortality are approximately 2 to 3 times higher for men than for women. Hepatocellular carcinoma (HCC) is the most common primary liver cancer and accounts for 75% to 85% of diagnoses, followed by intrahepatic cholangiocarcinoma (10%–15%), and other rare liver histologies. The improvement and safety of surgical techniques for liver resection and transplant, and advancements in ablation, transarterial chemoembolization

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(TACE), and systemic therapies have expanded the treatment options for patients with HCC. Liver transplant is the ideal treatment option for patients with HCC and poorly compensated liver disease because it removes both HCC and damaged liver and reduces the risk for early recurrence. However, shortages in donor liver and long waiting times to transplant are significant barriers to this treatment approach. As such, liver resection remains an effective treatment option for patients with HCC. The use of a multidisciplinary approach and the knowledge of each therapeutic option is critical in the management of patients with HCC. This article reviews the current evidence surrounding resection of HCC, including alternative and multimodal treatment approaches to the management of this disease.

TREATMENT GUIDELINES FOR HEPATOCELLULAR CARCINOMA: DIFFERENCES BETWEEN WEST AND EAST

The Barcelona Clinic Liver Cancer (BCLC) staging classification is widely used in Western countries. The classification recommends surgery only for patients with single HCCs in very early stage 0 disease[2] (solitary HCC <2 cm and Child-Pugh grade A) and in early stage A (single and Child-Pugh grade A–B) (**Fig. 1**A). It recommends ablation or liver transplant for patients with early stage A (largest HCC $\leq$3 cm and number of s $\leq$3).[3–5] Compared with Western countries, the selection criteria for liver resection are generally more lenient and indications for transplant are stricter in Eastern countries.[6,7] The Japanese clinical practice guidelines for HCC (fourth Japan Society of Hepatology [JSH] HCC guidelines) recommend both liver resection and radiofrequency ablation for patients who have less than or equal to 3 HCCs and Child-Pugh grade A to B, and recommend liver transplant for patients who have HCCs within Milan criteria and Child-Pugh grade C (**Fig. 1**B).[6] Importantly, these treatment guidelines are influenced by the availability of donors for liver transplant. Clearly, the treatment guidelines vary between Western and Eastern countries, taking into account local factors.

Liver Resection of Hepatocellular Carcinoma

Minimal future liver remnant requirements

Liver resection remains the treatment of choice for HCC. Two major preoperative considerations for HCC resection are the patient's liver function and the predicted future liver remnant (FLR). The intrinsic liver function of patients with HCC is often impaired because this patient population generally has chronic liver disease, including viral hepatitis, alcoholic hepatitis, and nonalcoholic steatohepatitis. As such, studies report that more FLR is needed for patients undergoing resection for HCC than for patients undergoing resection of secondary liver cancer (ie, metastatic disease).[8] The minimal requirement of FLR/standardized liver volume (standardized liver volume = $-794 + 1267.28 \times$ body surface area)[9] is 30% in patients with hepatic injury and fibrosis and 40% in patients with cirrhosis,[10] whereas it is 20% to 25% for patients with normal liver.[11,12]

New 3-level complexity classification

The assessment of FLR is important to avoid postoperative hepatic insufficiency. As a useful indicator for hepatic insufficiency, liver resection has historically been categorized in the binary fashion of major versus minor, from the number of resected segments. Major liver resection is generally defined as the resection of 3 or more contiguous Couinaud segments,[13–16] and is associated with higher rates of postoperative hepatic insufficiency than minor liver resection for both open and laparoscopic approaches.[17–21] However, the minor/major classification system does not necessarily stratify procedures effectively with respect to surgical and postoperative

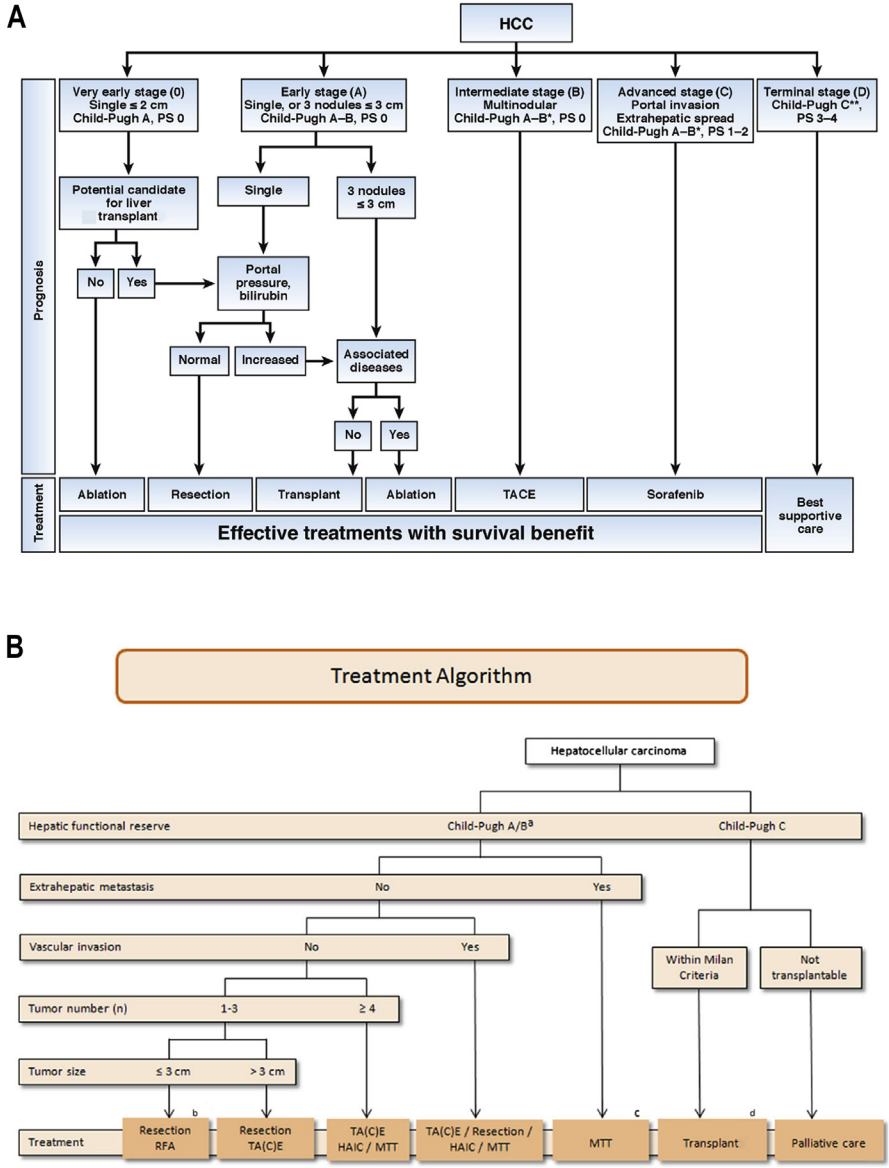

Fig. 1. Clinical practice guidelines in Western countries and Japan. (*A*) Staging and treatment according to the BCLC system.[96] (*B*) Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (fourth JSH-HCC guidelines) 2019 update.[6] *Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration. **Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stage with predictors of poor prognosis, high Model for End-Stage Liver Disease score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enlistment criteria. [a] Assessment based on liver damage is recommended in the case of hepatectomy. [b] For solitary hepatocellular carcinoma, resection is recommended as first-line therapy, and ablation as second-line therapy. [c] Patients with Child-Pugh A only. [d] Patients aged less than or equal to 65 years. HAIC, hepatic arterial infusion chemotherapy; MTT, molecular-targeted therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial

outcomes.[17,19,22,23] Our group has recently reported a 3-level complexity classification and categorized 11 common liver resection procedures as being of low, intermediate, or high complexity (grade) (**Fig. 2**).[19–21] Our data showed that the new 3-level classification system effectively stratified 11 liver resection procedures with respect to surgical and postoperative outcomes in Western and Eastern cohorts for both open and laparoscopic liver resections.[19–21,24] **Fig. 3** shows details related to duration of operation, estimated blood loss, and comprehensive complication index[25] for the procedures individually and stratified by grade using the 3-level classification scale. There was a clear, incremental increase in each of these factors as surgical complexity progressively increased from grade I to grade III. This scale predicts surgical complexity and postoperative morbidity better than the minor/major classification for both open and laparoscopic approaches.[20,21] Therefore, our 3-level classification may be useful as a training pathway for performing liver resections, and for tailoring management after liver resection (**Fig. 4**).

Anatomic resection versus nonanatomic resection

Anatomic resection of Couinaud segment for small HCC was reported in 1981 by Makuuchi and colleagues.[26] HCC frequently invades to the intrahepatic vascular structures and spreads through the portal vein. As such, the complete removal of tumor-bearing portal territory was reported to be theoretically superior to nonanatomic resection. The technique proposed by Makuuchi and colleagues[26] is detailed as follows: (1) under the guidance of intraoperative ultrasonography, the portal vein of interest is identified and punctured using a 22-gauge needle; (2) blue dye is injected into the portal vein; (3) the territory of the dyed surface is marked using electrocautery; and (4) liver resection is performed using ultrasonography guidance and intersegmental hepatic veins are exposed. This technique was recently refined using fluorescence imaging.[27–29] By using transportal injection or systemic intravenous injection of indocyanine green, the portal vein territory was more clearly visualized on the liver surface compared with the traditional method (**Fig. 5**). Many retrospective studies reported that anatomic resection was associated with better survival and lower recurrence than nonanatomic resection.[30–33] In contrast, other studies showed that survival did not differ significantly between patients undergoing anatomic resection and those undergoing nonanatomic resection.[34,35] Therefore, this clinical question remains unanswered and needs to be further elucidated.

Portal vein embolization

FLR is one of the most important factors when determining the technical resectability of HCC. To induce the hypertrophy of FLR and avoid the risk of postoperative hepatic insufficiency,[36] portal vein embolization (PVE) has been used.[8] The use of PVE was reported by Makuuchi and colleagues,[37] Matsuoka and colleagues,[38] and Kinoshita and colleagues[39] in the 1980s. PVE has now been adopted as a safe procedure frequently used to increase the volume of FLR for patients undergoing liver resection.[40–44]

chemoembolization. PS, posterosuperior. (*From* [*A*] Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology.* 2016;150(4):835-853; with permission; and [*B*] Kokudo N, Takemura N, Hasegawa K, et al. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatology research: the official journal of the Japan Society of Hepatology.* 2019, with permission.)

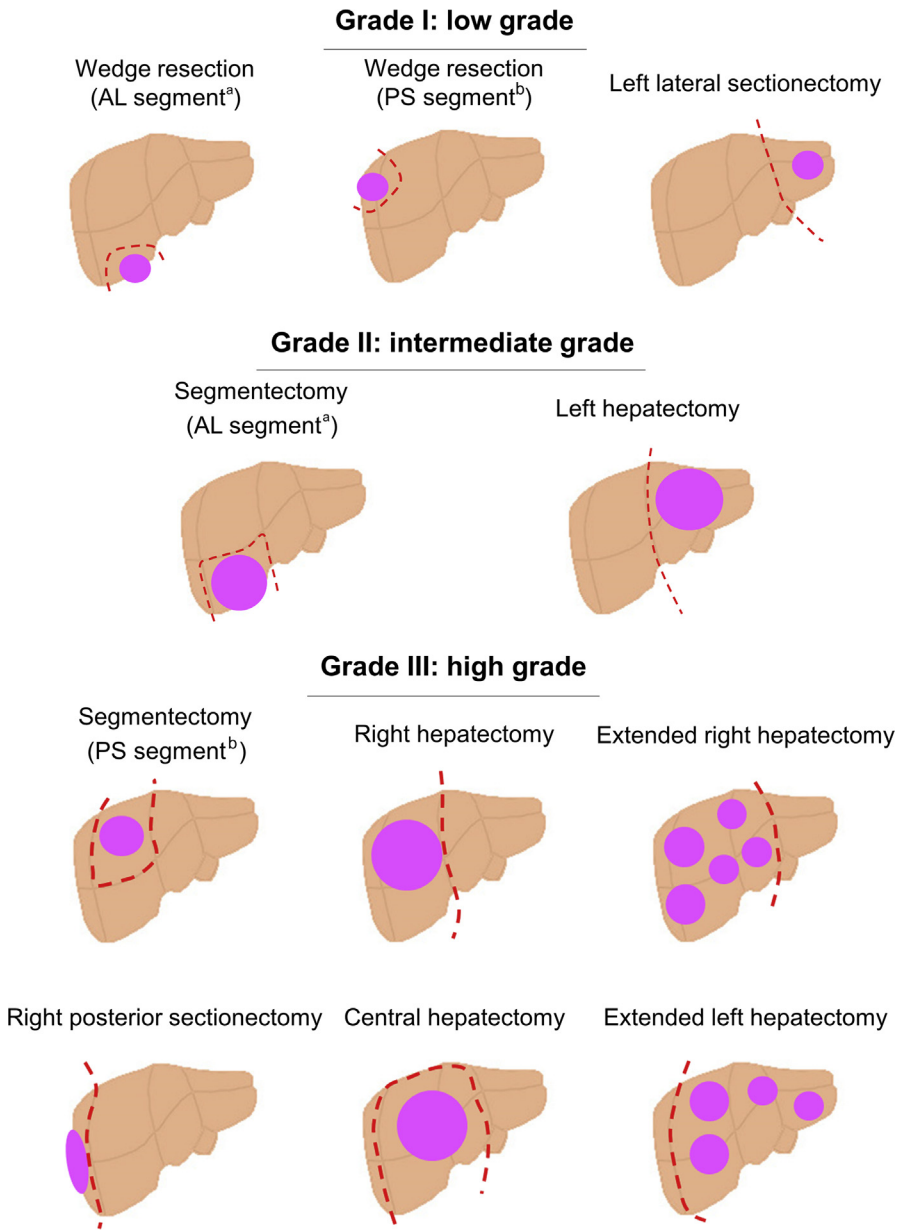

Fig. 2. New 3-level complexity classification. [a] Anterolateral (AL) segments are defined as Couinaud segments 2, 3, 4b, 5, and 6, and [b] PS segments are defined as Couinaud segments 1, 4a, 7, and 8.

Liver resection for HCC following PVE is feasible and safe, with reported morbidity rates of 19% to 55% and mortalities of 0% to 12% (**Table 1**).[41,45–52] The 5-year overall survival ranged from 44% to 72% in patients who underwent combined PVE and HCC resection. Studies also report that sequential TACE and PVE before liver resection is a feasible and useful treatment option.[53–56] This tactic prevents tumor progression and

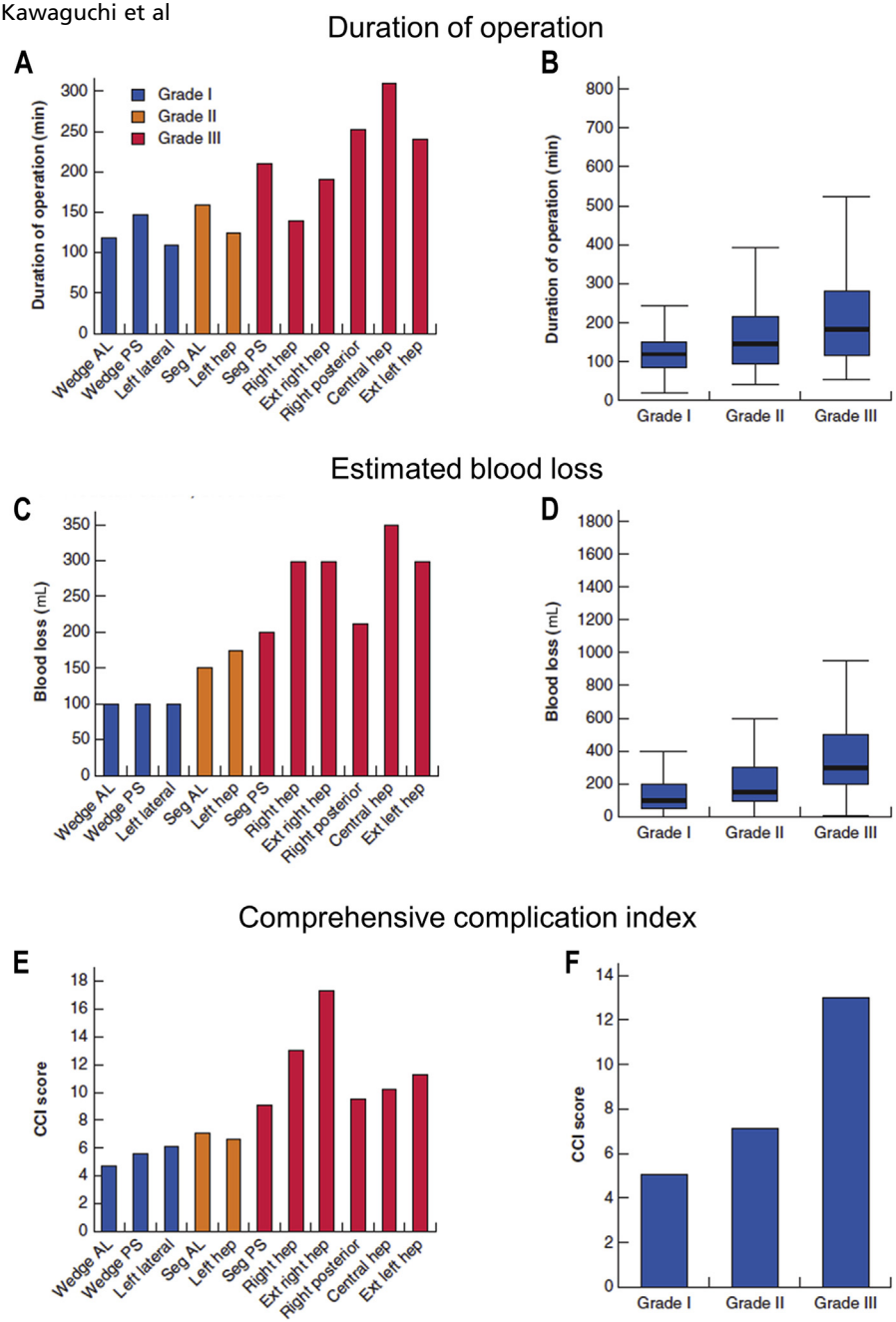

Fig. 3. Surgical and postoperative outcomes for 11 open liver resection procedures (*A*, *C*, *E*) and 3 grades (*B*, *D*, *F*) in our 3-level classification. (*A*, *B*) Duration of operation, (*C*, *D*) estimated blood loss, and (*E*, *F*) comprehensive complication index (CCI).[25] Central hep, central hepatectomy; Ext left hep, extended left hepatectomy; Ext right hep, extended right hepatectomy; Left hep, left hepatectomy; Left lateral, left lateral sectionectomy; Right hep, right hepatectomy; Right posterior, right posterior sectionectomy; Seg-AL, anterolateral segmentectomy; Seg-PS, PS segmentectomy; Wedge-AL, wedge resection of anterolateral segment; Wedge-PS, wedge resection of PS segment. (*Adapted from* Kawaguchi Y, Hasegawa K, Tzeng CD, et al. Performance of a modified three-level classification in stratifying open liver resection procedures in terms of complexity and postoperative morbidity. *The British journal of surgery.* 2020 Feb;107(3):258-267; with permission.)

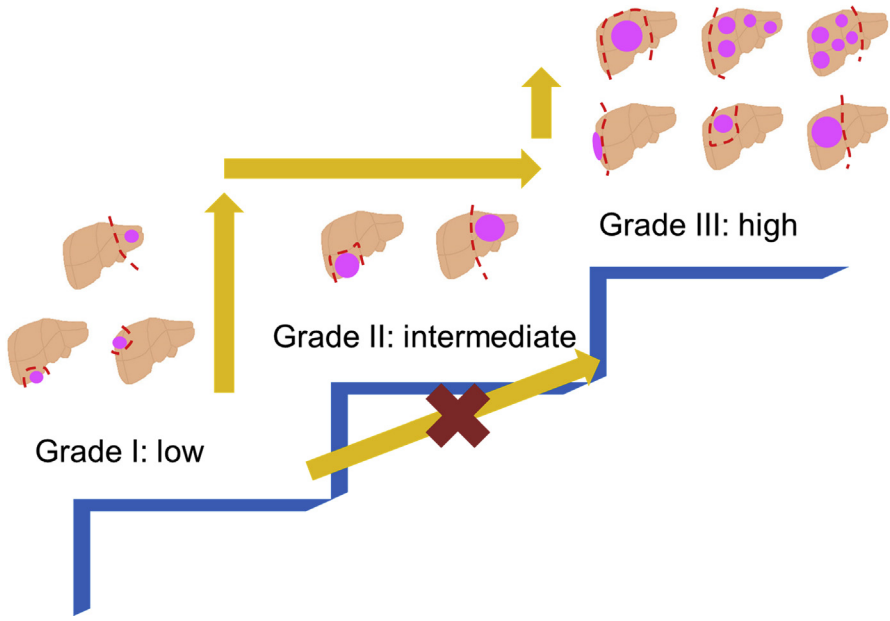

Fig. 4. Proposed training pathway based on 3-level complexity classification.

may increase hypertrophy in the FLR because arterial flow is also occluded. Ogata and colleagues[54] showed that the hypertrophy of the FLR was greater in patients who underwent TACE plus PVE than in patients who underwent PVE alone.

Laparoscopic liver resection

Laparoscopic liver resection (LLR) has been increasingly used worldwide.[57] In their systemic review, Nguyen and colleagues[58] reported on the safety of LLR with low rates of morbidity and mortality for both major and minor resections, as well as appropriate oncologic results compared with open liver resection (OLR). These results are most likely caused by patient selection and the advantages of the laparoscopic approach, including a magnified view[59,60] and the hemostatic effect caused by pneumoperitoneum.[61,62] Three retrospective studies including more than 200 patients showed that the 5-year overall survival (OS) was not significantly different between patients undergoing LLR for HCC and those undergoing OLR for HCC.[63–65] However, no randomized controlled trials (RCTs) comparing long-term outcomes in patients undergoing LLR versus OLR for HCC have been reported. For patients with colorectal liver metastases, a recent RCT (Oslo-CoMet study) showed that median OS in patients undergoing LLR was similar to those undergoing OLR: 80 months versus 81 months.[66]

Liver Resection Versus Ablation

It remains unclear whether liver resection or ablation is the most effective treatment of small HCC lesions. To answer this clinical question, 5 RCTs have been reported (**Table 2**).[67–71] Two of these studies showed that liver resection was associated with better survival than radiofrequency ablation[68,70] and 3 showed that survival did not differ significantly between patients undergoing resection and those undergoing ablation.[67,69,71] The shortcomings of these RCTs include insufficient patient follow-up; unclear treatment allocation; and different inclusion criteria, including tumor number,

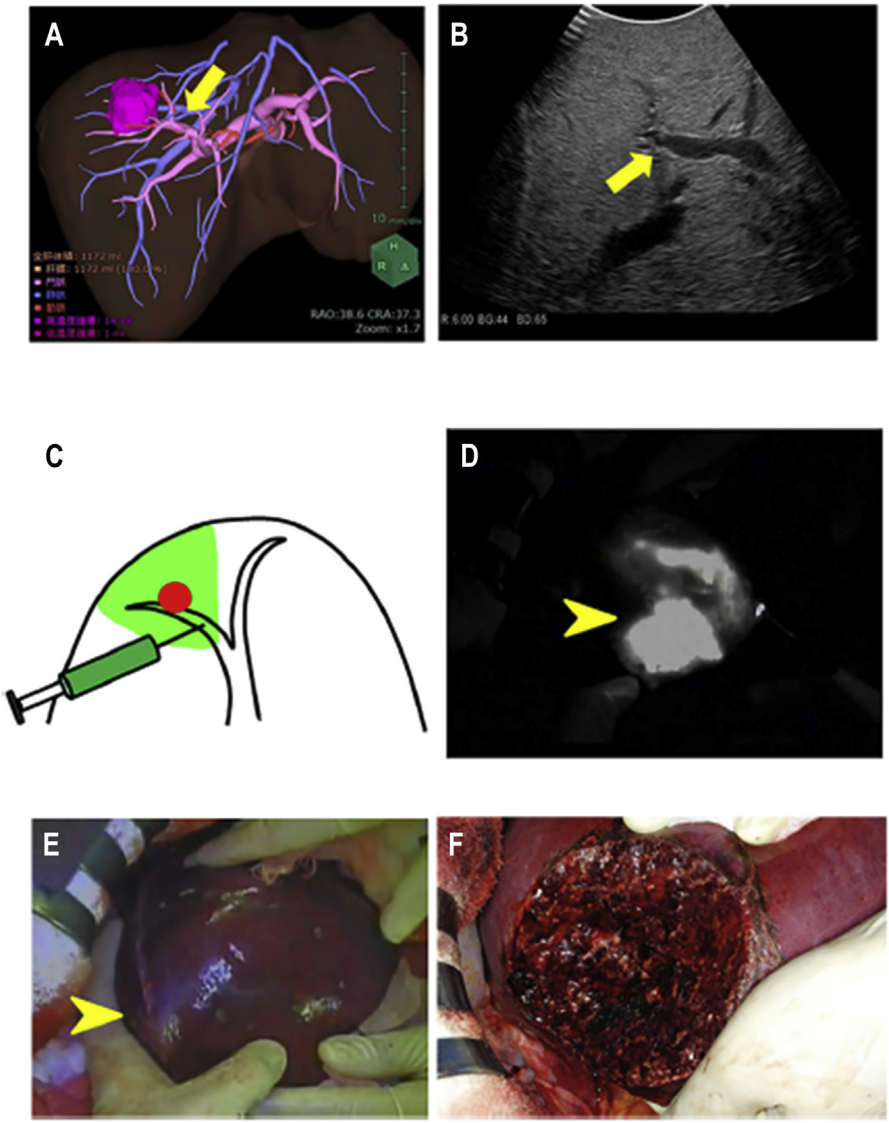

Fig. 5. Portal vein territory identification using fluorescence imaging. (*A*) P8 dorsal branch (*arrow*) was shown by three-dimensional simulation. (*B*) P8 dorsal branch (*arrow*) was visualized by intraoperative ultrasonography. (*C*) Schema of portal vein territory identification. (*D*) Fluorescence imaging clearly showed the territory of P8 dorsal branch (*arrowhead*). (*E*) Blue dye-stained regions (*arrowhead*) were unclear on gross examination of the liver. (*F*) Cut surface of the liver after anatomic resection of P8 dorsal branch territory. (*From* Kobayashi Y, Kawaguchi Y, Kobayashi K, et al. Portal vein territory identification using indocyanine green fluorescence imaging: Technical details and short-term outcomes. *Journal of surgical oncology.* 2017;116(7):921-931. with permission.)

Table 1
Outcomes of resection after preoperative portal vein embolization for hepatocellular carcinoma

Author, Year	Regions	N	Morbidity (%)	Mortality (%)	5-y DFS (%)	5-y OS (%)
PVE						
Azoulay et al,[41] 2000	Europe	10	55	0	21	44
Tanaka et al,[45] 2000	Asia	33	NA	2	33	50
Wakabayashi et al,[46] 2001	Asia	26	NA	12	40	46
Sugawara et al,[47] 2002	Asia	66	NA	0	38	59
Seo et al,[48] 2007	Asia	32	19	0	37	72
Palavecino et al,[49] 2009	United States	21	24	0	56	72
Siriwardana et al,[51] 2012	Asia	34	47	6	Approximately 40[a]	Approximately 60[a]
TACE + PVE						
Aoki et al,[53] 2004	Asia	24	24	0	47	56
Ogata et al,[54] 2006	Europe	18	39	NA	37	NA
Yoo et al,[55] 2011	Asia	68	NA	0	61	72
Ronot et al,[56] 2016	Europe	39	NA	8	NA	Approximately 30[a]

Abbreviations: DFS, disease-free survival; NA, not available; OS, overall survival.
[a] Estimated by the Kaplan-Meier curve.

tumor diameter, and Child-Pugh grade. Nonetheless, for patients with small HCCs (ie, <3 cm), the current evidence shows that both resection and ablation can be recommended.

Liver Resection Versus Transarterial Chemoembolization

There has been 1 RCT comparing the outcomes of patients undergoing resection for HCC with those undergoing TACE.[72] For patients outside of Milan criteria,[73] resection was associated with better survival than TACE (**Table 3**). The authors found 8 cohort studies comparing outcomes after resection with TACE using the propensity score adjustment.[72,74–81] Although the studies had different inclusion criteria, the data

Table 2
Liver resection versus ablation, randomized controlled trials

Author, Year	Regions	N	Tumor Number	Tumor Diameter (cm)	Child-Pugh Grade	Result
Chen et al,[67] 2006	Asia	180	1	≤5	A	Not significant
Huang et al,[68] 2010	Asia	230	Milan criteria[a]		A, B	Favor for resection
Feng et al,[69] 2012	Asia	168	≤2	≤4	A, B	Not significant
Liu et al,[70] 2016	Asia	200	Milan criteria[a]		A, B	Favor for resection
Izumi et al,[71] 2019	Asia	308	≤3	≤3	A, B	Not significant

[a] A solitary HCC nodule of 5 cm or less, or up to 3 nodules of 3 cm or less.[73]

show that resection is associated with better survival than TACE in selected patients who have multiple HCCs.

Liver Resection Versus Liver Transplant

Liver transplant is an established treatment option for patients who have early-stage HCC and poorly compensated cirrhosis and/or portal hypertension.[73,82] However, the preferred treatment of patients who have early-stage HCC and well-compensated cirrhosis is not established. Several retrospective studies have evaluated outcomes after liver resection for HCC in this setting, comparing them with those of transplant. However, most are limited by small sample sizes and low statistical power. No prospective studies have been performed on this topic given the inability to randomize patients to liver resection versus transplant. The authors found 2 studies including more than 200 patients (**Table 4**). They both suggest that transplant is associated with better survival than liver resection in patients within Milan criteria and Child-Pugh A or B.[83,84] Nonetheless, it should be noted that graft availability and waiting times for transplant differ between countries, which greatly influences the selection of liver resection versus transplant for patients with early-stage HCC.

New Medical Therapies and Liver Resection

In 2009, studies showed that sorafenib was an effective medical therapy for HCC.[85,86] The STORM trial compared patients who were assigned to receive either sorafenib or placebo after resection or ablation of HCC. The study did not show a significant survival benefit in those receiving sorafenib in the adjuvant setting.[87]

Recent studies have shown the effectiveness of new medical therapies for HCC as first and second lines (**Table 5**). These new therapies include multikinase inhibitors and immunotherapies. The REFLECT study showed that lenvatinib was noninferior to sorafenib for patients with untreated advanced HCC in first-line settings.[88] The CELESTIAL study, the REACH-II study, and the RESOURCE study respectively showed cabozantinib, ramucirumab, and regorafenib were associated with longer survival than placebo for the treatment of HCC in the second-line setting.[89–91] Recent results of immunotherapy trials are also promising in both first-line and second-line settings.[92–94] For first-line therapy in HCC, CheckMate-459 found that nivolumab was associated with better survival than sorafenib[92] and IMbrave150 showed that the

Table 3
Liver resection versus transarterial chemoembolization, randomized controlled trials and cohort studies using adjustment of propensity score

Author, Year	Regions	N	Tumor Number	Tumor Diameter (cm)	Child-Pugh Grade	OS
RCT						
Yin et al,[72] 2014	Asia	173	Outside of Milan criteria[a]		A, B	Favor for resection
Cohort Studies Using Adjustment of Propensity Score						
Hsu et al,[74] 2012	Asia	292	Outside of Milan criteria[a]		A, B	Favor for resection
Guo et al,[75] 2014	Asia	304	BCLC stage A[c]		A	Favor for resection
Zhu et al,[76] 2014	Asia	108	BCLC stage A[c]		A, B	Favor for resection
Yang et al,[77] 2014	Asia	118	1	≤3	A, B	Not significant
Shi et al,[78] 2014	Asia	1296	NA	NA	NA	Not significant
Liu et al,[79] 2014	Asia	216	Any with portal vein tumor thrombosis		A, B	Favor for resection
Lee et al,[80] 2015	Asia	118	1	≥ 5	A	Not significant
Zhong et al,[81] 2018	Asia	488	UICC stage (seventh) T3[b]		A, B	Favor for resection

[a] Milan criteria, a solitary HCC nodule of 5 cm or less, or up to 3 nodules of 3 cm or less.[73]
[b] Multiple lesions with any lesion larger than 5 cm (stage IIIa), or involving a major portal vein or hepatic veins (stage IIIb).
[c] A single tumor of any size or 2 to 3 tumors less than or equal to 3 cm.

Table 4
Liver resection versus transplant, retrospective studies including more than 200 patients

Author, Year	Regions	N	Tumor Number	Tumor Diameter (cm)	Child-Pugh Grade	5-y OS
Shah et al,[83] 2007	Europe	261	Milan criteria[a]		Child-Pugh A, B	Favor for transplant
Bellavance et al,[84] 2008	United States and Europe	379	Milan criteria[a]		Child-Pugh A, B	Favor for transplant

[a] Milan criteria, a solitary HCC nodule of 5 cm or less, or up to 3 nodules of 3 cm or less.[73]

Table 5
New medical therapy for hepatocellular carcinoma

Author, Year	Drug	Target	Study	Phase	Design	Median OS (mo) HR; 95% CI
First Line						
Kudo et al,[88] 2018	Lenvatinib	Multi-kinase	REFLECT	3	Vs sorafenib	13.6 vs 12.3 0.92; 0.79–1.06
Yau et al,[92] 2019	Nivolumab	PD-1	ChekMate-459	3	Vs Sorafenib	16.4 vs 14.7 0.85; 0.72–1.02
Cheng et al,[94] 2019	Atezolizumab + Bevacizumab	PD-L1 + VEGF	IMbrave150	3	Vs Sorafenib	6.8 vs 4.3 0.59; 0.47–0.76
Second Line						
Abou-Alfa et al,[89] 2018	Cabozantinib	Met/ VEGFR-2	CELESTIAL	3	Vs Placebo	10.2 vs 8.0 0.76; 0.63–0.92
Zhu et al,[90] 2019	Ramucirumab	VEGFR-2	REACH-II	3	Vs Placebo	8.5 vs 7.3 0.71; 0.53–0.95
Bruix et al,[91] 2017	Regorafenib	Multi-kinase	RESORCE	3	Vs placebo	10.7 vs 7.8 0.63; 0.50–0.79
Finn et al,[93] 2019	Pembrolizumab	PD-1	KEYNOTE240	3	Vs Placebo	13.9 vs 10.6 0.78; 0.61–0.998

Abbreviations: CI, confidence interval; HR, hazard ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; VEGFR, vascular endothelial growth factor receptor.

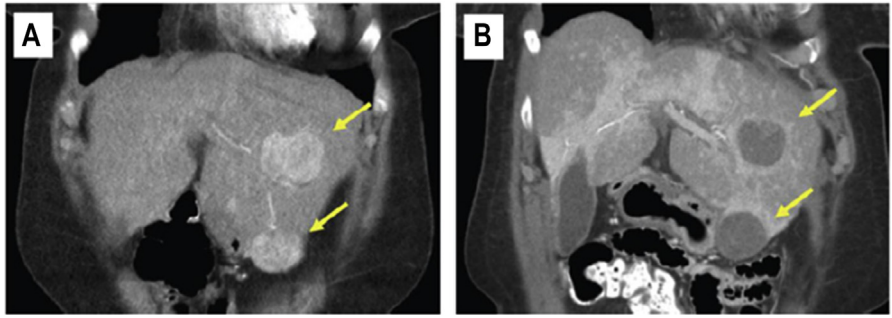

Fig. 6. Pretreatment and posttreatment computed tomography with arterial phase in patient with resectable hepatocellular carcinoma (*arrows*) treated with perioperative immunotherapy. (*A*) Pretreatment. (*B*) After 1 dose of nivolumab and ipilimumab followed by 1 dose of single-agent nivolumab. (*From* Kaseb AO, Vence L, Blando J, et al. Immunologic Correlates of Pathologic Complete Response to Preoperative Immunotherapy in Hepatocellular Carcinoma. *Cancer immunology research.* 2019;7(9):1390-1395; with permission.)

regimen of atezolizumab and bevacizumab was associated with better survival than sorafenib.[94] In the second-line setting, KEYNOTE240 showed that pembrolizumab provided better survival than placebo.[93]

Our group is conducting a randomized pilot study of perioperative immunotherapy for resectable HCC (ClinicalTrial.gov, NCT03222076). The clinical trial has 3 treatment arms: perioperative nivolumab alone in patients with resectable HCC (arm A), perioperative nivolumab plus ipilimumab in patients with resectable HCC (arm B), and perioperative nivolumab plus ipilimumab in patients with potentially resectable HCC (arm C). Our trial has accrued 9 patients, of whom 3 had complete response.[95] **Fig. 6** shows a representative case of a patient who showed complete response after treatment in arm B.[95] After 1 dose of nivolumab and ipilimumab followed by 1 dose of single-agent nivolumab, both lesions were downsized and had a cystlike appearance (see **Fig. 6**B). The patient underwent anatomic resection of segment 3. Histopathologic examination showed 2 hemorrhagic and necrotic liver lesions with no viable tumor cells.

SUMMARY

Liver resection remains an effective treatment option for HCC. The knowledge of liver function and minimal FLR requirement, combined with PVE when necessary, can help ensure the safety of liver resection for patients with HCC and underlying liver disease. The authors suggest a newly proposed 3-level classification system, which better categorizes procedures based on surgical complexity and perioperative morbidity. This classification can be used to guide the training for residents and fellows and improve postoperative management. LLR is one of the breakthroughs in liver resection for HCC in recent years and outcomes have been promising.

Note that guidelines for liver resection differ by country. In Western countries, liver resection is recommended for single lesions and ablation or liver transplant is recommended for small and multiple HCCs. In Eastern countries, liver resection is recommended for both single and multiple HCCs. Liver transplant is not generally performed for patients with well-compensated liver function because of donor shortages, especially in Eastern countries. The current evidence suggests that, for patients with small HCC lesions (<3 cm), OS is likely to be similar for patients undergoing liver resection versus ablation. For selected patients with multiple HCCs, liver resection may be associated with better OS than TACE. For the past 10 years, sorafenib has been the only effective medical therapy available for unresectable HCC. Recently, several promising new therapies, including multikinase inhibitors and immunotherapies, have been reported. Perioperative use of these new therapies may further improve outcomes in patients undergoing liver resection for HCC and potentially change the current treatment guidelines.

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DISCLOSURE

The authors have nothing to disclose.

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