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A Review on the Concepts for Initially Unresectable Liver Tumors - Bridge to Surgery

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Abbreviations:
ALPPS: associating liver partition and portal vein ligation for staged hepatectomy
CRC: colorectal cancer;
HCC: hepatocellular carcinoma;
FLR: future liver remnant;
MELD: model for end stage liver disease;
PVE: Portal vein embolization;
PVT: Portal vein thrombus;
TACE: Transarterial chemoembolization;
TARE: Transarterial radioembolization;
TSH: Two-staged hepatectomy;
Y-90: Yttrium-90.

Rezumat

Analiza managementului tumorilor hepatice inițial nerezecabile – proceduri premergătoare tratamentului chirurgical definitiv

Tratamentul chirurgical adresat tumorilor avansate a evoluat în ultimele două decenii ca urmare a progreselor în tehnicile chirurgicale, a metodelor avansate de radiologie intervențională, a îmbunătățirii dotărilor din unitățile de terapie intensivă şi a creşterii speranței de viață generale. Tumorile hepatice avansate reprezintă o categorie largă de diferite afecțiuni maligne, precum metastazele hepatice sau tumorile hepatice primare. Frecvent, aceste tumori nu pot fi tratate chirurgical curativ. Ca atare, necesită proceduri în vederea reducerii volumului tumoral sau pentru controlul extensiei loco-regionale a formațiunii decelate la momentul diagnosticului inițial. Scopul acestui review este de a prezenta metode terapeutice premergătoare tratamentului chirurgical definitive, precum: embolizarea venei porte (PVE), radioembolizarea transarterială (TARE) cu Yttrium-90 (Y-90), hepatectomia în doi timpi (TSH) şi partiția hepatică asociată cu ligatura venei porte pentru hepatectomia etapizată (ALPPS).

Cuvinte cheie: cancer hepatic, chirurgie hepatică, radioembolizare transarterială, embolizare venă portă, partiție hepatică

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Abstract

Surgical treatments of advanced tumors have expanded in the last two decades as a result of ad-vances in surgical techniques,

advanced interventional radiology methods, improved intensive care unit settings and increased overall life expectancy. Advanced liver tumors represent a broad category from various malignancies such as liver metastasis or native liver tumors. Not uncom-monly these tumors are not amenable to curative treatment and require down-staging, or local control at the initial diagnosis. Herein we discuss the portal vein embolization (PVE), transarterial radioembolization (TARE) with Yttrium-90 (Y-90), and surgical options namely, two-staged hepatectomy (TSH), and associating liver partition and portal vein ligation for staged hepatecto-my (ALPPS) as bridging strategies for definitive surgical treatment.

Key words: liver cancer, liver surgery, transarterial radioembolisation, portal vein embolisation, liver partition

Introduction

Radical liver resection has been the best way to achieve long term survival for hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) as well as secondary tumors such as metastatic colorectal cancer (CRC) or neuroendocrine tumors. However, many patients present in advanced stages with unresectable disease. One of the major reasons for unresectable disease is insufficient future liver remnant (FLR) and insufficient "functional volume". Today we know that not just absolute volume, but "functional volume" is the critical aspect for liver resection, particularly when the liver parenchyma is somewhat abnormal, damaged from chemotherapy or if there is an underlying/primary liver disease. There is abundant literature suggesting the added benefit of function measurement as well as volume calculations (1-4).

Portal Vein Embolization

Portal vein embolization (PVE) is mainly used to expand the indication for major hepatectomy in patients with initially insufficient FLR volume or function (5). Honjo et al. described PVE as a treatment for unresectable liver cancer in 1975 (6). It was performed in 20 patients. They reported that responses to ligation differed considerably, but significant palliation was attained in some patients and one survived six years. They stated that the effect of portal branch ligation on the tumor appears to be closely related to the degree of tumor vascularity, tumor malignancy, and portal circulatory disturbances such as cirrhosis, portal hypertension, or portal thrombosis (6). Later on, Kinoshita et al. reported PVE as a preoperative measure for HCC in 1986 (7). Shinkawa et al. reported that 99mTechnetium-galactosyl human serum albumin (99mTc-GSA) scintigraphy revealed that PVE induced a shift in hepatic function from the embolized part to the nonembolized part of the liver (5). Meier et al. demonstrated that PVE resulted not only increment in remnant liver volume but also improved liver function (8). For equivalent volumes, the immediate postoperative hepatic function appears to be better in livers prepared with PVE than in unprepared livers (8).

The indication for PVE is determined by the underlying liver function and standardized FLR volume. According to the expert consensus statement by Vauthey et al. PVE is indicated when the standardized FLR is $\leq$ 20% in a normal liver, $\leq$ 30% in liver with intermediate disease without cirrhosis, and $\leq$ 40% in liver with cirrhosis (9). Resection is generally considered safest when FLR volume reaches above targets and when the degree of FLR hypertrophy is adequate (at least 5% increase in FLR volume in normal liver and 10% increase in FLR volume in cirrhosis) (9). They also stated that preoperative PVE is appropriate in patients with chronic liver disease who are candidates for major

hepatectomy and recommended transarterial chemoembolization (TACE) to be followed by PVE in patients with chronic liver disease who are candidates for major hepatectomy (9).

Another point about PVE was the growth of the tumor as well as healthy parenchyma (10). In a recent extensive review by Bappu et al. authors overall state that PVE can result in tumor progression in both embolized and non-embolized livers; however, long term survival after liver resection following PVE is at least not inferior compared to liver resection alone despite the smaller future liver remnant volume (11). Further, PVE has multiple oncological advantages for both surgical and nonsurgical treatments. PVE can also enhance the anticancer effects of TACE and can avoid intraportal tumor cell dissemination (11). Also, systemic therapy administered after PVE and before hepatic lobectomy had no effect on FLR growth; however, it was associated with decreasing tumor volumes therefore it is recommended to continue chemotherapy after PVE (12).

Alvarez et al. reported long term (>20 years) results of PVE (13). They reviewed a total of 431 patients. Morbidity and mortality rates were 16.7% and 0.2% respectively. Morbidity was similar between percutaneous and ileocolic approaches or between histoacryl and ethanol as embolization materials (13). On the contrary, the percutaneous ipsilateral approach was associated with significantly fewer complications than the contralateral approach (10.3% vs 19.4%; P = 0.024) (13). Almost all patients (96%) achieved sufficient FLR volume after embolization, but only 66% finally underwent planned liver resection. Disease progression was the most common cause of unresectability (67%). Patients with extrahepatic biliary tumors experienced significantly higher unresectability rates compared to other entities (45.1% vs 31.4%; P = 0.019) (13). Overall PVE was not followed by hepatectomy in 34% of the patients. Biliary tumors displayed the higher dropout rates after PVE and the higher chances of tumor progression preventing curative resection (13). PVE-related complications prevented curative resection in 5% of patients (13). In a recent systematic review by Soykan et al. the authors reported increase in hypertrophy response when additional embolization of segment 4 was performed and that the use of N-butyl cyanoacrylate for PVE induced more hypertrophy than polyvinyl alcohol (14). There was no indication of a difference in degree of hypertrophy between patients who received neo-adjuvant chemotherapy and those who did not receive pre-procedural systemic therapy, or between male and female patients (14).

Currently PVE is a standard technique for patients with liver malignancies not amenable to liver resection due to small FLR. By doing so, contralateral liver hypertrophy is induced by redirecting the flow. Generally speaking, PVE is contraindicated if the patient's liver does not have the capacity to regenerate and these would be Childs B or C liver disease, severe hepatic fibrosis, biliary obstruction, or existing portal vein thrombosis. Major complications after PVE are rare. Disadvantages of PVE can be listed as following: relatively long waiting time until adequate FLR growth is achieved, stimulation of tumor growth, failure for optimal regeneration in some patients, risk of gastrointestinal bleeding for patients with existing high grade varices. PVE is not an option in the presence of portal vein tumor thrombus or tumor portal vein invasion.

Radioembolization

There are early reports from 1960s about the application of yttrium-90 (Y-90) intraarterial treatment for inoperable liver and pancreas tumors (15). Transarterial radioembolization (TARE) was approved by FDA in 2000 as a treatment option for unresectable liver tumors. Radioembolization with Y-90 causes tumoricidal effect predominantly due to radioactivity and not ischemia (16). There are various radioactive substances particularly 131I-lipiodol. Within 2 weeks following injection, >95% of the radiation is deposited causing irreversible cellular damage in the tumor epithelial and stromal cells (16).

In patients with large or intermediate-

stage HCC patients, tumor downsizing may convert the patient eligible for curative resection or for transplant (17). There are reports stating higher likeli-hood of downstaging after radioembolization compared to TACE (58% vs 31%, P = 0.023) (18). Similarly, Salem et al. demonstrated in their randomized phase 2 study of patients with HCC of BCLC stages A or B that Y-90 radioembolization provides significantly longer time to progression than TACE (>26 mo vs 6.8 mo, p=0.0012) (19). They demonstrated similar response to therapy, marked by necrosis (19). The median survival time, censored to liver transplantation, was also similar (17.7 months for the TACE group vs. 18.6 months for the Y90 group [P = .99]). They concluded that Y90 radioembolization provides better tumor control and could reduce dropout from transplant waitlists (19).

Another applicability of Y90 is the presence of portal vein thrombus (PVT). Spreafico et al. reported prognostic factors for survival in patients with HCC and PVT undergoing TARE (20). Bilirubin level, extension of PVT and tumor burden were independently related to posttreatment survival. Based on these variables, 3 prognostic categories were identified: favorable prognosis (0 points), intermediate prognosis (2-3 points) and dismal prognosis (>3 points). Median overall survival in the three categories was 32.2 months, 14.9 months, and 7.8 months respectively (p <0.0001). They concluded the proposed prognostic stratification may help to better identify good candidates for the treatment, and those for whom TARE may be futile (20).

Parikh et al. performed a systematic review and demonstrated that there was no significant difference comparing TACE versus TARE, but there were higher success rates in prospective versus retrospective studies (0.68 versus 0.44; P < 0.001) (21).

Radioembolization can induce a marked hypotrophy of the treated hepatic lobe, associated with an evident hypertrophy of the contralateral lobe - the so-called "radiation lobectomy" (22,23). Volumetric changes are comparable (albeit slightly slower, up to 9 months) to PVE while the right lobe tumor is treated synchronously (22-25) Therefore, radioembolization has been proposed as an alternative to PVE in HCC patients. In addition, radioembolization offers the advantage of treating the cancer itself, thus reducing the risk of pre-interventional tumor progression, and represents a therapeutic option also in patients with neoplastic venous thrombosis (24). Typically, 6-12 weeks or even longer in some cases are necessary to achieve radiation lobectomy; during this time, patients with more favorable biological behavior can be identified (24). This can allow a test-of-time approach that can disclose a tumor in the future liver remnant that would otherwise go undiagnosed at the time of resection if the interval between the procedure and liver resection were shorter. Another advantage of TARE over PVE is when there are tumors close to a vital structure such as cava or left portal vein, the treatment prevents growth of the tumor that leads to invasion of these structures at the time of surgery. Y-90 related fibrosis could be an additional challenge for the surgeons dealing with these tumors after Y-90 treatment.

From a healthcare-utilization perspective, radioembolization is definitely more complex and expensive than TACE; however, TACE requires more frequent, repeated treatments than radioembolization and may be associated with a less favorable safety profile, thus increasing indirect costs (24). El Fouly et al. has shown that radioembolization presents a similar efficacy, but a lower incidence of adverse events and need for hospitalization when compared to TACE (26). The number of treatment sessions, the average rate of treatment sessions per patient, total hospitalization time and rate of adverse events were significantly higher in the TACE cohort therefore they concluded TARE Y-90 was better tolerated and associated with fewer hospitalization and treatment sessions (26).

Riaz et al. reviewed radioembolization with Y-90 microspheres and side effects. They reported morbidity up to 25% and major complications < 2% (16). The degree of hypertrophy was 10-46%. They also commented on

local tumor progression as well as preexisting liver damage, which could lead to post-treatment liver failure (16).

Complications of radioembolization are either caused by delivering a toxic dose to non-tumoral tissues, or by procedural complications during the placement and manipulation of the catheter (24). The main complications include: (1) liver failure or radiation-induced liver disease (2) biliary complications; (3) post-radioembolization syndrome, characterized by fatigue, nausea, vomiting, anorexia, fever, abdominal pain 4) gastrointestinal complications, (5) radio-induced pneumonia, due to hepatopulmonary shunts. Another concern is the residual radiation dose at the time of the transplant or resection. Yttrium-90 has a relatively short half life of 64.2 hours. Therefore, in most institutions, even one month after TARE, the residual dose in the targeted area is considered negligible and not a risk for the surgeons.

We can summarize TARE indications as following:

1. Salvage therapy for almost all liver tumors;
2. Alternative therapy for down-staging before resection or transplant;
3. Particularly an alternative for large tumors;
4. Applicability of the technique with concomitant portal vein thrombus or tumor macro-vascular invasion, or concomitant cirrhosis (27);
5. An option for inoperable / unresectable tumors with small FLR (24-28).

Surgical Methods

Two-Staged Hepatectomy (TSH) means 2 sequential liver resections. There is a time period for liver regeneration between the 2 procedures. Main indication is bilobar liver tumors (i.e. colorectal liver metastasis) that is not amenable to resection by a single resection with or without PVE. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was performed in early 2000s (29). The first results of the international ALPPS registry were published in 2014 (30). The classic form of ALPPS consists of ligation of the right portal vein, limited resections on the left lobe if any, and splitting along the umbilical fissure; and the right lobe was removed one or two weeks later. The main concept is the auxiliary role of deportalized and diseased liver during the time interval between in situ splitting and the second operation (31).

Accelerated liver hypertrophy is attributed to prevention of collateral formation between remaining segments and intended resection part. In addition, portal deprivation and redistribution of hepatotropic factors cause the rapid growth of FLR (31,32).

Gauzolino et al. described modifications of ALPPS (33). Left ALPPS refers to ligation of the left portal vein, multiple resections on the right hemiliver and splitting along the main portal fissure. Rescue ALPPS, consists of splitting of the liver along the main portal fissure several months after a radiological PVE that did not allow satisfactory liver hypertrophy. Right ALPPS, consists of ligation of the posterolateral branch of right portal vein, left lateral sectionectomy, multiple resections on the right anterior and left medial section and splitting along the right portal fissure. In all cases auxiliary deportalized liver was removed 1 to 2 weeks week later. They concluded that the ALPPS technique, in its "classical" and modified forms, is a good option for selected patients with bilateral colorectal metastases and represents a feasible alternative to classical two-stage hepatectomy (33). There is also a concept called “mono-ALPPS”. Murtha-Lemekhova et al. reviewed 37 publications and 19 patients were identified to have undergone mono-ALPPS (34). Successful mono-ALPPS was possible in FLR above 8% standard liver volume. Eight out of 19 patients experienced post-hepatectomy liver failure grade A or B. There was no in-hospital mor-tality described. Recurrent disease has occurred in 7 of 19 patients and 3 died during follow-up. They concluded mono-ALPPS is an experimental procedure that provides a

reasonably safe opportunity to curatively treat extensive liver malignancies in patients with FLR as low as 8% standard liver volume (34).

The main concern has been the high morbidity rates after ALPPS. Schadde et al. reported age, tumor types, ISGLS criteria after stage-1, and MELD score before stage-2 stratify to different outcomes while FLR volume before stage-2 and center experience do not (35). Mortality was 14% for patients older than 60 years, 71% and 36% for patients with gallbladder cancer and cholangiocarcinoma, respectively, 20% for patients who fulfilled ISGLS criteria after stage 1, and 22% for patients with a MELD score more than10 before stage 2, highlighting the variable outcomes based on patient and disease process (35).

Sandstrom et al. conducted a prospective, multicenter RCT between 2014 and 2016 (36). It included 97 patients with CRLM and a standardized FLR (sFLR) of less than 30%. Primary outcome-resection rates (RR) were measured as the percentages of patients completing both stages of the treatment. The RR was 92% (44/48) in the ALPPS arm compared to 57% in the TSH arm [rate ratio 8.25 (95% CI 2.6-26.6); P <0.0001]. No differences in complications (Clavien-Dindo ≥3a), 90-day mortality, or R0-RRs were observed (36). Of the patients in the TSH arm that failed to reach an sFLR of 30%, 12 were successfully treated with ALPPS. They concluded ALPPS is superior to TSH in terms of resection rate, with comparable surgical margins, complications, and short-term mortality (36).

Moris et al. conducted a meta-analysis comparing TSH and ALPPS (37). Among the 634 records identified, 9 studies met the inclusion criteria. There were 657 patients with unresectable colorectal liver metastasis (ALPPS, n = 186 vs TSH, n = 471). There was no difference in final postoperative FLR between ALPPS versus TSH (mean difference: 31.72, 95% CI: -27.33 to 90.77, p =0.29). The kinetic growth rate was faster with the ALPPS vs TSH (mean difference 19.07 ml/day, 95% CI 8.12-30.02, p =0.0006). TSH had a lower overall and major morbidity vs ALPPS (overall morbidity: RR: 1.39, 95% CI: 1.07-1.8, p = 0.01; I 2: 58%, p = 0.01; major morbidity: RR: 1.57, 95% CI: 1.18-2.08, p = 0.002; I 2: 0%, p = 0.44) (37). Overall survival was comparable following ALPPS versus TSH. They concluded that while ALPPS may be a suitable approach for patients, the higher morbidity and mortality should be considered when determining the operative approach for patients with extensive CRC metastasis (37). Similar results were reported by the systematic review by Liu et al. ALPPS was associated with a greater increase in the future liver remnant (FLR) (RR: 4.87; 95%CI, 3.41-6.33) and more frequent completion of stage 2 resection (RR: 1.32; 95%CI, 1.21-1.44) (37). Compared to TSH, ALPPS had a trend toward higher morbidity (RR: 1.19, 95%CI, 0.96-1.47) and mortality (RR: 2.11, 95%CI, 1.02-4.33) after stage 2 resection (37). ALPPS was found to be associated with greater FLR hypertrophy and a higher rate of completion of stage 2, but with greater morbidity and mortality (37).

In summary indications of ALPPS could be summarized as: marginally resectable and locally advanced unresectable liver tumors of any origin with insufficient FLR, from either volume or quality perspective. Rescue ALPPS should be considered on an individual basis if PVE fails to provide targeted liver volume. ALPPS would be contraindicated in the presence of unresectable tumor in the FLR, unresectable extra-hepatic disease, severe portal hypertension, existing PVT or patients with poor performance status.

Conclusion

Bridge to surgery strategies should be prioritized for all initially unresectable tumors. All methods mentioned above offer a chance for secondary resectability for initially inoperable liver tumors. It must be kept in mind that optimal patient selection must occur at an individual level regarding patient and tumor characteristics and it is important to have these procedures performed at highly specialized and experienced centers in order to minimize morbidity.

Author's Contributions

Concept and design: YT. Data collection and manuscript preparation: OA, OO, YT.
Critical editing: OA, OO, YT
Final approval of the manuscript: OA, OO, YT

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