Transarterial Chemoembolization and Radioembolization across Barcelona Clinic Liver Cancer Stages

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Abstract

Keywords

- interventional oncology
- transarterial chemoembolization
- radioembolization

Transarterial chemoembolization (TACE) is a well-established treatment for hepatocellular carcinoma (HCC). TACE has a clearly delineated role within the Barcelona Clinic Liver Cancer (BCLC) staging framework, and TACE has been shown to bridge patients to transplantation and to downsize patients' tumor burden to meet transplantation criteria. Radioembolization (RE) also has an evolving role in the treatment of HCC. RE has evidence-based applications across the range of BCLC stages ranging from segmentectomy for patients with solitary lesions not amenable to ablation to lobar therapy for patients with multifocal HCC, and to treatment of advanced disease with portal vein thrombosis. This article aims to elucidate the evidence behind these therapies and to provide a rationale for their utilization across the spectrum of BCLC stages in the treatment of HCC.

Objectives: Upon completion of this article, the reader will be able to describe the indications for transarterial chemoembolization and radioembolization across the spectrum of Barcelona Clinic Liver Cancer stages.

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Currently, liver cancer is the second most frequent cause of cancer death among men worldwide and the sixth most frequent cause of cancer death among women worldwide with hepatocellular carcinoma (HCC) accounting for 70 to

85% of all liver cancers. The Barcelona Clinic Liver Cancer (BCLC) staging framework is a well-established algorithm for management of HCC.^{1,2} BCLC stage accounts for patient liver function, patient performance status, as well as extent of disease and provides guidelines for treatment depending on a composite of these factors. Transarterial chemoembolization (TACE) is recommended in the treatment of BCLC intermediate-stage patients—such as those patients with preserved performance status, Child-Pugh A or B liver function, and multinodular tumor burden. There is currently no specific recommendation for radioembolization (RE) in the BCLC staging guidelines. However, the BCLC stages provide a well-known framework for conceptualizing the clinical indications for RE and the evidence behind its utilization.

TACE was first described in the late 1970s for treatment of unresectable HCC by Yamada et al.³ It was described as a treatment option for unresectable HCC due to the tumor's predominant vascular supply from the hepatic arteries rather than the portal venous system. Following arteriography and identification of tumor feeding vessels, an emulsification of lipiodol and chemotherapy agents (cisplatin,

Adriamycin, and mitomycin-C) were administered followed by various embolization agents (e.g., Gelfoam and particles).³ In subsequent decades, TACE has become a common treatment for patients with intermediate BCLC stage HCC.

Generally, RE is a minimally embolic therapy allowing delivery of radiation doses greater than those achievable by external beam radiation to a liver mass. RE is accomplished by intra-arterial infusion of yttrium-90, a β -emitter with a half-life of approximately 64 hours, incorporated into resin or glass microspheres. Since the 1990s, yttrium-90 glass microspheres have been approved by the Food and Drug Administration (FDA) as neoadjuvant therapy prior to surgery or transplantation in patients with unresectable HCC. Resin-based yttrium-90 has been approved since the early 2000s for the treatment of unresectable metastatic colorectal cancer liver tumors.

Barcelona Clinic Liver Cancer Early Stage (A)

Patients designated BCLC A have preserved performance status (Eastern Cooperative Oncology Group [ECOG] 0), Child-Pugh A or B liver function, and either three or fewer HCC nodules all less than 3 cm or a solitary HCC without extrahepatic disease, and portal vein invasion. According to BCLC guidelines, these patients should be managed with transplantation, resection, or ablation. The choice of a therapeutic modality in these cases is dependent on assessment of portal pressure, bilirubin, and comorbid conditions.

TACE in BCLC Early Stage

Multiple studies have established the safety and efficacy of conventional TACE (c-TACE) performed as an adjunct therapy for ablation for this patient population.^{4–6} C-TACE is performed with contrast material, chemotherapeutic agent(s), and lipiodol, which stains the tumor allowing for improved visualization of the target lesion at the time of ablation, followed by an embolic agent. TACE with ablation has been shown to decrease long-term local tumor progression rates for BCLC stage A patients versus TACE alone, RFA alone, or transcatheter arterial embolization (TAE).^{4,6} Although curative treatment such as resection is the gold standard for the BCLC A patient population, when compared with TACE with RFA for patients who were not appropriate surgical candidates (e.g., inadequate functional reserve and small future liver remnant volume) or who did not prefer surgery, there was no difference in overall survival or tumor recurrence for patients with a solitary 2- to 5-cm HCC.⁵ The embolic aspect of c-TACE as well as drug-eluting bead TACE (DEB-TACE) alters tumor perfusion and may potentiate the effect of ablative therapy.⁷ The decreased systemic doxorubicin toxicity from DEB-TACE versus c-TACE is responsible for a significant reduction in liver toxicity and drug-related adverse effects between these modalities.^{7,8} Currently, however, no prospective studies have reported a significant difference in clinical efficacy between c-TACE and DEB-TACE.⁹

Although TACE is a well-established therapy for intermediate-stage BCLC, Burrel et al described the concept of “treatment stage migration”—the notion that all stages of

HCC require individually tailored treatment. For example, some patients with early-stage BCLC are ineligible for thermal ablation and may benefit from DEB-TACE.¹⁰ Burrel et al also demonstrated a median overall survival of 54.2 months in BCLC A patients treated with subselective DEB-TACE.¹⁰

Lastly, TACE has been utilized to maintain—or “bridge”—patients already within Milan criteria to liver transplantation.^{11,12} With the advent of the United Network for Organ Sharing (UNOS)-revised staging criteria in October 2015, for new HCC exception applications, candidates must be registered at calculated Model for End-stage Liver Disease (MELD) score for their first 3 months and for their first 3-month extension as well. At 6 months, the candidates then will receive a MELD score of 28; this essentially requires a 6-month waiting period for all HCC transplantation candidates.¹³ Given this waiting period for all new HCC transplantation candidates, locoregional therapies have an important role in maintaining patients within transplantation criteria.

RE in BCLC Early Stage

For patients with BCLC A disease and tumors not amenable to ablation, there is evidence supporting the use of RE to perform a “segmentectomy” in these cases. Close proximity of a tumor to vital structures such as the diaphragm, the porta hepatis structures, the inferior vena cava, or the gallbladder may increase the risks of percutaneous ablation. In these instances, patients may be offered segmental infusion of lobar-dosed RE. The term “RE segmentectomy” is a reference to surgical segmentectomy, as patients receiving radiation doses calculated for lobar infusion concentrated within a segmental vessel often demonstrate near-complete atrophy of the treated segment on follow-up imaging.

RE segmentectomy is complimentary to ablation in that RE provides a treatment option for BCLC A patients with an anatomically difficult to ablate lesion. Proximity to the diaphragm is the most commonly cited reason that ablation cannot be performed in a BCLC A lesion.¹⁴ Additional literature supports the safety and efficacy of RE segmentectomy in patients with moderate hepatic dysfunction and with advanced disease including portal vein invasion.¹⁵

The largest RE segmentectomy series showed that the technique achieved an objective response in 86% of patients with complete response in 47% of patients by modified Response Evaluation Criteria for Solid Tumors (mRECIST) standards. Median time to disease progression in this series was 33.1 months with new intrahepatic lesions responsible for disease progression in a majority of cases.¹⁶

Median overall survival for patients undergoing RE segmentectomy has been reported between 13.6 and 53.4 months^{14,16} with the variability likely related to the duration of these studies and the introduction of sorafenib in 2007. As RE segmentectomy is a complimentary therapy to ablation, comparison to overall survival in ablation studies is warranted. Vouche et al argued that overall survival and local control of tumor lesions in cases of RE segmentectomy are similar to overall survival seen in ablation cases following patient stratification by measure of baseline liver dysfunction.^{16–20} While controversies exist regarding the limitations

of percutaneous ablation, RE segmentectomy remains a treatment option for anatomically challenging lesions with the potential for complete pathological necrosis of the target tumor.^{21,22}

As previously discussed, the revised UNOS staging criteria now requires a 6-month waiting period for most HCC patients before undergoing liver transplantation. Just as TACE has been proven to be an effective means for bridging patients to transplantation, RE has also shown such potential.²³ In their cohort of 20 patients, Tohme et al reported that all 14 patients who initially met Milan criteria were maintained within Milan criteria utilizing RE (►Fig. 1).²³

BCLC Intermediate Stage B

As mentioned in the introduction, patients designated BCLC B have multifocal disease, ECOG performance status 0, are without vascular invasion or extrahepatic spread, and have preserved liver function (Child-Pugh A or B). The current BCLC recommendation calls for these patients to undergo

TACE. Patients with BCLC intermediate-stage disease have an expected median survival of approximately 16 months. The median survival improves to 20 months following treatment with TACE.²

TACE in BCLC Intermediate Stage

TACE remains the recommended and optimal therapy for intermediate-stage patients with unresectable HCC compared with best supportive care.^{24–27} As stated previously, an emulsification of lipiodol and chemotherapy agents are injected into tumor feeding vessels with the advantage of direct visualization of tumor staining at the parenchymal level.²⁸ With technological advances in the field of interventional radiology, selection of tumor feeding vessels and confirmation with cone-beam CT has demonstrated improved outcomes and increased overall survival in c-TACE compared with digital subtraction angiography alone.^{29,30}

With variations in technique pertaining to c-TACE and to improve the accuracy of dose delivery to tumor, drug-eluting platforms for embolization were established. The Precision V study, a phase II trial comparing DEB-TACE to c-TACE in intermediate-stage HCC, demonstrated a significant reduction in serious liver toxicity ($p < 0.001$) and a significantly lower rate of doxorubicin-related side effects ($p = 0.0001$) in the DEB-TACE arm with no difference in overall response at 6 months between the two groups. However, patients with Child-Pugh B, ECOG 1, bilobar disease, and recurrent disease showed a significant increase in objective response ($p = 0.038$) in the DEB-TACE arm.⁷

The SPACE study, a phase II trial, investigated the combination of DEB-TACE with sorafenib, a multikinase inhibitor, in BCLC B patients by comparing DEB-TACE to DEB-TACE plus sorafenib. The combination did not improve time to progression in a clinically meaningful manner compared with DEB-TACE alone (►Fig. 2).³¹

In addition to prolonging survival for patients with intermediate-stage disease, TACE has also been shown to successfully downstage patients initially beyond conventional criteria to meet transplantation requirements.^{32–34} Indeed, it has also been shown that patients who are successfully downstaged have overall survival similar to their counterparts who were always within transplantation criteria.³²

RE in BCLC Intermediate Stage

While TACE remains the BCLC recommendation for treatment of intermediate-stage disease, a growing body of evidence supports RE for the treatment of intermediate-stage patients. A comparative analysis between TACE and RE in BCLC B patients demonstrated no significant difference in overall survival, but a significant difference in postembolic syndrome, mainly abdominal pain, as well as Grade 3–4 laboratory toxicities with fewer side effects and toxicities in the RE arm.³⁵ RE also provided a longer time-to-progression in comparative analysis of 13.3 versus 9.4 months in the c-TACE arm, which may have implications for downstaging to transplantation.^{34,35}

Just as TACE has been shown to effectively downstage patients to meet conventional criteria for transplantation, RE

Fig. 1 Radioembolization segmentectomy in the treatment of a solitary hepatocellular carcinoma. (a) Pretreatment axial gadolinium-enhanced arterial phase MR demonstrates a 4-cm segment 4 lesion in close proximity to the heart and pericardium. (b) Posttreatment axial subtracted gadolinium-enhanced arterial phase MR showing complete response according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Fig. 2 DEB-TACE in the treatment of multinodular hepatocellular carcinoma (HCC). (a) Pretreatment axial gadolinium-enhanced arterial phase MR image reveals multiple HCC lesions in segment 6. (b) Intraprocedure subtracted angiogram demonstrates multiple enhancing HCC lesions in the right hepatic lobe. (c) Coronal reformatted intraprocedure contrast-enhanced cone beam CT showing multiple HCC lesions in the right hepatic lobe and several vessels supplying the tumors. (d) Posttreatment gadolinium-enhanced axial arterial phase MR image demonstrates complete response of the segment 6 lesions according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).

is also supported by several studies for downstaging HCC lesions.^{34,36,37} Furthermore, while larger cohort studies are required, there is some evidence to suggest that RE may be more effective at downstaging patients to meet UNOS T2 criteria compared with TACE.³⁴

In addition to downstaging to meet transplantation guidelines, patients with unilobar disease being considered for resection may benefit from RE “lobectomy.” Just as RE segmentectomy draws on the analogous surgical procedure, RE lobectomy causes atrophy in the treated lobe and hypertrophy of the contralateral lobe—the future liver remnant. There is a subset of patients with unilobar, multifocal HCC tumor burden who might be candidates for surgical lobectomy if not for a potentially inadequate future liver remnant. Minimal volumes for a future liver remnant have been described between 20 and 40% of total liver volume with a larger remnant deemed advisable for cirrhotic patients.^{38–41} RE lobectomy, then, offers this subset of patients a threefold benefit—treatment of the right-sided tumor(s), hypertrophy of the contralateral liver lobe through both redirection of portal venous flow and production of cytokines and growth factors, and allowance for a test of time to select for less aggressive tumors.^{36,42,43}

The concept behind RE lobectomy was established in 2008 when Jakobs et al evaluated volumetric changes in the liver

following lobar treatment with RE, and a subanalysis of those patients who received unilateral right lobar treatment demonstrated decreased right lobe volume with simultaneous left lobe hypertrophy.⁴⁴ Later, Vouche et al showed in their series of 83 patients that RE preceded definitive therapy with lobar resection or transplantation in 11 cases. Vouche et al also established that volumetric changes are apparent as early as 1 month after RE with maximum future liver remnant hypertrophy achieved at 9 months posttreatment.⁴⁰

BCLC Advanced Stage (C)

Patients with BCLC advanced-stage disease are characterized by vascular invasion and/or extrahepatic spread of tumor. Patients may also be considered BCLC stage C if they have a decline in their performance status (ECOG 1 or 2). The current recommendation for patients with BCLC stage C disease is systemic therapy with sorafenib. There is recent evidence to suggest that locoregional therapies—including TACE and RE—in addition to sorafenib provide a greater survival advantage than sorafenib alone.⁴⁵

Sorafenib, as mentioned earlier, is a tyrosine kinase inhibitor responsible for blocking the activity of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor to inhibit tumor angiogenesis and

tumor cell proliferation. TACE has been found to increase the expression of VEGFR following hypoxic injury of tumor cells, which has correlated with an increase in tumor recurrence.^{46,47} This correlation may be secondary to the overall tumor burden in these patients, but the combination of inhibition of VEGFR by sorafenib and TACE may provide additional benefits in the use of both therapies simultaneously.⁴⁷

The combination of systemic sorafenib and DEB-TACE has shown safety and increased efficacy in multiple studies, despite TACE typically being reserved for less advanced stages of HCC.^{47,48} The SHARP trial has demonstrated that sorafenib prolongs time to progression and improves median overall survival irrespective of baseline tumor burden, performance status, tumor stage, and prior therapy.^{49,50} The addition of sorafenib to TACE shows an additional effect in delaying tumor progression, although a survival benefit has not been reproduced in all studies.³¹

TACE in the setting of portal vein thrombus (PVT) remains controversial without strong evidence to support its utilization. There are, however, several studies that demonstrate improved survival in selected populations.⁵¹

RE in BCLC Advanced Stage

Employing TACE in the subset of patients with PVT carries the additional, theoretical risk of necrosis, as the dual blood

supply of the liver suffers two insults—limited portal flow secondary to PVT as well as iatrogenic limitation of hepatic arterial flow. While the safety of TACE performed in patients with PVT has been shown in several studies,^{52–54} RE is a minimally embolic therapy that further diminishes this risk of hepatic infarction. The minimally embolic effect of RE has been clinically established with a low incidence of postembolic syndrome following RE.^{55,56}

An early study regarding the use of RE for the treatment of HCC with portal vein invasion demonstrated that patients with branch/lobar PVT who underwent glass microsphere RE experienced improved survival compared to those with main PVT as well as compared with other studies of HCC treated with supportive therapy, TACE, and intra-arterial chemotherapy administration. This study also showed that adverse events such as bilirubin toxicity and development of ascites were more likely in patients with main PVT.⁵⁵ A later study showed that the location of PVT was of even greater importance for patients with better-preserved liver function. For patients with Child-Pugh A liver disease, lobar PVT was associated with improved overall survival compared with main PVT. This difference was not observed in Child-Pugh B patients; in this subset of patients, the authors argued that survival was driven by liver function more so than distribution of PVT.⁵⁷

Fig. 3 Radioembolization in the treatment of portal venous invasion. (a) Pretreatment axial gadolinium-enhanced arterial phase image demonstrates a segment 8 hepatocellular carcinoma lesion adjacent to the inferior vena cava. (b) Pretreatment axial gadolinium-enhanced portal venous phase image shows right portal vein tumor invasion. (c) Posttreatment axial gadolinium-enhanced arterial phase images reveal a complete response of the target lesion in segment 8 according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) and (d) flow restored to the right portal vein without evidence of residual tumor invasion, respectively.

Resin microsphere RE has also been shown to improve survival in patients with BCLC stage C disease characterized by PVT compared with studies of patients treated with supportive therapy and commensurate with survival times for BCLC stage C patients treated with sorafenib.⁵⁸ However, recent evidence suggests that resin microsphere RE may be associated with increased toxicity and decreased overall survival compared with glass microsphere RE in the setting of branch portal vascular invasion (► Fig. 3).⁵⁹

Conclusion

Currently, TACE is established as the recommended treatment modality for patients with BCLC intermediate-stage HCC. However, there is a large body of literature supporting the utilization of both TACE and RE across BCLC stages. TACE is beneficial as an adjunct to ablation in BCLC A patients, is well established in the treatment of BCLC B patients, and has (as some studies have shown) survival benefits for BCLC C patients. RE is beneficial in the treatment of BCLC A patients with lesions not amenable to ablation, has been shown to provide for tumor control as well as future liver remnant hypertrophy in unilobar BCLC B patients, and also may offer survival benefits for BCLC C patients with portal vascular invasion.

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References

- Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;19(03):329–338
- Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010;30(01):61–74
- Yamada R, Kishi K, Sato M, et al. Transcatheter arterial chemoembolization (TACE) in the treatment of unresectable liver cancer. *World J Surg* 1995;19(06):795–800
- Duan X, Zhou G, Han X, et al. Radiofrequency ablation combined with transcatheter therapy in rabbit VX2 liver tumors: effects and histopathological characteristics. *Acta Radiol* 2015;56(01):87–96
- Kim JW, Shin SS, Kim JK, et al. Radiofrequency ablation combined with transcatheter arterial chemoembolization for the treatment of single hepatocellular carcinoma of 2 to 5 cm in diameter: comparison with surgical resection. *Korean J Radiol* 2013;14(04):626–635
- Kim JW, Kim JH, Won HJ, et al. Hepatocellular carcinomas 2–3 cm in diameter: transarterial chemoembolization plus radiofrequency ablation vs. radiofrequency ablation alone. *Eur J Radiol* 2012;81(03):e189–e193
- Lammer J, Malagari K, Vogl T, et al; PRECISION V Investigators. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;33(01):41–52
- Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization of hepatocellular carcinoma with HepaSphere 30–60 µm. Safety and efficacy study. *Cardiovasc Intervent Radiol* 2014;37(01):165–175
- Han K, Kim JH. Transarterial chemoembolization in hepatocellular carcinoma treatment: Barcelona clinic liver cancer staging system. *World J Gastroenterol* 2015;21(36):10327–10335
- Burrell M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolization (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol* 2012;56(06):1330–1335
- Bouchard-Fortier A, Lapointe R, Perreault P, Bouchard L, Pomier-Layrargues G. Transcatheter arterial chemoembolization of hepatocellular carcinoma as a bridge to liver transplantation: a retrospective study. *Int J Hepatol* 2011;2011:974514
- Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003;9(06):557–563
- Kulik L. Criteria for liver transplantation in hepatocellular carcinoma. *Clin Liver Dis* 2015;6(04):100–102
- Riaz A, Gates VL, Atassi B, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys* 2011;79(01):163–171
- Padia SA, Kwan SW, Roudsari B, Monsky WL, Covelev A, Harris WP. Superselective yttrium-90 radioembolization for hepatocellular carcinoma yields high response rates with minimal toxicity. *J Vasc Interv Radiol* 2014;25(07):1067–1073
- Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. *Hepatology* 2014;60(01):192–201
- Pompili M, Saviano A, de Matthaeis N, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. *J Hepatol* 2013;59(01):89–97
- Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008;47(01):82–89
- Lencioni R, Della Pina C, Bartolozzi C. Percutaneous image-guided radiofrequency ablation in the therapeutic management of hepatocellular carcinoma. *Abdom Imaging* 2005;30(04):401–408
- Chen MH, Wei Y, Yan K, et al. Treatment strategy to optimize radiofrequency ablation for liver malignancies. *J Vasc Interv Radiol* 2006;17(04):671–683
- Salem R, Vouche M, Habib A, Kim E, Sato KT, Hickey R, Lewandowski R. Reply: To PMID 24691943. *Hepatology* 2015;61(01):407
- Seror O, Nault JC, Nahon P, N'Kontchou G, Trinchet JC. Is segmental transarterial yttrium 90 radiation a curative option for solitary hepatocellular carcinoma ≤5 cm? *Hepatology* 2015;61(01):406–407
- Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. *J Vasc Interv Radiol* 2013;24(11):1632–1638
- Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53(03):1020–1022
- Llovet JM, Real MI, Montaña X, et al; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359(9319):1734–1739
- Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35(05):1164–1171
- Satake M, Uchida H, Arai Y, et al. Transcatheter arterial chemoembolization (TACE) with lipiodol to treat hepatocellular carcinoma:

- survey results from the TACE study group of Japan. *Cardiovasc Intervent Radiol* 2008;31(04):756–761
- 28 Ahmadzadehfard H, Meyer C, Ezziddin S, et al. Hepatic volume changes induced by radioembolization with 90Y resin microspheres. A single-centre study. *Eur J Nucl Med Mol Imaging* 2013; 40(01):80–90
 - 29 Miyayama S, Yamashiro M, Hashimoto M, et al. Comparison of local control in transcatheter arterial chemoembolization of hepatocellular carcinoma ≤ 6 cm with or without intraprocedural monitoring of the embolized area using cone-beam computed tomography. *Cardiovasc Intervent Radiol* 2014;37(02):388–395
 - 30 Iwazawa J, Ohue S, Hashimoto N, Muramoto O, Mitani T. Survival after C-arm CT-assisted chemoembolization of unresectable hepatocellular carcinoma. *Eur J Radiol* 2012;81(12):3985–3992
 - 31 Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol* 2016;64(05):1090–1098
 - 32 Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008;248(04):617–625
 - 33 Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl* 2005;11(12):1505–1514
 - 34 Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant* 2009; 9(08):1920–1928
 - 35 Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011;140(02):497–507.e2
 - 36 Iñarrairaegui M, Pardo F, Bilbao JI, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. *Eur J Surg Oncol* 2012;38(07):594–601
 - 37 Kulik LM, Atassi B, van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006;94(07):572–586
 - 38 Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997;26(05):1176–1181
 - 39 Shindoh J, Tzeng CW, Aloia TA, et al. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol* 2013;20(08): 2493–2500
 - 40 Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J Hepatol* 2013;59(05):1029–1036
 - 41 Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007;94(03):274–286
 - 42 Salem R, Mazzaferro V, Sangro B. Yttrium 90 radioembolization for the treatment of hepatocellular carcinoma: biological lessons, current challenges, and clinical perspectives. *Hepatology* 2013; 58(06):2188–2197
 - 43 Gaba RC, Lewandowski RJ, Kulik LM, et al. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. *Ann Surg Oncol* 2009;16(06): 1587–1596
 - 44 Jakobs TF, Saleem S, Atassi B, et al. Fibrosis, portal hypertension, and hepatic volume changes induced by intra-arterial radiotherapy with 90yttrium microspheres. *Dig Dis Sci* 2008;53(09):2556–2563
 - 45 Sarpel U, Spivack JH, Berger Y, et al. The effect of locoregional therapies in patients with advanced hepatocellular carcinoma treated with sorafenib. *HPB (Oxford)* 2016;18(05):411–418
 - 46 Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. *World J Gastroenterol* 2004;10(19):2878–2882
 - 47 Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. *J Clin Oncol* 2011;29(30):3960–3967
 - 48 Weintraub JL, Salem R. Treatment of hepatocellular carcinoma combining sorafenib and transarterial locoregional therapy: state of the science. *J Vasc Interv Radiol* 2013;24(08):1123–1134
 - 49 Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012;57(04):821–829
 - 50 Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359(04):378–390
 - 51 Chern MC, Chuang VP, Liang CT, Lin ZH, Kuo TM. Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma with portal vein invasion: safety, efficacy, and prognostic factors. *J Vasc Interv Radiol* 2014;25(01):32–40
 - 52 Luo J, Guo RP, Lai EC, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. *Ann Surg Oncol* 2011;18(02):413–420
 - 53 Lee HS, Kim JS, Choi JJ, Chung JW, Park JH, Kim CY. The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. *Cancer* 1997; 79(11):2087–2094
 - 54 Georgiades CS, Hong K, D'Angelo M, Geschwind JF. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol* 2005;16(12):1653–1659
 - 55 Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008;47(01):71–81
 - 56 Sato K, Lewandowski RJ, Bui JT, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. *Cardiovasc Intervent Radiol* 2006;29(04):522–529
 - 57 Memon K, Kulik L, Lewandowski RJ, et al. Radioembolization for hepatocellular carcinoma with portal vein thrombosis: impact of liver function on systemic treatment options at disease progression. *J Hepatol* 2013;58(01):73–80
 - 58 Sangro B, Salem R, Kennedy A, Coldwell D, Wasan H. Radioembolization for hepatocellular carcinoma: a review of the evidence and treatment recommendations. *Am J Clin Oncol* 2011; 34(04):422–431
 - 59 Biederman DM, Titano JJ, Tabori NE, et al. Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: resin versus glass microspheres. *J Vasc Interv Radiol* 2016;27(06):812–821.e2