Yttrium-90 Radioembolization for Metastatic Colorectal Cancer: Outcomes by Number of Lines of Therapy

Andrew Marsala, MD¹ Edward W. Lee, MD, PhD¹ Siddharth A. Padia, MD¹

¹Division of Interventional Radiology, Department of Radiology, David Geffen School of Medicine at University of California, Los Angeles, California

Semin Intervent Radiol 2017;34:116–120.

Address for correspondence Siddharth A. Padia, MD, Division of Interventional Radiology, Department of Radiology, David Geffen School of Medicine at University of California, Los Angeles, 757 Westwood Plaza, Room 2125, Los Angeles, CA 90095 (e-mail: spadia@mednet.ucla.edu).

Abstract

Keywords

- colorectal cancer
- interventional radiology
- radioembolization
- chemotherapy
- transarterial therapy

Metastatic colorectal cancer represents the most common liver malignancy, and imparts a very poor prognosis for those who develop this disease. Unlike primary liver tumors such as hepatocellular carcinoma, which largely develops in patients with underlying cirrhosis, most metastatic liver tumor patients have normal underlying liver function. Owing to this, most will succumb to tumoral replacement of the liver rather than from underlying liver dysfunction. Radioembolization represents a treatment modality that can be used in multiple fashions to treat one or both lobes of the liver. Techniques depend on whether the procedure is used as first-line, second/third-line, or as salvage therapy. Outcomes and complications of radioembolization are presented in this article, as well as background information on colorectal cancer and systemic therapies.

Objectives: Upon completion of this article, the reader will be able to discuss the role of radioembolization in patients with colorectal cancer metastatic to the liver, including the indications for treatment, outcomes, and complications associated with the treatment.

Accreditation: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

Credit: Tufts University School of Medicine designates this journal-based CME activity for a maximum of **1 AMA PRA Category 1 Credit™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Radioembolization is an effective locoregional therapy used to treat liver metastases from colorectal cancer. Data of varied robustness support its use potentially across all lines of

chemotherapy. How to best integrate radioembolization into the treatment paradigm remains the subject of ongoing research. The benefits of radioembolization are well established in the salvage therapy population and guidelines published in 2016 by the European Society for Medical Oncology (ESMO) recommend consideration of radioembolization in this setting.¹ This review will discuss current standard-of-care treatment options for patients with metastatic colorectal cancer (mCRC) and the studies supporting the integration of radioembolization into various lines of chemotherapy.

Background: Colorectal Cancer and Systemic Therapy

Colorectal cancer is the fourth leading cause of cancer-related death in the United States. Approximately 134,490 new cases are diagnosed each year and up to 60% will develop liver metastases.^{2,3} Among patients with liver metastases, only 10 to 20% are resectable for a cure.⁴ The majority of remaining candidates undergo treatment with systemic chemotherapy, with the goal of tumor control to prolong

survival. While advances in chemotherapy and the addition of biologic agents have extended survival and may even increase the number of patients eligible for resection, chemorefractory liver metastases remain a life-limiting factor for most patients.⁵⁻⁸

Combination cytotoxic chemotherapy represents the current standard of care in the treatment of unresectable mCRC. A full discussion of all the chemotherapeutic regimens is beyond the scope of this document, but can be found in both the National Comprehensive Cancer Network (NCCN) and ESMO treatment guidelines for colorectal cancer.^{1,9} The most commonly used first-line systemic regimen is the combination of a fluoropyrimidine (intravenous 5-fluorouracil with leucovorin) and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Both regimens have been shown to have comparable survival times.¹⁰ Bevacizumab, a vascular endothelial growth factor A–targeting monoclonal antibody, is often added to these regimens.¹¹

Patients inevitably fail their initial chemotherapy regimen due to either tumor progression or intolerance to the medications. For second-line therapy, patients frequently switch to the other combined regimen (e.g., FOLFOX to FOLFIRI).¹⁰ Bevacizumab has also been studied in the second-line setting and shown to have benefit, although the results are less dramatic when compared with its use in the first-line setting.¹² Since individual agents are often added or subtracted to these regimens due to the desire to achieve higher efficacy or reduce toxicity, the definition of “lines of chemotherapy” is often blurred.¹³ For example, after an initial “induction” chemotherapy regimen of FOLFOX with bevacizumab, one may choose to change to a long-term maintenance regimen of an oral fluoropyrimidine (e.g., capecitabine) with bevacizumab (CAPOX).^{14,15} Furthermore, many patients may go on chemotherapy “holidays” due to long-standing toxicity, and may eventually resume their prior regimen.

Beyond second-line therapy, defined regimens become harder to define and therapy often centers on receptor types identified at biopsy. In patients who have a KRAS wild-type genetic profile, cetuximab and panitumumab, chimeric anti-EGFR antibodies have demonstrated improved response rates and progression-free survival when used in the second-line setting.^{16,17} It has also been shown to give an overall survival benefit over best supportive care in the chemorefractory patient population.¹⁸

BRAF mutations occur in 5% of patients with mCRC, and its presence confers an aggressive subtype of tumor biology. This mutation is typically associated with early chemotherapy resistance and inferior overall survival.¹⁹ As a result, many medical oncologists will consider a highly aggressive first-line regimen, such as combining oxaliplatin, irinotecan, and bevacizumab (FOLFOXIRI plus bevacizumab).²⁰ Similar to patients with KRAS mutant profiles, the benefit of anti-EGFR therapy (e.g., cetuximab, panitumumab) is limited.

In chemorefractory disease, several third-line agents can be considered, including cetuximab or panitumumab alone or in combination with irinotecan. Also approved for use in this setting is regorafenib, a multikinase small-molecule inhibitor. In chemorefractory disease, both of these agents demonstrated minimal improvement in survival, albeit with

significant rates of toxicity.^{21,22} The choice of regimen depends on several factors, such as efficacy and toxicity, previous treatment received, and tumor genetics.

Other biologic agents include ramucirumab, a human monoclonal antibody to the extracellular domain of VEGFR-2, and ziv-aflibercept, a recombinant fusion protein that inhibits VEGF. When used as a part of second-line therapy, ziv-aflibercept demonstrated modest improvements in survival.²³ However, significant toxicities associated with ziv-aflibercept have limited its use.

Radioembolization in the First-Line Setting

Several studies have been conducted and several are underway to determine where radioembolization best fits in the treatment algorithm of liver-dominant mCRC. Longer survival times from the first radioembolization treatment are expectedly observed when it is used early in the course of a patient's disease.^{24,25} However, when survival is calculated from the diagnosis of the primary tumor or from the diagnosis of hepatic metastases, a statistically significant difference has not been demonstrated when radioembolization is used early (two or less prior cytotoxic chemotherapy agents) versus later (three or more prior cytotoxic chemotherapy agents) in the course of disease.²⁴ A randomized phase II trial comparing first-line 5-fluorouracil/leucovorin plus radioembolization to 5-fluorouracil/leucovorin alone in 21 patients yielded positive results. Patients were stratified by the presence or absence of extrahepatic metastatic disease and the degree of liver involvement (<25% or >25%). Compared with chemotherapy alone, the 5-fluorouracil/leucovorin plus radioembolization group demonstrated significantly improved response rate (73% best objective response vs. 0%, $p < 0.001$), increased time to progression (18.6 vs. 2.6 months, $p < 0.0005$), increased overall survival (29.4 vs. 12.8 months, $p = 0.02$), and improved health-related quality of life compared with baseline.²⁶ However, since the publication of these pivotal trials, the addition of oxaliplatin or irinotecan to standard first-line systemic chemotherapy has significantly improved outcomes for chemotherapy-naïve patients. A subsequent single-arm phase I trial demonstrated an objective response rate of 90% and confirmed the safety of radioembolization administered as a part of an oxaliplatin-based chemotherapy regimen.²⁷

SIRFLOX, the first large-scale randomized phase III trial integrating radioembolization with first-line chemotherapy, compared the more modern FOLFOX-based regimen (plus or minus bevacizumab) to FOLFOX plus radioembolization.²⁸ A total of 530 patients were enrolled at 87 institutions with progression-free survival as the primary endpoint. Treatment with FOLFOX plus radioembolization significantly delayed disease progression in the liver (20.5 vs. 12.6 months, $p = 0.002$) but failed to improve overall progression-free survival compared with treatment with FOLFOX alone (10.7 vs. 10.2 months, $p = 0.43$). Given that radioembolization is a targeted locoregional therapy, Sangha et al postulated that failure to reach the primary endpoint may be related to extrahepatic metastatic disease that was present in 40% of patients enrolled.²⁹ Overall survival, a secondary endpoint

of the SIRFLOX trial, will be analyzed in combination with the FOXFIRE and FOXFIRE global trials currently underway. It should also be noted that toxicities were increased in the radioembolization group (grade ≥ 3 : 85 vs. 73%). In the radioembolization group, higher rates of neutropenia, thrombocytopenia, fatigue, and abdominal pain were noted. Gastric or duodenal ulcers occurred in 3.7% and hepatic failure or radiation hepatitis occurred in 2% of patients. Significant toxicities from radioembolization may preclude patients from receiving adequate systemic agents in the future, which may ultimately limit their overall survival.

Radioembolization in Second/Third-Line Therapy

Phase I trial data also support the use of radioembolization with second- and third-line chemotherapy regimens. Irinotecan plus radioembolization yielded an overall response rate of 48% and a disease control rate of 87% in patients who had failed prior 5-FU chemotherapy. One-third of patients had failed at least two lines of chemotherapy and almost two-thirds had failed oxaliplatin-based regimens. Median progression-free survival was 9.2 months in the liver and 12.2 months overall.³⁰ A randomized, prospective trial of radioembolization in patients who have failed first-line systemic chemotherapy is currently underway.

Radioembolization for Salvage Therapy

The vast majority of studies assessing the benefit of radioembolization for mCRC are in the salvage setting. Of course, the strict definition of “salvage” is not mutually agreed upon. But most studies consider “salvage” patients as those who have failed multiple lines of chemotherapy, are ineligible for other therapies, and continue to have progressive disease by imaging.⁵ Favorable prognostic factors in this population include an acceptable performance status (i.e., Eastern Cooperative Oncology Group (ECOG) 0, lower tumor burden, and the absence of extrahepatic disease.^{25,31}

A prospective, multicenter, randomized trial compared fluorouracil alone to fluorouracil plus radioembolization in the salvage setting.³² A total of 44 patients were included in the analysis, and radioembolization demonstrated superior progression-free survival (4.5 vs. 2.1 months, $p = 0.03$) and a trend toward improved overall survival (10.0 vs. 7.3 months, $p = 0.80$). Despite performing radioembolization in the salvage setting where patients had already been exposed to numerous lines of chemotherapy, radioembolization was well tolerated, and significant toxicities were lower than that in the control group.

In a comparative retrospective study of 339 patients with chemorefractory malignancies metastatic to the liver treated with radioembolization, a cohort of 224 patients with mCRC was subselected.⁶ The patients were primarily ECOG 0 (85%) and without extrahepatic disease (62%). Eighty-seven percent of patients had bilobar disease, though less than 25% of the liver was involved in most patients. After a single round of radioembolization, these patients were compared with a

smaller cohort who also had been referred for radioembolization but considered unsuitable due to variant arterial anatomy not correctable by prophylactic coil embolization, degree of hepatopulmonary shunting, refusal to consent, or having chosen another treatment option (e.g., a biologic agent). Median overall survival in the radioembolization cohort was 11.9 months, compared with 6.6 months in the supportive care cohort ($p = 0.001$). The ulceration rate in the treated population in this study was 3.2%, which may in part be due to some cases with poor arterial flow from multiple lines of systemic chemotherapy.

Similar results were described in a retrospective matched-pair comparison of radioembolization plus best supportive versus best supportive care alone.⁵ Following initial matching for prior treatment history and tumor burden, 29 matching pairs were identified based on percentage of liver involved, synchronous versus metachronous metastases, stable versus increasing alkaline phosphatase, and a carcinoembryonic antigen (CEA) greater than or less than 200 ng/mL. Sixteen (55.2%) matched all four criteria, 11 (37.9%) matched three criteria, and 2 pairs (6.9%) matched two criteria. Approximately 50% of all patients had extrahepatic disease, which, to undergo radioembolization, needed to be stable. Overall survival was significantly longer for the treatment group (8.3 vs. 3.5 months, $p < 0.001$). This was apparent at just 3 months at which time 97% of the treatment group was alive versus just 59% of the best supportive care (BSC)-only group. At 12 months, 24% of the treatment group was alive versus 0% of the BSC-only group. Univariate analysis determined that radioembolization and performance status significantly reduced the risk of death. Multivariate analysis determined that radioembolization predicted significantly prolonged survival and extent of liver involvement was associated with a significantly increased risk of death. Of note, almost one-third of patients who underwent radioembolization were later able to receive chemotherapy.

Radioembolization-induced liver disease (REILD) is an uncommon outcome after radioembolization, characterized by clinical onset of hepatic dysfunction, fatigue, and ascites, in the absence of tumor progression. While in some cases REILD can be reversible, in others this can progress to liver failure and death. Studies have shown that multiple lines of chemotherapy increase the risk of REILD.³³ Therefore, in the salvage setting after patients have been exposed to numerous chemotherapy agents, the risk of REILD is perhaps greater compared with a scenario where radioembolization is done earlier in the course of disease (—Fig. 1).

Interactions with Systemic Agents

Care must be taken when combining radioembolization with systemic agents to minimize toxicity and potentially maximize efficacy. For mCRC, recent exposure to biologic agents, especially bevacizumab, can result in significant vascular compromise. This manifests as small caliber hepatic arteries, poor hepatic arterial flow, or frequent spasm and dissection after catheterization (—Fig. 2).³⁴ In general, it is advisable to

Fig. 1 Radioembolization-induced liver disease. A 55-year-old woman with metastatic colorectal cancer had progressed after numerous lines of chemotherapy (a). Two months after radioembolization, she developed ascites, fatigue, and liver dysfunction (b).

hold bevacizumab for at least 4 to 6 weeks before mapping angiography.³⁵

Oxaliplatin, often used in first- and second-line systemic regimens, is a radiosensitizer which can potentiate the effects of radioembolization. In a phase I dose-escalation study of oxaliplatin when combined with radioembolization, grade 3 and 4 toxicities were observed at significant levels at the highest doses of oxaliplatin.²⁷ Based on this study, the authors advised a maximum oxaliplatin dose of 60 mg/m² when patients are treated with radioembolization.

Irinotecan, which is often used in first- and second-line regimens, has a known synergistic effect with external beam radiation in patients with lung cancer.³⁶ Van Hazel et al tested maximum tolerated dose of irinotecan when combined with radioembolization in a dose-escalation phase I study.³⁰ In this study of 25 patients, the maximum tolerated dose of irinotecan was not reached using resin microspheres

with body surface area dosimetry, and therefore the dose of irinotecan of 100 mg/m² was recommended.

Conclusion

Numerous studies have demonstrated the utility of radioembolization for patients with mCRC at various stages. Despite these results, there is currently no conclusive evidence for the use of radioembolization in combination with modern-day first-line chemotherapy in prolonging overall survival. The vast majority of evidence continues to support the use of radioembolization in the salvage setting, and promising results have been shown when used earlier in the course of patients' disease. Knowledge of patients' recent systemic agent exposure will help the interventionalist to minimize toxicity and potentially improve outcomes.

References

- 1 Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27(08):1386–1422
- 2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66(01):7–30
- 3 Sasson AR, Sigurdson ER. Surgical treatment of liver metastases. *Semin Oncol* 2002;29(02):107–118
- 4 Khatri VP, Chee KG, Petrelli NJ. Modern multimodality approach to hepatic colorectal metastases: solutions and controversies. *Surg Oncol* 2007;16(01):71–83
- 5 Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol* 2012;35(05):1066–1073
- 6 Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. *J Vasc Interv Radiol* 2012;23(01):96–105
- 7 Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005;23(36):9243–9249

Fig. 2 Effect of biologic agents on arterial vasculature. A 61-year-old woman with metastatic colorectal cancer underwent mapping angiogram for planned radioembolization, 3 weeks after her most recent dose of bevacizumab. The hepatic arterial branches are markedly diminutive in caliber with poor antegrade flow. A repeat angiogram (not shown) 3 weeks later showed normal caliber vessels, which were conducive to safe ⁹⁰Y microsphere delivery.

- 8 Nordlinger B, Sorbye H, Glimelius B, et al; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebertumoren und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;371(9617):1007–1016
- 9 Benson AB III, Venook AP, Bekaii-Saab T, et al; National Comprehensive Cancer Network. Colon cancer, version 3.2014. *J Natl Compr Canc Netw* 2014;12(07):1028–1059
- 10 Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22(02):229–237
- 11 Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350(23):2335–2342
- 12 Giantonio BJ, Catalano PJ, Meropol NJ, et al; Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25(12):1539–1544
- 13 Goldberg RM, Rothenberg ML, Van Cutsem E, et al. The continuum of care: a paradigm for the management of metastatic colorectal cancer. *Oncologist* 2007;12(01):38–50
- 14 Hegewisch-Becker S, Graeven U, Lerchenmüller CA, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 2015;16(13):1355–1369
- 15 Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet* 2015;385(9980):1843–1852
- 16 Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28(31):4706–4713
- 17 Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26(14):2311–2319
- 18 Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359(17):1757–1765
- 19 Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. *N Engl J Med* 2009;361(01):98–99
- 20 Loupakis F, Cremolini C, Salvatore L, et al. FOLFOXIRI plus bevacizumab as first-line treatment in BRAF mutant metastatic colorectal cancer. *Eur J Cancer* 2014;50(01):57–63
- 21 Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381(9863):303–312
- 22 Mayer RJ, Van Cutsem E, Falcone A, et al; RECURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372(20):1909–1919
- 23 Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012;30(28):3499–3506
- 24 Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging* 2014;41(10):1861–1869
- 25 Hickey R, Lewandowski RJ, Prudhomme T, et al. 90Y radioembolization of colorectal hepatic metastases using glass microspheres: safety and survival outcomes from a 531-patient multicenter study. *J Nucl Med* 2016;57(05):665–671
- 26 Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol* 2004;88(02):78–85
- 27 Sharma RA, Van Hazel GA, Morgan B, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 2007;25(09):1099–1106
- 28 van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol* 2016;34(15):1723–1731
- 29 Sangha BS, Nimeiri H, Hickey R, Salem R, Lewandowski RJ. Radioembolization as a treatment strategy for metastatic colorectal cancer to the liver: what can we learn from the SIRFLOX trial? *Curr Treat Options Oncol* 2016;17(06):26
- 30 van Hazel GA, Pavlakakis N, Goldstein D, et al. Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. *J Clin Oncol* 2009;27(25):4089–4095
- 31 Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer* 2009;115(09):1849–1858
- 32 Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol* 2010;28(23):3687–3694
- 33 Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, et al. Prognostic factors and prevention of radioembolization-induced liver disease. *Hepatology* 2013;57(03):1078–1087
- 34 Pieper CC, Willinek WA, Thomas D, et al. Incidence and risk factors of early arterial blood flow stasis during first radioembolization of primary and secondary liver malignancy using resin microspheres: an initial single-center analysis. *Eur Radiol* 2016;26(08):2779–2789
- 35 Padia SA, Lewandowski RJ, Johnson GE, et al; Society of Interventional Radiology Standards of Practice Committee. Radioembolization of hepatic malignancies: background, quality improvement guidelines, and future directions. *J Vasc Interv Radiol* 2017;28(01):1–15
- 36 Tamura K, Takada M, Kawase I, et al. Enhancement of tumor radio-response by irinotecan in human lung tumor xenografts. *Jpn J Cancer Res* 1997;88(02):218–223