Angiogenesis in ^{90}Y-Radioembolization of Colorectal Liver Metastases

Ahmed A. Alsultan, MD,* Maarten W. Barentsz, MD, PhD,* Maarten L.J. Smits, MD, PhD,*
Miriam Koopman, MD, PhD,† Marnix G.E.H. Lam, MD, PhD,* and
Charlotte E.N.M. Rosenbaum, MD, PhD*

In order to evaluate the role of angiogenesis in ^{90}Y-radioembolization for colorectal cancer liver metastasis an overview was provided of angiogenic growth factors and their function, the angiogenic mechanisms in colorectal cancer, the role of hypoxia, and the advances in antiangiogenic therapy. Last, the use of circulating angiogenic growth factors in ^{90}Y-radioembolization was reviewed. Two literature searches were conducted. A search query in PubMed on angiogenesis in colorectal cancer, and a systematic search in PubMed (Medline), Embase, and the Cochrane Library (October 2018) with synonyms for "radioembolization" and "angiogenic growth factor." The first search yielded 3 relevant publications on the role of angiogenic growth factors in colorectal cancer, hypoxia, and antiangiogenic therapy. The second search yielded two prospective studies on circulating angiogenic factors and their relationship with response and survival after ^{90}Y-radioembolization for colorectal cancer liver metastases. Rises in circulating angiogenic growth factors after radioembolization were seen in both studies. High baseline values of Ang-2 and IL-8 correlated with shorter survival and post ^{90}Y-radiembolization rises in Ang-2 and HGF correlated with early progression. Various angiogenic growth factors play a role in the development and progression of colorectal cancer. Several factors show correlation with poor outcomes after ^{90}Y-radioembolization and might be used for patient selection in the future, however, validation in larger comparative studies is required.
Semin Nucl Med 49:204-210 © 2019 Elsevier Inc. All rights reserved.

Introduction

Colorectal cancer is one of the most common diagnosed cancers in the Western world and is a leading cause of death.[1] Colorectal cancer metastases often spread to the liver and are a major cause of mortality. For patients with metastatic disease, surgical treatment is considered the only curative option, achieving 5-year survival rates of up to 40%.[2] Unfortunately, surgical treatment is often not possible and patients are left with palliative options, mainly consisting of systemic treatment with palliative intent. For patients failing systemic options, radioembolization (RE) should be considered.[3]

RE is a form of internal radiation therapy in which microspheres bearing radioactive isotopes (eg, yttrium-90 (^{90}Y) or holmium-166) are selectively injected into the hepatic arteries, where they embolize blood vessels and emit (primarily) ß-radiation. The duality of the hepatic blood supply allows for the delivery of high radiation doses to the tumor compared to the healthy liver tissue.[4] For the treatment of unresectable and chemorefractory colorectal cancer liver metastases (CRCLM), ^{90}Y-RE has proven to be a well-tolerated treatment with a median overall survival of approximately 12 months in CRCLM-patients.[5] However, response to treatment varies substantially despite seemingly homogeneous patient groups. We cannot predict which patients will respond to treatment due to the lack of predictive factors. However, it has been hypothesized that there might be a relationship between circulating angiogenic growth factors and treatment response after ^{90}Y-RE.[6] Measuring these biomarkers could have predictive value. In this review the role of angiogenesis in colorectal cancer, in relation with ^{90}Y-RE treatment was evaluated. To gain a better understanding of the process of angiogenesis we

*Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands.
†Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands.
Address reprint requests to A.A.N. Alsultan MD, Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht University, Huispost nr. E01.132, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. E-mail: A.A.N.Alsultan@umcutrecht.nl

appraised the most investigated angiogenic growth factors in colorectal cancer, the role of hypoxia, and antiangiogenic therapy. Furthermore, we reviewed the available literature on the use of angiogenic factors as predictive biomarkers in ^{90}Y-RE.

Methods

This review has 2 parts. The first describes the role of angiogenesis in colorectal cancer, its basic principles, and gives an overview on angiogenic growth factors. The second part addresses the role of angiogenic growth factors in ^{90}Y-RE.

Angiogenesis in Colorectal Cancer

In order to provide more insight into the angiogenic processes in colorectal cancer a search was conducted on PubMed. The search query was geared toward finding publications on angiogenesis in colorectal cancer and the prognostic and/or predictive value of angiogenic growth factors in colorectal cancer. Only reviews published in the last 5 years were considered. Screening for the most comprehensive reviews yielded three publications.[7-9] These were used to compile an overview of prominent angiogenic growth factors and their function. Furthermore, the role of hypoxia in cancer development, antiangiogenic treatment, and the value of circulating angiogenic growth factor measurements were reviewed. Only descriptive results were reported.

Angiogenesis in ^{90}Y-Radioembolization

A literature search was constructed to find all publications on the angiogenic growth factor response in relation with ^{90}Y-RE. The search query included synonyms for "Radioembolization" and "Angiogenic growth factor." These were adapted for PubMed (Medline), Embase, and the Cochrane Library. The search was performed in October 2018. Only original publications were selected. Exclusion criteria were: full text not available, review publications, letters to the editor, editorial papers, and case reports. Furthermore, a crosscheck of reference lists from identified publications was performed to identify papers missed by the initial search.

The screening of the 85 results on ^{90}Y-RE yielded three publications. Two studies that mainly included CRCLM patients[6,10] and one study focused on patients with hepatocellular carcinoma (HCC).[11] In this review we focus on CRCLM due to the large differences between the biology of CRCLM and HCC.

From the two studies we extracted data on patient characteristics and treatment details (eg, primary tumor type and the number of previous chemotherapy lines), the measured biochemical factors and their timepoints of measurement, and data on the relationship between angiogenic factors and survival/response. Survival data were described as medians with their 95% confidence interval. Incidence of increases in circulating angiogenic growth factors were described as percentages with corresponding P values.

Angiogenesis in Colorectal Cancer

Angiogenesis is a process in which new blood vessels are formed from pre-existing ones. Since the first description of the role of angiogenesis in tumor progression,[12] our understanding of the complex underlying processes has grown, but much remains unknown. Angiogenesis consists of a series of repeatable steps that ultimately lead to the development of blood supply to the tumor and it is considered to be a rate-limiting factor in cancer development, as it is necessary for tumor growth and metastasis.[7,13-15] The process is coordinated by a balance of inhibiting and activating factors, in which certain events tip the balance toward activation.[16,17]

In colorectal cancer, the first angiogenic activation occurs during the premalignant stages of the disease,[18] significant increases of circulating angiogenic growth factors and a corresponding increase of microvascular density were found at the onset of dysplasia. Angiogenic activation in colorectal cancer occurs mainly in two ways: (1) carcinogenic mutations cause permanent activation in proangiogenic signaling pathways and (2) as an adaptive mechanism to tumor growth induced hypoxia.[7]

Angiogenic Growth Factors

Angiogenic growth factors are naturally occurring molecules that promote proliferation and differentiation of endothelial cells and other cells that support angiogenesis. There are several different growth factor families. The most widely studied growth factors are the vascular endothelial growth factors (VEGF), for which several inhibiting agents have been developed that have been studied as anticancer treatments. Many other growth factors have been identified, not all underlying mechanisms of which are fully understood but it is presumed that these factors stimulate proliferation and migration of endothelial cells, attract cells that are essential to angiogenesis such as pericytes and macrophages, and create provisional matrices for growth of new blood vessels.[13,19] Table 1 provides an overview of several growth factors that have been investigated in colorectal cancer and what is known about their function.

Hypoxia and Angiogenesis

Activation of angiogenesis is closely linked to hypoxia, which is common in many solid tumors. During rapid growth, tumors disrupt the transport of oxygen by compressing and obstructing surrounding blood vessels. Moreover, cells located further away from a capillary vessel will become hypoxic, as the diffusion distance of oxygen is limited to 100-180 μm.[20] Hypoxia stimulates cells to undergo several changes that ensure their survival and thus increase the invasive potential of tumors, eg, inducing angiogenesis, shift toward glycolytic metabolism, gain of apoptosis

Table 1 Overview of Angiogenic Growth Factors in Colorectal Cancer

Growth Factor Family	Known Molecules	Receptors	Function	Role in Colorectal Cancer
VEGFs	VEGF-A, -B, -C, -D, and -E PIGF	TKIs: VEGFR-1, −2, and −3	VEGFR-1 and −2: EC survival, proliferation, and migration.[7,13,15] VEGFR-3: lymphangiogenesis. VEGFR-2, when phosphorylated by VEGF-A, is the most potent mediator of angiogenesis.[9,50] PIGF binds to VEGFR-1 and amplifies the effect of VEGFR-2.[51,52]	Significant VEGF and PIGF overexpression in advanced disease compared to early disease; correlating with disease progression.[53-56]
Angiopoietins	Ang-1 and Ang-2	Tie-2 receptor	The angiopoietins have antagonizing complementary roles. Ang-1 helps stabilize and mature vessels, through phosphorylating the Tie-2 receptor. Ang-2 binds to Tie-1 but does not phosphorylate it, antagonizing Ang-1 and destabilizing vessels.	Overexpression of Ang-2 in colorectal cancer cells.[57]
PDGFs	PDGF -AA, -BB, CC, DD, and -AB	PDGFR-$\alpha\alpha$, -$\beta\beta$, and -$\alpha\beta$	Wound healing and angiogenesis during the embryonic phase. PDGF-BB facilitates pericyte recruitment.	Overexpression of PDGFs and PDGFRs. PDGF-BB overexpression is associated with disease stage.[58-61]
HGF	HGF	Met-receptor	Hepatic regeneration, enhancement of cellular motility and suppression of apoptosis.	In colorectal liver metastasis HGF-Met binding correlates early recurrence CRLM after hepatectomy.[62]
FGFs	FGF-1 through FGF-23	FGFR-1, −2, −3, and −4.	Cell survival, growth, differentiation, and angiogenesis.[63] FGF-2, A.K.A. basic fibroblast growth factor (bFGF), induces a strong angiogenic response through stimulation of VEGF-A expression and modulation of VEGFR-2 function in ECs.[64,65] FGF-2 regulates HGF expression.[66]	Several FGFs as well as FGFRs were found to be overexpressed in colorectal cancer and are thought to promote tumor growth.[67,68]

Ang, angiopoietin; CRLM, colorectal liver metastasis; EC, endothelial cell; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; PDGF, platelet derived growth factor; PDGFR, platelet derived growth factor receptor; PIGF, placenta growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

resistance, and cell migration (toward less hypoxic zones).[21] There are several mechanisms through which these changes take place, the most important of which is the hypoxia inducible factor-1 (HIF-1) pathway.[9,22] HIF-1 is a DNA transcription factor that plays a central role in the cell's response to hypoxia. It consists of two subunits (HIF-1α and HIF-1β) and under normoxic conditions HIF-1α will undergo degradation almost immediately. In hypoxia however, this oxygen dependent degradation does not occur and HIF-1α will accumulate and bind to HIF-1β. Bound together they form an active compound that initiates transcription of more than sixty genes required for cell survival in hypoxic conditions.[23,24]

HIF-1 directly induces angiogenesis via upregulation of (among others): VEGF-A and VEGFR-2, TGF-β3, PDGF-, Ang-1 and Ang-2, and the Tie-2 receptor.[9,21] Furthermore, upregulation of cyclooxygenase-2 enzymes by HIF-1 leads to a rise of prostaglandin E2 which is associated with angiogenesis in colorectal cancer.[7,25,26]

Antiangiogenic Therapy

The initial hypothesis for antiangiogenic treatment was one of tumor starvation: impeding angiogenesis, leading to nutrient and oxygen deprivation, should slow down disease progression and improve survival.[12] However, this theory was soon abandoned as clinical studies with bevacizumab monotherapy—bevacizumab being the first used antiangiogenic agent—did not show any overall survival benefit over placebo.[27] Survival did improve when bevacizumab was combined with cytotoxic chemotherapy. This finding seems paradoxical as the function of chemotherapy relies on tumor perfusion.[27] This might be explained by the concept of vessel normalization, in which VEGF plays an important role. VEGF-inhibitors can restore the balance between anti- and proangiogenic factors. The leaky and abnormal tumor vessels are remodeled into vessels that resemble normal blood vessels, both in form and function. The normalized vessels have a higher pO2, improved pericyte coverage, lower macromolecular permeability, and improved delivery of chemotherapeutic agents.[7,8,27,28]

However, the increased overall survival of chemotherapy combined with VEGF-inhibitors still falls short, since it ranges between weeks to several months, as most tumors eventually develop resistance to anti-VEGF therapy.[27,29-31] The normalized vessels are sensitive to antiangiogenic drug dose and are only stable for a limited time, after which the hypoxia reoccurs and induces HIF-mediated angiogenesis through pathways that are not reliant on VEGF.[7,27] Furthermore, as less adapted cancer cells die due to hypoxia, more resilient and drug-resistant cell lines are "selected" leading to more aggressive tumor cells and disease progression.[8,23] More recent antiangiogenic agents, such as the tyrosine kinase inhibitors, influence multiple angiogenic targets (eg, regorafenib, which targets VEGFR 1-3, PDGFR, and FGFR). Regorafenib demonstrated survival benefit as monotherapy,[32] which supports the HIF-mediated VEGF-resistance theory.

In response to these findings, combining antiangiogenic agents with hypoxia inhibitors would make a promising treatment strategy. Several hypoxia inhibitors have been identified. These reduce the resistance mechanisms to antiangiogenic therapy by targeting the HIF-1 pathway or the mTOR pathway, which promotes angiogenesis through activation of HIF-1.[9] Animal studies with human colon cancer xenografts have shown that the cytotoxic agent irinotecan effectively inhibits angiogenesis.[33] One of these studies reported lower levels of HIF-1α in tumors treated with an irinotecan analogue.[9,34]

Measuring Angiogenic Factors

Angiogenesis is known to be essential to maintain tumor growth and progression. It was hypothesized that measurement of circulating angiogenic growth factors could reflect the degree of angiogenic activation and give insight into disease progression.[35,36]

Many attempts have been made to identify circulating biomarkers with predictive value for response to antiangiogenic treatment. However, due to heterogeneity in the methodology, there are no validated predictive factors for the success of antiangiogenic treatment.[37] VEGF-A and PlGF seem to be promising biomarkers. Early increases in VEGF-A levels after bevacizumab treatment were identified as predictive of poor prognosis in metastatic colorectal cancer patients.[38] Furthermore, a trial studying FOLFIRI $\pm$ aflibercept for metastatic colorectal cancer found that patients previously treated with bevacizumab had significantly higher baseline levels of VEGF-A and PlGF (both $P < 0.0001$); suggesting an association with acquired bevacizumab resistance.[39]

Angiogenesis and ⁹⁰Y-Radioembolization

Two studies on angiogenetic growth factors in ⁹⁰Y-RE have been included in this analysis, an overview of which can be found in Table 2.

In their pilot study, Carpizo et al sought to find a cause of early progression in patients treated with ⁹⁰Y-RE using resin microspheres (SIR-Spheres, Sirtex Medical, Sydney, Australia).[10,40] Based on earlier observations in HCC patients treated with transarterial chemoembolization, they hypothesized that progression might be caused by an upregulation of angiogenic growth factors.[10,41] The prospective pilot study included 15 CRCLM patients who had failed two to five lines of systemic therapy, as well as seven systemic therapy naïve HCC patients. A set of classic (VEGF, Ang-2, bFGF, PDGF-BB, and Tsp-1) and nonclassic angiogenic growth factors (IL-8, Leptin, Follistatin, HGF, and PECAM-1) were measured at baseline, at 6 hours, and at 3, 14, 30, 60, 90, and 120 days after treatment. The median overall survival was 8 months. Overall, 55%-77% of patients showed significant increases ($\geq$50% of baseline) of VEGF, Ang-2, PDGF-BB, and Tsp-1. A significant increase of angiogenesis related cytokines (eg, HGF, Follistatin, and IL-8) was seen in 55%-82%. Patients were stratified in short ($\leq$6 months) and long ($>$6 months) survival groups. Baseline levels of Ang-2 and IL-8 were significantly higher in the short survival group ($P = 0.033$ and 0.041, respectively). Furthermore, transient increases of VEGF, Ang-2, and PDGF-BB levels at various early time points after RE were correlated with shorter overall survival (VEGF at day 14, Ang-2 at 6 hours and 3 days, and PDGF-BB at 3 and 14 days after RE).

Rosenbaum et al included 42 patients treated with ⁹⁰Y-RE (SIR-Spheres) for chemorefractory CRCLM. They investigated the relationship between plasma levels of angiogenic growth factor and response to ⁹⁰Y-RE. The angiogenic growth factors (ie VEGF, Ang-2, bFGF, PDGF-BB, SDF-1a, and Tsp-1) were measured at baseline, directly after treatment through the indwelling femoral sheath, and at 1, 3, 7, and 30 days after treatment. The median overall survival was 9.3 months (95% confidence interval 6.1-12.4). Similar to Carpizo et al, plasma levels of VEGF, HGF, and Ang-2 were increased early after radioembolization. Baseline levels of Ang-2 were significantly higher in patients stratified into a short ($\leq$6 months) overall survival group ($P = 0.048$). In addition, Ang-2 and HGF levels after 3 and 7 days were significantly higher in early nonresponders ($P = 0.01$ and 0.007, respectively).

Discussion

Angiogenesis is a complex process that has been widely studied but remains not fully understood. It is a process that is necessary for tumor progression. Activation of angiogenesis occurs through oncologic mutations or as a response to hypoxia. The use of antiangiogenic agents in cancer treatment is an ongoing subject of research, with emphasis on multitargeted therapeutic approaches. There are several angiogenic growth factors that are promising prognostic biomarkers. However, until this day none have been validated for clinical use.

It is important to recognize that colorectal cancer is a heterogeneous disease. It has many subgroups that differ in their genetic makeup and histopathology, carrying different prognoses, and having a different response to treatment in each

Table 2 Overview of Studies on Angiogenic Factors and ^{90}Y-Radioembolization

Authors	No. of Patients	Measured Factors	Sample Collection	Outcome	Findings
Carpizo 2014[10]	CLM n = 15 HCC n = 7	VEGF, Ang-2, b-FGF, PDGF-BB, Tsp-1. IL-8, leptin, follistatin, HGF, PECAM-1.	Baseline 6 h and 3, 14, 30, 60, 90, and 120 days (last 4 time points ± 3 days) after treatment.	Survival	Baseline levels of Ang-2 and IL-8 were significantly higher in the short survival group (≤6 months) (respectively, $P = 0.033$ and 0.041) Short survival patients (≤6 months) had transient increases in VEGF, Ang-2, and PDGF-BB at various early time points.
Rosenbaum 2016[6]	CRCLM n = 42	VEGF, Ang-2, b-FGF, PDGF-BB, Tsp-1, SDF-1a, HGF.	Baseline 0 (directly after injection), 1, 3, 7, and 30 days after treatment.	Survival	Baseline levels of Ang-2 were significantly higher in the short survival group (<6 months) ($P = 0.048$)
				Response	Early nonresponders (at 1 month) had higher levels of Ang-2 and HGF at 3 and 7 days after treatment which was statistically significantly different from responders (respectively, $P = 0.01$ and 0.007).

Ang-2, Angiopoietin-2; b-FGF, basic fibroblast growth factor; CLM, colorectal liver metastasis; CRCLM, chemorefractory colorectal liver metastasis; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; IL-8, Interleukin-8; PDGF-BB, platelet derived growth factor-BB; PECAM-1, platelet endothelial cell adhesion molecule; SDF-1a, stromal cell-derived factor-1a; TSP-1, trombospondin-1; VEGF, vascular endothelial growth factor.

stage of the disease.[42] Prognostic and predictive factors are required to create treatment algorithms that are optimized for each patient. Ideally they would allow for prediction of the most efficacious treatment, reliable prognostic factors would aid in preventing overtreatment.

Currently, ^{90}Y-RE is mostly used in a salvage-treatment setting, where it has shown to be effective in prolonging the overall survival, while being well tolerated. However, as a localized liver-directed treatment, it may hold more benefit for patients with less advanced liver-only disease. In that scenario, ^{90}Y-RE is also being investigated as a neoadjuvant treatment. It can be used in cases where liver tumors are considered unresectable due to an insufficient future liver remnant (FLR). The FLR can be hypertrophied by means of radiation lobectomy (or radiation segmentectomy) using RE. In such a case the part of the liver that has to be resected is treated with RE, causing hypertrophy in the nontreated liver lobe while maintaining tumor control. Several angiogenic signaling pathways are important in liver regeneration. HGF plays a primary role in hepatocyte proliferation and HIF-1α, VEGF, PDGFR-β, and Ang-2 play auxiliary roles by inducing angiogenesis and protecting against liver injury.[43] The predictive value of angiogenic growth factors on FLR hypertrophy is yet to be researched.

Data showing that circulating angiogenic growth factors are correlated with response and overall survival after ^{90}Y-RE are limited. There is a correlation between high baseline levels of Ang-2 and IL-8 and shorter survival.[6,10] Unfortunately, generalization of these results is difficult due to the small sample sizes of both studies and the heterogeneous sample of Carpizo et al Larger patient cohorts are required to validate such findings and to create models to predict response to therapy. In addition, correlation between these factors and survival after ^{90}Y-RE does not necessarily prove a causative relation. Patients with high baseline levels of Ang-2 and IL-8 might have a poor survival whether they are treated with ^{90}Y-RE or not.

Both included studies demonstrated an angiogenic response to radioembolization. Carpizo et al found elevations of VEGF, Ang-2, TSP-1, IL-8, and follistatin, and Rosenbaum et al found post-treatment elevations of VEGF, Ang-2, and HGF. The latter rise in Ang-2 and HGF was statistically significantly higher in early nonresponders (at 1 month). Progressive disease in these patients was always due to new lesions or growth of non-target lesions. These lesions had probably received lower radiation doses due to preferential blood flow to the largest lesions. This supports the hypothesis that early disease progression is induced in untreated (or undertreated) micro- or macroscopic lesions by rising angiogenic growth factors.

In order to prevent overtreatment, better selection based on predictive factors is required. There have been several studies creating prediction models for the success of RE in

terms of survival.[44-46] These studies focused on pretreatment characteristics, including lesion size, CEA levels, prior liver surgery, and extrahepatic disease. Unfortunately, these models suffered from overfitting due to small sample sizes, possible selection bias due to their retrospective nature, or lacked validation.

To improve treatment response, radioembolization has been combined with an antiangiogenic agent in three large trials.[47,48] The SIRFLOX, FOXFIRE, and FOXFIRE-global were phase III, multinational, multicenter trials that included patients with unresectable liver metastases from primary colorectal cancer that were randomly assigned to first line systemic chemotherapy (mFOLFOX6) with or without treatment with ⁹⁰Y-resin microspheres (SIR-Spheres). In both of these arms bevacizumab (and in some instances cetuximab, an anti-EGFR agent) would be given at the discretion of the treating physician. The combined analysis of these studies, including 1103 patients, failed to demonstrate any added survival benefit for the combination of ⁹⁰Y-RE with systemic therapy.[48] This was attributed to several factors, one of which is the percentage of extrahepatic disease in the study population, being that 40% of patients had extrahepatic disease in whom progression could have been induced by the rise in circulating angiogenic factors. A subgroup analysis on antiangiogenic therapy has not been reported yet and may yield information on whether the use of antiangiogenic agents could improve progression free survival. Of note, the angiogenic factors that correlated with early progression and poor outcome are not limited to VEGF. Multitarget agents (eg, tyrosine kinase inhibitors such as regorafenib, or HIF-1 inhibitors such as irinotecan) might be better suited in coping with the rising angiogenic factors than bevacizumab.

For future studies a controlled trial design, in which patients are randomized to receive radioembolization with antiangiogenic therapy versus radioembolization alone, preferably in chemo- and bevacizumab naive patients may be a valuable option. The goal of antiangiogenic therapy would be the prevention of early progression and normalization of the vascular supply of the tumors. Vascular normalization increases the oxygenation of the tumors, which could lead to higher radiosensitivity due to increased availability of reactive oxygen species and prevention of hypoxia-induced adaptations.[49] Research on vascular normalization is still in the early phases, and will require more optimization before it can be successfully implemented.[7,27]

In conclusion, there is a variety of angiogenic factors that can play a role in the development and progression of CRCLM. Elevated angiogenic factors at baseline are associated with a relatively poor outcome after ⁹⁰Y-RE although this has not been evaluated in comparative studies. Increases in plasma levels of angiogenic factors shortly after treatment with ⁹⁰Y-RE are associated with early progressive disease. Future studies are needed to determine if angiogenic factors can be used as a selection criterion for RE. Whether the combined treatment with anti-angiogenic agents and RE may prevent early progression is yet to be investigated.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-E386, 2015
2. Silberhumer GR, Paty PB, Temple LK, et al: Simultaneous resection for rectal cancer with synchronous liver metastasis is a safe procedure. Am J Surg 209:935-942, 2015
3. Van Cutsem E, Cervantes A, Adam R, et al: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 27:1386-1422, 2016
4. Welsh JS, Kennedy AS, Thomadsen B: Selective internal radiation therapy (SIRT) for liver metastases secondary to colorectal adenocarcinoma. Int J Radiat Oncol 66:S62-S73, 2006
5. Rosenbaum CENM, Verkooijen HM, Lam MGEH, et al: Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: A systematic review. J Nucl Med 54:1890-1895, 2013
6. Rosenbaum CENM, van den Hoven AF, Braat MNGJA, et al: Yttrium-90 radioembolization for colorectal cancer liver metastases: A prospective cohort study on circulating angiogenic factors and treatment response. EJNMMI Res 6:92, 2016
7. Angelucci A, Delle Monache S, Cortellini A, et al: Vessels in the storm: Searching for prognostic and predictive angiogenic factors in colorectal cancer. Int J Mol Sci19, 2018
8. Ronca R, Benkheil M, Mitola S, et al: Tumor angiogenesis revisited: Regulators and clinical implications. Med Res Rev 37:1231-1274, 2017
9. Ulivi P, Marisi G, Passardi A: Relationship between hypoxia and response to antiangiogenic therapy in metastatic colorectal cancer. Oncotarget 7:46678-46691, 2016
10. Carpizo DR, Gensure RH, Yu X, et al: Pilot study of angiogenic response to yttrium-90 radioembolization with resin microspheres. J Vasc Interv Radiol 25:297-306, 2014
11. Lewandowski RJ, Andreoli JM, Hickey R, et al: Angiogenic response following radioembolization: Results from a randomized pilot study of yttrium-90 with or without sorafenib. J Vasc Interv Radiol 27:1329-1336, 2016
12. Folkman J: Tumor angiogenesis: Therapuetic implications. N Engl J Med 285:1182-1186, 1971
13. Dvorak HF, Nagy JA, Feng D, et al: Vascular permeability factor/vascular endothelial growth factor and the significance of microvascular hyperpermeabiltiy in angiogenesis. Curr Top Microbiol Immunol 237:97-132, 1999
14. Shahi PK, Pineda IF: Tumoral angiogenesis: Review of the literature. Cancer Invest 26:104-108, 2008
15. Hanrahan V, Currie MJ, Gunningham SP, et al: The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C, and VEGF-D in the adenoma-carcinoma sequence during colorectal cancer progression. J Pathol 200:183-194, 2003
16. Hanahan D, Folkman J: Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 86:353-364, 1996
17. Folkman J: Fundamental concepts of the angiogenic process. Curr Mol Med 3:643-651, 2003
18. Menakuru SR, Brown NJ, Staton CA, et al: Angiogenesis in pre-malignant conditions. Br J Cancer 99:1961-1966, 2008
19. Murdoch C, Muthana M, Coffelt SB, et al: The role of myeloid cells in the promotion of tumour angiogenesis. Nat Rev Cancer 8:618-631, 2008
20. Powis G, Kirkpatrick L: Hypoxia inducible factor-1alpha as a cancer drug target. Mol Cancer Ther 3:647-654, 2004
21. Masoud GN, Li W: HIF-1α pathway: Role, regulation and intervention for cancer therapy. Acta Pharm Sin B 5:378-389, 2015
22. Wouters BG, Koritzinsky M: Hypoxia signalling through mTOR and the unfolded protein response in cancer. Nat Rev Cancer 8:851-864, 2008
23. Semenza GL: Targeting HIF-1 for cancer therapy. Nat Rev Cancer 3:721-732, 2003
24. Rapisarda A, Uranchimeg B, Sordet O, et al: Topoisomerase I-mediated inhibition of hypoxia-inducible factor 1: Mechanism and therapeutic implications. Cancer Res 64:1475-1482, 2004
25. Kaidi A, Qualtrough D, Williams AC, et al: Direct transcriptional up-regulation of cyclooxygenase-2 by hypoxia-inducible factor (HIF)-1 promotes colorectal tumor cell survival and enhances HIF-1 transcriptional activity during hypoxia. Cancer Res 66:6683-6691, 2006

26. Tsujii M, Kawano S, Tsuji S, et al: Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell 93:705-716, 1998

27. Jain RK: Antiangiogenesis strategies revisited: From starving tumors to alleviating hypoxia. Cancer Cell 26:605-622, 2014

28. Carmeliet P, Jain RK: Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Discov 10:417-427, 2011

29. Saltz LB, Clarke S, Díaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 26:2013-2019, 2008

30. Kindler HL, Niedzwiecki D, Hollis D, et al: Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: Phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol 28:3617-3622, 2010

31. Giantonio BJ, Catalano PJ, Meropol NJ, et al: 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 25:1539-1544, 2007

32. Grothey A, Cutsem E Van, Sobrero A, et al: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:303-312, 2013

33. Guérin E, Raffelsberger W, Pencreach E, et al: In vivo topoisomerase I inhibition attenuates the expression of hypoxia-inducible factor 1α target genes and decreases tumor angiogenesis. Mol Med 18:83-94, 2012

34. Jeong W, Park SR, Rapisarda A, et al: Weekly EZN-2208 (PEGylated SN-38) in combination with bevacizumab in patients with refractory solid tumors. Invest New Drugs 32:340-346, 2014

35. Ranieri G, Coviello M, Patruno R, et al: Vascular endothelial growth factor concentrations in the plasma-activated platelets rich (P-APR) of healthy controls and colorectal cancer patients. Oncol Rep 12:817-820, 2004

36. Martins SF, Garcia EA, Luz MAM, et al: Clinicopathological correlation and prognostic significance of VEGF-A, VEGF-C, VEGFR-2 and VEGFR-3 expression in colorectal cancer. Cancer Genomics Proteom 10:55-67, 2013

37. Rodriguez-Pascual J, Cubillo A: Dynamic biomarkers of response to antiangiogenic therapies in colorectal cancer: A review. Curr Pharm Person Med 15:81-85, 2018

38. Hayashi H, Arao T, Matsumoto K, et al: Biomarkers of reactive resistance and early disease progression during chemotherapy plus bevacizumab treatment for colorectal carcinoma. Oncotarget 5:2588-2595, 2014

39. Tabernero J, Paccard C, Chiron M, et al: Placental growth factor and the angiogenic environment based on analysis of baseline plasma biomarkers from the VELOUR trial. J Clin Oncol 35, 2017. 592-592

40. Schonewolf Ca, Patel B, Gensure Rh, et al: Patterns of failure in colorectal patients with liver metastases after yttrium-90 radioembolization. Am J Clin Oncol 37:234-240, 2014

41. Korse CM, Bonfrer JMG, Prevoo W, et al: Increase of angiogenic growth factors after hepatic artery embolization in patients with neuroendocrine tumours. Tumor Biol 32:647-652, 2011

42. Punt CJA, Koopman M, Vermeulen L: From tumour heterogeneity to advances in precision treatment of colorectal cancer. Nat Rev Clin Oncol 14:235-246, 2017

43. Preziosi ME, Monga SP: Update on the mechanisms of liver regeneration. Semin Liver Dis 37:141-151, 2017

44. Fendler WP, Ilhan H, Paprottka PM, et al: Nomogram including pretherapeutic parameters for prediction of survival after SIRT of hepatic metastases from colorectal cancer. Eur Radiol 25:2693-2700, 2015

45. Damm R, Seidensticker R, Ulrich G, et al: Y90 Radioembolization in chemorefractory metastatic, liver dominant colorectal cancer patients: Outcome assessment applying a predictive scoring system. BMC Cancer 16:509, 2016

46. Kurilova I, Beets-Tan RGH, Flynn J, et al: Factors affecting oncologic outcomes of 90y radioembolization of heavily pre-treated patients with colon cancer liver metastases. Clin Colorectal Cancer. https://doi.org/10.1016/j.clcc.2018.08.004 (in press).

47. 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 34:1723-1731, 2016

48. Wasan HS, Gibbs P, Sharma NK, et al: First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): A combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol 18:1159-1171, 2017

49. Winkler F, Kozin SV, Tong RT, et al: Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation. Cancer Cell 6:553-563, 2004

50. Meadows KN, Bryant P, Pumiglia K: Vascular endothelial growth factor induction of the angiogenic phenotype requires ras activation. J Biol Chem 276:49289-49298, 2001

51. Adini A, Kornaga T, Firoozbakht F, et al: Placental growth factor is a survival factor for tumor endothelial cells and macrophages. Cancer Res 62:2749-2752, 2002

52. Autiero M, Waltenberger J, Communi D, et al: Role of PlGF in the intra- and intermolecular cross talk between the VEGF receptors Flt1 and Flk1. Nat Med 9:936-943, 2003

53. Beştaş R, Kaplan MA, Işıkdoğan A: The correlation between serum VEGF levels and known prognostic risk factors in colorectal carcinoma. Hepatogastroenterology 61:267-271, 2014

54. Divella R, Daniele A, DE Luca R, et al: Circulating levels of VEGF and CXCL1 are predictive of metastatic organotropismin in patients with colorectal cancer. Anticancer Res 37:4867-4871, 2017

55. Kwon KA, Kim SH, Oh SY, et al: Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. BMC Cancer 10:203, 2010

56. Sung CY, Son MW, Ahn TS, et al: Expression of placenta growth factor in colorectal carcinoma. J Korean Soc Coloproctol 28:315, 2012

57. Ahmad SA, Liu W, Jung YD, et al: The effects of angiopoietin-1 and -2 on tumor growth and angiogenesis in human colon cancer. Cancer Res 61:1255-1259, 2001

58. McCarty MF, Somcio RJ, Stoeltzing O, et al: Overexpression of PDGF-BB decreases colorectal and pancreatic cancer growth by increasing tumor pericyte content. J Clin Invest 117:2114-2122, 2007

59. Belizon A, Balik E, Horst PK, et al: Platelet-derived growth factor (subtype BB) is elevated in patients with colorectal carcinoma. Dis Colon Rectum 52:1166-1171, 2009

60. Ionescu C, Berindan-Neagoe I, Burz C, et al: The clinical implications of platelet derived growth factor B, vascular endothelial growth factor and basic fibroblast growth factor in colorectal cancer. J BUON 16:274-276, 2011

61. Ito M, Yoshida K, Kyo E, et al: Expression of several growth factors and their receptor genes in human colon carcinomas. Virchows Arch B Cell Pathol Incl Mol Pathol 59:173-178, 1990

62. Osada S, Matsui S, Komori S, et al: Effect of hepatocyte growth factor on progression of liver metastasis in colorectal cancer. Hepatogastroenterology 57:76-80, 2010

63. Korc M, Friesel RE: The role of fibroblast growth factors in tumor growth. Curr Cancer Drug Targets 9:639-651, 2009

64. Seghezzi G, Patel S, Ren CJ, et al: Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: An autocrine mechanism contributing to angiogenesis. J Cell Biol 141:1659-1673, 1998

65. Murakami M, Simons M: Fibroblast growth factor regulation of neovascularization. Curr Opin Hematol 15:215-220, 2008

66. Onimaru M, Yonemitsu Y, Tanii M, et al: Fibroblast growth factor-2 gene transfer can stimulate hepatocyte growth factor expression irrespective of hypoxia-mediated downregulation in ischemic limbs. Circ Res 91:923-930, 2002

67. Sonvilla G, Allerstorfer S, Stattner S, et al: FGF18 in colorectal tumour cells: Autocrine and paracrine effects. Carcinogenesis 29:15-24, 2007

68. Matsuda Y, Ueda J, Ishiwata T: Fibroblast growth factor receptor 2: Expression, roles, and potential as a novel molecular target for colorectal cancer. Patholog Res Int 2012:1-8, 2012