Combined [^{18}F]-Fluoroethylcholine PET/CT and ^{99m}Tc–Macroaggregated Albumin SPECT/CT Predict Survival in Patients With Intermediate-Stage Hepatocellular Carcinoma

Markus Hartenbach, MD, Stefan Weber,* Magdalena Pilz, PhD,* Sabrina Hartenbach, MD,† Mathias J. Zacherl,‡ Philipp M. Paprottka, MD,§ Reinhold Tiling, MD,‡ Peter Bartenstein, MD,‡ Marcus Hacker, MD,* Alexander R. Haug, MD,*‡ and Nathalie L. Albert, MD‡*

Aim: The aim of this study was to retrospectively analyze the prognostic value of combined ^{99m}Tc–macroaggregated albumin (MAA) SPECT/CT and [^{18}F]-fluoroethylcholine (FEC) PET/CT before radioembolization for survival of patients with intermediate-stage hepatocellular carcinoma.

Methods: Twenty-four patients with known hepatocellular carcinoma Barcelona Clinic Liver Cancer stage B were eligible for this analysis. All patients were scheduled for radioembolization and received a pretherapeutic [^{18}F]FEC PET/CT scan as well as ^{99m}Tc-MAA SPECT/CT for hepatopulmonary shunting. Laboratory and semiquantitative PET parameters and morphologic and metabolic (intersection) volumes of MAA and FEC were evaluated. Spearman correlation with overall survival, receiver operating curve analyses, univariate and multivariate Cox regression, and Kaplan-Meier-analysis was applied.

Results: All patients (5 female/19 male) are deceased within the observational period. Median survival was 395 days (±51 days; range, 23–1122 days). The percentage of hypervascularized metabolically active tumor volume (vascularized tumor ratio; defined as high MAA and FEC uptake) correlated significantly with survival. Vascularized tumor ratio was a significant predictor in univariate and multivariate analyses (P = 0.026; hazard ratio, 11.65; 95% confidence interval, 1.62–83.73; P = 0.015). Statistical significance was not reached by all other variables in multivariate analysis. Receiver operating curve analysis for 1-year survival revealed an area under the curve of 0.77 (P = 0.024) for vascularized tumor ratio. At a cutoff value of 9%, sensitivity, specificity, and positive and negative prediction were 83%, 67%, and 71% and 80% (P = 0.036). Patients with a higher tumor vascularization had a median survival of 274 ± 80 versus 585 ± 284 days (P = 0.015).

Conclusions: Hepatocellular carcinoma with high vascularization in metabolic active areas as assessed by combined FEC PET/CT and Tc-MAA SPECT/CT represents an unfavorable subgroup with reduced overall survival after radioembolization.

Key Words: FEC PET, intermediate-stage HCC, MAA SPECT, radioembolization, survival, vascularization

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Although having a 10 times higher incidence in Eastern Asia and Middle Africa, representing the third most common cause of cancer death worldwide, hepatocellular carcinoma (HCC) is still the fifth most common cause of cancer death in men in the United States.[1] It aggravates liver cirrhosis in more than 90% of the cases, and for these patients, HCC represents the foremost cause of death.[2]

The fact that HCC commonly afflicts patients with underlying liver disease, both tumor burden and liver function have to be carefully evaluated at the time of prognostic evaluation and therapy recommendation.[3]

Although major advances in the diagnosis and treatment of HCC were achieved, most patients suffering from HCC will die because of this neoplasm.[4] To assess prognosis and optimal therapy for HCC patients considering tumor stage, liver function, and physical status, the Barcelona Clinic Liver Cancer (BCLC) algorithm was established.[3,5,6] Following these recommendations, transarterial liver therapies are indicated in intermediate stages (BCLC stage B [BCLC-B]), where the liver function is preserved fitting into Child-Pugh A and B with single large HCCs and multifocal disease. Recent guidelines recommend treatment of intermediate-stage HCC with transarterial chemoembolization (TACE), but other emerging modalities of treatment are currently under evaluation, for example, ^{90}Y radioembolization.[5–7] Radioembolization with ^{90}Y has turned out as an efficient treatment option. On the basis of the hypervascularity of HCC, intra-arterial injection of microspheres will be primarily delivered to the tumor-bearing area and selectively emit high-energy, low-penetration radiation to the tumor.[4] Initial studies have already confirmed its antitumor activity.[3]

In addition, a number of study groups have tried to define and objectify the role of ^{99m}Tc-labeled macroaggregated albumin (MAA) uptake on SPECT for radioembolization.[8,9]

High tumor vascularization as indicated by MAA scintigraphy was not necessary for successful radioembolization of cholangiocellular carcinoma but was indeed associated with a tendency toward shorter survival.[8] In another study, the pretherapeutic and posttherapeutic [^{18}F]-fluoroethylcholine (FEC) PET/CT scans of patients with HCC scheduled for radioembolization have been evaluated. As FEC PET has demonstrated high detection rates in HCC[10–12] and thus seems to represent the metabolic active tumor areas also in lower-grade HCC, it seems to be a suitable imaging biomarker in HCC patients.

In patients with nonmetastatic but locally advanced HCC, FEC PET/CT showed high accuracy for response assessment in relation with radioembolization, allowing early monitoring of local therapies.[10] Its prognostic value on overall survival in these patients has not yet been evaluated, especially with regard to tumor vascularity as indicated with MAA scintigraphy.

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From the *Division of Nuclear Medicine, Department of Biomedical Imaging and Image Guided Therapy, Medical University of Vienna, Austria; †HistoConsulting, Ulm; and Departments of ‡Nuclear Medicine and §Clinical Radiology, Ludwig Maximilians University of Munich, Munich, Germany.
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All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.
Informed consent was waived by the ethics committee in this retrospective study, as far as all patients were not alive anymore at the time point of the evaluation.
Correspondence to: Markus Hartenbach, MD, Division of Nuclear Medicine, Department of Biomedical Imaging and Image Guided Therapy, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. E-mail: markus.hartenbach@meduniwien.ac.at.

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This encouraged us to retrospectively analyze the survival data in HCC BCLC-B patients with regard to MAA SPECT/CT and FEC PET/CT before radioembolization in order to evaluate the prognostic value of these 2 investigations.

PATIENTS AND METHODS

This retrospective study was approved by the local ethics committee of the LMU Munich, and the requirement to obtain informed consent was waived. Twenty-four patients with known HCC according to the European Association for the Study of the Liver criteria and/or histology as well as BCLC-B intermediate-stage HCC were identified for this analysis. All patients were scheduled for radioembolization and received a pretherapeutic FEC PET/CT scan as well as angiography with visceral catheterization to evaluate vascular anatomy and to identify aberrant vessels. Whenever deemed necessary, prophylactic embolization of these vessels was performed.[13] This investigation was simultaneously used for the injection of 100 MBq MAA into the hepatic artery followed by SPECT/CT for the evaluation of hepatopulmonary shunting and significant extrahepatic deposits. Relevant laboratory tests (liver function, coagulation profiles, metabolic panel, blood count, blood tumor marker α-fetoprotein) were obtained at this time point.

SIR-Spheres (SIRTeX Medical) were applied into the right and left hepatic arteries as previously described.[10] The activity was calculated using the body surface area method[13]: activity in GBq = (body surface area − 0.2) + (liver involvement [%]/100).

Seventy-five percent of the patients (n = 18) received a dual-time-point radioembolization (RE) with a (median) 4-week interval between right- and left-lobe therapy. Five patients had a single RE of both lobes, and 1 patient received only segmental RE in segments IVa + b. The median injected doses for the right lobe were 1 GBq (±283 MBq) and for the left lobe 479 MBq (±195 MBq). For single RE, it was 1505 MBq (±443 MBq).

Whole-body PET scans were acquired in 3-dimensional mode by using one of two 64-slice PET/CT scanners (Biograph 64 TruePoint [Siemens Medical Solutions, Knoxville, USA] or Discovery [GE Healthcare, Chalfont St Giles, England]). Prior to the CT scan, mean weight-adapted 120 mL of iodine-containing contrast agent (iopromide [Imeron 300]; Bracco, Milan, Italy) was intravenously administered at a rate of 2.5 mL/s. Initiation of the CT scan (200–250 mA, 120 kV, 5 × 5 and 3 × 3-mm collimation, pitch 0.6) was delayed by 50 seconds after starting contrast agent infusion in order to depict the venous contrast medium phase. The PET emission scan was initiated 60 minutes after intravenous injection of [^{18}F] FEC (3 MBq/kg body weight). Emission data were reconstructed with attenuation correction on the basis of concurrent diagnostic CT.

Fluoroethylcholine was produced and delivered by PETNet GmbH (Erlangen, Germany).

For image analysis, Siemens Syngo TrueD workstations were used. Detailed volume of interest (VOI) analysis, fusion of SPECT/CT and PET/CT images, and determination of intersection volumes were performed using Hermes Hybrid 3D (Hermes Medical Solutions, Stockholm, Sweden) as previously described.[10] Liver VOIs for total liver volume were drawn manually on CT images using region-of-interest interpolation. SUVmax, mean, and peak analysis were obtained with a 3-dimensional VOI and a 50% isocontour. The analysis of the intrahepatic FEC-positive tumor volume was measured threshold-based as described previously.[10] The lower threshold was defined as being 50% higher than the SUVmax taken from a cubic VOI out of a non-HCC affected area of the liver (defined by CT). As long as only venous phase CTs were performed in this PET/CT approach, other multiphase CTs or multiphase MRIs obtained in each patient before RE were taken into account to confirm these nonaffected areas.

In addition, tumor-to-background ratios (TBRs) were calculated. As the spleen is an organ with relatively high but homogenous FEC uptake, we defined a cuboid VOI of the spleen (5-voxel side length) and calculated TBRs for SUVmax, mean, and peak according to the following formula:

$$\mathrm{TBR} = \frac{\mathrm{SUV\ (tumor)}}{\mathrm{SUV\ (spleen)}}$$

The MAA SPECT/CT images were coregistered to the FEC PET/CT images. Again, a threshold-based VOI was drawn automatically using the reference region from PET/CT for defining the liver background MAA counts and taking twice the background maximum counts as the lower threshold for MAA-positive areas, representing highly vascularized areas (Fig. 1), adapted to previously described methods.[8] Intersection areas of MAA uptake and FEC uptake were calculated using the VOI intersection tool (Hermes Hybrid 3D). The ratio of highly vascularized tumor (vascularized tumor ratio [VTR]) among the metabolic active tissue was calculated according to the following:

$$\mathrm{VTR} = \frac{\mathrm{FEC + MAA\ intersection\ volume\ (mL)}}{\mathrm{FEC\ PTV\ (mL)}}$$

Statistical analysis was performed using IBM SPSS Statistics for Windows version 23.0 (IBM, Armonk, USA) and Sigma Plot 12.0 (Systat Tech Inc, San Jose, Calif). The Pearson correlation coefficient analysis was used for comparing survival rates with laboratory and PET-derived parameters. Data derived from SUV measurements were analyzed for correlation with 1-year survival using receiver operating characteristic (ROC) curve analysis and Youden index for the determination of the cutoff. Contingency tables were checked for independencies using χ^2 test. In addition, survival rates were assessed by Kaplan-Meier analysis using absolute time points of death. Variables were analyzed for an association with overall survival by the log-rank test. Cox regression proportional hazards models were used to obtain hazard ratio estimates of significant parameters derived from Spearman correlation using $P < 0.2$ for the parameters to qualify for multivariate analysis.

RESULTS

All patients (5 female and 19 male patients) deceased within the observational period with a median survival of 395 days (±50.65 days; maximum 1122 days, minimum 23 days; Fig. 2). Patients had a mean age of 65.7 ± 11.3 years. The characteristics of the functional laboratory and imaging parameters are given in Table 1. Eight patients had elevated bilirubin levels, and 3 patients presented already reduced albumin levels. All patients had an elevated γ-glutamyltranspeptidase (gGT).

Results of the Spearmen correlation analyses with overall survival are also given in Table 1. The percentage of hypervascularized metabolic active tumor volume (VTR) was the only parameter observed that correlated significantly with survival. Age, sex, liver size, bilirubin, albumin, and gGT, as well as SUV and total metabolic and total hypervascularized tumor volumes, did not significantly correlate with overall survival. With $P < 0.2$, only age, gGT, albumin, and VTR qualified for Cox regression analysis.

Only VTR was significant in univariate and multivariate analyses using the Cox regression proportional hazards model with a hazard ratio of 11.65 (95% confidence interval, 1.62–83.73; $P = 0.015$). Statistical significance was not reached by the other variables.

An ROC curve analysis of the respective parameters, applying 1-year survival as the dichotomous characteristic, revealed a significant area under the curve of 0.77 ($P = 0.024$) for VTR (Fig. 3).

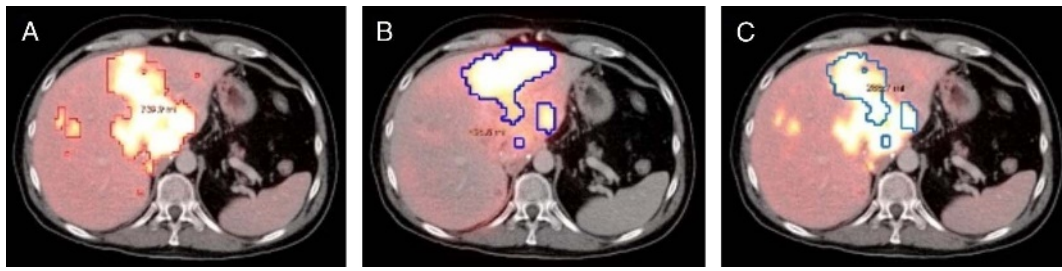

FIGURE 1. Example of a 56-year-old man (at the time point of PET imaging) who died 170 days later. He presented an FEC-positive volume of 743 mL (**A**) and an MAA-positive volume of 525 mL (**B**) with an intersection volume of 358 mL (**C**). This resulted in a VTR of 48% which is significantly correlated to shorter survival. MAA SPECT images are already fused to contrast enhanced CT images of the FEC PET/CT.

At a cutoff value of 9%, derived by the Youden index, the sensitivity, specificity, and positive and negative prediction were 83%, 67%, and 71% and 80% ($P = 0.036$).

The respective Kaplan-Meier curves are given in Figure 2. Patients with a higher tumor vascularization had a median survival of 274 ± 80 days, whereas patients with lower vascularized tumors survived 585 ± 284 days (log rank = 5.952, $P = 0.015$).

DISCUSSION

^{90}Y radioembolization in intermediate stages of HCC, represented by the BCLC-B, is an emerging treatment besides TACE and offers equal or superior survival rates while causing fewer adverse effects.[5,14] In the development of HCC, tumor vascularization and neoangiogenesis are hallmarks for tumor growth and accessibility to the hepatic arteries by the tumor. This is mainly driven by overexpression of the vascular endothelial growth factor and hypoxia-inducible factor 1a (HIF-1a) to ensure tumor oxygenation.[15,16] Both RE and TACE gain their therapeutic efficacy due to this arterial blood supply while preserving the normal liver tissue, which is to a larger amount supplied by the portal venous blood, thus implying that a high arterial blood supply might be beneficial for therapy response. On the other hand, the grade of intratumoral arteriole density, assessed by α-smooth muscle actin expression, was found to be significantly associated with histological grade, proliferative activity, and patient survival, suggesting its significance in tumor progression.[17]

In our retrospective analysis of a small cohort of BCLC-B patients, the survival rates differed from the published data (13 vs 20 months).[3] This might be due to the small sample size, but there might be other reasons in tumor biology that cause this heterogeneity in this subgroup of HCC patients and could have an impact on patient selection and/or multimodal therapeutic approaches.

Although FDG PET has demonstrated prognostic value for survival in presurgical HCC patients in a prospective study,[18] FEC PET/CT has proven to be significantly superior as compared with FDG PET/CT in the detection and staging of HCCs.[11,12,19] Therefore, FEC PET/CT was routinely used for diagnosis and staging in our clinic. As there is already knowledge about its potential for assessing therapy response of RE in HCC BCLC-B patients,[10] this metabolism might also be a surrogate for predicting survival. Interestingly, the uptake of FEC in terms of standardized uptake value as well as the total amount of metabolic active HCC did not have any significance concerning survival in this study (Table 1). Thus, we postulate that an up-regulated choline uptake of HCC cells is not a surrogate for tumor aggressiveness.

The standard therapy for advanced HCC BCLC-C, representing a metastatic stage, is sorafenib. Sorafenib mediates the inhibition of HIF-1a synthesis and harbors also a strong antiangiogenic mechanism of action by inhibiting vascular endothelial growth factor protein expression.[20] As mentioned before, vascularization is associated with survival, thus being an important target for therapies, as well as for tumor characterization in pretherapeutic diagnostics. Contrast enhancement on MRI or CT is not a surrogate for neovascularization.[21] MAA has a median size of 10 to 90 μm and is trapped in the small arterioles of the tumoral vessels when being injected through the hepatic artery. As MAA is trapped in relation to the arterial blood flow, it might serve as a surrogate for tumor vascularization.

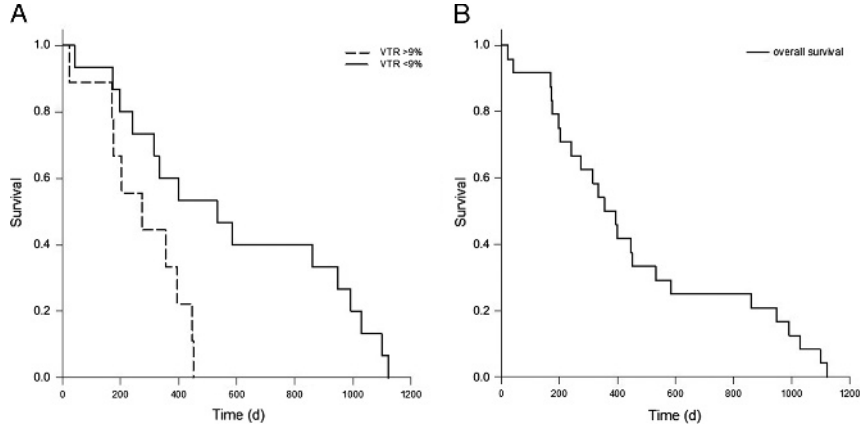

FIGURE 2. Kaplan-Meier plot for VTR (**A**) with a cutoff of 9% received by ROC curve analyses (Fig. 3) demonstrates a significant survival benefit for lower vascularized tumors (585 ± 284 vs 274 ± 80 days, log rank: 5.952, $P = 0.015$). All patients are deceased within the observational period (**B**) with a median survival of 395 days (±50.65; maximum 1122 days, minimum 23 days).

TABLE 1. Results of the Assessed Volumetric, Laboratory, and Semiquantitative Parameters and Their Correlation With Overall Survival

	Mean	SD	Reference Range	Correlation With Overall Survival (Spearman)	*P*
Liver volume, mL	2028	593		−0.039	0.856
MAA volume, mL	131	120		−0.145	0.498
FEC volume, mL	161	181		0.057	0.793
VTR, %	18	19		−0.591	0.002*
SUVpeak	21.5	8.6		0.085	0.692
SUVmean	14.9	4.6		0.051	0.812
TBRpeak	5.1	2.5		−0.176	0.412
TBRmean	4	1.3		−0.025	0.908
Albumin	4	0.5	3.5–5.0 g/dL	0.360	0.084
Bilirubin	1.1	0.9	≤1.0 mg/dL	−0.192	0.370
gGT	365.5	314.2	≤40 U/L	−0.277	0.189
AFP	10,121	30,231	≤7.0 ng/mL	−0.132	0.539
Age, y	65.7	11.3		0.284	0.178

*Significant result.
AFP indicates α-fetoprotein.

While the total amount of MAA-positive HCC alone was not significantly associated with survival in our cohort, the intersection volume of FEC- and MAA-positive HCC areas could be identified as predictive marker for patient outcome. This intersection volume, defined as VTR in our study, is supposed to represent the metabolically active tumor areas with higher vascularity (Fig. 3, Table 1). As compared with histopathologic findings in other studies,[17] this could be a promising minimally invasive diagnostic approach to select patient groups with favorable outcome of RE. Even in our relatively small patient cohort, this parameter proved to be highly significant for survival. Patients with a VTR of less than 9% reached survival rates that were comparable to those reported by other studies for HCC BCLC-B patients after treatment, whereas patients with higher VTR demonstrated significantly shorter survival (Fig. 2). As our cohort had a mean VTR of 18% (Table 1), this might explain the comparatively low overall survival.

Our results might seem counterintuitive at first sight, as one could assume that more ^{90}Y resin microspheres might be delivered to the tumor with higher vascular density, which should result in a better posttherapeutic outcome; however, there are several possible explanations for our contrary results; high tumor vascularization is also a consequence of hypoxia via the previously mentioned HIF-1a mechanism. As hypoxia is known to increase resistance to ionizing radiation,[22] this might be one of the factors reducing therapeutic effectiveness. Furthermore, the distribution of MAA in the pretherapeutic SPECT/CT does not necessarily reflect the distribution of ^{90}Y microspheres during radioembolization.[9] In addition, highly vascularized HCC might represent a more aggressive tumor biology outweighing the higher tumor dose reached by the higher amount of microspheres delivered.

Some limitations of the presented data have to be mentioned. First, the presented cohort is small. Nevertheless, all eligible patients are deceased in the observational period; thus, being available for a Spearman correlation analysis that provides more stable correlative statistics than Cox regression or Kaplan-Meier analyses as far as no censored data has to be taken into account. For illustration purposes, these analyses are also presented.

Also possibly because of the small sample size, parameters that have a known impact on survival in HCC patients after RE are not significant in our analysis.[23] This is true for age, bilirubin, albumin, and α-fetoprotein. Portal vein thrombosis was present in only 1 patient in our cohort and was not analyzed. Because of the

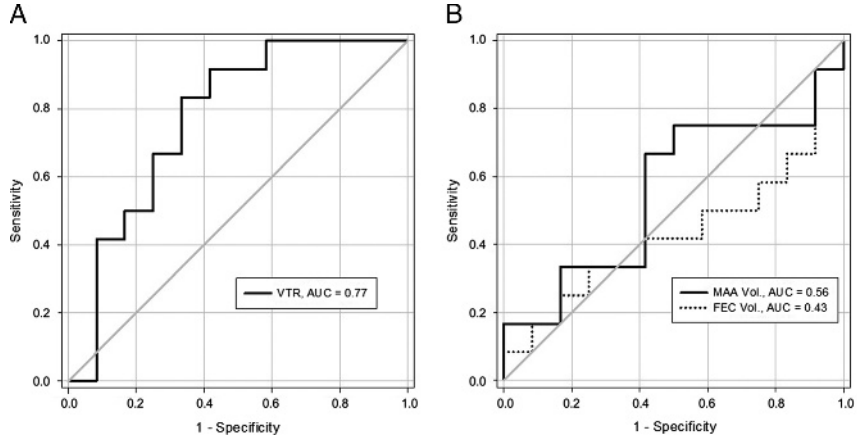

FIGURE 3. Receiver operating characteristic curve analysis for 1-year survival demonstrated a significant AUC of 0.77 ($P = 0.024$) for VTR (**A**), whereas absolute MAA and FEC volumes did not reach significance (**B**). AUC indicates area under the curve.

retrospective design of the study and therefore incomplete medical history in some cases, other confounders such as concomitant or previously applied medications could unfortunately not be evaluated on multivariate analysis. This is also true for the histological differentiation grade as only 11 patients had biopsy-proven HCC. However, this retrospective analysis did not intend to elaborate clinical parameters that affect survival but to analyze the performance of noninvasive or minimally invasive imaging biomarkers in this context. Even more remarkable is the level of significance for VTR in this cohort. With a negative predictive value of 80%, this could be a criterion for patient selection in a prospective study design for a multimodal therapeutic approach, combining the antiangiogenetic potential of sorafenib with the lower adverse effect profile of RE as already applied in an ongoing randomized multicenter trial.[24]

CONCLUSIONS

In a cohort of 24 patients with HCC BCLC-B treated with radioembolization, the combination of FEC PET/CT and MAA SPECT/CT demonstrated a significantly shorter survival for metabolic active tumors with larger areas of high vascularization. This could serve as a selection criterion for a new subgroup of high-risk patients who should receive a multimodal treatment regimen (eg, sorafenib and RE).

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