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INTERVENTIONAL ONCOLOGY (DC MADOFF, SECTION EDITOR)

Tumor Biomarkers and Interventional Oncology: Impact on Local Outcomes for Liver and Lung Malignancy

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Abstract

Purpose of Review Interventional oncology (IO) loco-regional treatments are widely utilized in clinical practice. However, local tumor control rates are still widely variable. There is a need to identify and develop novel biomarkers prognosticators following IO therapies. Here, we review the current literature on molecular tumor biomarkers in IO, mainly focusing on patients with liver and lung cancers.

Recent Findings RAS mutation is a prognosticator for patients with colorectal liver metastases. Several promising serum metabolites, gene signatures, circulating tumor nucleotides, and peptides are being evaluated for patients with hepatocellular carcinoma. Ki-67 and RAS mutation are independent risk factors for local tumor progression in the ablation of lung cancer.

Summary The relevant interplay between specific tumor biomarkers and IO loco-regional therapies outcomes has brought a new vision in the management of cancer. Further evolution of personalized interventional oncology accordingly to tumor biomarkers should improve oncologic outcomes for patients receiving IO therapies.

Keywords Biomarkers · Interventional oncology · Liver cancer · Lung cancer · Prognosis · Recurrence

Introduction

Significant improvements in interventional oncology (IO) therapies have been recently achieved for various types of cancers. Although surgical resection remains the local modality of choice for several types of cancers, a significant number of patients are not eligible for surgical resection. Therefore, locoregional therapies, including IO therapies, have been developed and optimized for those who do not fulfill the criteria for surgical resection.

Such IO therapies include percutaneous and transarterial techniques such as thermal ablation, transarterial embolization (TAE), chemoembolization (TACE), and radioembolization (TARE). Image-guided percutaneous ablation is a curative technique suitable for small and early-stage tumors and has been clinically utilized for many tumor treatments. TAE and TACE are techniques centered on the principle of obstruction of blood supply to the tumor, inducing ischemic effect combined with the impact of locally delivered chemotherapy with minimal systemic effects, and they are usually reserved for patients with intermediate or advanced tumor status. TARE allows the delivery of radioactive microspheres directly to hepatic tumors. It is most commonly used as salvage therapy in HCC or metastatic liver disease. Despite of its widespread clinical use, limitation remains on proper patient selection for such therapies in order to maximize rates of local tumor control [1, 2].

The identification of robust tumor biomarkers correlating with the outcome of locoregional treatment may help to determine the prognosis, identify patients most likely to benefit from specific treatments, and guide clinicians to design personalized treatment strategies. So far, the main known predictive factors of recurrence are based on the tumor's morphological characteristics and the severity of the underlying disease, but little focus has been given on the influence of tumor biology. For this purpose, recent studies have identified serum

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or tissue biomarkers that could be indicative of treatment efficacy and prognosis, potentially allowing locoregional therapy patient personalization. Furthermore, refining the staging systems by incorporating biomarkers based on molecular or cellular tumor features remains a goal in precision oncology. In this article, we provide a review of the most recent literature in respect the predictive biomarkers for local outcomes after locoregional therapy in the liver and lung of the past years.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide [3, 4]. Although hepatic resection remains the first-line treatment for patients with early-stage HCC as defined by the Barcelona Clinic Liver Cancer staging system, a substantial number of patients who are not eligible for curative surgery at presentation may benefit from locoregional treatments, such as percutaneous image-guided ablation and transcatheter arterial-directed procedures [5–7]. Tumor biomarkers for appropriate treatment selection or response prediction have been widely studied recently.

Several studies focused on the serum level of alpha-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and des-γ-carboxy-prothrombin (DCP) to predict the response of locoregional treatment in HCC. AFP is the first biomarker widely used as an independent factor to predict treatment outcomes and OS. In percutaneous image-guided ablation, low pre- and post-therapeutic levels of AFP have been associated with better clinical outcomes [8, 9]. However, there is controversy regarding which cut-off value of AFP should be used. Dynamic AFP changes before and after ablation have also been associated with OS and disease-free survival following ablation. It was reported that patients with AFP levels decreasing more than 50% at 1 week after ablation had better disease-free survival irrespective of achieving complete ablation [10]. Another study found that patients with a post-therapeutic AFP reduction level of less than 20% from baseline had a higher rate of tumor recurrence and poor OS following radiofrequency ablation (RFA) [11]. For patients submitted to TACE as the initial treatment modality, AFP response (defined as a reduction of more than 50% from the baseline level 1 month after TACE) has been found as a predictor of improved OS [12]. Recently, a study of 74 patients undergoing TARE found that the pre-therapeutic level of AFP more than 37 ng/mL was a poor prognostic factor of OS [13]. However, in this study, there was no association of AFP level with radiographic improvement based on modified response evaluation criteria in solid tumors criteria. In a study of 125 patients treated with TACE or TARE, a reduction of post-therapeutic AFP level more than 50% compared with baseline was a prognostic factor for tumor imaging response, longer time to tumor progression (TTP) and PFS [14].

AFP-L3, which is an isoform of AFP, and DCP, which is known as a protein induced by vitamin K absence or antagonist II, are both associated with larger HCC, poor HCC differentiation, and vascular invasion [15–17]. Elevated AFP-L3 levels have been associated with a higher risk of recurrence [18, 19] and poor OS [9] following ablation. High levels of DCP have been associated with a higher risk of local tumor progression (LTP), intrahepatic recurrence, and poor survival after ablation [9, 20–22]. In an analysis of 1057 patients, it was reported that the level of DCP and AFP-L3 were predictors of vascular invasion after RFA [23]. However, the prognostic values of AFP-L3 and DCP have been evaluated with different cut-off values. In another study, the patients with three positive biomarkers (AFP >20 ng/mL, AFP-L3 >10%, and DCP >40 mAU/dL) had lower 2-year recurrence-free survival (27.1% versus 83.1%, respectively, P <0.001) and lower 5-year OS (47.6% versus 83.3%, respectively, P = 0.001) when compared with non-positive patients following RFA [24]. Regarding TACE, another study of 327 treatment-naïve patients reported that reduced levels of AFP and DCP greater than 50% from baseline were correlated with objective response one month after TACE, and with longer TTP and higher OS [25]. Moreover, the trend of pre- and post-therapeutic levels of DCP was correlated with treatment response and OS [26]. In terms of AFP-L3, the reduction of at least 20% from baseline after two cycles of TACE was associated with better radiological response and higher OS [27].

The detection of plasma microRNA and circulating tumor cells (CTC), which are encompassed by the term "liquid biopsy," have been related to oncogenesis and tumor metastasis. The circulating microRNAs have roles in the prediction of clinical outcomes in HCC treated by RFA. The low serum levels of miR-26a and miR-29a were found as a risk factor for poor disease-free survival and the high serum level of miR-122 (>100) was a negative predictor of OS following RFA [28, 29]. In patients responding to TACE, the serum levels of miR-106b, miR-107, and miR-133b were significantly elevated, while the level of miR-26a was elevated in non-responded patients [30•]. Other studies revealed that the expression of a specific combination of microRNAs (miR-21, miR-26a, and miR-29a-3p) and the lower level of miR-199a/b-3p at baseline could predict the poor response of TACE [31, 32]. Recently, the high CTC number (≥6) was found as a predictor of lower PFS and OS in TACE treatment of unresectable HCC [33].

Genetic expression of HCC may have a predictive value of treatment response in TACE. Studies have shown the polymorphism in the SERPINE1 gene promoter region, and glutathione S-transferase O2 gene was associated with poor prognosis in patients undergoing TACE [34, 35]. Another study showed that patients with ADAMTS5 polymorphism had a decreased risk of tumor recurrence in aflatoxin-related HCC

following TACE [36]. A panel of 60 genes analyzed in a study from 38 tumors treated with TACE reported that genes related to DNA transcription (ATF4, NFX1, TOP2A, TOP2B), cell mitosis (CCNE1, KIF11), apoptosis (BAX), angiogenesis (VEGFA), and other biological functions (CXCL10, PPP3CA, SNX1) were related to the radiological response after TACE [37]. Recently, the nuclear factor E2-related factor 2 (NRF2) pathway mutation, which supports cell survival in hypoxemia, was found to be associated with shorter TTP after TAE compared to wild-type HCC, and the 6-month cumulative incidence of local progression was 56% versus 22%, respectively ($P < 0.001$) (Fig. 1) [38••]. In the same study, the cell lines with NRF2 mutation were susceptible to in vitro ischemia condition when treated with NRF2 inhibitor.

Other serum biomarkers also revealed potential prognostic values in the locoregional treatment of HCC. The vascular endothelial growth factor (VEGF), an angiogenetic factor, is a key factor for the expansion of HCC [39]. An analysis of 120 patients found that the pre-therapeutic serum level of VEGF greater than 240 pg/mL was a significant prognostic factor of both OS and recurrence-free survival after RFA [40]. The VEGF also plays a role in the hypoxic tumor environment induced by TACE. A report found that the pre-therapeutic VEGF levels were significantly higher in patients having progressive disease compared with stable or responsive disease after TACE [41]. The post-therapeutic serum level of VEGF more than 16.7 pg/mL measured 7 days after TACE has been shown as a predictor of rapid tumor growth in 3 months [42]. The serum ferritin, which reflects the hepatic iron accumulation, is a factor that influences hepatocarcinogenesis [43]. A study analyzing 103 patients undergoing RFA reported that the serum ferritin level less than or equal to 244 ng/mL was a predictor of lower OS and shorter time to recurrence [44]. The insulin-like growth factor-1, which is mainly synthesized by the liver, is a surrogate of liver function reserve in HCC [45]. A study of 145 treatment-naïve patients had longer TTP and higher OS in patients having higher pre-therapeutic IGF-1 levels (≥57.3 ng/mL) after TACE [46]. The osteopontin is a biomarker associated with dedifferentiation and vascular invasion of aggressive HCC and a higher early recurrence rate [47]. The low baseline osteopontin level and the reduction of more than 10% 4 weeks after TACE compared with baseline had better treatment response and survival, although they were not statistically significant in multivariate analysis [48]. Some serum biomarkers which are released into the circulation directly after locoregional treatment and represent the high cell turnover or cell death were studied. For example, the increase of the serum levels of circulating nucleosomes 24 h after TACE was one of those biomarkers found to be associated with local treatment response [49].

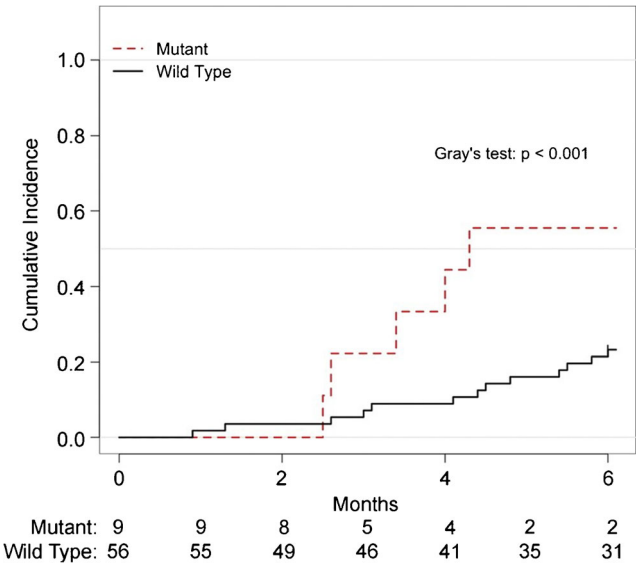


Fig. 1 Comparison of cumulative incidence of local progression after transarterial embolization in NRF2 and KEAP1 wild-type and NRF2 and KEAP1–mutant tumors

Reproduced from Ziv E, Zhang Y, Kelly L, Nikolovski I, Boas FE, Erinjeri JP, et al. NRF2 dysregulation in hepatocellular carcinoma and ischemia: a cohort study and laboratory investigation. Radiology. 2020:200201. Used with permission.

A few studies are addressing the prediction of treatment outcomes regarding tissue samples retrieved from percutaneous ablation. The microRNA-34a, an aberrant microRNA, is associated with the development and progression of cancer [50]. A study found that a low level of microRNA-34a (<0.87) was a predictor of recurrence after RFA [51]. The endothelial cell-specific molecule 1, a gene expression correlated to tumor angiogenesis and invasion, has been found independently related to early recurrence of early-stage single HCC treated with RFA [52]. In the same study, keratin 19, which is considered to be a hepatic progenitor cell maker, and glutamine synthetase, which is associated with the nuclear Wnt/β-catenin pathway, were not found to be related to the recurrence or survival. But in the other studies of early-stage HCC treated with RFA, keratin 19 has been found as a risk factor for recurrence after ablation [53] and glutamine synthetase was correlated with reduced mortality [54].

Locoregional therapy could cause tumor necrosis and stimulate the immunomodulatory effect. The neutrophil-to-lymphocyte ratio (NLR), which is a proposed inflammatory score, can be used as an independent prognostic factor in HCC treatment. A recent study of 86 patients treated with TACE or TARE found that NLR greater than 3 was significantly associated with early disease progression [55]. The increase of circulating T helper 17 cells 30 days after TACE was a predictor of longer TTP and higher OS [56]. A study analyzing 111 patients treated with cryoablation found that the increase of circulating regular T cells which are associated with antitumor immune response was an independent predictor of tumor progression and recurrence [57]. On an animal study, hepatic arterial bland embolization has also been shown to induce local and systemic increased infiltration of Th17 cells,

highlighting the potential application of transarterial embolic therapies as an immunomodulator of the tumor microenvironment [58].

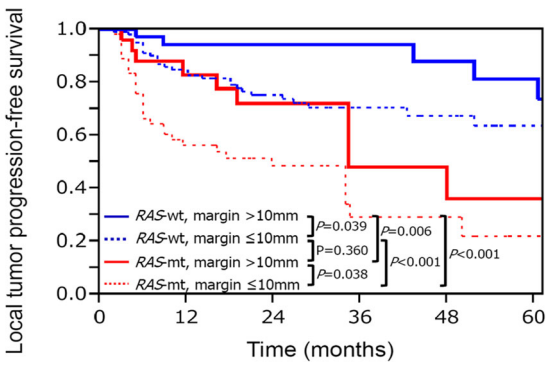
Colorectal Cancer Liver Metastases

Colorectal cancer is the fourth most common malignancy and the third leading cause of cancer-related death in the world [59]. The liver is the most common site of metastases, and colorectal liver metastases (CLM) contribute to the leading cause of mortality [60, 61]. Although surgical resection is considered the gold standard treatment modality for curative intent, percutaneous ablation is a well-established locoregional therapy for patients who are poor surgical candidates [62–64].

Local tumor control is the main goal for an effective percutaneous image-guided ablation. Low tumor progression rates are desirable due to the relationship between progression-free survival and disease-free survival, which are considered to influence overall survival [65, 66]. Several factors have been evaluated that may predict local outcomes of ablation in CLM. Tumor size and the minimal ablation margins are two of the most recognized morphological factors [63, 67–69]. Recently, researchers have focused on exploring the prognostic of molecular biomarkers in the treatment of CLM. The RAS gene family (KRAS, NRAS, and HRAS) mutation is one of the relevant prognostic biomarkers among patients undergoing CLM treatment, such as resection or percutaneous image-guided ablation [70–73]. Mutations in the RAS gene family are present in up to 40% of the patients with colorectal cancers [74]. Mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) signaling pathways are two well-established downstream effectors of the epidermal growth factor receptor (EGFR). The RAS GTPase, a membrane-bound GTP-binding protein that stimulates cellular growth and proliferation, is a downstream component of the MAPK pathway.

Patients with RAS mutations have worse survival when compared to patients with wild-type RAS colorectal cancer [75, 76]. Various studies have revealed that mutant RAS was a risk factor for LTP in patients undergoing percutaneous image-guided ablation [70–73]. In 2017, a study analyzed 92 patients with 137 ablated CLM and showed that mutant RAS patients had worse 3-year local tumor progression-free survival (LTPFS) compared to wild-type RAS patients (35% versus 71% respectively, $P < 0.001$) [71]. Furthermore, in ablated CLM with LTP, patients with mutant RAS had earlier progression and smaller size of the ablated CLM compared with wild-type RAS. In 2018, the patients of the above-mentioned study were combined into a two-institutional analysis of 136 patients [70••]. The authors showed that achieving minimal ablation margins >10 mm can significantly improve the LTPFS among mutant RAS CLM ($P = 0.038$) (Fig. 2). In another study, Shady et al. reported a higher LTP rate for mutant RAS CLM with minimal ablation margins of 1–5 mm compared with wild-type RAS of the same minimal ablation margins (43% versus 80%, respectively, $P = 0.02$), and the risk of progression was 15.6-fold when compared with wild type tumors with margins ≥6 mm [72]. According to these findings, minimal ablation margins of ≥10 mm should be achieved in particular for mutant RAS CLM to offer the appropriate local tumor control [70, 72]. Besides, KRAS mutation was found as a risk factor of new liver metastases development and peritoneal metastases in colorectal cancer patients [72]. For overall survival, KRAS mutation was a predictor and retained significance on multivariate analysis (Hazard ratio: 2, 95% confidence interval: 1.2–3.3, $P = 0.009$) [72]. Recently, a retrospective analysis of 154 CLM also reported that KRAS mutation status and minimal ablation margin were significant predictors for LTP [73].

The impact of RAS mutant status on treatment outcomes of transcatheter arterial-directed treatments has also been reported. Two retrospective studies reported that KRAS mutation was a negative predictor of progression-free survival (PFS) (91days, RAS-mutant vs. 166 days, RAS-wild type; [$P = 0.002$]) and OS (4.8 months, RAS-mutant vs. 9.5 months, RAS-wild type; [$P = 0.041$]) in patients undergoing TARE [77, 78]. The PI3K signaling pathway mutation, another EGFR downstream effector, was reported as a negative predictor of LTP in an analysis of 40 CLM patients treated with TARE [79]. However, recently another retrospective analysis



Patients at risk

RAS-wt, margin >10mm	35	33	24	20	14	12
RAS-wt, margin ≤10mm	103	79	51	28	21	11
RAS-mt, margin >10mm	25	17	13	6	4	3
RAS-mt, margin ≤10mm	55	28	17	6	5	2

Fig. 2 Comparison of local tumor progression-free survival among patients of colorectal liver metastasis with different RAS mutant status and minimal ablation margins treated by ablation. Legend: RAS-wt: RAS wild-type; RAS-mt: RAS mutant

Reproduced from Calandri M, Yamashita S, Gazzera C, Fonio P, Veltri A, Bustreo S, et al. Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. Eur Radiol. 2018;28(7):2727-34. Used with permission.

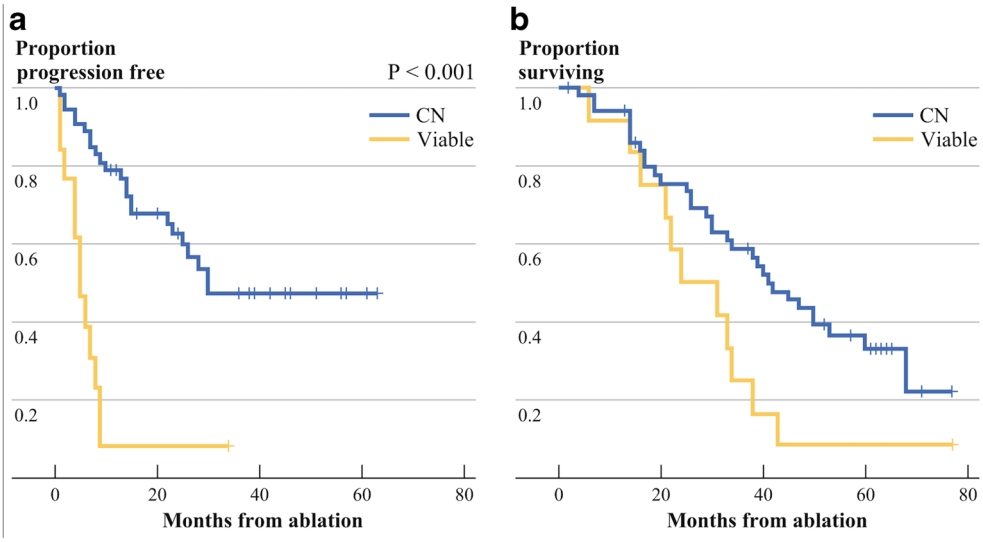


Fig. 3 Comparison of local tumor progression-free survival (**a**) and overall survival (**b**) among patients with viable Ki-67 tumor cells or coagulation necrosis (CN) on the electrode after liver primary or secondary tumor RFA Reproduced from Sofocleous CT, Garg S, Petrovic LM, Gonen M, Petre EN, Klimstra DS, et al. Ki-67 is a prognostic biomarker of survival after radiofrequency ablation of liver malignancies. Ann Surg Oncol. 2012;19(13):4262-9. Used with permission.

of 103 patients reported that KRAS, PI3KCA, or BRAF mutations were neutral predictors of LTPFS and OS [80].

There are some serum biomarkers reported affecting the clinical outcome of TARE in the treatment of CLM. For example, circulating nucleosomes and immunogenic cell death markers measured from the peripheral blood were found to be prognostic predictors for OS in two reports [81, 82]. And the high level of high-mobility group box 1 (HMGB1), an immunogenic cell death marker, measured before and after the radioembolization was found to be associated with poor OS and treatment response [82].

Miscellaneous Hepatic Tumors

The Ki-67 is an antigen associated with cell proliferation and has been used as an independent predictor of outcomes in different types of cancer [83–87]. Two studies analyzing the primary or metastatic hepatic tumor tissue adherent to the electrode after RFA reported that expression of Ki-67 was an independent predictor of LTP and OS [88, 89]. Besides, the fraction of Ki-67-positive tumor cells (Ki-67 index) is a reliable pathological grading marker for neuroendocrine tumors [90]. In a study of 45 patients who had undergone

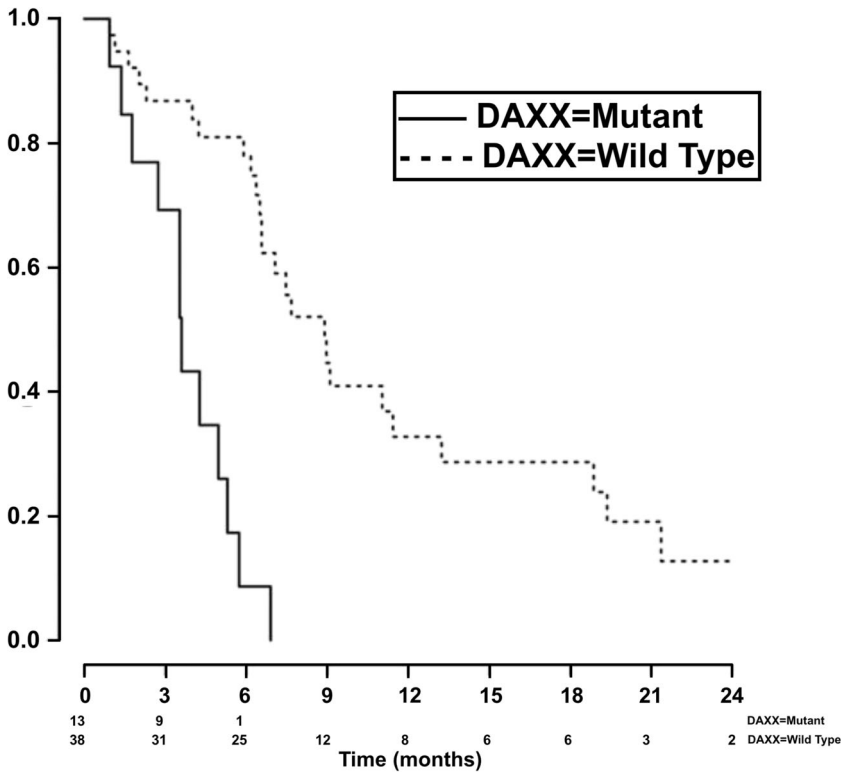


Fig. 4 For patients with neuroendocrine liver metastases treated by transarterial embolization, the median hepatic progression free-survival for DAXX mutant was 108 days compared with 267 days for DAXX wild type patients Reproduced from Ziv E, Rice SL, Filtes J, Yarmohammadi H, Boas FE, Erinjeri JP, et al. DAXX mutation status of embolization-treated neuroendocrine tumors predicts shorter time to hepatic progression. J Vasc Interv Radiol. 2018;29(11):1519-26. Used with permission.

TARE for neuroendocrine liver metastases, the Ki-67 index less than or equal to 2% was associated with longer PFS than a Ki-67 index of more than 2% (Fig. 3) [91]. Another study that analyzed 17 patients with primary or metastatic hepatic tumors reported that genes associated with the Wnt/β-catenin and hypoxia signaling pathways were highly expressed in patients having no radiographic response following TAE [92]. Other biomarkers such as the DAXX gene mutation in pancreatic neuroendocrine tumor liver metastases (Fig. 4) and the PI3K pathway mutation in breast invasive ductal carcinoma liver metastases have been shown to have impacts on the prediction of treatment response and local tumor control following TAE and TARE, respectively [93, 94].

Lung Cancers

The traditional prognostic predictors of local recurrence in percutaneous image-guided ablation include tumor size and ablation margin [95, 96]. The role of tumor biomarkers in predicting treatment response in percutaneous image-guided ablation of lung cancer is limited to a few studies. One study analyzed the presence of Ki-67 tumor cells from the adherent tissue on the electrodes of RFA after the ablation of primary or metastatic lung tumors up to 5 cm. The 1- and 3-year LTPFS rates of patients with viable tumor cells positive to Ki-67 were less than patients with negative results (34% versus 75%, and 0 versus 31%, respectively, $P = 0.003$). The 3-year disease-specific survival rates were 33% and 73% for patients with positive and negative Ki-67, respectively ($P = 0.007$). In large (>2 cm) and small (≤2 cm) tumor size groups, the presence of Ki-67 tumor cells was an independent predictor of shorter LTPFS and disease-specific survival (Fig. 5) [97]. In a study of treating primary lung adenocarcinoma with RFA,

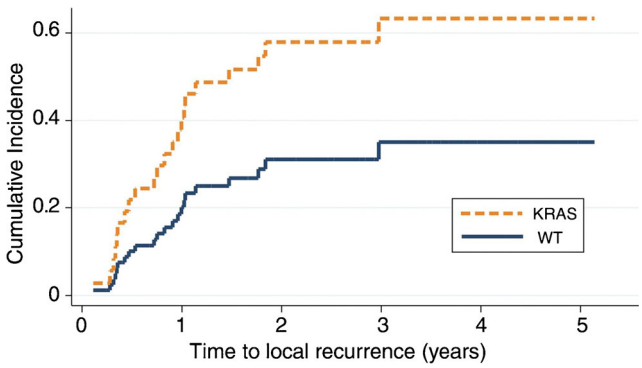


Fig. 5 Comparison of cumulative incidence function of time to local recurrence among patients of primary lung adenocarcinoma with KRAS mutation (KRAS) or wild-type (WT) treated by ablation
Reproduced from Ziv E, Erinjeri JP, Yarmohammadi H, Boas FE, Petre EN, Gao S, et al. Lung adenocarcinoma: predictive value of KRAS mutation status in assessing local recurrence in patients undergoing image-guided ablation. Radiology. 2017;282(1):251-8. Used with permission.

Table 1 Summary of biomarkers and impacts on locoregional treatment

Biomarkers	Impacts on local tumor treatment	Relevant references
Hepatocellular carcinomas		
Alpha-fetoprotein	The low pre- and post-therapeutic levels and more reduction of AFP after ablation were associated with less tumor recurrence and higher overall survival The high pre-therapeutic level and less reduction of AFP after TACE or TARE were predictors of lower progression-free survival and overall survival	Casadei et al. [8], Shiina et al. [9], Tsai et al. [10], Kao et al. [11], Lee et al. [12], Bhutiani et al. [13], Riaz et al. [14], Tateishi et al. [18], Park et al. [25]
Lens culinaris agglutinin-reactive fraction of α-fetoprotein (AFP-L3)	The increase of AFP-L3 level was associated with a higher risk of recurrence and lower overall survival following ablation The reduction of AFP-L3 level after TACE was associated with better radiological response and higher overall survival	Shiina et al. [9], Tateishi et al. [18], Ogawa et al. [19], Huang et al. [27]
(Des-gamma carboxy-prothrombin) DCP	The high level of DCP was associated with a higher risk of local tumor progression, intrahepatic recurrence, and poor survival following ablation The pre-therapeutic level and reduction of DCP after TACE were associated with objective response, longer time to progression, and higher overall survival	Shiina et al. [9], Lee et al. [12], Kobayashi et al. [20], Lee et al. [21], Okuwaki et al. [22], Park et al. [25], Arai et al. [26]
MicroRNAs	The serum level of microRNAs was a risk factor of disease-free survival and overall survival following ablation and it was also associated with treatment response following TACE The low level of tissue microRNAs was a predictor of recurrence after RFA	Cho et al. [28, 29], Ali et al. [30•], Kim et al. [31], Luo et al. [32]
Circulating tumor cells	The high circulating tumor cell count was a predictor of lower progression-free	Shen et al. [33]

Table 1 (continued)

Biomarkers	Impacts on local tumor treatment	Relevant references
	survival and overall survival after TACE	
The genetic polymorphism of SERPINE1, GSTO2, and ADAMTS5	The genetic polymorphism was associated with treatment response following TACE	Divella et al. [34], Wang et al. [35], Huang et al. [36]
NRF2 signaling pathway	The patients with mutation had shorter time to progression after TAE	Ziv et al. [38••]
Genes related to chemotherapy--sensitivity, hypoxia, mitosis, and inflammatory	The genes were associated with the radiological response after TACE	Gaba et al. [37]
Endothelial cell-specific molecule 1 (ESM-1) gene	The gene was related to early recurrence following RFA	Ziol et al. [52]
Vascular endothelial growth factor (VEGF)	The high pre-therapeutic level of VEGF was a prognostic factor of both recurrence-free survival and overall survival following RFA	Poon et al. [40, 41], Hsieh et al. [42]
	The high pre- and post-therapeutic levels of VEGF were associated with tumor progression after TACE	
Ferritin	The low serum ferritin level was a predictor of shorter time to recurrence and lower overall survival after RFA	Facciorusso et al. [44]
Insulin-like growth factor-1 (IGF-1)	In TACE, patients having a high pre-therapeutic IGF-1 level had longer time to progression and higher overall survival	Liu et al. [46]
Osteopontin	The low baseline osteopontin level and less reduction after TACE had better treatment response and survival	Kim et al. [48]
Circulating nucleosomes	The serum level of circulating nucleosomes after TACE was associated with local treatment response	Kohles et al. [49]
Immune cells	The high neutrophil-to--lymphocyte ratio was associated with early disease progression after TACE or TARE	Taussig et al. [55], Liao et al. [56], Zhou et al. [57]
	The increase of circulating T helper 17 cells after TACE was a predictor of longer time to progression and higher overall survival	
	In cryoablation, the increase of circulating regular T cells was a predictor of tumor recurrence	
Colorectal liver metastases		
RAS gene	Mutant RAS patients had earlier local tumor progression, worse overall survival, and a higher risk of new liver metastases after ablation	Calandri et al. [70••], Odisio et al. [71], Shady et al. [72], Jiang et al. [73], Lahti et al. [77], Magnetta et al. [78]
	The KRAS mutation was a negative predictor of progression-free survival and overall survival following TARE	
PI3K signaling pathway	In TARE, the PI3K signal pathway mutation was associated with longer time to progression	Ziv et al. [79]
Circulating nucleosomes and immunogenic cell death serum markers	The high level of biomarkers was associated with poor treatment response and lower overall survival in patients undergoing TARE	Fahmueller et al. [81, 82]
Primary or metastatic liver tumors		
Ki-67	Expression of Ki-67 in the tissue adherent to the electrode of RFA was a predictor of shorter local tumor progression and lower overall survival	Sofocleous et al. [88, 89]
Wnt/β-catenin and hypoxia signaling pathways	The signaling pathways were highly expressed in patients having no treatment response following TAE	Ziv et al. [92]
Neuroendocrine liver metastases		
Ki-67 pathologic grading index	The low Ki-67 index was associated with higher progression-free survival in neuroendocrine liver metastases	Sommer et al. [91]
DAXX gene	The expression of the gene was a predictor of treatment response and	Ziv et al. [93]

Table 1 (continued)

Biomarkers	Impacts on local tumor treatment	Relevant references
	local tumor control after TAE	
Breast invasive ductal carcinoma liver metastases		
PI3K signaling pathway	The expression of the signaling pathway was a predictor of treatment response and local tumor control after TARE	Deipolyi et al. [94]
Primary or metastatic lung tumors		
Ki-67 gene	The presence of Ki-67 tumor cells on the electrode of RFA was a predictor of local tumor progression and lower disease-specific survival	Sofocleous et al. [97]
Primary lung adenocarcinomas		
KRAS gene	The KRAS mutant status was a predictor of local tumor recurrence after ablation	Ziv et al. [98]

microwave ablation, or cryoablation, the 1- and 3-year local recurrence rates of KRAS mutant tumors were 40% and 63% compared with 20% and 35% for KRAS wild-type tumors (P = 0.05). Furthermore, the KRAS mutant status, tumor size, and eastern cooperative oncology group status were significant independent predictors of local tumor recurrence. However, there was no significant association with minimum ablation margins [98].

Conclusion

Interventional oncology is rapidly evolving and playing an increasing role in oncology. Precision and personalized interventional oncology therapies based on specific tumor biomarkers have brought a new vision in the management of cancer (Table 1). Besides using conventional clinical and histological features, combining serum or tissue biomarkers will tailor the development of individualized therapies. The identification of patients with a higher risk of recurrences will be useful to allocate appropriate treatments. It is expected that including prognostic biomarkers will expand and enhance current guidelines in the treatment of specific cancers. Moreover, as the rapidly evolving technology gives advancement in biomarkers collecting, such as liquid biopsy, there is a need to identify novel biomarkers to understand the behavior of the tumor and the susceptibility of each therapeutic strategy. Further evolution of personalized interventional oncology should potentiate the synergies with biomarkers to improve oncologic outcomes.

Compliance with Ethical standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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