



# The Number of Positive Tumor Marker Status Is Beneficial for the Selection of Therapeutic Modalities in Patients with Hepatocellular Carcinoma

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## Abstract

Hepatic resection (HR) and radiofrequency ablation (RFA) are popular local therapies for early-stage hepatocellular carcinoma (HCC). Alpha-fetoprotein, *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein, and des-c-carboxy prothrombin are well-known and useful tumor markers for HCC. The positive number status of these tumor markers has recently been demonstrated as beneficial for predicting outcome for HCC patients treated with local therapy. Although the normal ranges reported have differed by institution, the positivity of tumor markers is consistent and can easily be assessed. Kumamoto and Wakayama's group clearly demonstrated the following: 1) Regardless of the degree of tumor stage, a triple-positive tumor marker profile can predict poor outcome in HCC patients undergoing HR; 2) For RFA alone, HCC patients with double- and triple-positive status, having less than three lesions and lesions  $\leq 3$  cm in diameter show comparably insufficient outcomes; 3) For HCC patients with lesions  $\leq 5$  cm in Child-Pugh grade A, HR is preferred over RFA; 4) Microvascular invasion rates increased even in the double-positive patients, while poorly differentiated HCC was frequently observed only in the triple-positive patients; and 5) RFA with chemoembolization, anatomical liver resection, and postoperative adjuvant chemoembolization or hepatic arterial chemotherapy might improve the outcome for patients with highly malignant HCC with multiple positive tumor markers. However, the impacts of these therapies still need to be evaluated in prospective comparative studies.

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**Abbreviations:** AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; DCP, des-c-carboxy prothrombin; DSS, disease-specific survival; HCC, hepatocellular carcinoma; HR, hepatic resection; HZR, hazard ratio; MI, microvascular invasion; OS, overall survival; RFA, radiofrequency ablation; RFS, recurrence-free survival; TD, tumor differentiation.

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## Introduction

Hepatic resection (HR) and radiofrequency ablation (RFA) are common and curative treatments for early-stage hepatocellular carcinoma (HCC).<sup>1–3</sup> Numerous papers have been published about various tumor markers as indicators of postoperative outcomes.<sup>4–10</sup> Among them, alpha-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and des-c-carboxy prothrombin (DCP) are well-known useful tumor markers. Various cutoff levels of these tumor markers have been used; however, the normal limits reported from the various institutes are often different. Thus, optimal cutoff levels cannot be universally applied in studies. On the other hand, the determination of negativity or positivity for tumor markers is quite easy and can be performed regardless of the institutional cutoff values. Recently, the status of three positive tumor markers (AFP, AFP-L3 and DCP) was established as a beneficial prognostic factor for HCC patients treated with HR or RFA.<sup>11–15</sup>

Histological HCC, characterized by features including microvascular invasion (MI) and tumor differentiation (TD), is a great prognostic factor for HR<sup>16–20</sup> and RFA.<sup>21–24</sup> Highly malignant tumors have worse postoperative outcomes; however, the curability of the two treatment modalities might be different according to the grade of tumor malignancy. It has been recently reported that the expression status of positive markers can predict histological tumor malignancy.<sup>11,12,14</sup>

In this review, we have summarized the correlation between the expression number of positive markers and the therapeutic effects of local therapy in HCC patients.

## Number of positive tumor markers and prognosis in HCC patients undergoing HR

Two studies have reported on the expression number of positive tumor markers and prognosis in HCC patients treated with HR<sup>11,12</sup> (Table 1). The tumor markers studied were AFP, AFP-L3, and DCP. Kiriya and colleagues<sup>11</sup>

**Table 1. Positive tumor marker number and outcome in HCC patients who underwent HR and RFA**

REF number	Treatment	Patient number	Classification	Patient ratio	2-year RFS	3-year RFS	5-year RFS	5-year OS	5-year DSS
11	HR	199	TP	14%			17%	61%	
			Non-TP	86%			30%	80%	
12	HR	185	TP	21%	19%				36%
			Non-TP	79%	38–56%				55–83%
14	HR	136	TP	21%	60%			76%	
			Non-TP	79%	50–71%			54–78%	
	RFA	160	TP	20%	27%			48%	
			Non-TP	80%	43–83%			62–83%	
15	RFA	160	DP	19%		16%		33%	
			TP	6%		11%		19%	
			Non-DP and -TP	75%		19–30%		78–82%	

**Abbreviations:** DP, double positive; DSS, disease-specific survival; HCC, hepatocellular carcinoma; HR, hepatic resection; OS, overall survival; REF, reference; RFA, radiofrequency ablation; RFS, recurrence-free survival; TP, triple positive.

evaluated 185 resected HCC patients, known as the Wakayama cohort. Our group also evaluated 199 resected HCC patients that met the Milan criteria, the Kumamoto cohort<sup>12</sup> which included a larger number of early-stage HCC patients (in comparison with the Wakayama cohort). In the Kumamoto cohort, the number of positive tumor markers was significantly associated with larger tumor size (>3 cm) and multiple tumors. Based on a qualitative assessment of these three tumor markers, there were 29.6% and 13.0% negative, 37.2% and 40.5% single positive, 19.1% and 25.4% double positive, and 14.1% and 21.1% triple positive, respectively in the Kumamoto and Wakayama cohorts.

In the Kumamoto cohort, the 5-year recurrence-free survival (RFS) rate was significantly worse for the triple positive group compared to the non-triple positive group (17.1% vs. 29.5%,  $p = 0.038$ ). The 5-year overall survival (OS) rates were 61.4% and 80.2% for the triple positive and non-triple positive groups, respectively ( $p = 0.013$ ). The 5-year OS rate was about 20% worse for the triple positive group. By multivariate analysis, independent predictive factors for poor RFS were positivity for hepatitis C virus-antibody [hazard ratio (HZR), 1.65;  $p = 0.015$ ], non-initial treatment (HZR, 1.87;  $p = 0.005$ ), and triple positive tumor markers status (HZR, 1.68;  $p = 0.038$ ); and, for poor OS, the independent predictive factors were indocyanine green 15-min retention rate >12.6% (HZR, 2.46;  $p = 0.0146$ ), maximum tumor diameter >3 cm (HZR, 2.71;  $p = 0.004$ ), and triple positive tumor markers status (HZR, 2.57;  $p = 0.020$ ).

In the Wakayama cohort, the 2-year RFS rates were 19.4%, 38.2%, 55.5%, and 50.7% in the triple positive, double positive, single positive, and triple negative groups, respectively. The 5-year disease-specific survival (DSS) rates were 35.9%, 54.7%, 82.9%, and 62.8% in the same groups. Multivariate analysis demonstrated that independent risk factors for poor RFS included Child–Pugh class B [HZR, 2.00; 95% confidence interval (CI), 1.03–3.87], presence of multiple tumors (HZR, 2.53; 95% CI, 1.73–3.71), and triple positive markers status (HZR, 1.78; 95% CI, 1.10–2.86); and, for poor DSS, the independent risk factors were presence of multiple tumors (HZR, 2.38; 95% CI, 1.31–4.33) and triple positive markers status (HZR, 2.41; 95% CI, 1.20–4.83).

Thus, regardless of the degree of tumor stage, a triple positive tumor marker profile was an independent predictive factor for both recurrence and long-term survival in HCC patients who underwent HR.

#### Number of positive tumor markers and prognosis in HCC patients undergoing RFA

We recently reported the utility of determining the number of positive tumor markers for HCC patients treated with RFA<sup>15</sup> (Table 1). A total of 160 patients with less than three lesions and with lesions no more than 3 cm in diameter were selected and treated with percutaneous, endoscopic or open RFA. The pre-treatment positive rates of these markers were 31.9%, 43.1%, 19.4%, and 5.6% in the negative, single positive, double positive, and triple positive tumor marker groups, respectively. The frequency of triple positive patients was less in the RFA group than in the HR group.<sup>11,12</sup> Interestingly, in the RFA group, the double and positive tumor marker HCCs provided similarly insufficient outcomes. The 3-year RFS rates were 30%, 19%, 16%, and 11% ( $p = 0.02$ ) and the OS rates were 94%, 88%, 67%, and 37% ( $p < 0.001$ ) in the negative, single, double, and triple positive groups, respectively. The 2-year local recurrence rates at the adjacent area of initial ablated lesion were 6.5%, 0%, 41.2%, and 61.9%, respectively in these groups ( $p < 0.001$ ). By multivariate analysis, a double or triple positive tumor marker status was an independent risk factor for poor OS (HZR, 4.21; 95% CI, 1.89–9.37;  $p < 0.001$ ) and local recurrence (HZR, 5.48; 95% CI, 2.44–12.33;  $p < 0.001$ ).

#### Selection of HR or RFA for HCC patients by assessment of the number of positive tumor markers

The Wakayama group<sup>14</sup> recently reported the utility of positive conditions of tumor markers for treatment selection of patients with HCC (Table 1). A total of 296 patients with solitary HCC of  $\leq 5$  cm and presenting Child–Pugh grade A (136 HR and 160 RFA) were analyzed. Actually, in the HR group, the frequency of patients undergoing anatomical resection was increased among patients with positive status for three

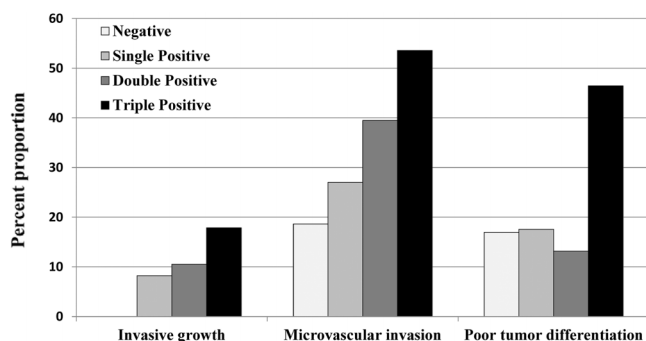
tumor markers, while in the RFA group, the frequency of patients treated with RFA following chemoembolization was increased among patients with positive status for three tumor markers.

The 5-year OS rates of HR and RFA were similar, 70.1% and 69.8%, respectively ( $p = 0.14$ ). Conversely, when we analyzed their outcome according to the positive number of three tumor markers, the 5-year OS rates were 60.6%, 78.2%, 54.2%, and 75.9% in the HR group, whereas the rates were 83.3%, 75.7%, 62.2%, and 47.6% in the RFA group, respectively, in patients with negative, single positive, double positive, and triple positive tumor markers. The  $p$ -values were different between patients treated with HR and RFA: 0.45 in negative, 0.10 in single positive, 0.77 in double positive, and  $<0.01$  in triple positive. By multivariate analysis, RFA application was an independent poor prognostic factor only in the triple positive group (HZR, 1.78; 95% CI, 1.16–2.72); and, for HCC patients, HR was preferable to RFA for a tumor size of  $\leq 5$  cm in Child–Pugh grade A.

### Number of positive tumor markers and histological malignancy of HCC

Three studies have reported on the expression number of positive tumor markers and histological HCC malignancy.<sup>10,12,14</sup> We presented the data from patients with HCC who met the Milan criteria in the Kumamoto cohort<sup>12</sup> and from patients with solitary HCC  $\leq 5$  cm in diameter in the Wakayama cohort.<sup>14</sup> Positive data from the Kumamoto cohort is depicted in Fig. 1.<sup>12</sup> MI rates rose significantly in a stepwise manner according to the increased number of positive tumor markers expressed. For the Kumamoto and Wakayama cohorts, respectively, these were 18.6% and 16.7% in the negative group, 27.0% and 29.3% in the single positive group, 39.5% and 46.8% in the double positive group, and 53.6% and 56.4% in the triple positive group.

The percentage of poor TD was significantly increased only in the triple positive group in the Kumamoto cohort (negative, 17.0%; single positive, 17.6%; double positive, 13.2%; triple positive, 46.4%). Similarly, tumors representing the Edmondson–Steiner classification grades III or IV were significantly different among the four groups in the Wakayama cohort (negative, 12.5%; single positive, 13.3%; double positive, 25.5%; triple positive, 35.9%). The rate of invasive growth showed a stepwise increase among the four groups in the Kumamoto cohort (negative, 0%; single positive, 8.2%; double positive, 10.5%; triple-positive, 17.9%).



**Fig. 1. Association between histological factors and number of positive tumor markers.**

### Treatment strategy in consideration of the positive tumor marker number profile

The positive tumor marker number profile can clearly estimate recurrence and prognosis in HCC patients who have undergone local therapy, like HR and RFA.<sup>11–15</sup>

Preoperative assessment for higher recurrence risk allows for planning of an appropriate treatment strategy. According to the histological examination, MI rates increased even in the double positive patients. Both poor differentiation and MI were frequently observed in the triple positive patients. These characteristics were poor prognostic factors after HR<sup>16–20</sup> and potent predictors for local recurrence or tumor cell seeding after RFA.<sup>21–24</sup>

The prognosis of HCC after HR was excellent, if the positive number of tumor markers were within a value of 2. For the RFA-treated group in the Kumamoto cohort, double-positive patients showed equally poor prognosis compared to triple-positive patient.<sup>15</sup> Conversely, in the Wakayama cohort—limited to double-positive patients—the prognoses were similar in patients undergoing HR and RFA.<sup>14</sup> For double positive and triple positive patients, if hepatic function is sufficient then HR should be a first-choice therapy, instead of RFA. If hepatic function is insufficient, RFA in combination with chemoembolization might be recommended, which can improve survival over RFA alone.<sup>25</sup> Prior chemoembolization can reduce arterial blood flow and reduce the heat-sink effect with RFA.<sup>26</sup> Similarly, RFA plus percutaneous alcohol injection or sorafenib administration can enhance the effect of RFA.

Triple positive tumor marker status was an independent poor prognostic factor even after curative HR. In patients with good liver functional reserve, anatomical HR is advocated based on better outcome for HCC patients with MI.<sup>27,28</sup> Post-operative adjuvant chemoembolization or hepatic arterial chemotherapy for highly malignant HCC might be useful to reduce recurrence in the remnant liver.<sup>29–31</sup>

In conclusion, preoperative estimation of positive tumor marker number is strongly recommended for HCC patients who undergo local therapy, including HR and RFA.

### Conflict of interest

The authors have no conflict of interests related to this publication.

### Author contributions

Conceived the study and drafted the manuscript (TB, SN, HN), performed the analysis and interpretation of data (SN, HN, HO, TK, KI, HH, YK, KK, DH, YY, AC), revised the paper for important intellectual content (HB, TI). All authors participated in the acquisition of data and approved the final manuscript.

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