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TP53 Alteration and its Effect on Pathologic Response are Associated with Survival After Resection of Colorectal Liver Metastases

Harufumi Maki, MD, PhD[1], **Antony Haddad, MD**[1], **Reed I. Ayabe, MD**[1], **Mateo Lendoire, MD**[1], **Isha Khanduri, MD**[2], **Dipen M. Maru, MD**[2], **Jean-Nicolas Vauthey, MD**[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[2]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Keywords

colorectal cancer; liver metastasis; liver resection; pathologic response; TP53; somatic gene alteration

INTRODUCTION

Pathologic response (PR) to preoperative chemotherapy has been shown to be associated with improved overall survival (OS) in patients who undergo hepatectomy for colorectal liver metastasis (CLM).[1, 2] The role of biological factors, including RAS, TP53, APC, SMAD4, BRAF, and FBXW7, on the prognosis is well established, but the effect of these gene mutations on pathologic response has been scarcely studied.[3] Only RAS alteration was previously reported to decrease the rate of PR.[4] In this study, we assessed the effect of known gene alterations on PR and the correlation between gene mutations and PR on OS in patients with CLM.

Corresponding Author: Jean-Nicolas Vauthey, MD, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1484, Houston, TX 77030, USA, jvauthey@mdanderson.org.

AUTHOR CONTRIBUTIONS

Study concept: **Harufumi Maki** and **Jean-Nicolas Vauthey**
Study design: **Harufumi Maki** and **Jean-Nicolas Vauthey**
Data acquisition: **Harufumi Maki, Antony Haddad, Mateo Lendoire, Isha Khanduri** and **Dipen M. Maru**
Quality control of data and algorithms: **Harufumi Maki** and **Jean-Nicolas Vauthey**
Data analysis and interpretation: **Harufumi Maki, Antony Haddad**
Statistical analysis: **Harufumi Maki**
Article preparation: **Harufumi Maki, Antony Haddad** and **Reed I. Ayabe**
Article editing: **All authors**
Article review and approval: **All authors**

CONFLICT OF INTEREST DISCLOSURES

Nothing to disclose.

PATIENTS AND METHODS

The Institutional Review Board at MD Anderson Cancer Center approved this study protocol (#2023-0050). From a prospectively maintained database, we collected data on patients who underwent initial R0 or R1 hepatectomy for CLM after receiving a maximum of 12 cycles of first-line preoperative chemotherapy between January 2004 and December 2020. Patients with missing data were excluded. Next-generation sequencing using tumor DNA from primary or CLM specimens was performed with an AmpliSeq cancer-related multigene panel including at least 46 genes using the Ion Torrent Personal Genome Machine (Life Technologies, Carlsbad, CA) in a Clinical Laboratory Improvement Amendment–certified molecular diagnostic laboratory. Major pathologic response (majorPR) was defined as tumor viability of less than 50%. Minor pathologic response (minorPR) was defined as tumor viability above 50%.[2] Clinicopathologic and biologic factors associated with majorPR and OS were evaluated by multivariate analyses, using backward elimination with $P < 0.05$ to select variables. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Median [interquartile range (IQR)] follow-up and OS of the whole cohort (N = 458) was 3.8 [2.3-5.4] and 6.9 [3.4–not reached] years, respectively. During the follow-up period, 167 patients (36.5%) died. MajorPR was achieved in 252 (55.0%) patients. Median [IQR] percentage of pathological tumor viability was significantly lower in patients with TP53 wild-type than those with TP53 alteration (30 [10–50] % vs 47 [24–70] %, $P < 0.001$) (Figure 1). Multivariate analysis revealed that oxaliplatin-containing regimen (risk ratio (RR): 2.54, 95% confidence intervals (CI): 1.58–4.07, $P < 0.001$), bevacizumab-containing regimen (RR: 2.15, 95%CI: 1.36–3.39, $P = 0.001$) and TP53 alteration (RR: 0.42, 95%CI: 0.27–0.66, $P < 0.001$) were independently associated with majorPR (Table 1).

The cohort was divided into 3 groups: TP53 wild-type with majorPR (N = 91, 19.9%), TP53 alteration with majorPR (N = 161, 35.2%), and minorPR (N = 206, 45.0%). Five-year OS of the different groups is shown in Figure 2. Multivariate analysis revealed that patients in the TP53 wild-type with majorPR group (hazard ratio (HR): 0.49, 95%CI: 0.31–0.77, $P = 0.002$) and those in the TP53 alteration with majorPR group (HR: 0.70, 95%CI: 0.49–1.00, $P = 0.048$) had significantly better OS compared to those in the minor PR group (Table 2).

DISCUSSION

This is the first study showing TP53 alteration is associated with worse PR. This effect can be due to TP53-mediated resistance to chemotherapy as this has been shown in colorectal cancer cell lines.[5] On the other hand, the statistical difference between the Kaplan-Meier curve (Figure 2) and multivariate analysis (Table 2) can be explained by the factors in the multivariate analysis such as chemotherapy regimen, co-existing mutations, or extrahepatic disease. Further studies targeting the combined association of TP53 and these factors with pathologic response and survival can help clarify the role of TP53 in CLM.[6]

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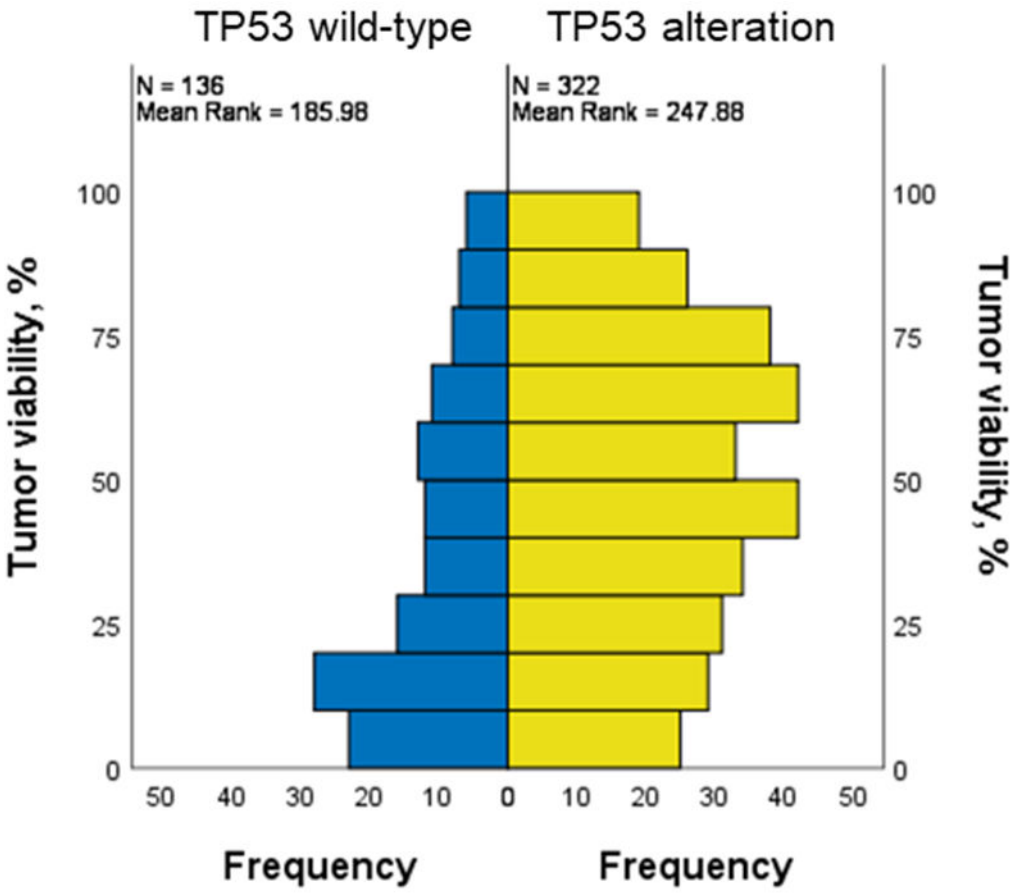
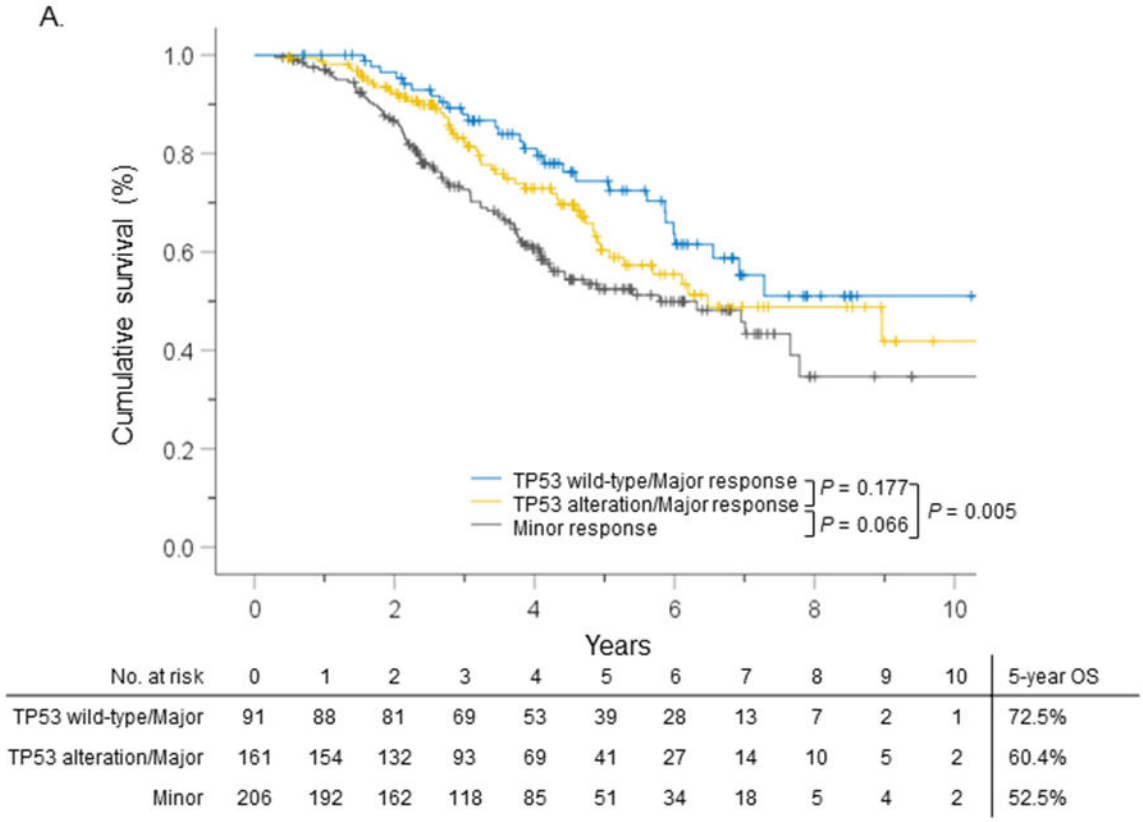


Figure 1.
Histogram of pathological tumor viability categorized by TP53 alteration.



No. at risk	0	1	2	3	4	5	6	7	8	9	10	5-year OS
TP53 wild-type/Major	91	88	81	69	53	39	28	13	7	2	1	72.5%
TP53 alteration/Major	161	154	132	93	69	41	27	14	10	5	2	60.4%
Minor	206	192	162	118	85	51	34	18	5	4	2	52.5%

Figure 2.
Overall survival (OS) stratified by TP53 alteration and pathologic response.

Table 1.

Factors associated with major pathologic response

Factors	No. of Patients	No. of Events	Multivariable RR[†]	95% CI	*P* value
Oxaliplatin-containing					
Yes	353	213	2.54	1.58–4.07	< 0.001
No	105	39	1 (referent)		
Bevacizumab-containing					
Yes	343	205	2.15	1.36–3.39	0.001
No	115	47	1 (referent)		
TP53 alteration					
Yes	322	161	0.42	0.27–0.66	< 0.001
No	136	91	1 (referent)		

Abbreviations: RR, risk ratio; CI, confidence interval

[†]The Binary logistic model analysis initially included age (continuous), sex, primary T stage (> T3 vs. ≤ T3), oxaliplatin-containing regimen, bevacizumab-containing regimen, RAS or BRAF, APC, TP53, PIK3CA, SMAD4 and FBXW7 alterations.

Table 2.

Factors associated with overall survival

Factors	No. of Patients	No. of Events	Multivariable HR[†]	95% CI	*P* value
Extrahepatic metastasis					
Yes	101	48	1.63	1.15–2.33	0.007
No	357	119	1 (referent)		
RAS or BRAF alteration					
Yes	264	102	1.43	1.03–1.99	0.035
No	194	65	1 (referent)		
SMAD4 alteration					
Yes	50	26	1.96	1.26–3.03	0.003
No	408	141	1 (referent)		
APC alteration					
Yes	248	82	0.62	0.45–0.86	0.004
No	210	85	1 (referent)		
Combination of TP53 alteration and PR					
TP53 wild-type/Major PR	91	28	0.49	0.31–0.77	0.002
TP53 alteration/Major PR	161	52	0.70	0.49–1.00	0.048
Minor PR	206	87	1 (referent)		

Abbreviations: HR, hazard ratio; CI, confidence interval; PR, pathologic response;

[†]The Cox proportional hazard model analysis initially included age (continuous), sex, primary T stage (> T3 vs. ≤ T3), primary lymph node metastasis, synchronous liver metastasis, extrahepatic metastasis, tumor size (continuous), tumor number (continuous), oxaliplatin-containing regimen, bevacizumab-containing regimen, surgical margin (R0 vs R1), posthepatectomy chemotherapy, RAS or BRAF, APC, PIK3CA, SMAD4 and FBXW7 alteration and combination of TP53 alteration and PR.