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SSAT PLENARY PRESENTATION

Alteration of *FBXW7* is Associated with Worse Survival in Patients Undergoing Resection of Colorectal Liver Metastases

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Abstract

Background For patients undergoing resection of colorectal liver metastases (CLMs), the prognostic role of somatic gene alterations is increasingly recognized. F-box/WD repeat–containing protein 7 (*FBXW7*) is a tumor suppressor gene found in approximately 10% of patients with colorectal cancer. The aim of this study is to assess the association of *FBXW7* with overall survival after CLM resection.

Methods Patients who underwent initial CLM resection during 2001–2016 and had genetic sequencing data were studied. Risk factors for overall survival (OS) were evaluated with Cox proportional hazards models using backward elimination.

Results Of 2045 patients who underwent CLM resection during the study period, 476 were included. The majority (90.5%) underwent prehepatectomy chemotherapy. A total of 27 patients (5.7%) had *FBXW7* alteration, along with 240 (50.4%) *RAS*, 337 (70.8%) *TP53*, 51 (10.7%) *SMAD4*, and 27 (5.7%) *BRAF*. Cox proportional hazards model analyses including 5 somatic gene alteration status and 12 clinicopathologic factors revealed *FBXW7*(hazard ratio [HR] 1.99, $P = 0.015$), *BRAF* (HR 2.47, $P = 0.023$), *RAS* (HR 2.42, $P < 0.001$), *TP53* (HR 2.00, $P < 0.001$), and *SMAD4* alterations (HR 1.90, $P = 0.004$) as significantly associated with OS, together with three clinicopathologic factors, prehepatectomy chemotherapy > 6 cycles (HR 1.51, $P = 0.021$), number of CLM (HR 1.05, $P = 0.007$), and largest liver metastasis diameter (HR 1.07, $P = 0.023$). The covariate-adjusted 5-year OS was significantly lower in patients with *FBXW7* alteration than in patients with *FBXW7* wild-type (40.4% vs.59.4%, $P = 0.015$).

Conclusions *FBXW7* alterations are associated with worse survival after CLM resection. The information on multiple somatic gene alterations is imperative for risk stratification and patient selection for CLM resection.

Keywords Liver resection · Metastatic colorectal cancer · Somatic gene alteration · Mutation · Genetic sequencing

Introduction

Liver resection remains the only curative treatment option for patients with colorectal liver metastases (CLMs). Clinicopathologic factors, such as number and diameter of CLM, concomitant extrahepatic metastases, carcinoembryonic antigen level, and surgical margins, are known to be associated with survival following CLM resection.[1,2] Evidence suggests that somatic gene alterations in *RAS*, *TP53*, and *SMAD4* are associated with survival following CLM resection and provide additional data that augments decision on treatment sequencing and patient selection.[3–12] However, the impact of rare alterations on oncologic outcomes has been recently described, such as those in *BRAF*, and thus their detection is critical for surgical decision-making and informed discussion on prognosis for patients with CLM.[13,14]

Yoshikuni Kawaguchi and Timothy E. Newhook contributed equally to this work.

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F-box/WD repeat–containing protein 7 (*FBXW7*) is a tumor suppressor gene implicated in the degradation of mediators of cell cycle progression. A previous study with extensive genetic analysis showed that *FBXW7* was altered in various human tumor types, with an overall alteration frequency of approximately 6%.[15] Of these, *FBXW7* alteration was found in 35% of cholangiocarcinoma, 31% of T cell acute lymphocytic leukemia, 10% of colorectal cancer, and 9% of endometrial cancer.[15] For patients with metastatic colorectal cancer, overall survival (OS) was significantly worse in patients with *FBXW7* alteration than in patients with *FBXW7* wild-type.[16] However, for patients who undergo resection of CLM, the prognostic role of *FBXW7* has not been reported. We hypothesized that *FBXW7* alterations would negatively impact survival for patients with resected CLM. Within this context, the primary aim was to evaluate the survival impact of *FBXW7* alteration for patients undergoing CLM resection.

Materials and Methods

Study Population

We identified patients who underwent initial CLM resection in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center from 2001 to 2016, from a prospectively maintained database. Patients who had genetic sequencing data more than 46 genes were included. Demographic and clinicopathologic characteristics, and survival outcomes, were collected. This study was approved by the institutional review board.

Surgical Management of CLM

As previously described,[9] our group performs preoperative chemotherapy followed by liver resection and postoperative chemotherapy in most patients with CLM. Preoperative chemotherapy generally consists of oxaliplatin- or irinotecan-containing regimens plus bevacizumab and is administered for 4 cycles. Postoperatively, 8 cycles of the same regimens without bevacizumab are administered.[17] CLMs are deemed resectable if negative surgical margins can be achieved while preserving an adequate standardized future liver remnant volume[18] If the future liver remnant is insufficient, preoperative portal vein embolization and two-stage hepatectomy are used. [19] Patients are followed after CLM resection with axial imaging every 3–4 months for the first 2 years and every 4–6 months for the subsequent 3 years.[20]

Somatic Gene Alteration Profiling

As previously described,[21] tumor DNA was isolated from 5-mm-thick unstained sections on the basis of tumor tissue blocks or slides from primary colorectal cancer or CLM specimens. Macrodissection was performed in cases of low tumor cellularity. Next-generation sequencing was performed with an AmpliSeq gene panel related to cancer (Supplementary Table 1) using the Ion Torrent Personal Genome Machine (Life Technologies, CA) in a Clinical Laboratory Improvement Amendment–certified molecular diagnostic laboratory.[22]

Definitions

We defined synchronous metastases as metastases diagnosed within 12 months of primary tumor diagnosis and a positive surgical margin as the presence of tumor cells within 1 mm of the transection line. Primary tumors were staged according to the *AJCC Cancer Staging Manual*, eighth edition.[23]

Statistical Analysis

KRAS and *NRAS* alterations were grouped in a single category, *RAS* alteration, and analyzed as previously described[24,25] and are supported by the fact that survival after CLM resection was worse in patients who had metastatic colorectal cancer and *NRAS* alteration.[26–28]

Categorical variables were expressed in numbers and percentages and were compared among groups using Fisher's exact test or the chi-square test, as appropriate. Continuous variables were expressed as median values with the interquartile range. A Cox proportional hazards model analysis was performed with clinicopathologic factors, somatic genes which were associated with prognosis (*BRAF*, *RAS*, *TP53*, and *SMAD4*),[29] and *FBXW7*. A Cox proportional hazards model analysis initially included age (continuous variable), sex, primary tumor location, T category, primary lymph node metastasis, prehepatectomy carcinoembryonic antigen level (continuous variable), timing of metastasis (synchronous vs. metachronous), prehepatectomy chemotherapy, extrahepatic disease, number of CLM (continuous variable), largest liver metastasis diameter (continuous variable), surgical margin status (R1 vs. R0), *BRAF* alteration, *RAS* alteration, *TP53* alteration, *SMAD4* alteration, and *FBXW7* alteration. A backward elimination with a threshold P value of 0.05 was used to select variables for the final models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each factor. We estimated the 5-year OS time and survival curves adjusted for covariates by using direct adjusted survival estimation.[30,31] This method uses the Cox regression model to estimate survival probabilities at each time point for each individual and averages them to obtain an OS estimate. The proportional hazards assumption was tested by using Schoenfeld residuals. $P \leq 0.05$ was considered to indicate statistical significance. Statistical analysis was conducted with SAS (SAS Institute, Cary, NC).

Table 1 Demographic and clinicopathologic characteristics in 476 patients who underwent resection of CLM from 2001 to 2016

Characteristic	Value
Patient factors	
Age, median (IQR), year	55 (46–62)
Sex, male:female, *n*	269:207
ASA score ≥ 3, *n* (%)	413 (86.8%)
Primary lesion factors	
Location, colon:rectum, *n*	326 : 150
T category ≥ 3, *n* (%)*	412 (87.5)
Lymph node metastasis, *n* (%)*	329 (70.9)
Liver metastases clinical factors	
Prehepatectomy CEA level, median (IQR), ng/mL	4.0 (2.2–12.3)
Synchronous metastasis, *n* (%)	364 (76.5%)
Extrahepatic metastasis, *n* (%)	79 (16.6%)
Prehepatectomy chemotherapy, *n* (%)	431 (90.5%)
> 6 cycles, *n* (%)	136 (28.6%)
With anti-VEGF agent, *n* (%)	338 (71.0%)
With anti-EGFR agent, *n* (%)	37 (7.7%)
Liver metastases histopathologic factors	
Tumor number, median (IQR)	2 (1–4)
Maximum diameter, median (IQR), cm	2.5 (1.5–4.0)
R1 surgical margin, *n* (%)	97 (20.4%)
Somatic gene alteration	
BRAF, *n* (%)	11 (2.3%)
RAS, *n* (%)	240 (50.4%)
TP53, *n* (%)	337 (70.8%)
SMAD4, *n* (%)	51 (10.7%)
FBXW7, *n* (%)	27 (5.7%)

Abbreviations: *IQR*, interquartile range; *ASA*, American Society of Anesthesiologists; *CEA*, carcinoembryonic antigen; *VEGF*, vascular endothelial growth factor; *EGFR*, epidermal growth factor receptor

*Data not available for T category in 5 patients and lymph node metastasis in 12 patients

Results

Study Population

Of 2045 patients who underwent CLM resection during the study period, 476 met inclusion criteria (Supplementary Figure 1). Because genetic sequencing was not frequently performed before 2010, 407 (85.5%) of the 476 patients underwent CLM resection from 2011 to 2016.

Table 1 shows demographic and clinicopathologic characteristics. A total of 431 patients (90.5%) underwent prehepatectomy chemotherapy. Of these, 338 (71.0%) received anti-vascular endothelial growth factor (*VEGF*) agent-containing regimen, and 37 (7.7%) received anti-epidermal growth factor receptor (*EGFR*) containing regimen. *BRAF*, *RAS*, *TP53*, *SMAD4*, and *FBXW7* were altered in 11 patients (2.3%), 240 patients (50.4%), 337 patients (70.8%), 51 patients (10.7%), and 27 patients (5.7%), respectively. Of the 27 patients with *FBXW7* alteration, 26 (96.3%) had mutation of *FBXW7* including 25 single nucleotide variation and 1 duplication, and 1 patient missed the detailed information. No amplification was found in patients with *FBXW7* alteration (Fig. 1a). Co-alteration of *FBXW7* and other somatic genes are shown in Fig. 1b. The frequency of *RAS* alteration was significantly higher in patients with *FBXW7* alteration than in patients with *FBXW7* wild-type (77.8% vs. 44.8%, $P = 0.005$). The frequencies of *BRAF*, *TP53*, and *SMAD4* were similar between patients with and without *FBXW7* alteration.

The median duration of follow-up was 3.1 years (interquartile range, 2.1–4.8 years). During the follow-up period, 170 (35.7%) patients died and 388 (81.5%) patients experienced recurrence, including 24 patients with *FBXW7* alteration and 364 patients with *FBXW7* wild-type. Recurrence rates in the liver alone, lung alone, and two or more sites were 20.8%, 33.3%, and 29.2% in patients with *FBXW7* alteration as compared to 36.5%, 28.9%, and 21.4% in patients with *FBXW7* wild-type.

A Cox Proportional Hazards Model Analysis for OS After CLM Resection

We evaluated *FBXW7* alteration status in a Cox proportional hazards model analysis, together with reported prognostic somatic gene (*BRAF*, *RAS*, *TP53*, and *SMAD4*) in this patient group and clinicopathologic factors. A multivariable Cox proportional hazards model analysis revealed that alterations of *FBXW7* was an independent predictor of OS together with *BRAF*, *RAS*, *TP53*, and *SMAD4* (Table 2). Additionally, prehepatectomy chemotherapy > 6 cycles, number of CLM, and largest liver metastasis diameter were associated with OS (Table 2).

OS Estimates Stratified by Alteration Status of *FBXW7*

OS curves with and without adjustment for other prognostic factors are shown in Fig. 2. The 5-year OS was significantly lower in patients with *FBXW7* alteration than in patients with *FBXW7* wild-type: 29.7% vs. 61.2%, $P = 0.005$. After adjustment for other prognostic factors, the covariate-adjusted 5-year OS remains significantly lower in patients with *FBXW7* alteration than in patients with *FBXW7* wild-type: 40.4% vs. 59.4%, $P = 0.015$.

OS Estimates Stratified by Alteration Status of *RAS* and *FBXW7*

Because the frequency of FBXW7 alteration was significantly higher in patients with *RAS* alteration than in patients with *RAS* wild-type, we evaluated OS stratified by *RAS* and

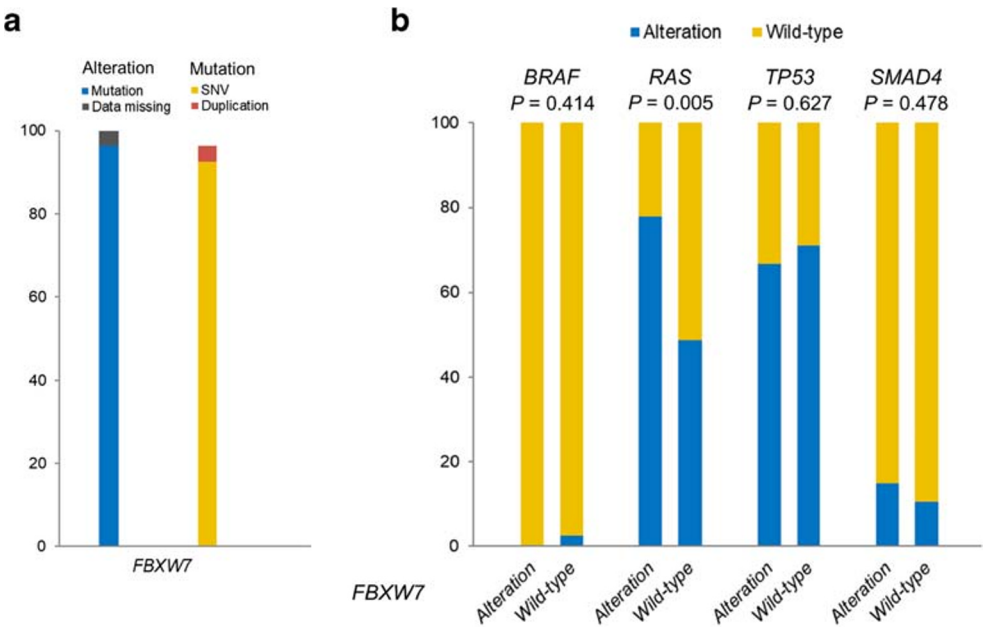


Fig. 1 Types of alterations and mutations in *FBXW7* (**a**) and co-alteration of *FBXW7* with *BRAF*, *RAS*, *TP53*, and *SMAD4* (**b**). Abbreviation: SNV, single nucleotide variation

FBXW7 alteration (Fig. 3). The 5-year OS was lower in patients with co-alteration of *RAS* and *FBXW7* alteration than in patients with *RAS* alteration and *FBXW7* wild-type (27.1% vs. 53.4%, $P = 0.066$) and in patients with *RAS* wild-type (27.1% vs. 67.0%, $P < 0.001$). After adjustment for other prognostic factors, the covariate-adjusted 5-year OS was significantly lower in patients with co-alteration of *RAS* and *FBXW7* alteration than in patients with *RAS* alteration and *FBXW7* wild-type (26.1% vs. 47.0%, $P = 0.036$) and in patients with *RAS* wild-type (26.1% vs. 70.6%, $P < 0.001$). We repeated the analysis of OS stratified by *TP53* and *FBXW7* alteration. Similarly, the 5-year OS with and without adjustment for other prognostic factors was lower in patients with co-alteration of *TP53* and *FBXW7* alteration (Supplementary Figure 2). The 5-year OS without adjustment of patients with alterations in *FBXW7*, *RAS*, and *TP53* (triple alteration, 17.9%) was worse than alterations in *FBXW7* and *RAS* or *FBXW7* and *TP53* or *RAS* and *TP53* (double alteration, 38.2%) although the number of patients with alteration in *FBXW7*, *RAS*, and *TP53* was small ($n = 12$).

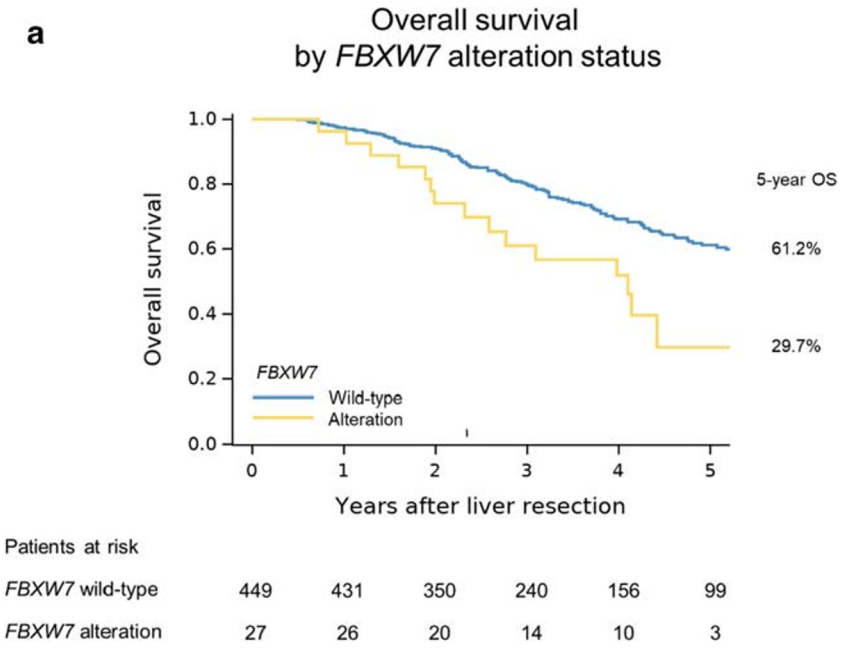
Table 2 Multivariable Cox proportional hazards model analysis for OS in 476 patients*

Factor	No. of patients	No. of events	Multivariable HR†	95% CI	*P* value
Gene alteration					
FBXW7	27	15	1.99	1.15–3.45	0.015
BRAF	11	7	2.47	1.13–5.40	0.023
RAS	240	93	2.42	1.70–3.45	< 0.001
TP53	337	130	2.00	1.36–2.95	< 0.001
SMAD4	51	26	1.90	1.22–2.96	0.004
Clinicopathologic factors					
Prehepatectomy chemotherapy > 6 cycles	136	54	1.51	1.06–2.15	0.021
Number of CLM	–	–	1.05	1.01–1.09	0.007
Largest liver metastasis diameter	–	–	1.07	1.01–1.14	0.023

Abbreviations: *HR*, hazard ratio; *CI*, confidence interval; *CLM*, colorectal liver metastasis

*Of the 476 patients, 462 patients were analyzed because data were unavailable for T category in 5 patients and lymph node metastasis in 12 patients.

† The Cox proportional hazards model analysis initially included age (continuous variable), sex, primary tumor location, T category, primary lymph node metastasis, prehepatectomy carcinoembryonic antigen level (continuous variable), timing of metastasis (synchronous vs. metachronous), prehepatectomy chemotherapy, extrahepatic disease, number of CLM (continuous variable), largest liver metastasis diameter (continuous variable), surgical margin status (R1 vs. R0), *FBXW7* alteration, *BRAF* alteration, *RAS* alteration, *TP53* alteration, and *SMAD4* alteration. A backward elimination with a threshold *P* value of 0.05 was used to select variables for the final models



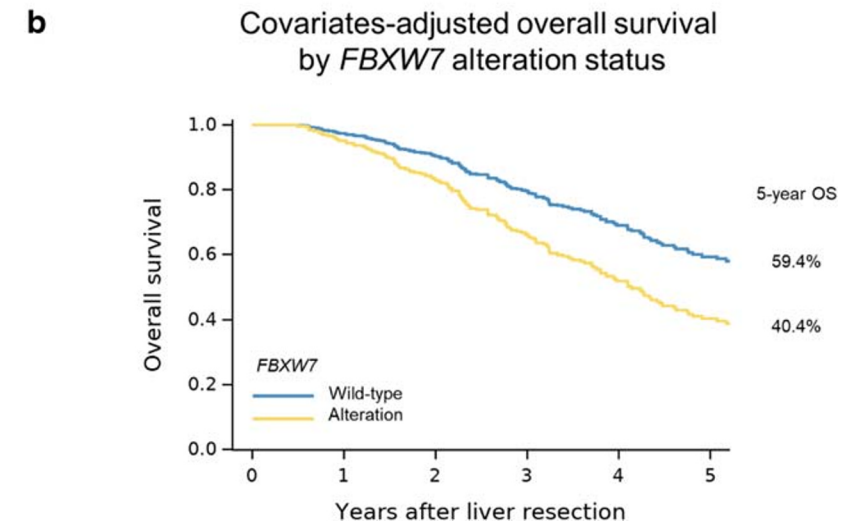


Fig. 2 Overall survival (OS) by *FBXW7* alteration status. **a** OS curves. **b** OS curves after adjustment for somatic gene alteration status (*BRAF*, *RAS*, *TP53*, and *SMAD4*), prehepatectomy chemotherapy (> 6 cycles vs. ≤ 6 cycles or no prehepatectomy chemotherapy), number of CLM, and largest liver metastasis diameter

Discussion

Patients with *FBXW7* alteration experienced worse OS after CLM resection compared to *FBXW7* wild-type patients. When grouped by *RAS* and *FBXW7*, or *TP53* and *FBXW7* alteration status, the stratification of prognosis was more refined. Of the 12 clinicopathologic factors, only 3 factors (prehepatectomy chemotherapy > 6 cycles, number of CLM, and largest liver metastasis diameter) were associated with OS when assessed with somatic gene alteration status of *FBXW7*, *BRAF*, *RAS*, *TP53*, and *SMAD4*. Our findings confirm the prognostic importance of knowing the status of multiple potential somatic gene alterations in CLM patients due to the genomic heterogeneity of colorectal cancer.

FBXW7 is a tumor suppressor gene associated with the Notch signaling pathway (Fig. 4).[32] Our study showed that the frequency of *FBXW7* alteration was 5.7% in patients with CLM, in line with previous studies that reported frequency rates of 6–10%.[15,33] Importantly, this alteration was more frequent among CLM patients than *BRAF* alteration, which is

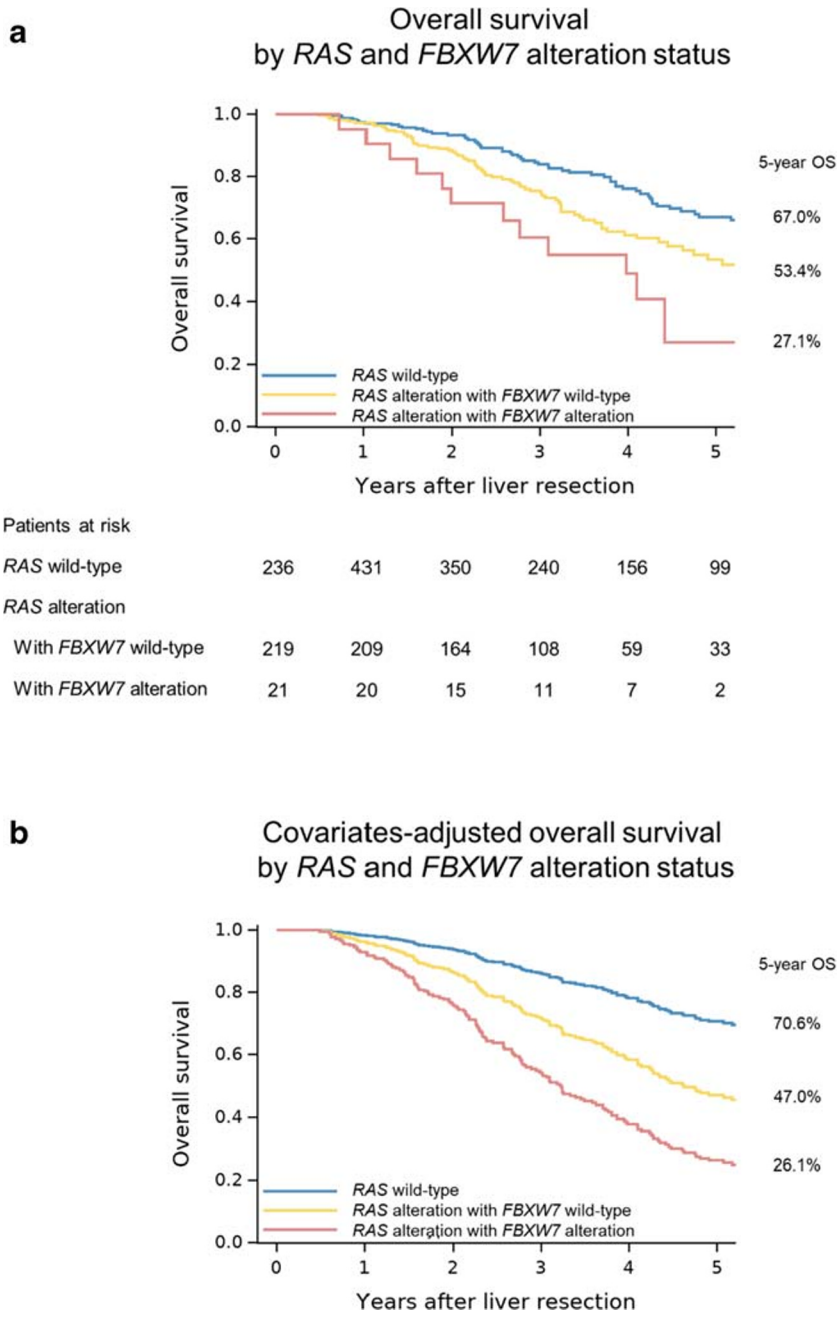


Fig. 3 Overall survival (OS) by *RAS* and *FBXW7* alteration status. **a** OS curves. **b** OS curves after adjustment for somatic gene alteration status (*BRAF*, *TP53*, and *SMAD4*), prehepatectomy chemotherapy (> 6 cycles vs. ≤ 6 cycles or no prehepatectomy chemotherapy), number of CLM, and largest liver metastasis diameter

well recognized to be a poor prognostic marker: the percentage of patients with *BRAF* alteration was 2.3% in our study and 2–5% in a large series including patients with CLM.[29] In line with previous reports,[15,34] our study found that the frequency of *FBXW7* alteration was significantly higher in patients with *RAS* alteration than in patients who were *RAS* wild-type. The Notch pathway is a regulator of cell growth and differentiation.[35] Inactivation of *FBXW7* causes abnormal accumulation of the intracellular domain of Notch1 and influences cell growth.[36] As such, alteration of *FBXW7* may result in uncontrolled cell growth and proliferation and thus, a deleterious effect on survival through the Notch pathway. The resultant negative survival impact has been reported for patients with metastatic colorectal cancer.[16] Nonetheless, our study is the first to show that OS after CLM resection was significantly worse in patients with *FBXW7* alteration than in patients with *FBXW7* wild-type.

The Cancer Genome Atlas project has detailed the landscape of somatic gene alteration of colorectal cancer in the context of cancer-related signaling pathways.[37] Our group reported that alteration of *RAS*, *TP53*, and *SMAD4* and co-alteration of *RAS* and *TP53* were associated with worse survival.[4,8–10,21] *RAS*, *TP53*, and *SMAD4* belong to three cancer-related signaling pathways: the mitogen-

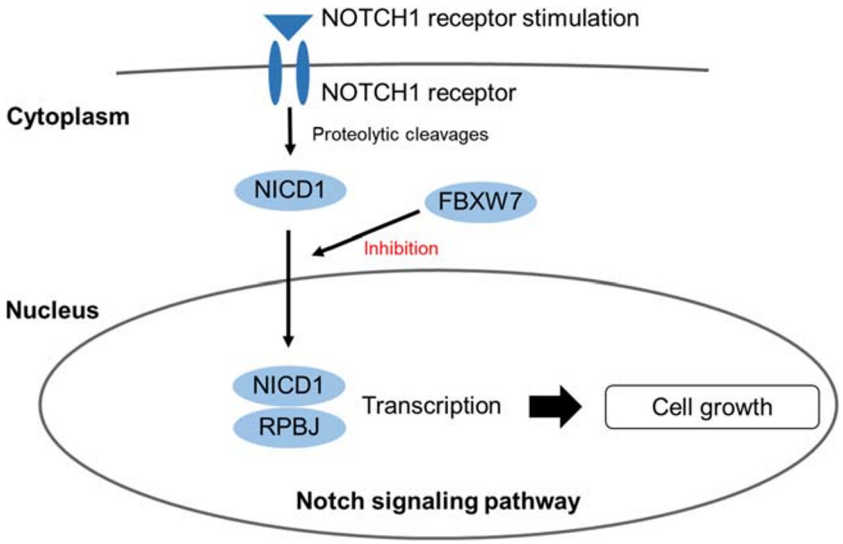


Fig. 4 Overview of NOTCH signaling pathway. Abbreviations: NICD1, intracellular domain of Notch1

activated protein kinase (MAPK) pathway, the p53 pathway, and the transforming growth factor-β (TGF-β) pathway, respectively.[37] Because these three pathways are associated with tumor-cell growth, it may be plausible that the malfunction of these pathways influences prognosis in patients with CLM. The information on alterations in these pathways may have high impact on clinical practice because the alterations of *RAS* and *TP53* were found in more than 50% of this patient group.

Alterations of *FBXW7* and *BRAF* are less frequent than alterations of *RAS*, *TP53*, and *SMAD4*. However, we believe that it is important to identify rare deleterious alterations in order to more succinctly predict CLM patients' prognosis. It is being increasingly recognized that the interplay of multiple altered signaling pathways in CLM may cause deleterious effect and result in observable differences in tumor phenotype, response to therapy, and pattern of recurrence after resection. Therefore, it is imperative that we identify the status of the rare alterations, such as that of *BRAF* and *FBXW7*, because they not only allow for prognostication on their own, but when preset in combination with others provide more accurate data for patients with CLM. This is clearly demonstrated in our previous reports[8,21] and here with the survival differences in *RAS* alteration patients with or without a co-alteration in *FBXW7*. The data presented emphasizes the importance of multiple gene testing as single gene alterations are insufficient for accurate prognostication after CLM resection. Whether these somatic alterations can definitively direct patient selection for surgery and treatment sequencing is an evolving subject. We may use this information to identify patients who have CLM with favorable molecular biology (i.e., wild-type in *FBXW7*, *BRAF*, *RAS*, *TP53*, and *SMAD4*) and may be best suited for aggressive surgery and local therapies. For example, patients with poor clinicopathologic factors (e.g., number of CLMs > 10, largest diameter of CLM > 10 cm, multiple primary lymph node metastases, extrahepatic metastases) but with favorable molecular biology may expect oncological benefits using aggressive treatment strategies.

Our study should be understood in the context of limitations. First, the retrospective single-institution design makes it difficult to preclude all biases. Nonetheless, the large size of the study cohort with complete data regarding the status of 46 somatic gene alterations allowed the analysis of patients with *FBXW7* alteration. Second, we analyzed patients who had complete data of 5 somatic genes (*FBXW7*, *BRAF*, *RAS*, *TP53*, and *SMAD4*). As such, we included only patients who underwent the 46-gene panel test in the study. Third, we did not analyze specific types of genetic alteration because the majority of *FBXW7* alterations were single nucleotide variations followed by duplication. Last, we studied patients who underwent CLM resection for a relatively long period from 2001 to 2016. However, this may be a limited impact because genetic sequencing has only been performed with regularity in the past several years, and 85.5% of the patients in the study underwent CLM resection after 2011 and had similar management of CLM. Further study including more patients may elucidate the interaction of multiple alterations in *FBXW7* and other somatic genes.

Conclusion

In conclusion, *FBXW7* alteration was found in 5.7% of patients undergoing CLM resection and was associated with worse survival. This finding further supports the genetic heterogeneity of colorectal cancer and the importance of determining the status of multiple somatic gene alterations for risk stratification for patients with CLM considering resection.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-020-04866-2.

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Statement of Author Contribution Substantial contributions to:

The conception or design of the work: YK, TN, JNV

The acquisition, analysis, or interpretation of data for the work: YK, TN, HT, CWT, YSH, TA, SK, JNV

Drafting the work or revising it critically for important intellectual content: all authors

Final approval of the version to be published: all authors

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors

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Compliance with ethical standards

Conflicts of interest Nothing to disclose.

Abbreviations CLM, colorectal liver metastases; *FBXW7*, F-box/WD repeat–containing protein 7; OS, overall survival; HR, hazard ratio; CI, confidence intervals; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; TGF-β, transforming growth factor-β

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