



# Improved Survival over Time After Resection of Colorectal Liver Metastases and Clinical Impact of Multigene Alteration Testing in Patients with Metastatic Colorectal Cancer

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Received: 28 April 2021 / Accepted: 20 June 2021 / Published online: 10 September 2021

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## Abstract

**Background** The past 20 years have seen advances in colorectal cancer management. We sought to determine whether survival in patients undergoing resection of colorectal liver metastases (CLM) has improved in association with three landmark advances: introduction of irinotecan- and/or oxaliplatin-containing regimens, molecular targeted therapy, and multigene alteration testing.

**Methods** Patients undergoing CLM resection during 1998–2014 were identified and grouped by resection year. The influence of alterations in *RAS*, *TP53*, and *SMAD4* was evaluated and validated in an external cohort including patients with unresectable metastatic colorectal cancer.

**Results** Of 1961 patients, 1599 met the inclusion criteria. Irinotecan- and/or oxaliplatin-containing regimens and molecular targeted therapy were used for more than 50% of patients starting in 2001 and starting in 2006, respectively, so patients were grouped as undergoing resection during 1998–2000, 2001–2005, or 2006–2014. Liver resectability indications expanded over time. The 5-year overall survival (OS) rate was significantly better in 2006–2014, vs. 2001–2005 (56.5% vs. 44.1%,  $P < 0.001$ ). *RAS* alteration was associated with worse 5-year OS than *RAS* wild-type (44.8% vs. 63.3%,  $P < 0.001$ ). However, OS did not differ significantly between patients with *RAS* alteration and wild-type *TP53* and *SMAD4* and patients with *RAS* wild-type in our cohort ( $P = 0.899$ ) or the external cohort ( $P = 0.932$ ). Of 312 patients with genetic sequencing data, 178 (57.1%) had clinically actionable alterations.

**Conclusion** OS after CLM resection has improved with advances in medical therapy and surgical technique. Multigene alteration testing is useful for prognostication and identification of potential therapeutic targets.

**Keywords** Hepatectomy · Metastatic colorectal cancer · Chemotherapy · Molecular targeted therapy · Perioperative chemotherapy

## Abbreviations

CLM Colorectal liver metastases  
VEGF Vascular endothelial growth factor  
EGFR Epidermal growth factor receptor

HR Hazard ratio  
OS Overall survival  
IQR Interquartile range

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## Introduction

The past 20 years have seen a number of advances in the management of colorectal cancer. These include refinement of the techniques for resection of colorectal liver metastases (CLM),<sup>1–6</sup> which have expanded indications for CLM resection, and adoption of irinotecan, oxaliplatin, anti-vascular endothelial growth factor (VEGF), and anti-epidermal growth factor receptor (EGFR) for medical treatment of metastatic colorectal cancer on the basis of evidence from

phase III trials,<sup>7–11</sup> These advance in surgical techniques and medical therapy have in turn led to improvements in survival for patients with metastatic colorectal cancer.<sup>12</sup>

Another breakthrough in the management of metastatic colorectal cancer is increasing knowledge of molecular biology. *RAS* alteration status garnered attention because *RAS*-altered disease is resistant to anti-EGFR therapy.<sup>13</sup> *BRAF* mutation has been consistently shown to be associated with a worse prognosis in patients with metastatic colorectal cancer.<sup>14,15</sup> For patients undergoing CLM resection, alterations in *RAS*, *BRAF*, *TP53*, and *SMAD4* were demonstrated to have prognostic importance.<sup>16–20</sup> With the recent development of next-generation sequencing, testing of multiple gene alterations has become more accessible in clinical practice. Studies have shown that the status of multiple somatic alterations is superior to the status of *RAS* alteration alone for predicting prognosis in patients undergoing CLM resection.<sup>19,21</sup>

At present, it remains unknown whether survival in patients undergoing resection of CLM with curative intent has improved in step with the above-described advances in management of metastatic colorectal cancer.

To answer this question, we evaluated the changes in survival over time of patients undergoing CLM resection in relation to three breakthroughs: introduction of irinotecan- and/or oxaliplatin-containing regimens, molecular targeted therapy, and multigene alteration testing. We also investigated the clinical implications of multigene alteration testing.

## Materials and Methods

### Study Populations

Patients who underwent initial liver resection for CLM with potentially curative intent at MD Anderson Cancer Center from 1998 to 2014 were identified from a prospectively compiled database. To validate the influence of multiple gene alterations, we also analyzed an independent cohort of patients who received non-surgical treatments for metastatic colorectal cancer at Memorial Sloan Kettering Cancer Center from April 2014 through September 2016. The dataset is publicly available through the cBioPortal for Cancer Genomics ([http://www.cbioportal.org/study?id=crc\\_msk\\_2017](http://www.cbioportal.org/study?id=crc_msk_2017)).<sup>22</sup> The study was approved by the Institutional Review Board at MD Anderson Cancer Center (PA17-0564).

### Analysis of Multivariable Hazard Ratios and Adjusted Overall Survival Curves

Multivariable hazard ratios (HRs) and adjusted overall survival (OS) curves were assessed for the entire cohort and subgroups with special reference to time periods, *RAS*

mutation status, and multigene alteration status. For the assessment of multigene alteration status, we focused on co-existence of somatic alterations in *RAS*, *TP53*, and *SMAD4*, which are associated with prognosis after CLM resection according to our previous studies.<sup>16,19,21,23</sup>

### Surgical Management of CLM

Our institutional approach to surgical management of CLM was detailed previously.<sup>24</sup> CLM are deemed resectable when a hepatectomy can achieve a negative margin and preserve more than 30% of the standardized total liver volume.<sup>25</sup> Patients with an anticipated insufficient future liver remnant are offered preoperative portal vein embolization and staged hepatectomy. Postoperative chemotherapy is typically administered to complete 12 cycles, including the cycles of preoperative chemotherapy.<sup>5</sup> Patients are routinely followed after resection with history, physical examination, laboratory evaluation, and axial imaging every 3 to 4 months for the first 2 years and every 4 to 6 months for the subsequent 3 years.<sup>26</sup>

### Somatic Gene Mutation Profiling

Tumor DNA was isolated from 5-mm-thick unstained sections from tumor tissue blocks or slides. Next-generation sequencing was performed with an AmpliSeq multigene panel (Supplementary Table A.1) using the Ion Torrent Personal Genome Machine (Life Technologies, CA) in a Clinical Laboratory Improvement Amendment–certified molecular diagnostic laboratory.<sup>27</sup> Single alterations in the various codons of *KRAS* and *NRAS* were analyzed together and reported as *RAS* mutations.

### Clinical Actionability of Genomic Alterations

Genomic alterations were classified using the OncoKB classification system (oncokb.org).<sup>28</sup> OncoKB categorize genomic alterations on the basis of published evidence about “clinical actionability” (i.e., the level of evidence that an alteration predicts response or resistance to a particular drug).

### Definitions

Liver resection procedures were graded according to a three-level classification (grade I, low complexity; grade II, intermediate complexity; grade III, high complexity).<sup>29–32</sup> Synchronous metastases were defined as metastases diagnosed within 12 months of primary tumor diagnosis. Positive surgical margin was defined as the presence of tumor cells < 1 mm from the transection line. The number and diameter of liver metastases were determined from surgical

pathology specimens. Primary tumor T category and N category were classified according to the *AJCC Cancer Staging Manual*, eighth edition.<sup>33</sup> Preoperative chemotherapy regimens were recorded and further categorized based on anti-VEGF or anti-EGFR agent use.

## Statistical Analysis

Categorical variables were summarized using frequencies and percentages and were compared among groups using Fisher's exact test or  $\chi^2$  test, as appropriate. Continuous variables were summarized using median values with the interquartile range (IQR) and were compared using the Kruskal–Wallis test. Trends of surgical outcomes with a stepwise increase in periods were evaluated using the Cochran–Armitage trend test.<sup>34</sup> For our cohort, OS is defined as the time interval between date of CML resection and the date of death due to any cause. Patients who were alive at the end of 5 years after CLM resection were censored at 5 years. For the external cohort, OS is defined as the time interval between date of diagnosis of metastasis and the date of death due to any cause. Patients who were alive at 5-year follow-up were censored at that time. Using a multivariable Cox proportional hazards model, prognostic factors were assessed and model-adjusted survival rate was estimated. A backward elimination with a threshold *P* value of 0.05 was used to select variables for the final models. HRs and 95% confidence intervals (CIs) were calculated for each factor. *P* ≤ 0.05 was considered to indicate statistical significance, and all tests were two-sided. Statistical analysis was conducted with SAS (SAS Institute, Cary, NC).

## Results

### Study Population

Of 1961 patients who underwent CLM resection during the study period, 1599 patients met the inclusion criteria (Supplementary Figure A.1). Figure 1 shows chronological trends in perioperative chemotherapy regimens, molecular targeted therapy, *RAS* alteration testing, and next-generation sequencing. Regimens including irinotecan and/or oxaliplatin were used in more than 50% of patients starting in 2001 (Fig. 1A), and anti-VEGF and/or anti-EGFR agents were used in more than 50% of patients starting in 2006 (Fig. 1B). As such, we divided the 1599 patients into 3 groups: 149 patients who underwent liver resection in 1998–2000, 443 who underwent liver resection in 2001–2005, and 1007 who underwent liver resection in 2006–2014 (Supplementary Figure A.1). Demographic and clinicopathologic characteristics of the patients by group are summarized in Table 1. The proportion of patients with American Society of Anesthesiologists

score ≥ 3 differed by group. Primary lesion factors did not differ significantly by group. In contrast, all liver metastasis factors differed significantly among the three groups. Synchronous metastasis and concomitant extrahepatic metastasis were more frequent in patients who underwent resection in 2006–2014, compared to those who underwent resection in 1998–2000.

During the follow-up period, 946 patients (59.2%) died. The median duration of follow-up was 4.2 years (IQR 2.3–7.0 years) for the entire cohort, 4.3 years (IQR 1.9–10.8 years) for patients undergoing CLM resection during 1998–2000, 4.1 years (IQR 2.2–10.1 years) for patients with CLM resection during 2001–2005, and 4.2 years (IQR 2.3–6.3 years) for patients with CLM resection during 2006–2014.

### Changes in Morphologic Factors and Surgical Techniques

Figure 2 shows the changes in morphologic factors and surgical techniques over time. The rates of multiple CLM and largest CLM diameter < 2 cm were significantly associated with a stepwise increase from 1998–2000 to 2006–2014 (both, *P* < 0.001) (Fig. 2A A and 2B). The rate of grade III (high-complexity) procedures did not differ significantly between the time periods (*P* = 0.205) (Fig. 2C), whereas the rate of a parenchymal-sparing approach increased significantly over time (*P* < 0.001) (Fig. 2D). The rate of resection with use of intraoperative ablation decreased significantly (Fig. 2E) and the rate of two-stage hepatectomy increased significantly (Fig. 2F) in a stepwise fashion from 1998–2000 to 2006–2014 (both, *P* < 0.001).

### Predictors of OS After CLM Resection

A multivariable Cox proportional hazards model analysis revealed that CLM resection in 2006–2014 was significantly associated with lower risk for OS than CLM resection in 2001–2005, whereas HR for OS did not differ significantly between CLM resection in 1998–2000 and 2001–2005 (Supplementary Table A.2). Also associated with OS were age, primary tumor location, T category, primary lymph node metastasis, prehepatectomy chemotherapy, extrahepatic disease, number of CLM, largest liver metastasis diameter, and surgical margin status (Supplementary Table A.2).

For patients undergoing CLM resection during 2006–2014, a multivariable Cox proportional hazards model analysis was repeated including alteration status of *RAS* and *BRAF* (Supplementary Table A.3). *RAS* alteration and undetermined *RAS* alteration status were associated with higher risk for OS than *RAS* wild-type.

**Fig. 1** Chronological trends in **A** prehepatectomy chemotherapy, **B** molecular targeted therapy, **C** *RAS* alteration testing, and **D** next-generation sequencing and **E** a summary of trends in treatment from 1998 to 2014. Prehep-chemo, prehepatectomy chemotherapy; 5-FU, 5-fluorouracil



### Adjusted OS Estimates by Time Period and by *RAS* Mutation Status During 2006–2014

OS curves after adjustment for other prognostic factors are shown in Fig. 3. CLM resection in 2006–2014 was associated with better OS than CLM resection in 2001–2005, whereas OS did not differ significantly between CLM resection in 1998–2000 and 2001–2005 (Fig. 3A). In patients undergoing CLM resection during 2006–2014, the OS rates were significantly better in patients with *RAS* wild-type than in patients with *RAS* alteration, and the OS rate for patients with *RAS* alteration status undetermined was intermediate (Fig. 3B).

### Adjusted OS Estimates by Alteration Status of *RAS*, *TP53*, and *SMAD4* in Patients Undergoing CLM Resection and Patients Receiving Nonsurgical Treatments

OS curves after adjustment for other prognostic factors were further stratified by alteration status of *RAS*, *TP53*, and *SMAD4* in patients undergoing CLM resection during 2006–2014. Patients with *RAS* alteration with wild-type *TP53* and *SMAD4* and patients with *RAS* wild-type had similar 5-year OS rates, but patients with *RAS* alteration and *TP53* and/or *SMAD4* alteration had a significantly

**Table 1** Demographic and clinicopathologic characteristics overall and by year of CLM resection

Characteristic	All patients	1998–2000	2001–2005	2006–2014	<i>P</i>
<b>Number of patients</b>	1599	149	443	1007	
<b>Patient factors</b>					
Age, median (IQR), year	57 (49–65)	60 (51–70)	58 (50–67)	56 (49–64)	0.001
Sex, male : female, <i>n</i>	958 : 641	86 : 63	280 : 163	592 : 415	0.241
ASA score $\geq 3$ , <i>n</i> (%) <sup>*</sup>	1099 (69.6)	49 (36.0)	239 (54.9)	811 (80.5)	< 0.001
<b>Primary lesion factors</b>					
Location, colon : rectum, <i>n</i>	1164 : 435	112 : 37	322 : 121	730 : 277	0.815
T category $\geq 3$ , <i>n</i> (%) <sup>*</sup>	1391 (88.5)	134 (91.2)	368 (85.4)	889 (89.5)	0.052
Lymph node metastasis, <i>n</i> (%) <sup>*</sup>	1024 (66.0)	91 (64.5)	266 (62.0)	667 (68.0)	0.086
<b>Liver metastasis factors</b>					
Prehepatectomy CEA level, median (IQR), ng/mL	3.7 (1.7–13.3)	6.0 (2.1–23.3)	4.3 (1.7–20.5)	3.3 (1.7–10.6)	< 0.001
Synchronous metastasis, <i>n</i> (%)	1129 (70.6)	82 (55.0)	309 (69.8)	738 (73.3)	< 0.001
Extrahepatic metastasis, <i>n</i> (%)	165 (10.3)	5 (3.4)	28 (6.3)	132 (13.1)	< 0.001
Prehepatectomy chemotherapy, <i>n</i> (%)	1260 (78.8)	72 (48.3)	320 (72.2)	868 (86.2)	< 0.001
With preoperative irinotecan or oxaliplatin, <i>n</i> (%)	1138 (71.1)	23 (15.4)	278 (62.8)	837 (83.1)	< 0.001
With preoperative anti-VEGF agent, <i>n</i> (%)	754 (47.2)	0	73 (16.5)	681 (67.6)	< 0.001
With preoperative anti-EGFR agent, <i>n</i> (%)	91 (5.7)	0	3 (0.7)	88 (8.7)	< 0.001
R1 surgical margin, <i>n</i> (%)	179 (11.2)	10 (6.7)	25 (5.6)	144 (14.3)	< 0.001
<b>Somatic mutation data</b>					
RAS status determined	717 (44.8)	0	34 (7.7)	683 (67.8)	< 0.001
Multigene mutation testing data available	312 (19.5)	0	4 (0.9)	308 (30.6)	< 0.001

Abbreviations: *IQR* interquartile range; *ASA* American Society of Anesthesiologists; *CEA* carcinoembryonic antigen; *VEGF* vascular endothelial growth factor; *EGFR* epidermal growth factor receptor; *CLM* colorectal liver metastasis; *SD* standard deviation

<sup>\*</sup>Date missing on ASA score for 21 patients, T category for 28 patients, and lymph node metastasis for 48 patients

worse 5-year OS rate than patients with *RAS* wild-type (Supplementary Table A.4).

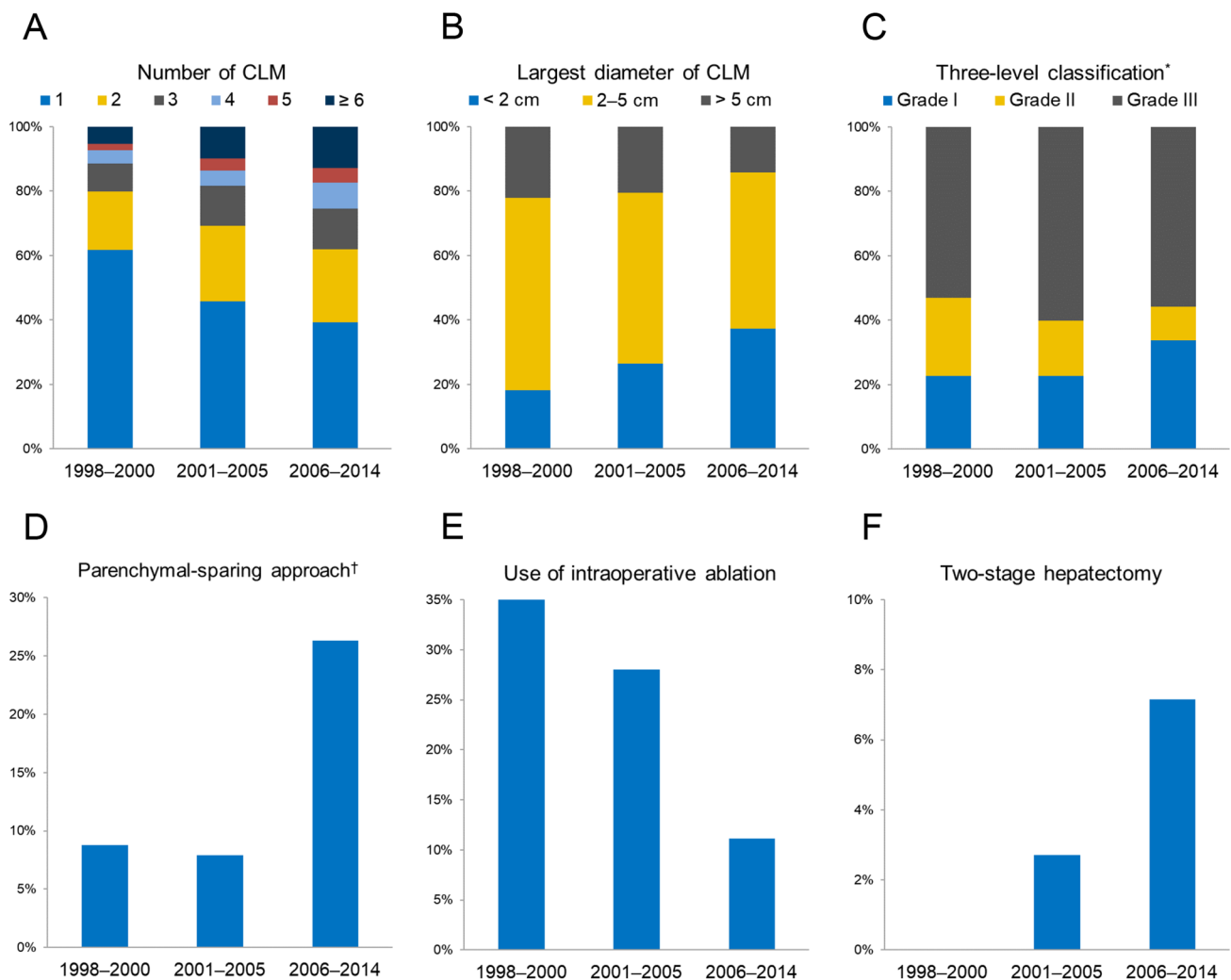
A similar analysis was repeated for the external validation cohort including 499 patients who underwent nonsurgical treatments for metastatic colorectal cancer and did not have missing data. Demographic and clinicopathologic characteristics of the cohort are summarized in Supplementary Table A.5. Median (IQR) age was 56 (46–65) years. The number of sites involved at first diagnosis of metastasis was 1 for 294 patients (58.9%), 2 for 138 patients (27.7%), and 3 or more for 67 patients (13.4%). The median duration of follow-up was 1.7 years (IQR, 1.1–2.6 years). During the follow-up period, 254 patients (50.9%) died. Similar to the results of our cohort of resected patients, the 5-year OS rates for these unresectable metastatic patients did not differ significantly between patients with *RAS* alteration and wild-type *TP53* and *SMAD4* and patients with *RAS* wild-type, whereas the 5-year OS rate was significantly worse in patients with *RAS* alteration and *TP53* and/or *SMAD4* alteration than in patients with *RAS* wild-type (Supplementary Table A.4).

### Changes in 5-Year OS Rates by Year of CLM Resection, *RAS* Alteration Status, and Multiple Gene Alteration Status

The changes in adjusted 5-year OS rates after CLM resection in our cohort and after the diagnosis of metastasis from colorectal cancer in the external cohort by year of CLM resection and by gene alteration status are shown in Fig. 4.

### Clinical Actionability of 312 Patients with the Next-Generation Sequencing Data

Of the 312 patients with the next-generation sequencing data, 178 (57.1%) had clinically actionable gene alterations. Of these 178 patients, 77 (24.7%) had one or more actionable genes other than *RAS* or *BRAF* (Fig. 5).



**Fig. 2** Changes over time in **A** number of CLM, **B** largest CLM diameter, **C** complexity of liver resection, **D** use of a parenchymal-sparing approach, **E** concomitant use of intraoperative ablation, and **F**

two-stage hepatectomy. \*Grade I, low complexity; grade II, intermediate complexity; grade III, high complexity.<sup>29</sup> †Defined as frequency of multiple resections ( $\leq 1$  Couinaud segment) for multiple CLM

## Discussion

Our study demonstrates that OS after adjustment for risk factors was significantly better in patients undergoing CLM resection during 2006–2014 (a period when irinotecan- and/or oxaliplatin-containing chemotherapy regimens and molecular targeted therapy were each used in more than 50% of patients) than in patients undergoing CLM resection during 1998–2000 (before the introduction of irinotecan/oxaliplatin chemotherapy) and patients undergoing CLM resection during 2001–2005 (after the introduction of irinotecan/oxaliplatin chemotherapy but before the introduction of molecular targeted therapy). Over the years of our study, indications for CLM resection were expanded to patients with worse performance status, multiple CLM, and extrahepatic disease. The survival gain that we observed despite these expanding

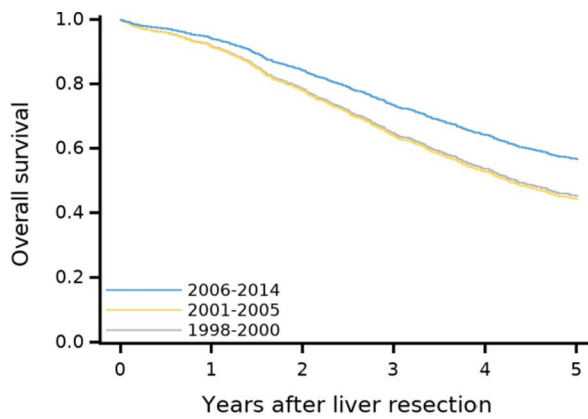
indications for CLM resection may be attributable to the concomitant advances in medical therapy and refinements of surgical technique.

RAS alteration testing is another development in the management of metastatic colorectal cancer that occurred during the study period. However, the findings of our study show that RAS mutation testing alone is not sufficient for prognostication. Instead, testing of multiple gene alterations is essential for accurately predicting prognosis in both patients undergoing CLM resection and patients with unresectable metastatic colorectal cancer.

Improvements in survival after CLM resection were multifactorial. The gain in OS during 2006–2014 correlated with an increasing use of oxaliplatin and anti-VEGF agent for prehepatectomy chemotherapy (Figs. 1 and 3). Patients undergoing CLM resection during 2006–2014 had higher

**A**

By year of CLM resection



Patients at risk							5-year OS (95% CI)	HR (95% CI)	P value
Period	0	1	2	3	4	5			
2006–2014	979	908	802	669	552	409	56.5% (53.3%–59.6%)	0.97 (0.73–1.29)	.845
2001–2005	425	389	332	272	219	184	44.1% (39.5%–48.6%)	1 (reference)	–
1998–2000	141	128	104	83	75	69	45.1% (36.5%–53.2%)	0.68 (0.57–0.81)	< .001

**B**

By RAS alteration status

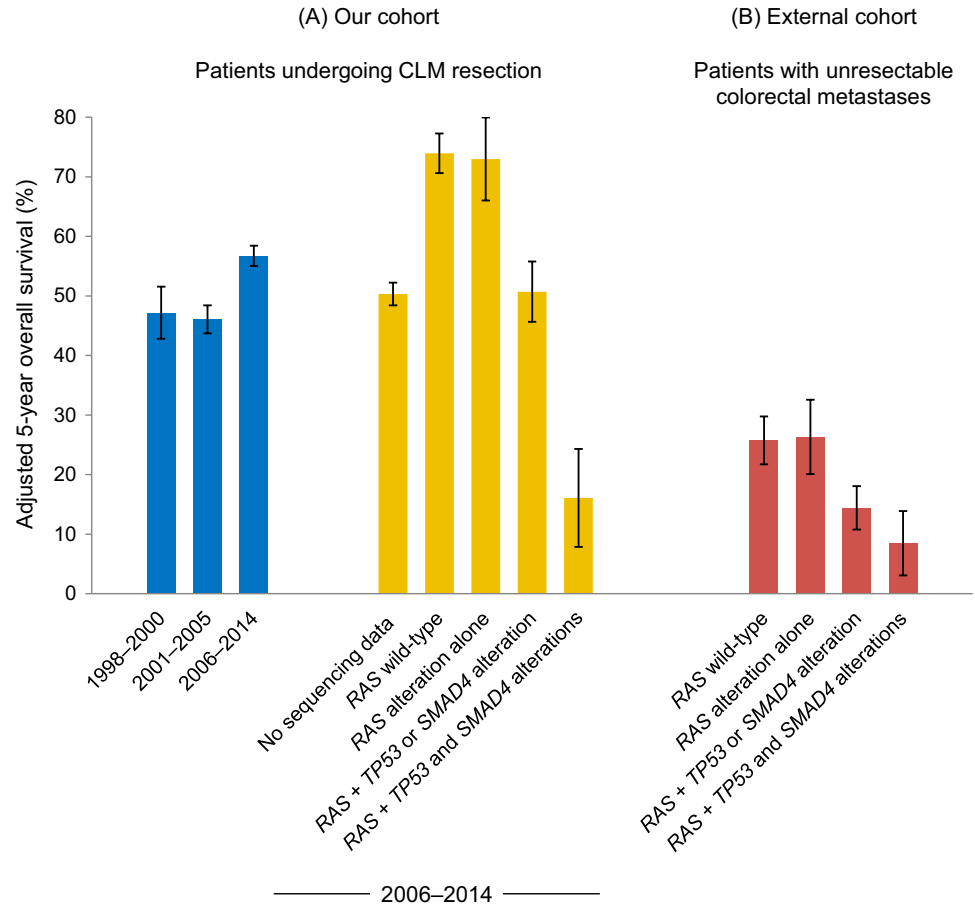


Patients at risk							5-year OS (95% CI)	HR (95% CI)	P value
RAS status	0	1	2	3	4	5			
Wild-type	366	349	327	277	237	173	63.3% (58.3%–67.9%)	1 (reference)	–
Undetermined	313	276	236	208	176	145	54.7% (48.7%–60.2%)	1.34 (1.04–1.73)	.024
Alteration	302	283	239	184	139	91	44.8% (39.3%–50.1%)	1.82 (1.44–2.30)	< .001

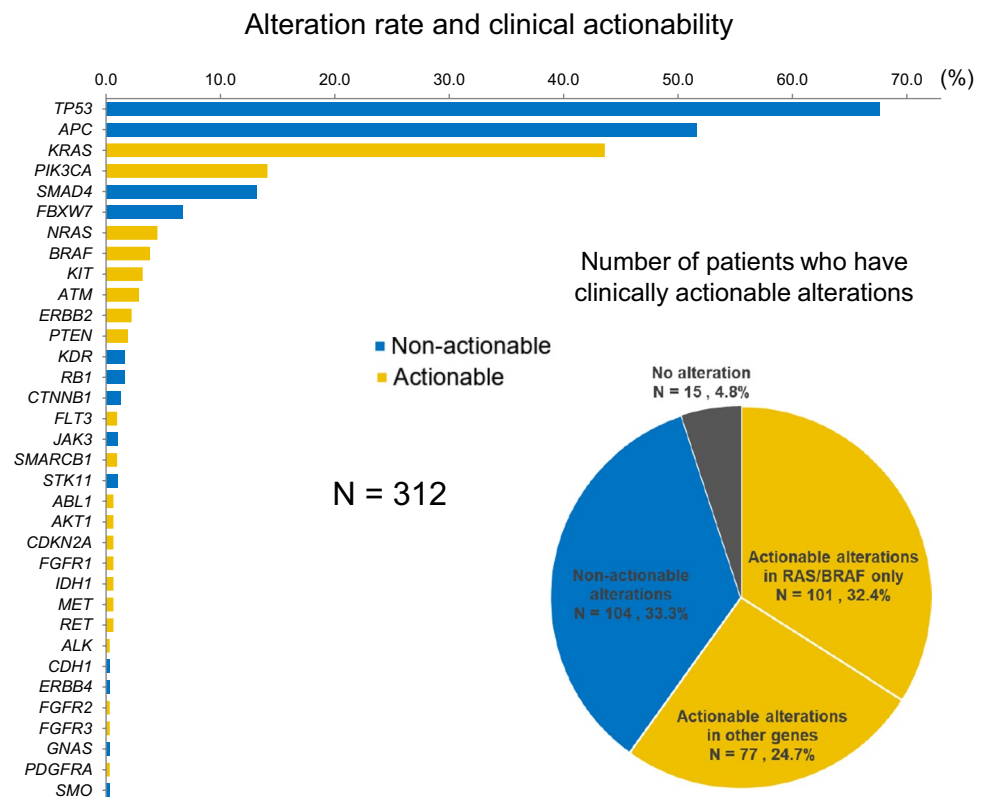
**Fig. 3** Overall survival (OS) by **A** year of resection and **B** RAS alteration status in patients with CLM resection during 2006–2014. (A) OS curves after adjustment for age, primary tumor location, T category, lymph node metastasis, prehepatectomy chemotherapy, extrahepatic disease, number of CLM, largest liver metastasis diameter, and sur-

gical margin status. (B) OS curves after adjustment for age, lymph node metastasis, prehepatectomy chemotherapy, extrahepatic disease, number of CLM, largest liver metastasis diameter, and surgical margin status

**Fig. 4** Adjusted 5-year overall survival **A** by year of CLM resection and multiple gene alteration status in our cohort and **B** by multiple gene alteration status in the external cohort



**Fig. 5** Alteration rate and clinical actionability in 312 patients with the next-generation sequencing data





number of CLM but smaller largest CLM diameter than patients undergoing CLM resection during 2001–2005 and during 1998–2000 (Fig. 2). The smaller diameter of CLM during 2006–2014 is most likely attributable to effective prehepatectomy chemotherapy regimens. Downsizing of CLM diameter can facilitate tumor detachment from hepatic vasculature to preserve parenchyma. These effects of prehepatectomy chemotherapy may have expanded surgical indications for patients who had multiple CLM. Another important change between the earlier years of the study and 2006–2014 was refinement of surgical technique, which was reflected by increased use of a parenchymal-sparing approach and decreased use of intraoperative ablation. Our group previously demonstrated that use of a parenchymal-sparing approach<sup>6</sup> and lack of use of intraoperative ablation<sup>2</sup> were associated with better prognosis in patients undergoing CLM resection. Development of two-stage hepatectomy has also improved resectability of bilateral CLM.<sup>35</sup> Taken together, our findings from the current study indicate that advances in medical therapy and refinements of surgical technique were associated with improved OS in patients undergoing CLM resection despite expanding eligibility for CLM resection. These findings emphasize the importance of a multimodality approach to achieve optimal long-term outcomes.<sup>36</sup>

Another important finding of our study was the clinical implications of multigene alteration testing. *RAS* alteration status is clearly important for predicting response to anti-EGFR therapy<sup>37,38</sup> and OS after CLM resection (Fig. 3). However, *RAS* alteration status with coexisting alterations in *TP53* and *SMAD4* may better stratify prognosis not only in patients undergoing CLM resection but also in patients with unresectable colorectal metastases. Importantly, we found that patients with *RAS* alteration and wild-type *TP53* and *SMAD4* did not have significantly shorter OS than patients with wild-type *RAS*. Patients with *RAS* alteration and wild-type *TP53* and *SMAD4* accounted for 31.7% (45 of 142) of the patients with *RAS* alteration in our cohort and 28.6% (74 of 259) of the patients with *RAS* alteration in the external cohort (Supplementary Table 4). Patients with *RAS* alteration with wild-type *TP53* and *SMAD4* and patients with *RAS* wild-type had the most favorable survival probability: the 5-year OS rate after adjustment was approximately 73% in patients undergoing CLM resection and 26% in patients with unresectable colorectal liver metastases (Fig. 4). In contrast, patients with triple alterations in *RAS*, *TP53*, and *SMAD4* had the worst prognosis.

The findings of our study showed that advances in chemotherapy and molecular targeted therapy were associated with improved survival in patients undergoing CLM resection. Our findings yield three main messages regarding care for patients with resectable CLM and unresectable metastatic colorectal cancer. First, curative resection of CLM remains associated with better survival than unresectable metastatic colorectal

cancer. Eligibility criteria for liver resection have evolved over time. With advances in medical therapy and surgical technique, patients with non-ideal performance status, multiple CLM, synchronous metastases, and extrahepatic disease may be considered for resection when the eligibility criteria for liver resection is determined by specialized liver surgeons. Second, it is important for liver surgeons to keep up to date with knowledge regarding the current optimal chemotherapy regimens, novel agents, and advances in surgical technique. Further development of novel agents and refinement of surgical technique may lead to further improvement in survival for patients with metastatic colorectal cancer. Third, multigene alteration testing is useful for better prognostication and may change clinical decision making, for example, by leading to a decision to extend the period of posthepatectomy chemotherapy or to adjust surveillance frequency and intensity. Because the prognosis of patients with stage IV colorectal cancer may be influenced by alterations in multiple somatic genes, independent from clinicopathologic factors, information about gene alteration status may also be important to balance the background of groups studied in future clinical trials. Finally, multigene alteration testing is expected to provide potentially clinically actionable therapeutic information.<sup>28</sup> We found that approximately 60% of patients in our cohort had clinically actionable alterations in genes and 25% had actionable alterations in genes other than *RAS* or *BRAF*. *RAS* mutation status is established as a predictive molecular biomarker for response to anti-EGFR therapy for colorectal cancer.<sup>13</sup> Targeted therapies for *BRAF*, *PIK3CA*, and *ERBB2* are expected to become potential therapeutic options for colorectal cancer.<sup>39–41</sup>

Our study should be understood in the context of potential limitations. First, it was a retrospective cohort study in a single institution. The selection process for liver resection is complex and considers patient factors and tumors factors including tumor biology. We do not exclude patients based on specific genetic mutations. Patients who underwent CLM resection during each of the three periods had sufficient follow-up, and the results showed improvement of survival with advances in medical therapy and surgical technique, and expanding surgical indications. Furthermore, prognostication based on *RAS*, *TP53*, and *SMAD4* was reproduced in an independent external cohort including patients with unresectable colorectal metastases. A secondary limitation is that barriers may exist to incorporation of medical therapy and surgical resection because close coordination among the medical oncologist, radiologist, pathologist, and surgeon is needed for each patient.

## Conclusions

In conclusion, in the past 20 years, advances in medical therapy and surgical technique have improved survival after CLM resection such that 5-year OS rates are approximately

70% for patients with favorable tumor biology despite expanding surgical indications. Multigene alteration testing allows better prognostication than *RAS* mutation testing alone and provides information on clinically actionable genes for patients with metastatic colorectal cancer.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11605-021-05110-1>.

**Acknowledgements** The authors thank Mario De Bellis for reviewing the data used in the study, Ms. Ruth Haynes for administrative support in the preparation of this manuscript, and Ms. Stephanie Deming, an employee of the Research Medical Library at MD Anderson Cancer Center, for copyediting the manuscript.

**Author Contribution** Substantial contributions to:

The conception or design of the work: YK and JNV.

The acquisition, analysis, or interpretation of data for the work: YK, SK, EP, HH, XW, HT, CWT, YSH, TA, and 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.

**Funding** This research was supported in part by the National Institutes of Health through MD Anderson Cancer Center Support Grant, CA016672.

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