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Anatomic Resection Is Not Required for Colorectal Liver Metastases with *RAS* Mutation

Katharina Joechle[1] · Timothy J. Vreeland[1] · Eduardo A. Vega[1] · Masayuki Okuno[1] · Timothy E. Newhook[1] · Elena Panettieri[1] · Yun Shin Chun[1] · Ching-Wei D. Tzeng[1] · Thomas A. Aloia[1] · Jeffrey E. Lee[1] · Jean-Nicolas Vauthey[1]

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Abstract

Background Non-anatomic resection (NAR) has emerged as a safe and effective technique for resection of colorectal liver metastases (CRLM). More recently, *RAS* mutation has been identified as an important indicator of aggressive disease, which may require anatomic resection (AR). In this retrospective study, we compared the long-term outcomes of AR versus NAR in CRLM patients with and without *RAS* mutations.

Methods Patients with known *RAS* mutation status who underwent AR or NAR for CRLM between 2006 and 2016 were included. Differences in baseline characteristics were adjusted using 1:1 propensity score matching, including the most important factors that contributed to the decision to use the resection technique. Overall survival (OS), recurrence-free survival (RFS), and liver-specific recurrence-free survival (L-RFS) were compared between cohorts.

Results Among 622 total patients, 338 (54%) underwent AR and 284 (46%) NAR. There was no difference in OS or L-RFS between the AR and NAR groups, regardless of mutation status. There was increased RFS in the *RAS* WT patients with NAR ($P = 0.034$), but no difference in RFS in the whole cohort or *RAS* mutant group. After propensity score matching, 360 patients were analyzed, and no differences in OS, RFS, or L-RFS rates were seen between any groups. There was also no difference in margin recurrence.

Conclusions Similar outcomes can be achieved with both AR and NAR, regardless of *RAS* mutation status. These data do not support a universal requirement for AR in *RAS* mutant CRLM when not necessary to achieve an R0 resection.

Keywords Non-anatomic resection (NAR) · Colorectal liver metastases (CRLM) · Anatomic · Resection (AR)

Introduction

Liver resection is acknowledged as the only curative treatment for colorectal liver metastases (CRLM). There has been a steady movement away from mandatory anatomic resection (AR) and toward non-anatomic resection (NAR) in situations in which the latter can achieve an R0 resection. While a recent review of 12 studies examining short- and long-term outcomes of both techniques did not show any survival differences,[1] NAR is associated with lower risk of postoperative liver failure and morbidity after surgery.[1–6] Additionally, the appropriate use of NAR offers equivalent risk of intrahepatic recurrence, but allows a higher chance to perform a re-resection if recurrence occurs, which may lead to longer survival after recurrence.[2]

While most favor NAR over AR, assuming a margin-negative resection can be achieved, some authors have suggested that a more aggressive resection strategy may be required on the basis of the disease biology. In particular, *RAS* mutation has been identified as an important risk factor for worse long-term outcomes in patients with metastatic colorectal cancer,[7] leading some to question the appropriateness of applying NAR in patients harboring *RAS* mutation, whether for lung or for liver metastases.[8,9] In this context, the primary

Katharina Joechle and Timothy J. Vreeland contributed equally to this work.

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✉ Jean-Nicolas Vauthey
jvauthey@mdanderson.org

[1] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1484, Houston, TX 77030, USA

aim of this study was to compare the outcomes of patients undergoing AR versus NAR for CRLM, stratified by *RAS* mutation status.

Patients and Methods

Study Population

After obtaining approval from the Institutional Review Board of The University of Texas MD Anderson Cancer Center (protocol #PA19-0242), we retrospectively identified patients with known *RAS* mutation status who underwent AR or NAR for CRLM between 2006 and 2016 from a prospectively maintained departmental database. Patients who underwent simultaneous ablation at the time of resection, two-stage hepatectomy, R2 resection, or a combined AR and NAR were excluded.

AR was defined as segmentectomy, multi-segmentectomy, sectionectomy, or segmentectomy plus sectorectomy, as described by Couinaud[10] and *The Brisbane 2000 Terminology of Liver Anatomy and Resections.*[11] Thus, formal segmentectomy, sectorectomy, right hepatectomy, left hepatectomy, extended right hepatectomy, and extended left hepatectomy were considered an AR. A NAR was defined as the resection of at least one metastasis, which includes a margin of microscopically normal liver tissue, regardless of hepatic anatomy.

Perioperative Management

The decision to perform an AR or NAR was made by the surgeon and determined during preoperative evaluation. Intraoperative liver ultrasound was performed. A resection margin on final pathological examination of < 1 mm was defined as an R1 resection. Follow-up, including physical examination, laboratory testing, and cross-sectional imaging, was conducted every 3–4 months.

Data Collection

The following patient data were recorded: sex, age, American Society of Anesthesiologists (ASA) physical status classification, body mass index, CRLM characteristics (number of tumors, largest tumor diameter, unilobar vs bilobar location, and timing of metastasis), type of hepatectomy, pre-hepatectomy chemotherapy, and perioperative outcomes (blood loss, operative time, resection margin, postoperative complications, length of hospital stay, unplanned readmission 45 days after discharge,[12] primary tumor location, and primary nodal status). Postoperative complications were classified according to Clavien-Dindo classification,[13] with grade IIIa or higher being considered a major complication.

Recurrence Definitions

Patients were considered to have experienced recurrence when imaging showed an area of concern that was either biopsy proven to be recurrent disease or was treated as such by the treatment team. Intrahepatic recurrence was defined as evidence of metastatic disease within the liver at the time of first recurrence, whether or not synchronous extra-hepatic recurrence was also present. In patients with intrahepatic recurrence, we closely examined the site of recurrence. Local recurrence was defined as an intrahepatic recurrence at the resection margin or within the same segment of the liver, as determined by imaging review.

Propensity Score Matching

Propensity score (PS) matching without replacement in an optimal algorithm was used to adjust for differences in baseline characteristics between AR and NAR patients and was separately applied for *RAS* wild-type and *RAS*-mutated patients. The variables that were considered most clinically relevant and directly associated with undergoing AR or NAR were included in a logistic regression model to calculate the PS. These variables were age, sex, ASA score, body mass index, bilateral vs unilateral liver metastases, number of metastases, largest tumor diameter (as a continuous variable), neoadjuvant chemotherapy, extrahepatic disease, and repeated hepatectomy. After PS generation, AR and NAR patients underwent 1:1 nearest available matching of the logit of the PS, with a caliper width of 0.05 of the standard deviation of the score. If both AR and NAR patients did not meet the matching criteria, they were excluded.

Statistical Analysis

Statistical analysis was performed using JMP Pro 14 software (SAS Institute, Inc., Cary, NC). Continuous variables were analyzed using a Wilcoxon signed-rank test and expressed as medians and ranges. Categorical variables were compared using χ^2 test or Fisher's exact test, as appropriate, and expressed as absolute values and percentages. Recurrence-free survival (RFS), liver-specific recurrence-free survival (L-RFS), and overall survival (OS) rates were calculated from the day of liver surgery and estimated using the Kaplan-Meier method. The 1-, 3-, and 5-year RFS, L-RFS, and OS rates were compared using log-rank statistics. All tests were two-sided, and $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

Between 2006 and 2016, 1474 patients underwent hepatectomy for CRLM at our institution. The *RAS* mutation status was known in 1025. After exclusion criteria were applied, 622 patients were included in analysis (Fig. 1). Of these, 338 (54%) underwent AR and 284 (46%) underwent NAR. *RAS* mutation was found in 274 (40%) patients, with a similar distribution of AR and NAR (55% and 45%, respectively). The remaining 348 (60%) patients were *RAS* wild type, again with a similar distribution of AR and NAR (54% and 46%, respectively). As expected, NAR patients presented with fewer metastases ($P = 0.002$), a smaller median tumor diameter ($P < 0.0001$), and were more likely to undergo repeat hepatectomy ($P = 0.002$). These differences persisted when patients were evaluated according to *RAS* mutation status, except for repeat hepatectomy, which was similar between AR and NAR in the *RAS* mutation patients (Supplementary Table 1).

PS-Matched Patient Characteristics

After 1:1 PS matching, 360 patients (180 AR vs 180 NAR) were included in the analysis, 210 (58%) with *RAS* wild-type and 150 (42%) with *RAS* mutation; exactly half in each group underwent AR and NAR. The differences in patient characteristics between AR and NAR in the original cohort were well adjusted (Supplementary Table 1).

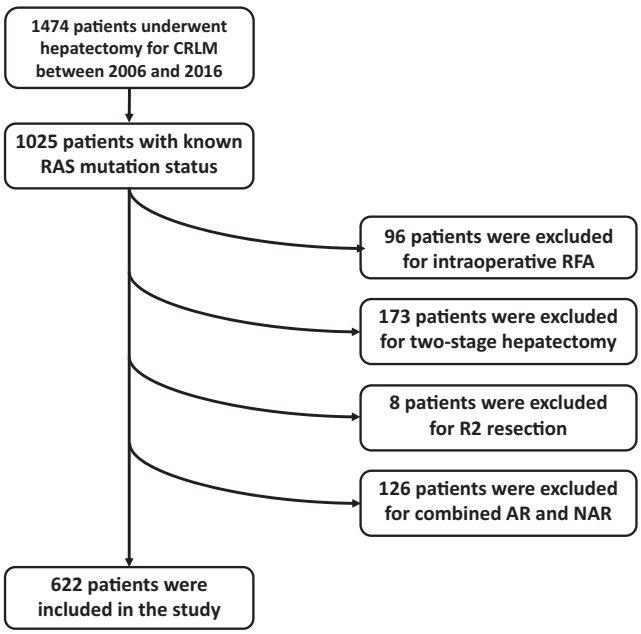

Fig. 1 Flowchart of patient selection

Perioperative Outcomes

Patients' perioperative outcomes are shown in Table 1. In the original cohort, patients with AR had greater intraoperative blood loss ($P < 0.001$), were more likely to develop major complications ($P = 0.001$), and had a longer hospital stay ($P < 0.001$); this was true regardless of *RAS* status. In the *RAS* mutation group, patients who underwent NAR were more likely to have an R1 margin ($P = 0.036$). After PS matching, significant differences in intraoperative blood loss ($P = 0.001$) and length of hospital stay ($P = 0.006$) persisted. R1 resection rates were similar in patients who underwent AR and NAR.

Survival Analysis Before Matching

The median follow-up period in the original cohort was 43.9 months, with 45 months in the AR group and 43 months in the NAR group. Patients who underwent NAR had a significantly longer OS duration than did those who underwent AR for the whole cohort ($P = 0.021$); the same trend was found for *RAS* mutation patients ($P = 0.052$). No difference was found for patients with *RAS* wild-type (Supplemental Fig. 1a, 1b, 1c). While the RFS rate was similar for AR and NAR in the entire cohort and for *RAS* mutation patients, it was higher for NAR in patients with *RAS* wild-type ($P = 0.034$) (Fig. 2a–c). The L-RFS rates were similar between NAR and AR for all groups (Fig. 3a–c).

Survival Analysis After Matching

After PS matching, the median follow-up duration was 43.1 months, with 45.3 months for patients undergoing AR and 40.8 months for patients undergoing NAR. The OS was similar between NAR and AR for the whole cohort, *RAS* wild-type, and *RAS* mutation groups (Supplemental Fig. 1d, 1e, 1f). The RFS rate was similar between NAR and AR for all groups, (Fig. 2d–f), as was L-RFS for all groups (Fig. 3d–f).

Local Recurrence

Three hundred forty-two patients (54.9%) in the original cohort developed intrahepatic recurrence, with no difference in the *RAS* mutation group between AR and NAR (55.0% vs 57.7%, $P = 0.647$). In the matched cohort, 187 patients (51.9%) developed intrahepatic recurrence, again with no difference in the *RAS* mutation group between AR and NAR (49.0% vs 54.7%, $P = 0.513$). There were no differences in local recurrence after AR or NAR in either the *RAS* wild-type (14.3% vs 7.6%, $P = 0.122$) or *RAS* mutation (10.7% vs 5.3%, $P = 0.229$) groups (Table 2).

Of 622 patients in the overall cohort, 96 (15.4%) had R1 resections. In the matched cohort, 35 patients (9.7%) had R1 resections. There was no difference in R1 resection rate

Table 1 Perioperative outcomes after anatomic vs non-anatomic resection by *RAS* mutation status

Outcome	All patients $n = 622$	*RAS* wild type			*RAS* mutant		
		AR $n = 187$	NAR $n = 161$	p value	AR $n = 151$	NAR $n = 123$	P value
Operating time, median (range), min	222 (41–714)	236 (53–595)	201 (55–647)	0.586	233 (50–714)	222 (41–593)	0.7664
Blood loss in ml, median (range)	200 (10–1850)	250 (30–1700)	150 (10–1700)	< 0.0001	270 (10–1850)	100 (10–1500)	< 0.0001
Pringle maneuver°, no. (%)	227 (67)	81 (65)	50 (66)	0.946	59 (68)	37 (74)	0.447
R1 resection, no. (%)	96 (15.4)	34 (18)	26 (16)	0.617	14 (9)	22 (18)	0.036
Major pathological response‡, no. (%)	246 (50)	73 (51)	64 (53)	0.669	61 (48)	48 (47)	0.839
Length of stay, median (range), days	6 (0–28)	6 (1–28)	5 (1–28)	< 0.0001	6 (1–24)	5 (0–21)	0.0004
45-day readmission, no. (%)	45 (8)	18 (10)	7 (5)	0.095	11 (8)	9 (9)	0.818
Dindo-Clavien > 3, no. (%)	72 (12)	29 (16)	13 (9)	0.047	23 (15)	7 (6)	0.012

AR anatomic resection, *NAR* non-anatomic resection

° Evaluated for 337 patients

‡ Evaluated for 492 patients

§ Evaluated for 573 patients

between NAR and AR in the *RAS* wild-type group (10.5% vs 11.4%, $P = 0.825$) or the *RAS* mutation group (6.7% vs 8.0%, $P = 0.754$) (Table 2). Local recurrence was not more common after R1 resection than R0 resection for the *RAS* mutation group (9.1% vs 7.9%, $P = 0.838$).

Discussion

In this study, we demonstrated that both AR and NAR can be performed with similar oncologic outcomes, regardless of *RAS* mutation status. After PS matching, we found no difference in OS, RFS, or L-RFS rates and durations after AR or NAR in the overall cohort or in patients with wild-type or mutant *RAS*. Moreover, there was no difference in local recurrence between AR and NAR, before or after matching.

The superiority of NAR or AR as the optimal surgical approach for resection of CRLM has been evaluated in several retrospective studies. DeMatteo et al. showed a benefit from more extensive resection in a retrospective review published in 2000, but this study pre-dated the ubiquitous use of modern perioperative chemotherapy and thus is not likely applicable in the current era.[14] While no prospective, randomized trials have compared these two techniques, more recent studies have shown no detriment in oncologic outcomes with NAR, but have shown improved salvageability and survival after recurrence for patients who have undergone NAR for small, solitary metastases.[1,2,5,15,16] Meanwhile, multiple studies have shown increased morbidity and mortality with AR,[5,17] just as we observed increased blood loss, complications, and length of stay in the current study. Considering the decrease in perioperative risk without sacrificing oncologic outcomes, we advocate for NAR for CRLM, assuming a negative margin can be obtained.

While NAR has become an acceptable approach in most patients with CRLM, some have argued that the decision for AR or NAR should be different for patients harboring *RAS* mutations, as these mutations are known to be a marker of more aggressive disease.[18–20] In a recently published study that evaluated the impact of AR vs NAR for colorectal lung metastases,[9] patients with *RAS* mutation who underwent NAR had a significantly higher resection-margin recurrence rate, shorter time to pulmonary recurrence, and lower OS compared to those undergoing AR. This finding in the setting of lung metastases calls into question the appropriateness of NAR for patients with *RAS* mutant CRLM. Indeed, a recently reported study of AR versus NAR in patients with known *RAS* mutation showed a significant improvement in disease-free survival and intrahepatic disease-free survival for *RAS*-mutated patients treated with AR, while there was no difference in *RAS* wild-type patients.[8] The authors hypothesized that *RAS* mutation CRLM may spread through the portal system, and would thus benefit from *en bloc* removal of the segmental portal pedicle, mandating an AR. While there is evidence for such spread in hepatocellular carcinoma,[21] this has not been shown in CRLM.[22]

In contrast, our study did not show improved OS or RFS with AR in patients with *RAS* mutation, but instead shorter OS in the overall cohort, and a trend toward a shorter OS in *RAS*-mutated patients. This finding is somewhat related to more aggressive disease at baseline in the AR group, but, at minimum, this shows that AR does not significantly improve OS or RFS. In an effort to account for these differences, we performed PS matching, but we still found no benefit from AR in terms of OS or RFS in *RAS*-mutated patients or any other

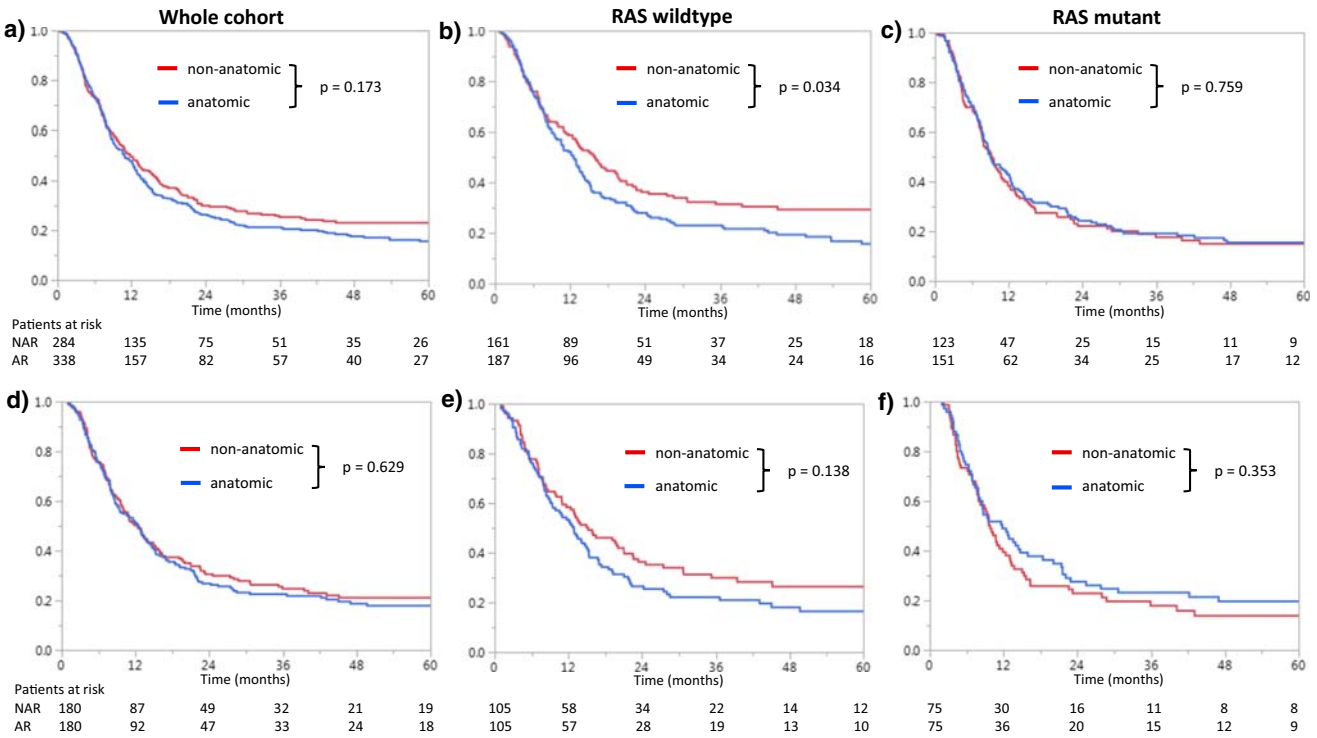

Fig. 2 Recurrence-free survival in patients after anatomic (AR) vs non-anatomic resection (NAR) according to *RAS* mutation status, before matching for **a** the whole cohort, **b** *RAS* wild-type, and **c** *RAS* mutation and after matching for **d** the whole cohort, **e** *RAS* wild-type, and **f** *RAS* mutation

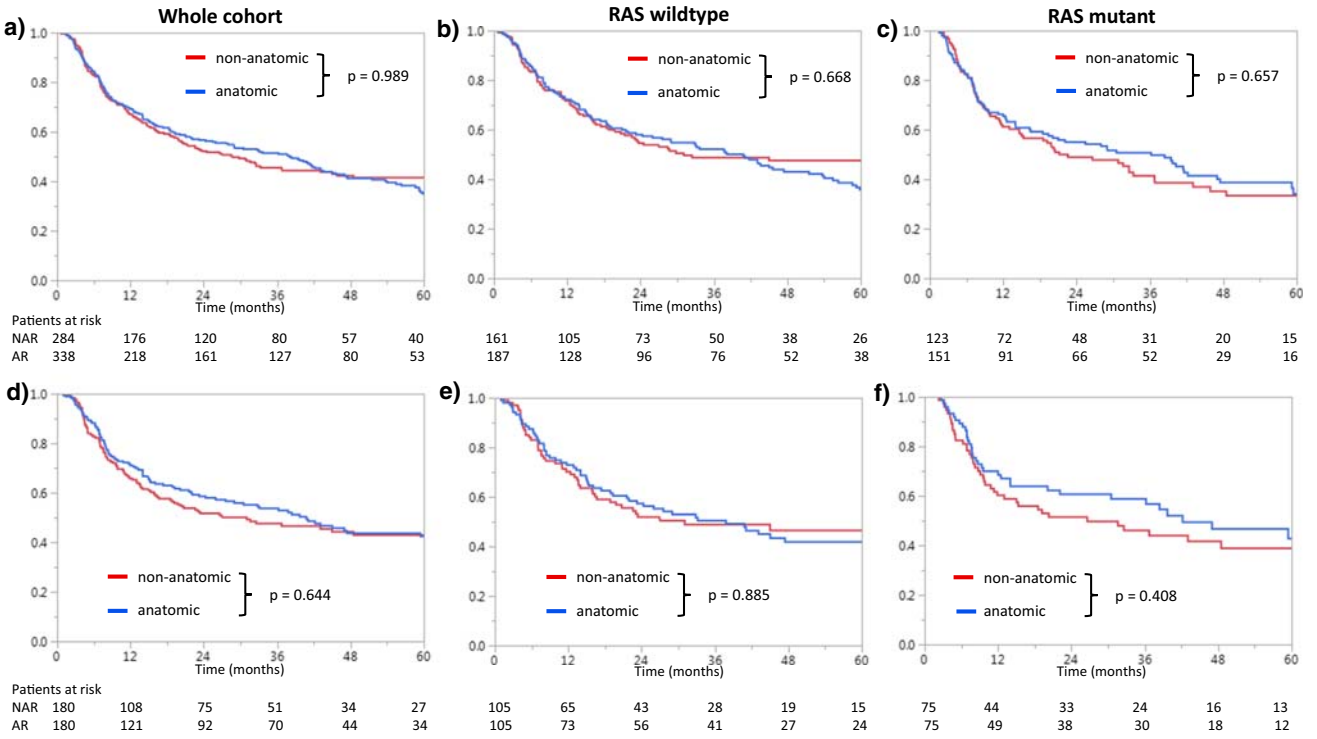

Fig. 3 Liver-specific recurrence-free survival in patients with anatomic (AR) vs non-anatomic resection (NAR) according to *RAS* mutation status, before matching for **a** the whole cohort, **b** *RAS* wild-type, and **c** *RAS* mutation and after matching for **d** the whole cohort, **e** *RAS* wild-type, and **f** *RAS* mutation

Table 2 R1 resection, and intrahepatic and local recurrence after matching

Outcome	All patients 360	*RAS* wild type			*RAS* mutant		
		AR $n = 105$	NAR $n = 105$	*P* value	AR $n = 75$	NAR $n = 75$	*P* value
Intrahepatic recurrence, *n* (%)	187 (51.9)	59 (56.2)	47 (44.8)	0.098	37 (49.0)	41 (54.7)	0.513
Local recurrence, *n* (%)	35 (9.7)	15 (14.3)	8 (7.6)	0.122	8 (10.7)	4 (5.3)	0.229
R1 resection, no. (%)	34 (9.4)	11 (10.5)	12 (11.4)	0.825	5 (6.7)	6 (8.0)	0.754
Local recurrence after R1, *n* (% of patients with R1 resection)	6 (17.6%)	2 (18.2)	3 (25.0)	0.692	1 (20.0)	0 (0.0)	–

AR anatomic resection, *NAR* non-anatomic resection

group. This finding is consistent with previous data demonstrating that, while *RAS* mutation is a risk factor for more aggressive systemic disease and likely predicts poor response to chemotherapy, this risk is not specific to intrahepatic recurrence and is not prevented by AR.[7] Thus, a more aggressive liver resection will not affect overall outcomes such as OS and RFS, and may actually decrease the ability to perform a re-resection when these patients experience recurrence in a remote site within the liver.[2]

Perhaps most importantly, there was no difference in L-RFS between groups, before or after matching. This contradictory result when compared to previous work may directly reflect our exclusion of patients undergoing intraoperative ablation, which likely accounted for at least some of the intrahepatic recurrences.[23] Most importantly, we closely evaluated patients with intrahepatic recurrence and examined the site of recurrence. We found no decrease in local recurrence, which we defined to include any recurrence at the resection margin or within the same segment as the resected lesion, with AR. If *RAS*-mutated CRLM required an AR to clear the segmental portal pedicle, this outcome would be the most likely to show a difference. While previous studies have shown that 40% of CRLM present with microvascular invasion and 20% with micrometastases, mostly occurring in a 2- to 4-mm area around the tumor,[24,25] there is no clear relation to the presence of *RAS* mutation.[22] Moreover, there is no convincing evidence that colorectal liver metastases spread via the portal pedicle, which would require an AR. Therefore, an adequate surgical margin, rather than an AR, is required to fully remove these sites of metastatic disease, even with *RAS* mutation.

Our study has some important limitations that should be considered. First, we used a retrospective design, evaluating a selected cohort of patients at a single institution, which introduced selection bias. Patients who underwent AR had more aggressive disease with more tumors, larger tumors, and potentially tumors that were closer to major vascular structures, biasing surgeons against NAR. We did attempt to account for this bias using PS matching, but it still must be considered when interpreting our data. Second, the definitions of AR and NAR are not universal. For this study, we specifically addressed the concern of tumor spread via the segmental pedicle; therefore, we included any formal segmentectomy and sectionectomy in the AR group. We used a prospectively maintained database with this data point filled by the faculty surgeon in each case. When ambiguity existed, operative reports were read to determine whether or not an AR was performed. Despite these limitations, this study represents the largest to date addressing this important question of AR vs NAR for RAS-mutated patients.

Conclusion

In conclusion, both AR and NAR can be performed with similar long-term outcomes in patients with CRLM, regardless of *RAS* mutation status. While *RAS* mutation may be a risk factor for more aggressive systemic disease, it did not impact outcomes between AR or NAR. These data do not support a universal requirement for AR in *RAS* mutant CRLM when R0 resection can be achieved with NAR.

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Compliance with Ethical Standards

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References

1. Moris D, Ronnekleiv-Kelly S, Rahnemai-Azar AA, Felekouras E, Dillhoff M, Schmidt C, et al. Parenchymal-sparing versus anatomic liver resection for colorectal liver metastases: A systematic review. J Gastrointest Surg 2017;21:1076–85.

2. Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. Ann Surg 2016;263:146–52.
3. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, et al. Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma. Am J Surg 2001;181:153–9.
4. Stewart GD, O'Suilleabhain CB, Madhavan KK, Wigmore SJ, Parks RW, Garden OJ. The extent of resection influences outcome following hepatectomy for colorectal liver metastases. Eur J Surg Oncol 2004;30:370–376.
5. Gold JS, Are C, Kornprat P, Jarnagin WR, Gonen M, Fong Y, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 2008;247:109–117.
6. Lalmahomed ZS, Ayez N, van der Pool AE, Verheij J, JN IJ, Verhoef C. Anatomical versus nonanatomical resection of colorectal liver metastases: is there a difference in surgical and oncological outcome? World J Surg 2011;35:656–661.
7. Vauthey JN, Zimmitti G, Kopetz SE, Shindoh J, Chen SS, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg 2013;258:619–626.
8. Margonis GA, Buettner S, Andreatos N, Sasaki K, Ijzermans JNM, et al. Anatomical resections improve disease-free survival in patients with KRAS-mutated colorectal liver metastases. Ann Surg 2017;266:641–649.
9. Renaud S, Seitlinger J, Lawati YA, Guerrera F, Falcoz PE, et al. Anatomical resections improve survival following lung metastasectomy of colorectal cancer harboring KRAS mutations. Ann Surg 2018; https://doi.org/10.1097/SLA.0000000000002829.
10. Couinaud C. [Liver lobes and segments: notes on the anatomical architecture and surgery of the liver]. Presse Med 1954;62:709–712.
11. The Brisbane 2000 Terminology of Liver Anatomy and Resections. Terminology Committee of the International Hepato-Pancreato-Biliary Association. HPB. 2000;2 (3): 333–39.
12. Brudvik KW, Mise Y, Conrad C, Zimmitti G, Aloia TA, et al. Definition of readmission in 3,041 patients undergoing hepatectomy. J Am Coll Surg 2015;221:38–46.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.
14. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, et al. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. J Gastrointest Surg 2000;4:178–184.
15. Matsumura M, Mise Y, Saiura A, Inoue Y, Ishizawa T, et al. Parenchymal-sparing hepatectomy does not increase intrahepatic recurrence in patients with advanced colorectal liver metastases. Ann Surg Oncol 2016;23:3718–3726.
16. Memeo R, de Blasi V, Adam R, Goere D, Azoulay D, et al, French Colorectal Liver Metastases Working Group AFdC. Parenchymal-sparing hepatectomies (PSH) for bilobar colorectal liver metastases are associated with a lower morbidity and similar oncological results: a propensity score matching analysis. HPB (Oxford) 2016;18:781–790.
17. Donadon M, Cescon M, Cucchetti A, Cimino M, Costa G, et al. Parenchymal-sparing surgery for the surgical treatment of multiple colorectal liver metastases is a safer approach than major hepatectomy not impairing patients' prognosis: A Bi-institutional propensity score-matched analysis. Dig Surg 2018;35:342–349.
18. Passot G, Denbo JW, Yamashita S, Kopetz SE, Chun YS, et al. Is hepatectomy justified for patients with RAS mutant colorectal liver metastases? An analysis of 524 patients undergoing curative liver resection. Surgery 2017;161:332–340.
19. Margonis GA, Spolverato G, Kim Y, Karagkounis G, Choti MA, et al. Effect of KRAS mutation on long-term outcomes of patients undergoing hepatic resection for colorectal liver metastases. Ann Surg Oncol 2015;22:4158–4165.
20. Brudvik KW, Jones RP, Giuliante F, Shindoh J, Passot G, et al. RAS mutation clinical risk score to predict survival after resection of colorectal liver metastases. Ann Surg 2019;269:120–126.
21. Shindoh J, Makuuchi M, Matsuyama Y, Mise Y, Arita J, et al. Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. J Hepatol 2016;64:594–600.
22. Vigano L, Costa G, Toso C, Cimino M, Andres A, et al. "Precision Surgery" for colorectal liver metastases: Is the time ripe? Ann Surg 2018; https://doi.org/10.1097/SLA.0000000000002855
23. Brudvik KW, Vauthey JN. Surgery: KRAS mutations and hepatic recurrence after treatment of colorectal liver metastases. Nat Rev Gastroenterol Hepatol 2017;14:638–639.
24. Vigano L, Capussotti L, De Rosa G, De Saussure WO, Mentha G, et al. Liver resection for colorectal metastases after chemotherapy: impact of chemotherapy-related liver injuries, pathological tumor response, and micrometastases on long-term survival. Ann Surg 2013;258:731–740.
25. Kokudo N, Miki Y, Sugai S, Yanagisawa A, Kato Y, et al. Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 2002;137:833–840.