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Short Report

Resectability and resection rates of colorectal liver metastases according to *RAS* and *BRAF* mutational status: prospective study

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Introduction

Resection of colorectal liver metastases (CRLMs) improves survival and may lead to cure. Resectability rates can be improved with conversion therapy[1,2].

RAS and *BRAF* mutations are found in 50 and 5–20 per cent of tumours respectively in patients with metastatic colorectal cancer[3,4]. These mutations limit systemic therapy alternatives[5] and have been associated with worse outcomes in patients with CRLMs[6]. Patients with the *BRAF* V600E mutation clearly have shorter median survival, but some may survive without recurrence[7].

Multidisciplinary teams (MDTs) have emerged to facilitate cooperation between medical specialties to ensure optimal care for the patient[8–11]. The aim of this study was to evaluate how *RAS* and *BRAF* mutational status affected resectability and conversion assessments performed by local hospitals and by a centralized MDT, and how this information could be used to improve resection rates and survival in patients with CRLMs.

Methods

Study design

RAXO was a prospective, investigator-initiated, nationwide Finnish study (NCT01531621, EudraCT 2011-003158-24) that included 1086 patients with metastatic colorectal cancer between 2012 and 2018. The main protocol[12], liver metastases group[13], and *RAS*/*BRAF* mutations in studies of metastatic colorectal cancer[14] have been published previously. This substudy included patients with known *RAS*/*BRAF* status and CRLMs. Further details are available in the *supplementary material*. Patients with non-V600E *BRAF* mutations were excluded. The patients were assessed as having liver-only metastatic disease or liver and extrahepatic disease at the time of inclusion in the study. The central MDT at Helsinki University Hospital tertiary centre evaluated each patient's technical resectability as described previously[12,13] and in the *supplementary material*. The mutational status was mostly known to the local team, but only

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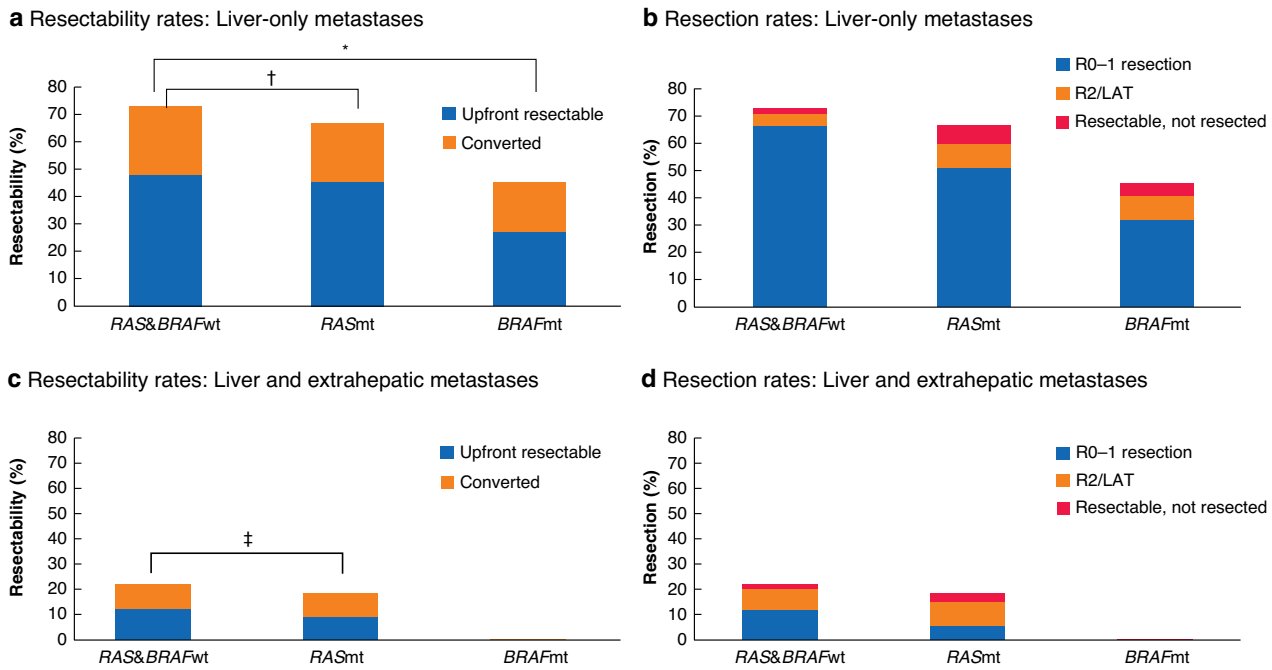

Fig. 1 Resectability, conversion, and resection rates according to mutational status

a Resectability and **b** resection rates for patients with liver-only metastases, and **c** resectability and **d** resection rates for patients with liver and extrahepatic metastases. wt, Wild type; mt, mutation; LAT, local ablative therapy. *OR 0.31 (95% c.i. 0.12 to 0.77); †OR 0.74 (0.46 to 1.22); ‡OR 0.79 (0.44 to 1.44).

occasionally to the central MDT. Patients were classified into the following resection outcome groups: R0–1, R2/local ablative therapy (LAT) or systemic therapy only. The study was approved by the Ethics Committee at Helsinki University Hospital and all patients provided written informed consent. Statistical methodology is presented in the *supplementary material*.

Results

Of 672 patients included, 226 (33.6 per cent) had *RAS&BRAF* wild-type (wt) tumours, 392 (58.3 per cent) *RAS* mutation (mt) tumours, and 54 (8.0 per cent) *BRAF*mt tumours. Median follow-up was 55 (95 per cent c.i. 50–59; minimum 18) months. Patient demographics are summarized in *Table S1*.

Upfront resectability and conversion rates in the central assessment of 354 patients with liver-only and 318 with liver and extrahepatic metastases are shown in *Fig. 1*. In the liver-only group, the central MDT considered the metastases to be upfront resectable in 48.0, 45.5, and 27.3 per cent of patients with *RAS&BRAF*wt, *RAS*mt, and *BRAF*mt tumours respectively. Conversion rates for the borderline or unresectable liver-only group were 48.4, 39.5, and 25.0 per cent respectively. Conversion rates for patients with initially borderline liver-only CRLMs were 78.9 per cent for *RAS&BRAF*wt (reference), 81.5 per cent for *RAS*mt (OR 1.17, 95 per cent c.i. 0.42 to 3.32), and 40.0 per cent for *BRAF*mt (OR 0.18, 0.04 to 0.79) subgroups. The overall R0–1 resection rates for patients with liver-only CRLMs were 67.5 per cent for those with *RAS&BRAF*wt tumours (reference), 51.2 per cent for patients with *RAS*mt tumours (OR 0.51, 0.32 to 0.80), and 31.8 per cent for those with *BRAF*mt tumours (OR 0.22, 0.09 to 0.60). The influence of tumour location on conversion is shown in *Table S2*.

Patients with liver and extrahepatic *RAS&BRAF*wt and *RAS*mt metastases had similar upfront resectability and conversion rates. There was, however, a difference in R0–1 resection rates between the *RAS&BRAF*wt (12.6 per cent; reference) and *RAS*mt (4.9 per cent; OR 0.35, 0.15 to 0.87).

When patients with liver-only disease were considered to have upfront resectable tumours by the central MDT, the local hospital underestimated resectability in 39, 41, and 83 per cent for *RAS&BRAF*wt, *RAS*mt, and *BRAF*mt tumours respectively (*Fig. 2a*). If the central MDT considered a patient to have borderline resectable disease, 16, 15, and 0 per cent respectively of the local assessments were scored as never resectable.

Among patients with liver and extrahepatic metastases considered upfront resectable by the central MDT, the local teams underestimated resectability in 69 and 53 per cent of those with *RAS&BRAF*wt and *RAS*mt tumours respectively (*Fig. 2b*). The rate of underestimation for borderline liver and extrahepatic metastases was 31 per cent for *RAS&BRAF*wt and 50 per cent for *RAS*mt tumours. Reasons for not resecting technically resectable metastases are listed in *Table S3*.

Forty-two patients (6.3 per cent) had CRLMs that the local team considered never resectable. These were considered upfront or borderline resectable in central assessment, and 28 became technically resectable. Nine of these patients underwent resection with curative intent, including six with *RAS&BRAF*wt tumours (5 with liver-limited and 1 with liver and extrahepatic metastases) and three with *RAS*mt tumours (2 liver-limited, and 1 liver and extrahepatic metastases).

Median overall survival (OS) after the first resection of metastases for 197 patients with liver-only metastases who underwent R0–1 resection was 82, 73, and 28 months according to *RAS&BRAF*wt (reference), *RAS*mt (HR 1.55, 0.91 to 2.65), and *BRAF*mt status (HR 7.24, 2.38 to 22.00) respectively ($P < 0.001$). Corresponding 5-year OS rates were 68, 60, and 0 per cent respectively (*Fig. S1*). For 22 patients with *RAS&BRAF*wt and *RAS*mt status who underwent R0–1 resection of liver and extrahepatic metastases, median OS was 79 and 71 months respectively ($P = 0.847$). Corresponding 5-year OS rates were 79 and 88 per cent. Recurrence-free survival, survival

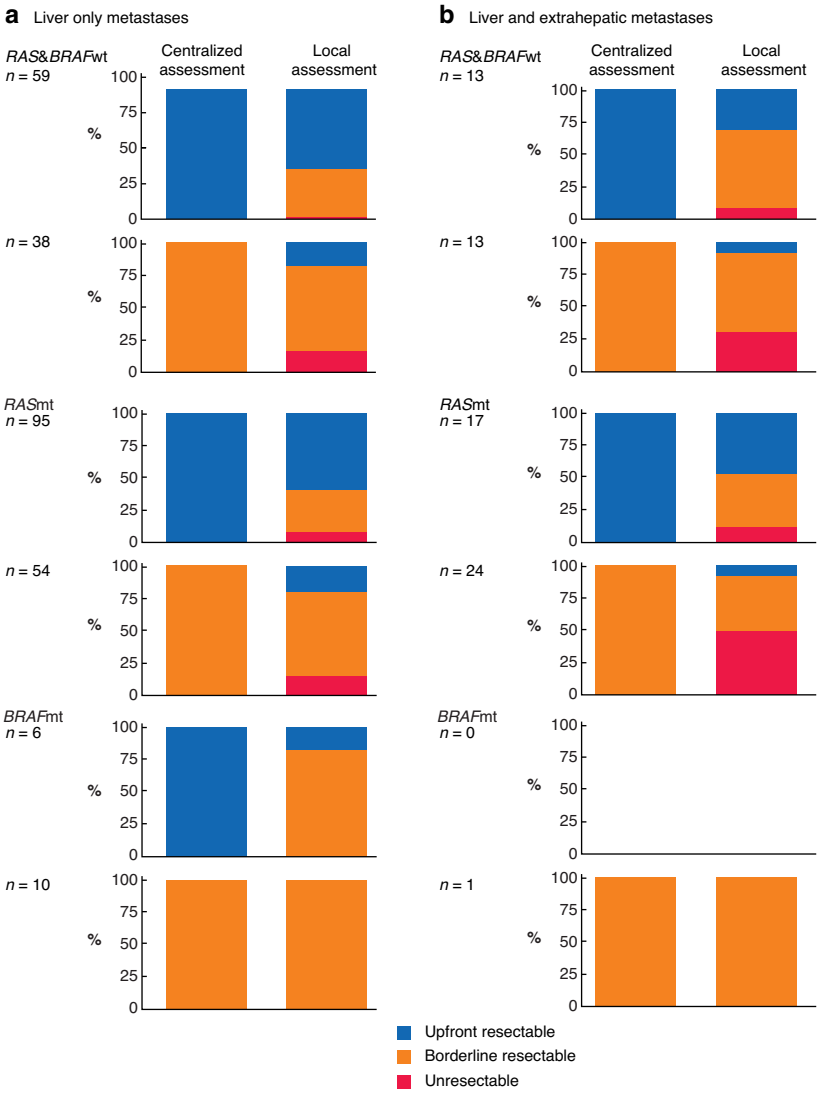

Fig. 2 Centralized resectability assessment compared with local assessment according to mutational status for patients with liver-only metastases and those with liver and extrahepatic metastases

a Patients with liver-only metastases and **b** patients with liver and extrahepatic metastases. wt, Wild type; mt, mutation.

according to resection status, mutational status, and extent of disease, and a 12-month conditional landmark analysis of OS are shown in *Figs S2–S4*.

In multivariable analysis of risk factors for OS, assessment as unresectable by the central MDT appeared to be a strong risk factor. The second most notable factor was mutational status (*Table 1*).

Discussion

With the help of centralized multidisciplinary assessment, high resectability, conversion, and resection rates are achievable for patients with RAS&BRAFwt and RASmt CRLMs. Selected patients with unfavourable *BRAF* mutation or with extrahepatic metastases may even undergo potentially curative resection.

Prospective studies of highly selected patients, often with RASwt tumours, have reported a conversion rate of 44–64 per cent and secondary resection/LAT rates of 44–61 per cent for patients with initially borderline or unresectable CRLMs[2,15–17]. In patients who also underwent hepatic artery infusion as induction therapy, conversion and secondary resection/LAT rates were 32 per cent for patients with RAS&BRAFwt tumours, 39 per cent for those with RASmt lesions, and 0 per cent for those with BRAFmt disease[18]. In a retrospective neoadjuvant therapy response assessment[19], disease in up to 53 per cent of patients, mostly with RASwt tumours, was considered resectable upfront or after conversion, but only 29 per cent of these patients actually underwent resection. The present prospective study has shown comparable secondary resection/LAT rates for patients with liver-only RAS&BRAFwt and RASmt metastases, and a secondary resection/LAT rate as high as 25 per cent for patients with BRAFmt tumours.

In the literature, resectability and resection rates range from 18 to 71 per cent and from 16 to 54 per cent respectively for patients with liver-only metastases[1,9,19,20]. This study has shown that the chance of curative resection is highest for liver-only RAS&BRAFwt metastases, then RASmt metastases. Even for patients with tumours harbouring a *BRAF* mutation, a resectability rate of 45 per cent and corresponding resection rate of 32 per cent provided at least a chance of prolonged survival.

Table 1 Multivariable analysis of risk factors for overall survival

	HR	
	Univariable analysis	Multivariable analysis
Age > 70 years	1.22 (1.01, 1.48)	1.27 (1.04, 1.56)
Female sex	1.04 (0.86, 1.26)	
ECOG score		
PS 0	1.00 (reference)	1.00 (reference)
PS 1	1.89 (1.50, 2.39)	1.47 (1.16, 1.87)
PS 2–3	3.38 (2.54, 4.48)	2.29 (1.70, 3.09)
Charlson Co-morbidity Index score		
0	1.00 (reference)	
1–2	1.20 (0.96, 1.48)	
3–5	1.25 (0.47, 3.36)	
BMI (kg/m^2)		
< 20	1.00 (reference)	
20–30	0.96 (0.67, 1.36)	
> 30	0.85 (0.57, 1.27)	
Primary tumour in right colon	1.76 (1.44, 2.14)	1.76 (1.42, 2.18)
Primary tumour not operated at baseline (yes *versus* no)	1.89 (1.53, 2.27)	1.49 (1.20, 1.85)
Synchronous metastases*	1.10 (1.20, 1.88)	1.35 (1.04, 1.77)
≥ 3 liver segments involved	2.37 (1.91, 2.94)	1.54 (1.21, 1.98)
Extrahepatic metastases	2.41 (2.00, 2.91)	1.21 (0.97, 1.50)
Mutational status		
RAS and *BRAF* wild type	1.00 (reference)	1.00 (reference)
RAS mutation	1.57 (1.27, 1.93)	1.62 (1.30, 2.00)
BRAF mutation	3.34 (3.09, 6.07)	2.55 (1.78, 3.64)
Upfront resectability assessment by central MDT		
Resectable	1.00 (reference)	1.00 (reference)
Borderline	1.50 (1.09, 2.06)	1.11 (0.79, 1.55)
Unresectable	5.54 (4.28, 7.18)	3.69 (2.68, 5.08)

Values in parentheses are 95% confidence intervals. Co-variables significant in univariable analyses were entered into the multivariable analysis. *Within 2 months of diagnosis of primary tumour. ECOG, Eastern Cooperative Oncology Group; PS, performance status; MDT, multidisciplinary team.

Other groups have reported up to 44 per cent resectability, but resection rates of only 5–11 per cent for patients with multiorgan metastases[19,20]. The present study has shown that such patients are indeed less likely to undergo resection. After conversion therapy, curative resection of all diseased organs could still be completed in 13 and 5 per cent of patients with *RAS*&*BRAF*wt and RASmt tumours respectively.

Reported disagreements between surgeons assessing resectability of 35–52 per cent, including 7–11 per cent major disagreements, have stressed the importance of a multidisciplinary team[9,15]. Disagreement between local teams and central MDT was considerable in the present study, with most major disagreements relating to borderline resectable or extrahepatic disease, suggesting that patients with more advanced disease could benefit even more from centralized MDT assessment. In multivariable survival analysis, central MDT assessment was associated with survival. This indicates that the central MDT is capable of including important clinical and radiological information in their decision, and underlines the potential additional value of multidisciplinary assessment of patients with liver-only or liver-dominant CRLMs.

Collaborators

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This paper reports subgroup study results of the preregistered RAXO study (NCT01531621, EudraCT 2011-003158-24). The preregistration can be accessed at https://clinicaltrials.gov/ct2/show/NCT01531621. Understanding of the significance of molecular pathology has increased greatly since the RAXO study was originally conceived. The analysis plan for molecular pathology has been developed partially during the course of the study, and can be found in the RAXO Protocol version 3.2, dated 7 May 2017[12].

Disclosure

The authors declare no conflict of interest. The funders had no role in the study design, analysis, interpretation of the data, decision to publish, or writing of this report.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The original study database is not publicly available, but an anonymized version of the original data can be requested from the authors.

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