What defines long-term survival in patients after liver resection for colorectal metastases?

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BACKGROUND

Colorectal cancer is the third most frequent malignant disease, with 1,800,000 people affected worldwide (1). At diagnosis, the disease is disseminated in 15% to 25% of patients, and the liver is the most frequent site of distant metastases (1). Another 25% of patients develop metachronous metastases (1). The 5-year overall survival (OS) after radical resection of colorectal liver metastases (CLMs) in well-selected patients is 47–60%. However, the disease recurs in 40–75% of patients, and the liver is involved in half of such patients (1). Traditionally, factors associated with prognosis in patients with CLM were explored that derived from the characteristics of a primary tumor or the CLM, including somatic mutations (2). So far, more than a dozen prognostic scoring systems (PSSs) were developed, and some were externally validated (3). Recently, the paradigm of prognostication shifted toward a host immune system (4). Furthermore, ratios between blood cells or proteinaceous inflammatory markers (PIMs) of the acute phase response could express an inflammatory response (5, 6). These could be C-reactive protein (CRP), albumins, and fibrinogen (7, 8). In 2019, Dupre et al. (9) developed and validated the Liverpool score. It is a PSS that includes the systemic inflammatory response expressed as the neutrophil-to-lymphocyte ratio (NLR) to predict the survival of patients undergoing surgical therapy for CLM (9). Although prognostic factors used in PSSs are usually part of routine processing, missing variables, which cannot be obtained retrospectively, represent a challenging issue for validation (3). The aim of the study was to rank original variables and candidate PIMs that could replace the NLR in further validating the PSS for patients treated with curative intent for CLM.

MATERIALS AND METHODS

In our research we conducted a retrospective review of a prospectively maintained database of 632 patients who underwent surgical treatment of CLM. For this study, a cohort of 371 patients who had undergone the first liver resection was selected. The study was based on the intention-to-treat principle. Routinely available variables were obtained from the database and analyzed since the patients were subjected to routine diagnostics. The diagnostics included a colonoscopy, blood work, and medical imaging and has already been described elsewhere (10). Patients were considered by a multidisciplinary team (1), and those with metastases confined to the liver were considered

for liver resection, radiofrequency ablation, or a combination (1). A major liver resection involves three or more adjacent liver segments. The routine blood work did not include determining the white blood cell count but PIMs: CRP, albumins and fibrinogen (8). PIMs were measured by automatized analyzers from the peripheral vein blood of patients one day before the scheduled liver procedure. Fibrinogen was obtained in a standard coagulation panel. A postoperative histopathological examination confirmed the diagnosis of CLM in all patients.

The study's endpoint was to find the most appropriate PIM by ranking the variables of the Liverpool score and candidate PIMs. For each variable, the cohort was divided into two groups. The main assumption was that the greater the two groups differed in OS, the greater was the importance of the variable in the OS of a patient. Nine variables were analyzed by the Kaplan–Meier method, by the integral between the Kaplan–Meier curves, by univariate Cox regression analysis, and by multivariate Cox regression analysis and ranked for survival.

Table 1. Four ways of ranking of survival factors

	Kaplan-Meier		**Integral I_p**		**Univariate Cox analysis**		**Multivariate Cox analysis**	
Variable	**Chi-square**	**Rank**	**I_p [months]**	**Rank**	**Hazard ratio (Exp(b))**	**Rank**	**Hazard ratio (Exp(b))**	**Rank**
Infiltrated lymph nodes of a primary tumor	21.6	1	26.6	2	2.04	1	1.79	1
Positive resection margin	20.0	2	28.1	1	1.65	2	1.55	2
C-reactive protein > 6 mg/L	16.5	3	20.6	3	1.53	3	1.35	3
ASA classification 2/3	8.4	4	16.6	4	1.35	4	1.33	4
Albumins < 38 g/L	6.7	5	14.7	5	1.33	5	1.14	8
The multiplicity of liver metastasis	5.1	6	12.3	7	1.30	6	1.24	5
The largest liver metastasis > 3.30 cm	4.8	7	11.1	8	1.26	7	1.21	6
Primary tumors on the right side	4.2	8	13.3	6	1.25	8	1.14	7
Fibrinogen > 4.1 g/L	0.5	9	3.2	9	1.080	9	0.982	9

ASA, American Society of Anesthesiologists

RESULTS

There were 243 (65.5%) males and 128 (34.5%) females. Their median age was 65 (27–85, IQR 15) years. There were 263 (70.9%) minor and 108 (29.1%) major liver resections.

Ranking is given in Table 1.

DISCUSSION

The most important finding of our study was that elevated CRP levels were ranked high using all four statistical methods.

First rank was radicality of liver resection in terms of whether R0 resection could be achieved, where an R1 resection was linked to a significantly worse OS (1). Second was lymph node infiltration by the primary colorectal cancer with infiltration contributing to lower survival rates (3). Third was elevated CRP, which was shown to increase the chance for worse OS (7). Fourth was the American Society of Anesthesiologists (ASA) classification, where ASA grade 2 or 3 was linked with worse OS than ASA 1. Fifth was the site of primary colorectal cancer, specifically right-sided cancer, which showed a worse prognosis than left-sided colorectal cancer (3). Sixth was the multiplicity of CLM, with multiple metastases being linked with worse OS, followed by the size of CLM at seventh, specifically with the size of the lesion greater than 3.3 cm (1). Blood albumin levels, specifically lower levels were linked with a worse outcome and placed at eighth (6). Finally, fibrinogen levels, specifically hyperfibrinogenemia, were placed at number nine with no statistical significance (8).

CONCLUSION

CRP levels were ranked high using all four statistical methods, which showed that it could be a promising factor in predicting outcomes for patients with CLM and could prove to be a proper replacement for NLR in future research regarding the validation of the Liverpool score.

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