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A novel preoperative risk score to optimize patient selection for performing concomitant liver resection with cytoreductive surgery/HIPEC

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Abstract

Background: While parenchymal hepatic metastases were previously considered a contraindication to cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC), liver resection (LR) is increasingly performed with CRS/HIPEC.

Methods: Patients from the US HIPEC Collaborative (2000–2017) with invasive appendiceal or colorectal adenocarcinoma undergoing primary, curative intent CRS/HIPEC with CC0-1 resection were included. LR was defined as a formal parenchymal resection. Primary endpoints were postoperative complications and overall survival (OS).

Results: A total of 658 patients were included. About 83 (15%) underwent LR of colorectal (58%) or invasive appendiceal (42%) metastases. LR patients had more complications (81% vs. 60%; $p = .001$), greater number of complications (2.3 vs. 1.5; $p < .001$) per patient and required more reoperations (22% vs. 11%; $p = .007$) and readmissions (39% vs. 25%; $p = .014$) than non-LR patients. LR patients had decreased OS (2-year OS 62% vs. 79%, $p < .001$), even when accounting for peritoneal carcinomatosis index and histology type. Preoperative factors associated with decreased OS on multivariable analysis in LR patients included age < 60 years (HR, 3.61; 95% CI, 1.10–11.81), colorectal histology (HR, 3.84; 95% CI, 1.69–12.65), and multiple liver tumors (HR, 3.45; 95% CI, 1.21–9.85) (all $p < .05$). When assigning one point for each factor, there was an incremental decrease in 2-year survival as the risk score increased from 0 to 3 (0: 100%; 1: 91%; 2: 58%; 3: 0%).

Conclusions: As CRS/HIPEC + LR has become more common, we created a simple risk score to stratify patients considered for CRS/HIPEC + LR. These data aid in striking the balance between an increased perioperative complication profile with the potential for improvement in OS.

Keywords

appendiceal adenocarcinoma; colorectal cancer; HIPEC; liver resection; risk score

1 | INTRODUCTION

Liver metastases have historically been a contraindication for cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) for synchronous peritoneal metastases from colorectal cancer. Liver metastases represent systemic dissemination of disease, while

the surgical rationale supporting CRS/HIPEC centers around peritoneal metastases representing locoregional disease spread.[1] However, with long term survival proven possible after liver resection (LR) for colorectal metastases, concomitant LR and CRS/HIPEC is increasingly performed.[2]

Several single institutions have reported the feasibility and safety of concomitant LR and CRS/HIPEC. In a study of 24 patients undergoing concurrent LR and CRS/HIPEC for colorectal cancer, Elias and colleagues reported morbidity of 58%, 2-year overall survival (OS) of 61%, and 2-year disease-free survival of 42%. Number of liver lesions was found to be the only predictor of decreased OS, and the authors concluded that concomitant LR and CRS/HIPEC was feasible for selected patients, specifically those with <3 liver lesions.[3] Navez et al.[4] and Alzahrani et al.[1] found no difference in major complication rates following LR and CRS/HIPEC compared to patients undergoing CRS/HIPEC alone, though both reported decreased OS in patients undergoing LR. In contrast, Cloyd et al.[5] reported increased operative time, longer length of stay, increased rates of reoperation, and increased postoperative morbidity in patients undergoing concomitant LR and CRS/HIPEC and encouraged a staged operative approach for patients with synchronous peritoneal and liver metastases.

Though controversy remains regarding differences in complication rates, published studies agree that patients with isolated peritoneal metastases enjoy a longer OS compared to patients with peritoneal and liver metastases undergoing concomitant resection. However, the survival after LR and CRS/HIPEC is meaningful, with estimates reported up to 74% at 1 year and 16%-18% at 5 years compared to a median OS in patients with peritoneal and liver metastases treated with systemic chemotherapy alone of approximately 12 months and minimal survival at 5 years,[1,3,6] with the caveat that patient selection for concomitant resection is paramount. General consensus requires patients to have three or fewer liver lesions, with good performance status, and minimal comorbidities to be considered for concomitant LR and CRS/HIPEC.[7–9]

To aid in patient selection, Elias et al.[10] developed a nomogram to estimate survival in patients considered for concomitant LR and CRS/HIPEC. Criteria included in the nomogram were number of liver metastases, peritoneal carcinomatosis index (PCI), and type of surgery (CRS/HIPEC alone, LR alone, or concomitant LR and CRS/HIPEC). However, though radiographic PCI has been shown to correlate with intraoperative PCI, use of radiographic PCI remains controversial, and its measurement in clinical practice is not standard practice.[11] Thus, our aim was to determine purely preoperative predictors associated with OS in patients considered for concomitant LR and CRS/HIPEC using a large, multi-institutional database.

2 | MATERIALS AND METHODS

The United States HIPEC Collaborative is a collaboration of 12 academic tertiary and quaternary referral centers: Emory University, The Ohio State University, University of California San Diego, University of Cincinnati, City of Hope National Medical Center, Johns Hopkins University, University of Massachusetts, Mayo Clinic, Medical College of

Wisconsin, Moffitt Cancer Center, University of Texas MD Anderson Cancer Center, and University of Wisconsin. Institutional Review Board approval was obtained at each study site before data collection. Patients who underwent CRS with or without HIPEC between 2000 and 2017 were included. Pertinent baseline intraoperative, pathologic, and postoperative outcome data were collected. Staging was based on the American Committee on Cancer (AJCC) 7th edition guidelines. Data regarding neoadjuvant and adjuvant therapy, disease recurrence, and survival were also recorded.

Patients who underwent curative-intent CRS with HIPEC for invasive appendiceal or colorectal adenocarcinoma were included. Completeness of cytoreduction was estimated by the operating surgeon at each institution after CRS. Each patient was assigned a completeness of cytoreduction score (CCR) of 0 (no visible peritoneal disease), 1 (remaining tumor nodules <2.5 mm), 2 (remaining tumor nodules 2.5 mm–2.5 cm), or 3 (remaining tumor nodules >2.5 cm). Patients with CCR of 2 or 3 were excluded.

Patients were categorized into two groups based on whether or not they had an LR, defined as a formal parenchymal resection. Patients who had a liver capsule resection without parenchymal resection were placed in the “no liver resection” group. “Multiple” liver tumors was defined as >1 distinct lesion. Primary outcomes were postoperative complications and OS.

2.1 | Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software (IBM Inc.). Descriptive analyses were performed for the entire cohort. χ^2 analysis was used to compare categorical variables, and Student’s *t* test or one-way analysis of variance was used for continuous variables, where indicated. The univariate and multivariable associations between each covariate with study outcomes including postoperative complications and OS were assessed using binary or Cox logistic regression, where appropriate. Statistical significance was predefined as $p < .05$. Median follow up was 23 months.

3 | RESULTS

3.1 | Patient characteristics

Of 2372 patients in the database, 658 met inclusion criteria. Fifteen percent ($n = 83$) of patients underwent formal LR. Seventy-seven percent of these patients underwent wedge resection and 23% major hepatectomy. The average number of wedge resections per patient was 1.6 ± 1.2. Patients who underwent LR were more likely to be male (58% vs. 44%, $p = .026$), to have colorectal histology (58% vs. 39%, $p = .002$), and to have moderately or poorly differentiated tumors (40% vs. 21% and 24% vs. 18%, respectively, $p = .032$). They were more likely to have received neoadjuvant chemotherapy (59% vs. 44%, $p = .014$). This difference is likely due to differences in histology however, as the majority of patients with colorectal histology (83%) received neoadjuvant chemotherapy, compared to the minority of patients with appendiceal histology (26%, $p < .001$). Patients who underwent LR were also more likely to have a postoperative complication (81% vs. 60%, $p = .001$), to have a greater number of postoperative complications (mean 2.31 vs. 1.5, $p < .001$), were more likely to

need a reoperation (22% vs. 11%, $p = .007$), and to be readmitted (39% vs. 25%, $p = .014$) (Table 1). LR was also associated with having a postoperative complication and with multiple postoperative complications on both univariate and multivariable analysis (any complication: OR, 2.990; 95% CI, 1.601–5.584; $p = .001$; multiple complications: OR, 2.156; 95% CI, 1.259–3.691; $p = .005$) (Table 2).

LR was associated with decreased OS compared to patients who did not have a LR (2-year OS, 62% vs. 79%; $p < .001$) (Figure 1), which persisted in multivariable analysis accounting for PCI, histology type, tumor differentiation, and completeness of cytoreduction (HR, 1.728; 95% CI, 1.124–2.657; $p = 1.013$) (Table 3).

3.2 | Preoperative predictors of OS

Due to the increased complication profile and decreased OS associated with concomitant LR and CRS/HIPEC, we sought to determine preoperative predictors of decreased OS in patients undergoing the combined procedure. Preoperative factors associated with decreased OS included age less than 60 years (HR, 3.608; 95% CI, 1.101–11.819; $p = .034$), colorectal histology (HR 3.844; 95% CI, 1.168–12.650; $p = .027$), and multiple liver lesions (HR, 3.454; 95% CI, 1.211–9.851; $p = .020$) (Table 4). Based on similar hazard ratios in a multivariable model we assigned each risk factor a score of 1 and created a simple risk score to preoperatively risk-stratify patients considered for concomitant liver resection and CRS/HIPEC. Using this model, there is an incremental decrease in 2-year OS as the score increases from 0 to 3 (0: 2-year OS 100%; 1: 91%; 2: 58%; 3: 0%; $p = .001$) (Figure 2).

4 | DISCUSSION

Using a large, multi-institutional database of high-volume tertiary and quaternary referral centers, we sought to determine complication rates associated with concomitant LR and CRS/HIPEC and to provide a decision-making tool using solely preoperative factors to aid patient selection for this controversial, but increasingly performed, combined procedure.

4.1 | Complication and survival rates

Concomitant LR and CRS/HIPEC was found to be associated with increased postoperative complication rates, increased number of complications, increased rates of reoperation, and increased readmission compared to patients undergoing CRS/HIPEC alone. This mirrors the findings of Cloyd et al, but contradicts results of previous studies which reported no difference in postoperative morbidity.[1,3–5] However, studies reporting no difference in postoperative morbidity with concomitant resection are single-institution studies with relatively small numbers of patients. The physiologic basis for increased complications is convincing, including conflicting intraoperative resuscitation goals for the two procedures, unknown absorption and toxicity implications of intraperitoneal chemotherapy by raw liver margins, and increased extent of cytoreduction associated with LR.[5,12–15] It should be considered that comparing patients with peritoneal metastases alone with patients with both peritoneal and liver metastases compares two different groups of patients, one group with locoregional spread and one with hematogenous dissemination of disease. This alone may

explain the survival difference between patients undergoing concomitant LR and CRS/HIPEC with those undergoing CRS/HIPEC alone.

4.2 | Risk score

Regardless of the appropriateness of a direct comparison, patients undergoing concomitant LR and CRS/HIPEC represent a unique group facing a potentially morbid operation. We created a simple, preoperative risk score to aid with patient selection and to better inform the consent process. Three easily determined preoperative factors, age < 60, colorectal rather than appendiceal histology, and multiple (>1) liver lesions, are associated with decreased OS following concomitant LR and CRS/HIPEC, with incrementally decreased survival with the presence of each additional risk factor. To our knowledge this is the only risk score available for this patient population that utilizes only preoperatively determined factors.

Further examining the risk factors in our model, decreased OS seen for patients less than 60 years old can potentially be explained by differing tumor biology in cancers diagnosed in young people. Early onset colorectal cancer, defined as a diagnosis before the age of 50, is increasing in incidence, and tends to present at a later stage, likely due to recommendations for colon cancer screening beginning at age 50 absent a family history.[16] Younger patients are more likely than older patients to be symptomatic at diagnosis and to have a longer time interval between symptom onset and diagnosis, presumably due to lower clinical suspicion due to age. There is also some evidence that cancers diagnosed in younger patients are biologically different than those in older patients. Early onset colon cancers have been found to have different molecular characteristics, with increased rates of poorly differentiated and signet-cell histology, and are much more likely to be left sided, compared to a right-sided predominance in older patients.[16] Though more research is needed into the underlying mechanisms and characteristics of early onset colon cancer, our results indicate that younger patients with peritoneal and liver metastases are a distinct risk group compared to older patients with the same metastatic pattern.

Data directly comparing colorectal and appendiceal neoplasms are scarce, which, given the heterogeneity of the two malignancies and rarity of appendiceal adenocarcinoma, is unsurprising. Son et al.[17] conducted a retrospective review and comparative analysis of 2875 patients with sporadic appendiceal and colorectal cancer who underwent curative resection. They found appendiceal adenocarcinoma to be associated with increased risk of perforation (OR, 2.602; $p = .009$) and decreased 5-year disease-free survival (58% vs. 85%; $p = .001$) compared to colon cancer, however the recurrence patterned differed significantly, with appendiceal adenocarcinoma recurring more commonly in the peritoneum due to direct locoregional spread.[17] Importantly, this study excluded stage IV disease and did not report OS. The majority of other long-term outcome studies tend to group appendiceal and colorectal tumors, making direct comparison of survival after CRS/HIPEC between the groups difficult. Furthermore, PCI and CCR, both of which are major contributors to survival, likely fail to correlate between the two disease processes, further contributing to unbalanced comparisons.[18] Additional research is needed to elucidate differences between the two histologies, as colorectal histology appears to be associated with OS after concomitant LR and CRS/HIPEC.

Finally, multiple liver tumors, rather than a single metastasis is associated with decreased OS. Elias et al.[7] first showed that tumor burden was prognostic; patients with 1–3 colorectal resected liver metastases had improved OS compared to those with 4–6 and >6 tumors. Looking specifically at patients undergoing concomitant LR and CRS/HIPEC, Downs-Canner et al.[19] also found that patients with >3 colorectal liver metastases had a decreased OS compared to patients with 1–3 tumors (median OS 5 vs. 21 months). Using our multi-institutional database, we found that not only were >3 tumors associated with decreased OS, but that multiple tumors of any number portend worse prognosis after concomitant LR and CRS/HIPEC. This is likely due to increased liver metastatic burden representing more advanced systemic spread compared to the isolated metastasis.

Limitations to this study include its retrospective design and associated risk of selection bias, however the US HIPEC Collaborative consists of high-volume centers allowing for data from a large number of patients treated by similarly trained and experienced surgeons to be used to analyze long term outcomes. Though we recognize that the expertise of the collaborative members also limits generalizability to patients seen at lower-volume centers, it also ensures a relative standardization of care across institutions. Additionally, while the database included KRAS mutation status and sidedness of colon cancer, factors known to affect patient prognosis, the majority of patients meeting selection criteria did not have this data available and thus these variables were not included in our risk score. This is another limitation to the retrospective nature of our database. Furthermore, though PCI is an important prognostic indicator for these patients, because there is no universally accepted method to accurately determine PCI pre-operatively, nor is preoperative radiographic determination of PCI routinely performed, we did not include PCI in our risk score. Once preoperative determination of PCI becomes standardized and reliable, our risk score should be modified to include this important clinical information. Finally, data regarding response to neoadjuvant chemotherapy before surgery is an important variable allowing insight to disease biology and prognosis. Unfortunately, this variable was not available in our database, which should be considered a limitation. However, progression of disease is generally considered a contraindication to surgical management of malignancy, and patients with disease progression on systemic therapy were likely not included in our database. Our risk score also should be externally and prospectively validated before clinical implementation.

5 | CONCLUSION

As concomitant LR and CRS/HIPEC is increasingly performed for concurrent liver and peritoneal metastases, tools are needed to aid in patient selection and risk stratification. A simple risk score including the preoperative factors of age (<60 vs. ≥60), histology (colorectal vs. appendiceal), and number of liver tumors (single vs. multiple) is associated with incremental decreases in OS with increasing number of factors present. Though prospective external validation is needed, this risk score will help facilitate an informed decision by considering the increased complication profile associated with concomitant LR and CRS/HIPEC with the potential improvement in OS.

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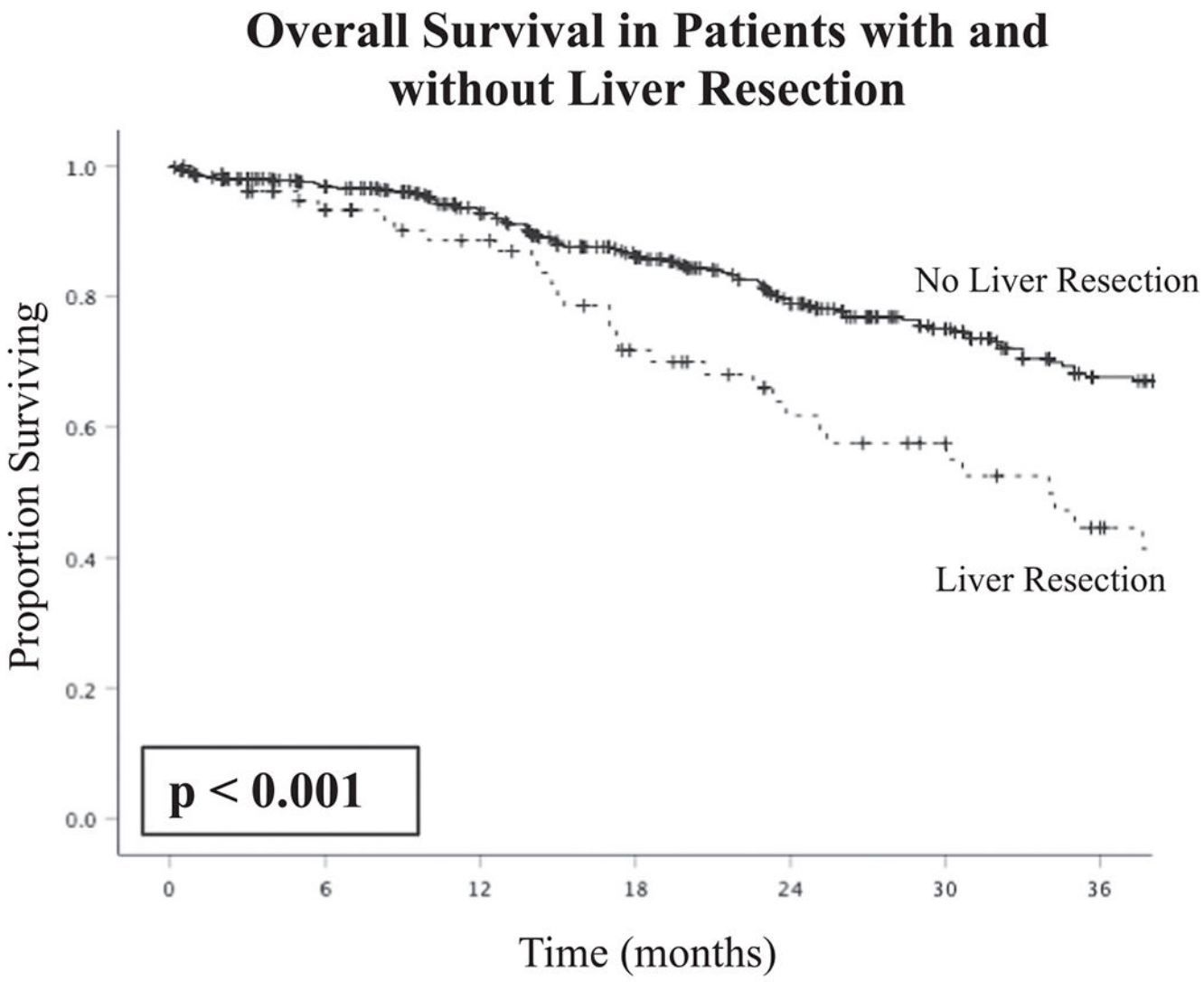

FIGURE 1.
Overall survival in patients with and without formal liver resection

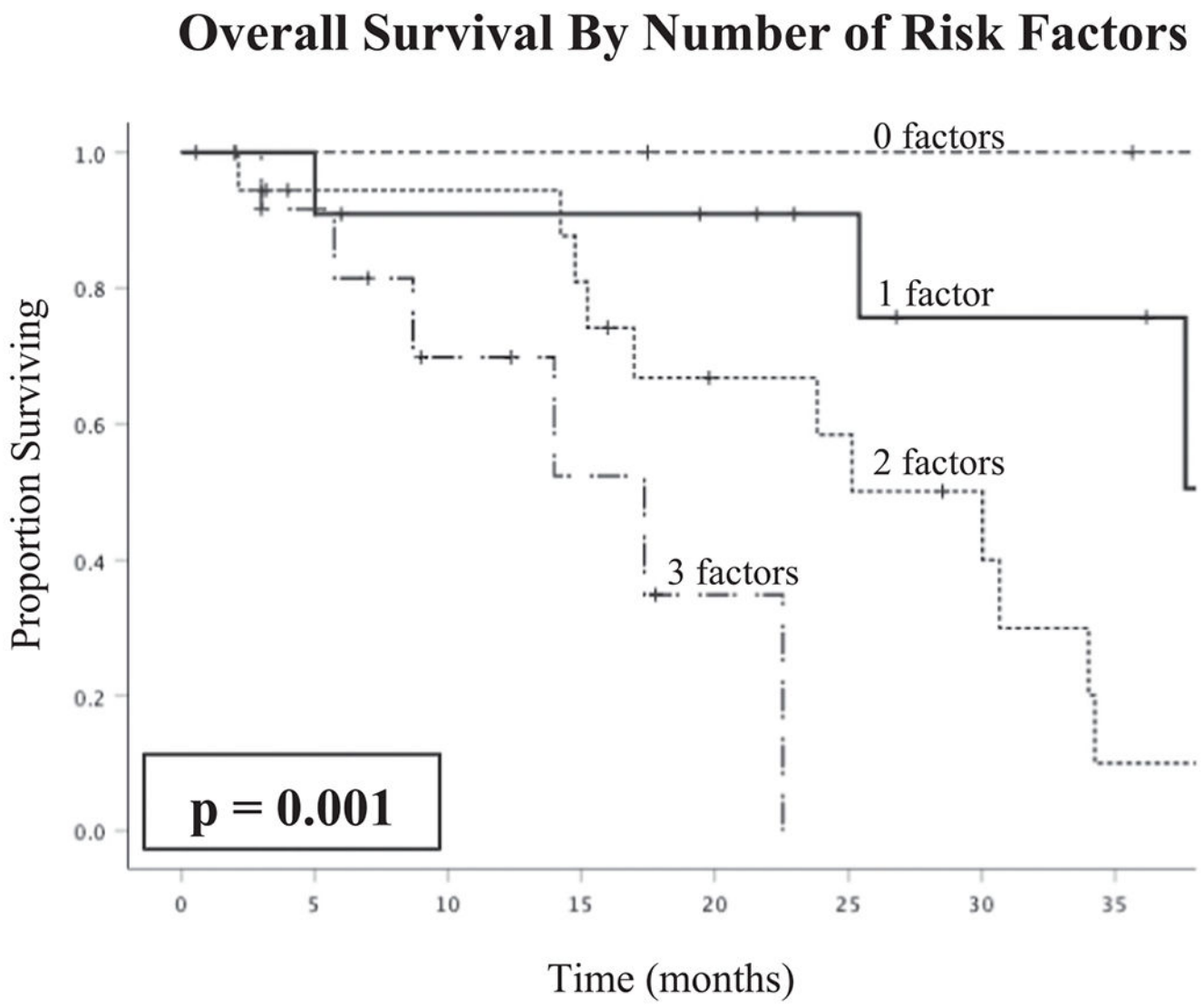

FIGURE 2.
Overall survival by risk factor group (risk factors include: age < 60 years, colorectal histology, multiple (>1) liver lesions)

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TABLE 1

Baseline characteristics and comparative data

Variable	All patients *n* = 658 *n* (%)	Liver resection *n* = 83 *n* (%)	No liver resection *n* = 575 *n* (%)	*p* value
Age	53.9 ± 12.3	55.2 ± 11.4	54.1 ± 12.4	.463
Gender				**.026**
Male	297 (45.1)	48 (57.8)	213 (43.9)	
Female	361 (54.9)	35 (42.2)	272 (56.1)	
ECOG				1.000
0–1	465 (95.5)	57 (98.3)	331 (97.4)	
2–4	22 (4.5)	1 (1.7)	9 (2.6)	
Histology				**.002**
Appendiceal	410 (62.3)	35 (42.2)	298 (61.4)	
Colorectal	248 (37.7)	48 (57.8)	187 (38.6)	
Neoadjuvant chemotherapy	305 (46.4)	49 (59.0)	212 (43.8)	**.014**
Tumor differentiation				**.032**
Well	185 (28.1)	19 (22.9)	152 (26.4)	
Moderate	161 (24.5)	33 (39.8)	118 (20.5)	
Poor	125 (19.0)	20 (24.1)	104 (18.1)	
Missing	187 (28.4)	11 (13.2)	201 (35.0)	
PCI	12.68 ± 7.8	12.81 ± 7.3	12.82 ± 8.1	.989
Operative time	8.12 ± 2.6	8.41 ± 2.4	8.28 ± 2.7	.698
EBL	468.53 ± 592.8	498.2 ± 421.8	455.87 ± 632.2	.557
Any complication	402 (61.1)	67 (80.7)	291 (60.1)	**.001**
Total # complications	1.52 ± 1.5	2.31 ± 1.7	1.50 ± 1.5	**<.001**
Reoperation	70 (10.6)	18 (21.7)	51 (10.5)	**.007**

Variable	All patients $n = 658$ n (%)	Liver resection $n = 83$ n (%)	No liver resection $n = 575$ n (%)	p value
Readmission	159 (24.2)	32 (38.6)	120 (24.9)	**.014**

Abbreviations: EBL, estimated blood loss; ECOG, Eastern Cooperative Oncology Group; PCI, peritoneal carcinomatosis index.

TABLE 2

Univariate and multivariable analysis for postoperative complications

	Univariate analysis		Multivariable analysis	
Variable	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Any postoperative complication				
Age	1.010 (0.997–1.023)	.134	–	–
Gender			–	–
Female	Reference			
Male	0.981 (0.716–1.345)	.907		
ECOG			–	–
0–1	Reference			
2–4	2.175 (0.789–5.997)	.133		
Histology			–	–
Appendiceal	Reference			
Colorectal	0.983 (0.721–1.378)	.983		
PCI	1.052 (1.029–1.076)	**<.001**	1.024 (0.991–1.057)	.157
Operative time	1.146 (1.069–1.228)	**<.001**	1.017 (0.923–1.120)	.732
EBL	1.001 (1.000–1.001)	**<.001**	1.001 (1.000–1.002)	**.005**
Liver resection	2.777 (1.563–4.935)	**<.001**	2.990 (1.601–5.584)	**.001**
Multiple postoperative complications				
Age	1.006 (0.992–1.021)	.418	–	–
Gender			–	–
Female	Reference			
Male	1.084 (0.758–1.549)	.660		
ECOG			–	–
0–1	Reference			

	Univariate analysis		Multivariable analysis	
Variable	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
2–4	1.587 (0.611–4.121)	.343		
Histology				
Appendiceal	Reference		Reference	
Colorectal	1.476 (1.030–2.115)	**.034**	1.738 (1.122–2.691)	**.013**
PCI	1.043 (1.018–1.068)	**.001**	1.028 (0.994–1.064)	.111
Operative time	1.161 (1.077–1.250)	**<.001**	1.071 (0.968–1.185)	.182
EBL	1.000 (1.000–1.001)	**.022**	1.001 (1.000–1.000)	.685
Liver resection	2.277 (1.468–3.790)	**.002**	2.156 (1.259–3.691)	**.005**

Abbreviations: CI, confidence interval; EBL, estimated blood loss; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; PCI, peritoneal carcinomatosis index.

TABLE 3

Univariate and multivariable Cox regression analysis for overall survival

	Univariate analysis		Multivariable analysis	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age	0.994 (0.982–1.007)	.358	–	–
Gender				
Female	Reference		Reference	
Male	1.344 (1.001–1.804)	**.049**	1.019 (0.694–1.496)	.925
Histology				
Appendiceal	Reference		Reference	
Colorectal	2.578 (1.915–3.471)	**<.001**	3.134 (2.002–4.905)	**<.001**
Tumor differentiation				
Well	Reference		Reference	
Moderate	3.537 (2.230–5.611)	**<.001**	2.611 (1.494–4.565)	**.001**
Poor	4.572 (2.810–7.328)	**<.001**	3.583 (2.061–6.229)	**<.001**
PCI	1.028 (1.009–1.047)	**.004**	1.043 (1.015–1.071)	**.002**
CCR				
0	Reference		Reference	
1	1.835 (1.339–2.516)	**<.001**	1.693 (1.050–2.730)	**.031**
Liver resection	2.037 (1.386–2.993)	**<.001**	1.728 (1.124–2.657)	**.013**

Abbreviations: CCR, completeness of cytoreduction score; CI, confidence interval; HR, hazard ratio; PCI, peritoneal carcinomatosis index.

TABLE 4

Univariate and multivariable cox regression analysis for overall survival using only preoperative factors

	Univariate analysis		Multivariable analysis	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age		**.011**		
<60	Reference		Reference	**.034**
≥60	0.353 (0.158–0.790)		0.277 (0.085–0.908)	
Gender				
Male	Reference	.328		
Female	1.422 (0.703–2.877)			
ECOG				
0–1	Reference	.697		
2+	1.493 (0.199–11.224)			
Histology				
Appendiceal	Reference	.171	Reference	**.027**
Colorectal	1.629 (0.810–3.276)		3.844 (1.168–12.650)	
Number of liver lesions				
Single	Reference	**.019**	Reference	**.020**
Multiple	2.712 (1.177–6.247)		3.454 (1.211–9.851)	

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.