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Posthepatectomy liver failure after simultaneous versus staged resection of colorectal cancer and synchronous hepatic metastases*

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SUMMARY: **Posthepatectomy liver failure after simultaneous versus staged resection of colorectal cancer and synchronous hepatic metastases.**

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Background. *Posthepatectomy liver failure (PHLF) is the third most frequent complication and the major cause of postoperative mortality after resection of colorectal cancer liver metastases (CRLM). In case of synchronous resectable CRLM, it is still unclear if surgical strategy (simultaneous versus staged resection of colorectal cancer and hepatic metastases) influences the incidence and severity of PHLF. The aim of this study was to evaluate the impact of surgical strategy on PHLF and on the early and long-term outcome.*

Patients and Methods. *Retrospective study on 106 consecutive patients undergoing hepatectomy for synchronous CRLM between 1997 and 2012.*

Results. *Of 106 patients, 46 underwent simultaneous resection and 60 had staged hepatectomy. The rate of PHLF was similar between groups (16.7% vs 15.2%; p=1) and subgroup analysis restricted to patients undergoing major hepatectomy confirmed this observation (31.8% vs 23.8%; p=0.56). Propensity-score analysis showed that preoperative total bilirubin level and the amount of intra-operative blood transfusion were independently associated with an increased risk of PHLF. Nevertheless, the risk of severe PHLF (grade B - C) was increased in patients who underwent simultaneous resection and major hepatectomy (OR: 4.82; p=0.035). No significant differences were observed in severe (Dindo – Clavien 3 – 4) postoperative morbidity (23.9% vs 20.0%; p=0.64) and survival (3 and 5-year survival: 55% and 34% vs 56% and 33%; p=0.83).*

Conclusions. *The risk of PHLF is not associated with surgical strategy in the treatment of synchronous CRLM. Nevertheless, the risk of severe PHLF is increased in patients undergoing simultaneous resection and major hepatectomy.*

KEY WORDS: Liver resection - Liver failure - Colorectal hepatic metastases - Liver remnant - Propensity score.

Introduction

Posthepatectomy liver failure (PHLF) is the third most frequent complication after resection of colorectal cancer liver metastases (CRLM) and accounts for nearly 20% of postoperative deaths (1, 2). With the exception of liver transplantation, which is generally not indicated in this setting for oncological reasons (3), no effective treatment of severe PHLF exists nowadays.

Approximately 20% of patients with a newly diagnosed colorectal cancer present synchronous liver metastases (4). Only 15%-30% of CRLM are initially resectable (5), whereas a further 13%-63% will become resectable after chemotherapy (6). Despite the fact that preoperative chemotherapy (CT) including oxaliplatin and irinotecan is associated with histological hepatic alterations and increased postoperative morbidity (7), especially in case of major hepatectomy (8), surgical resection represents the standard of care in the treatment of CRLM, with a 5-year survival rate attaining 45-57% in recent series (9, 10).

The classical strategy for the treatment of synchronous resectable CRLM is staged resection of the primary colorectal cancer and hepatic metastases, interspaced by a 3-6 months period during which chemotherapy is usually administered (10). This strategy is based on the reported increased mortality and morbidity after simultaneous resection of the primary tumor with liver metastases, and on the possibility of sparing an unnecessary liver resec-

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tion in patients with a rapidly progressive disease (5, 11-13). Nevertheless, several studies suggest that simultaneous resection of colorectal cancer and hepatic metastases is safe, even if a major hepatectomy is needed (14-18). Most recently, the reversed liver-first approach has been described (10), which allows outcomes similar to those of the classical strategy when successfully completed (19).

Unfortunately, previous papers comparing staged versus simultaneous resection of colorectal cancer and CRLM (5, 13-16, 18, 20-27) lack an univocal definition and grading of PHLF and an analysis of the risk factors associated with PHLF in this setting. Furthermore, postoperative complications are not clearly defined and the grading of postoperative morbidity is frequently not specified, making results hard to interpret.

The aim of our study was to assess the incidence and risk factors of PHLF after simultaneous *vs* staged resection of colorectal cancer and hepatic metastases. In order to evaluate the global safety and oncological validity of both approaches, postoperative morbidity along with long-term survival and disease-free survival were also analyzed.

Patients and methods

Patients

This is a retrospective study on one-hundred six patients who underwent liver resection for synchronous CRLM in the period of February 1997 - June 2012 at our department. These patients represent 38% of the patients operated on for CRLM during the same period. Prospectively collected data based on medical records and outpatient clinic reports were retrospectively reviewed. Data regarding pre-operative work-up, type and duration of pre-operative CT, surgical strategy and technique, post-operative mortality and morbidity, and long-term survival were analyzed. Patients were divided in two groups according to the surgical strategy: the "SIM" group (n = 46) included patients in which resection of the primary tumor and resection of hepatic metastases were carried out simultaneously, whereas the "STA" group (n = 60) included patients in whom the two operations were performed sequentially in a staged approach.

Patients management

Simultaneous colorectal and hepatic resection was proposed to all patients with synchronous resectable CRLM regardless of the location of the primary tumor, with the exception of five patients who were considered initially unfit for combined surgery because of advanced age and comorbidities. As a consequence, all but five patients in the STA group were secondarily referred from other institutions, after resection of the primary colorectal cancer. Pre-operative work-up included total colonoscopy, thoraco-abdominal contrast-enhanced computed tomography (CT) and hepatic magnetic resonance imaging, if indicated. An estimation of the volume of the future liver remnant was obtained only in selected cases, mostly after portal vein embolization. Carcinoembrionic antigen (CEA), carbohydrate antigen 19.9 (CA19.9) baseline biochemical levels were obtained prior to operation. After operation, CEA and CA19.9 levels were measured every three months; a computed tomography scan was obtained every 6 months for the first five years and yearly thereafter.

Surgical technique

A bilateral subcostal incision was used in most cases of staged hepatic resection or in case of right colon cancer, whereas a median incision with a right transverse extension was preferred in case of simultaneous resection of a rectal or left-sided primary cancer. During simultaneous resections, the primary colorectal cancer was resected first, deferring the colonic anastomosis after the completion of the hepatic resection. A direct transparenchymal approach was used in most cases; parenchymal transection was carried out by finger fracture or crush-and-clamp technique or by means of an Harmonic dissector (SonoSurg®, Olympus, Southend-on-Sea, UK). An intermittent Pringle maneuver was performed in case of major bleeding.

Definitions

Hepatic resections were defined according to the Brisbane 2000 classification (28, 29). Major hepatectomy was defined as the resection of three or more Couinaud segments. Postoperative liver failure was defined and graded according to the International Study Group of Liver Surgery classification (30, 31). Briefly, PHLF was defined as a "postoperatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR (> 1.7) and concomitant hyperbilirubinemia (> 3mg/dL) on or after postoperative day 5" (30). Grade A PHLF was defined as a mild liver failure with no deviation from the patient's usual management; grade B identified a situation requiring a modification in patient's management, but without the need for invasive procedure; finally, grade C corresponded to a severe PHLF requiring invasive procedure as hemodialysis, mechanical ventilation, extracorporeal liver support, or transplantation. Surgical complications were graded according to the Dindo-Clavien classification: grade 3 and 4 complications were defined as severe (32). Survival and disease free survival (DFS) were calculated from the date of hepatic resection.

Statistical analysis

Continuous variables were expressed as mean and standard deviation and were compared using Mann-Whitney U test; categorical variables were summarized as counts and percentages and the χ^2 test was performed for comparison. Variables which showed a significant association with PHLF were entered in a multivariate logistic regression model. Due to the observed differences in patients' characteristics between the treatment groups, a propensity score analysis was carried out by the use of a logistic regression model for treatment, using demographic and clinical patient variables associated with the treatment.

Survival and disease free survival (DFS) were also studied using a multivariate Cox regression model. The propensity score was entered as a covariate to adjust for the differences in patients' characteristics between the treatment groups. $P<0.05$ was deemed statistically significant. The variables with more than 30% of missing values were not considered in the multivariate analysis. Statistical analyses were carried out using "R" software statistical package version 2.15.

Results

In the STA group, hepatic resection was performed 9 ± 6 months after the primary operation. In this group, 51 (85%) patients received a chemotherapy before hepatic resection; three patients underwent percutaneous radiofrequency ablation of a liver CRLM as a bridging towards hepatic resection and in five patients a partial resection of hepatic metastases had been performed at the time of primary colic resection.

TABLE 1 - PATIENTS AND TUMOR CHARACTERISTICS.

	Whole series			Major hepatectomy subgroup		
	SIM n = 46	STA n = 60	p	SIM n = 22	STA n = 42	p
Age	63.6 ± 11.5	60.9 ± 9.1	0.20	62.9 ± 12.8	60.5 ± 8.8	0.24
Sex (Female/Male)	22/24	23/37	0.33	9/13	16/26	1
Body Mass Index	24.6 ± 4	25.1 ± 4.1	0.48	23.8 ± 3.6	25 ±4.3	0.25
Diabetes	63.6 ± 11.5	60.9 ± 9.1	0.20	0	6 (14.3%)	0.086
Rectal primary (n)	8 (17.4%)	13 (22%)	0.63	5 (22.7%)	10 (23.8%)	1
Complicated primary	0 (0%)	13 (22%)	<0.001	0	8 (30.7%)	0.005
Extrahepatic metastases	7 (15.2%)	6 (10%)	0.55	4 (18.2%)	3 (7.1%)	0.220
≥ 3 liver metastases	13 (28.3%)	28 (46.7%)	0.14	6 (28.6%)	19 (46.3%)	0.274
Diameter > 5 cm	17 (37%)	19 (32%)	0.30	14 (70%)	16 (53.3%)	0.38
CT prior to hepatic resection	13 (28.3%)	51 (85%)	< 001	9 (41%)	34 (81%)	0.002
CEA>200	12(26.1%)	11 (18.3%)	0.35	5 (22.7%)	10 (23.8%)	1
Total bilirubin	0.76 ± 0.56	0.88 ± 0.79	0.23	1 ± 0.7	0.9 ± 0.9	0.31
Portal vein embolization	2 (4.3%)	4 (6.7%)	0.69	2 (9%)	4 (9.5%)	1
Major hepatectomy	22 (47.8%)	42 (70%)	0.03	22 (100%)	42 (100%)	1
Total vascular exclusion	1 (2.2%)	1 (1.7%)	1.000	0	1 (2.4%)	1
Pringle maneuver	5 (10.9%)	18 (30%)	0.02	5 (22.7%)	17 (40.5%)	0.179
Duration (min)	243 ±117	194 ± 79	<0.001	286 ± 73	199 ± 76	<0.001
Blood transfusion (patients)	30 (65.2%)	36 (60%)	0.69	19 (86.4%)	29 (69%)	0.223
Blood transfusion (ml)	621 ± 335	1055 ± 699	0.004	579 ± 425	803 ± 810	0.58

Data are expressed as mean ± standard deviation or number (percentage). Categorical and continuous variables are compared by one-sided Fisher's exact test or Mann-Whitney test, as appropriate. SIM, simultaneous resection; STA, staged resection.

The two groups were comparable regarding demographic and pre-operative characteristics (Table 1), with the exception that only patients in the STA group had a complicated primary tumor and that they received more frequently a CT prior to hepatic resection. This observation was confirmed also in major hepatectomy subgroup analysis. Due to the large time span of the study, chemotherapy regimens were largely heterogeneous (Fig. 1). Concerning operative variables, the duration of the operation was longer in the SIM group (243 ± 117 *vs* 194 ± 79 minutes, p < 0.001). Patients in the STA group underwent more frequently a major hepatectomy, a Pringle maneuver, and they experienced more abundant blood losses (Table 1). The volume of future liver remnant was estimated pre-operatively in only eight patients and was invariably above 22.5% of total liver volume or 0.7% of patient weight.

Pathological examination showed no differences between groups concerning the radicality of liver resection: R0 resection was achieved in 80.5% *vs* 75% (p = 0.61) in the SIM and STA group, respectively. In comparison with the SIM group, in the STA group steatosis (37% *vs* 60%, p = 0.02), inflammatory infiltrates (4.4% *vs* 16.7%, p = 0.04) and sinusoidal congestion (4.3 *vs* 25%, p = 0.003) were observed more frequently. Histological damage, defined as the presence of sinusoidal congestion or non-alcoholic steatohepatits, was more frequent in patients having received oxaliplatin or irinotecan (31% *vs* 6.5%, p = 0.02).

Postoperative outcomes are shown in Table 2. The overall mortality rate was 0.9%, due to one patient in the SIM group who died of PHLF after a right hepatectomy associated with a right hemicolectomy. Mortality rate was not significantly different between groups (2% *vs* 0% p=0.251). No differences in terms of complications and re-operation rate were observed; in particular, grade 3 and 4 complication rate was similar between groups (23.9% *vs* 20%, p = 0.64), and this was confirmed also by major hepatectomy subgroup analysis.

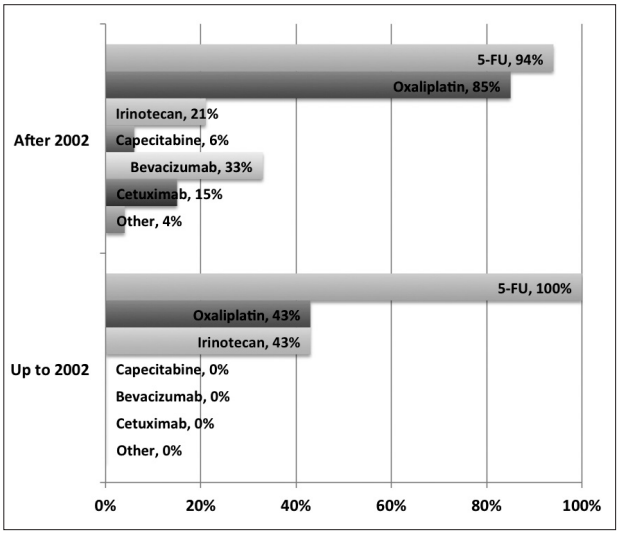

Fig. 1 - Chemotherapy regimens. The series has been split in two periods, 1997-2002 and 2002-2012.

TABLE 2 - POSTOPERATIVE OUTCOME.

	Whole series			Major hepatectomy subgroup		
	SIM (n = 46)	STA (n = 60)	p	SIM (n = 22)	STA (n = 42)	p
Mortality	1 (2.2%)	0	0.43	1 (4.5%)	0	0.34
PHLF	7 (15.2%)	10 (16.7%)	1	7 (31.8%)	10 (23.8%)	0.56
Grading of PHLF	A=0 B=6 (13%) C=1 (2.2%)	A=5 (8.3%) B=5 (8.3%) C=0	0.09	A=0 B=6 (27.3%) C=1 (4.5%)	A=5 (11.9%) B=5 (11.9%) C=0	0,06
Postoperative complications	27 (58.7%)	32 (53.3%)	0.69	20 (90.9%)	31 (73.8%)	0.19
Grade 3 - 4 complications	11 (23.9%)	12 (20%)	0.64	8 (36.4%)	12 (28.6%)	0.58
Anastomotic leak	2 (4.3%)	2 (3.3%)	1	1 (4.5%)	2 (4.8%)	1
Postoperative hemorrhage	2 (4.3%)	2 (3.3%)	1	2 (9.1%)	2 (4.8%)	0.60
Abdominal abscess	2 (4.3%)	0	0.19	1 (4.5%)	0	0.34
Surgical site infection	1 (2.2%)	2 (3.3%)	1	1 (4.5%)	2 (4.8%)	1
Pulmonary complications	4 (8.7%)	8 (13.3%)	0.55	4 (18.2%)	8 (19%)	1
Re-operation	2 (4.3%)	2 (3.3%)	1	1 (4.8%)	2 (4.8%)	1
Length of stay after hepatic resection	13.4 ± 8.6	10 ± 4	0.001	14 ± 9	10 ± 4	0.004

Data are expressed as mean ± standard deviation or number (percentage). Categorical and continuous variables are compared by one-sided Fisher's exact test or Mann-Whitney test, as appropriate. SIM, simultaneous resection; STA, staged resection.

The rate of PHLF was 15.2% (7/46) in the SIM group and 16.7% (10/60) in the STA group (p = 1). Only patients having undergone a major hepatectomy presented PHLF. Subgroup analysis restricted to patients who underwent a major hepatectomy confirmed this observation: PHLF rate was 31.8% versus 23.8% (p = 0.56) in the SIM and STA group, respectively. Due to the observed differences in patients characteristics between the treatment groups, a propensity score analysis was carried out using a logistic regression model for treatment. The logistic model by which the propensity score was estimated showed good predictive value (Somers's Dxy = 0.863, which corresponds to an area under the ROC curve of 93%, after bootstrap validation with 100 repetitions) and calibration characteristics by the Le Cessie and Houwelingen test (p = 0.468). The score was incorporated into the multivariate model as a covariate: after adjusting, the odds ratio for PHLF of simultaneous versus sequential resection was 0.76 (95% confidence interval: 0.12, 4.80; p=0.77), indicating the non-significant effect of the allocation to a group of treatment in developing PHLF. At multivariate analysis, the risk of PHLF was positively correlated with the level of pre-operative total bilirubin, the extent of liver resection (major hepatectomy) and with the amount of intra-operative blood transfusion. The risk of PHLF was 40% in patients with a pre-operative total bilirubin level > 1.96 mg/dl (Fig. 2A).

Concerning the grading of PHLF, in the SIM group six patients (13%) presented a grade B PHLF, whereas one (2%) presented and died of a grade C PHLF. In the STA group five (8%) and five (8%) patients presented a liver failure of grade A and B, respectively, and no grade C PHLF was observed. Severity of PHLF seemed unequally distributed as there was a borderline significant trend (p = 0.06) towards a more severe PHLF in the SIM group. Thus, we carried out a subgroup analysis of the incidence of 'clinically relevant' PHLF (i.e. grade B and C only, excluding grade A) considering only the patients having received a major hepatectomy. Logistic regression with Firth's adjustment showed that 'clinically relevant' PHLF was significantly associated with both pre-operative total bilirubin (OR 2.8, p = 0.012) and assignment to the SIM group (OR 4.82, p = 0.035) (Table 3). There was a linear relationship between the increase of pre-ope-

TABLE 3 - LOGISTIC MODEL WITH FIRTH'S CORRECTION FOR SEVERE (GRADE B OR C) PHLF AFTER MAJOR HEPATECTOMY.

Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Pre-operative total bilirubin	2.80	1.21	8.49	0.012
Intra-operative blood transfusion	1.001	1.0003	1.002	0.009
Simultaneous versus staged	4.82	1.10	30.17	0.035

Logistic regression with Firth's correction was used to avoid problems due to separation or quasi-separation of events among different groups. In patients undergoing a major hepatectomy, the risk of developing a severe PHLF was increased by 4.82 times.

rative bilirubin level and the incidence of severe PHLF (Fig. 2B). Increasing age seemed to be associated with a higher risk of severe PHLF for equal levels of pre-operative bilirubin, although this observation did not reach statistical significance (Fig. 2C).

The overall median survival was 44 months. Three and 5-year survival rate was 55% and 34 % and 56% and 33% in the SIM and STA group, respectively (log rank test, p = 0.83) (Fig. 3). Cox regression analysis showed that the presence of extra-hepatic metastases and a non-R0 resection were factors independently associated with a reduced survival (Fig. 3).

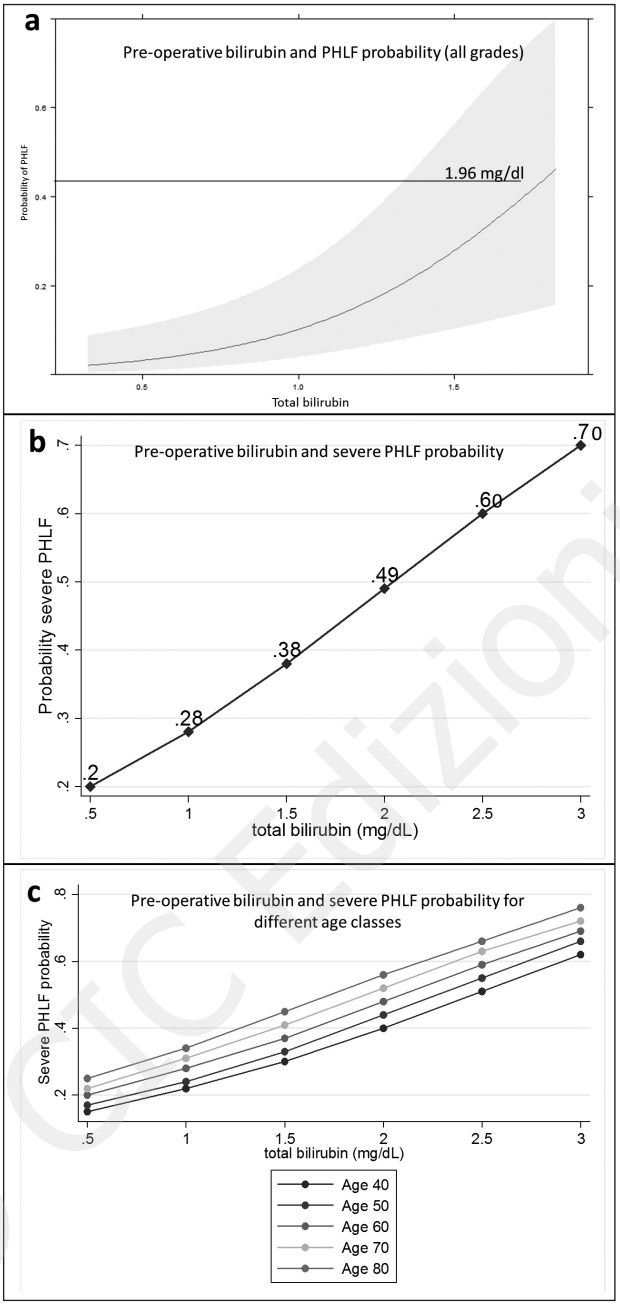

Fig. 2 - A) The plot shows the relationship between preoperative total bilirubin level and the risk of any grade of PHLF. B) Linear relationship between preoperative total bilirubin level and the risk of severe PHLF in patients having undergone a major hepatectomy. C) The plot shows the effect of increasing age on the relationship between PHLF and preoperative bilirubin.

Discussion

Postoperative liver failure is undoubtedly one of the most feared complications of hepatic resections. A considerable amount of literature has been dedicated to identify the risk factors for PHLF and to establish the limits of a "safe" hepatic resection. In the setting of liver resections for CRLM, incidence of PHLF in recent series is around 8% (33, 34). In the systematic review by Simmonds et al. (1) PHLF rate is 2.8% and represents the most frequent cause of death in the postoperative period. The question if simultaneous colon and liver resections are burdened by an increased rate and severity of PHLF has not been clearly assessed by the existing literature. Many articles have assessed the global feasibility of simultaneous resections in selected patients based on postoperative and long-term outcomes, but the incidence of PHLF and of PHLF-related mortality have been inconstantly reported. In the multi-institutional study by Reddy et al. (5) mortality and severe morbidity were increased after colorectal resection associated with major hepatectomy, but PHLF rate was not specified and hepatic related morbidity was equal between the two groups of treatment. In the series by Goyer et al. (23) incidence of PHLF, defined according to the so-called "50 – 50" criteria (31), was 21.5% and PHLF was the only cause of postoperative death. Capussotti et al. (14) observed a PHLF rate (defined as a prothrombin time < 50% and a serum bilirubin level > 5 mg/dl after postoperative day 4) of 0% and 4.2% after simultaneous and staged resection, respectively.

In our study, the risk of presenting any grade of PHLF was not associated with the group of treatment and this observation was also confirmed in the major hepatectomy subgroup. Propensity score analysis and logistic regression showed that patients with an increased pre-operative total bilirubin level, undergoing a major hepatectomy and experiencing more abundant blood losses were at risk of developing a PHLF. The amount of intra-operative bleeding is a well-known risk factor for PHLF, due to the depression of the immune system favoring bacterial translocation (35). However, despite optimal surgical and anesthetic patient management, intra-operative bleeding is often unavoidable and unpredictable. Based on our results, the type of hepatectomy and the pre-operative bilirubin level are the two prognostic factors for PHLF that can be considered in the choice of the surgical strategy. The fact that an important increase in the risk of PHLF

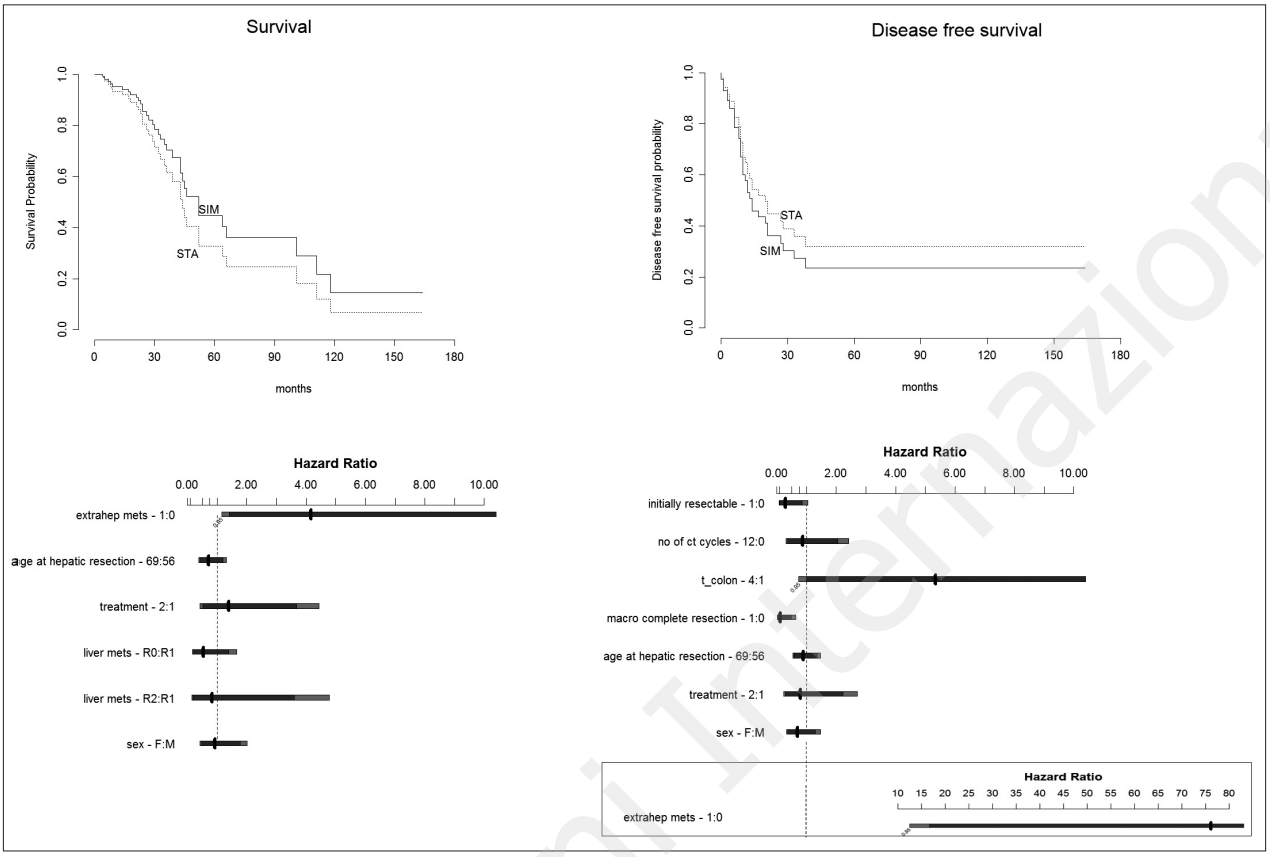

Fig. 3 - Survival and disease free survival curves estimated from Cox regression model plotted along with hazard ratio for covariates entered in the model. Differences between simultaneous (SIM) and staged resection (STA) are not statistically significant for both survival (p=0.802) and disease free survival (p=0.51).

was observed for a modest elevation of pre-operative bilirubin is intriguing, especially for the patients who receive a CT prior to hepatic resection. Thus, regardless of the strategy adopted, procedures aimed at enhancing the function of the future liver remnant (36-38) should be implemented in these patients.

The most original finding of our study is that, although the risk of presenting any grade of PHLF was not associated with the group of treatment, the incidence of 'clinically relevant' (grade B and C) PHLF in patients undergoing a major hepatectomy was significantly associated with the simultaneous approach. In particular, this risk was increased almost five-fold in patients undergoing a major hepatectomy and a simultaneous colorectal resection. This is quite surprising, as we could expect that patients in the STA group (i.e. having received more frequently CT prior to hepatic resection and presenting more frequently features of non-alcoholic steatohepatitis and sinusoidal congestion in the non-tumor-bearing liver) would develop PHLF more frequently. The explanation for this observation is not clear. In our experience we did not observe a different rate of bile leakage or sepsis between the two groups explaining the different incidence of PHLF. Experimental works have shown an impairment of hepatic regeneration after simultaneous liver and bowel resection in rats in relation with higher levels of endotoxin, which inhibits liver regeneration through its effects on Kupffer cells and hepatocytes (39, 40). Anyhow, our study was not designed to establish causal relationships and further studies are needed to clarify the mechanism of increased risk of severe PHLF after simultaneous resection. However, it should be noted that the clinical relevance of this observation was modest: all but one patient in the SIM group recovered from PHLF and there was no significant difference in PHLF-related mortality.

Postoperative morbidity was similar in the two groups, also considering only severe complications. This was true in the major hepatectomy subgroup as well. At multivariate analysis, the risk factors for postoperative morbidity were the same as for PHLF, i.e. pre-operative total bilirubin, major hepatectomy and intra-operative hemorrhage. This is not surprising, as PHLF can either favor the onset of postoperative complications or be a consequence, as in the case of biliary leak or abdominal abscess. The only difference between the two groups was the length of stay after hepatectomy, which was increased in patients undergoing a simultaneous resec-

tion (13.4 *vs* 10 days). Unfortunately, as the length of stay after colorectal resection was often unknown, it was not possible to analyze the pooled data of both operations. Anyhow, the length of stay is often dictated by many factors unrelated to the clinical postoperative course and, especially in our country, it does not represent a reliable marker of postoperative morbidity.

Finally, the analysis of survival and disease-free survival showed no difference between the study groups. These results are even stronger if our policy is considered, i.e. proposing to all patients a simultaneous resection regardless of the location of the primary tumor and of the hepatic lesions, unless their comorbidities contraindicate major abdominal surgery. Indeed, it has been previously observed that, despite similar postoperative outcomes, long-term survival of patients treated with a simultaneously strategy may be lower (41). This is conceivable, as the patients treated with a staged strategy represent a selection of patients with synchronous CRLM, i.e. those not presenting a disease progression after resection of the primary tumor and for whom a better prognosis could be expected. In this context, Capussotti et al. observed that male sex, advanced primary tumor and more than three metastases are factors associated with reduced survival in patients undergoing simultaneous resection and suggest that a staged approach should be preferred for patients presenting these risk factors. Though our study was not intended to analyze which surgical strategy is better in terms of survival and disease-free survival, these were almost identical between the groups and surgical strategy did not have a significant impact on survival at multivariate analysis.

The strength of our conclusions is limited by the retrospective nature of our study and by the very limited availability of data concerning one of the more important prognostic factors of PHLF, that is the volume of the future liver remnant. However, although this was seldom formally measured, all major hepatic resections were planned to preserve a sufficient portion of liver parenchyma. Furthermore, it should be noted that pre-operatively assessed future liver remnant does not necessarily correspond to the actual liver remnant, as operative strategy may vary according to intra-operative ultrasonography findings and other technical reasons. Ideally, a randomized controlled trial would be required to assess which is the best surgical strategy for these patients in terms of postoperative complications and long-term outcomes but, as it has been observed, it would be difficult to perform and probably unethical (24).

Conclusions

In conclusion, overall incidence of PHLF is not increased after simultaneous resection of primary colorectal cancer and CRLM. Postoperative morbidity and long-term outcomes are comparable to those of patients treated with a staged strategy. Still, the surgical strategy should be evaluated with caution in patients needing a major hepatectomy, especially in presence of an increased bilirubin level, because in this setting the simultaneous approach exposes to an increased risk of 'clinically relevant' PHLF.

Conflict of interest. The Authors declare that they have no conflict of interest.

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