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Surgical outcomes in patients with hepatic synchronous and metachronous colorectal metastasis

AIM: *To evaluate the impact of several clinical and pathological factors on the outcomes of surgery for hepatic colorectal cancer metastasis.*
METHODS: *Eighty-four liver metastasectomies in 77 consecutive patients with 90 colorectal cancer hepatic metastases were performed in our institution from 2009 to 2014. Surgery was carried out in 75 cases, as two patients were not eligible for surgery. Among them 43 (Group A) were affected by synchronous, and 32 (Group B) by metachronous lesions. Furthermore, 9 reoperations were performed in patients with initially synchronous lesions. The follow-up after surgery included total body CT scans every 3 months for the first year, and every 6 months for 4 years thereafter. Blood level of CEA was determined every 3 months.*
RESULTS: *The univariate analysis evidenced significantly more recurrences in patients with synchronous lesions (p=0.011), and higher grade, pN stage and CEA blood levels. In multivariate logistic regression analysis the statistically significant parameters found were: the pT stage (OR: 3.92, p = 0.039), the use of adjuvant chemotherapy for the colonic tumor (OR: 0.19, p = 0.025), and the adjuvant chemotherapy (OR: 4.11, p = 0.048). The global survival was 32 patients (41.5%), 17 with synchronous and 15 with metachronous lesions, and a significant difference in long term survival between these two groups was found (p = 0.008).*
CONCLUSIONS: *The most relevant prognostic factor in patients with hepatic colorectal cancer dissemination is the timing of metastasis; the metachronous lesions present better survival when surgically treated.*

KEY WORDS: Colorectal cancer, Liver, Metastasis, Surgery

Introduction

Colorectal cancer (CRC) is one of the most common neoplastic diseases in the world with more than 1,200,000 annual cases estimated [1]. Approximately 65% of patients with CRC are affected by metastasis at the time of diagnosis or will develop metastasis later; the liver is mostly involved (40–60%) in a synchronous or metachronous manner, but only 25% of hepatic metastatic lesions are resectable at the first evaluation [2]. In recent years, the latter percentage, and the prognosis of patients with colorectal cancer liver metastasis (CRCLM) have substantially improved, thanks to the development of multidisciplinary protocols combining neoadjuvant chemotherapy and surgery, which increased both the overall survival and the disease free survival [3,4]. Currently, the 5-years survival after metastasectomy varies between 24% and 64%, depending on selection criteria and preoperative

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risk factors, while the 5-years survival after chemotherapy alone is approximately 10-11% [5-11]. Several factors may influence the outcomes of CRCLM resections, like the number and volume of the hepatic lesions, their anatomical localization, and the timing of their detection in relation to the diagnosis of the primary CRC. This last factor, impacts substantially the choice of the treatment strategy; in cases of synchronous CRCLM both the primitive and secondary lesions can be surgically treated in a single stage, or a two stage approach can be adopted, with an initial resection of the colonic lesion, and a subsequent hepatic resection after chemotherapy. The choice of the appropriate therapeutic approach is more challenging in these patients, in relation to those with metachronous lesions.

The aim of this study is to evaluate the differences in survival and recurrence in patients with synchronous and metachronous hepatic colorectal cancer metastasis, in relation to the type of surgery, the number, volume, and distribution of the lesions, and finally the chemotherapeutic treatment employed.

Materials and Methods

Eighty-four liver metastasectomies in 77 consecutive patients with 90 CRCLM were performed in our institution from 2009 to 2014. The initial surgery was carried out in 75 cases, as two patients were not eligible for surgery on the basis of the extension of the disease and their performance status. Among them 43 had synchronous lesions (group A), and 32 metachronous metastases (group B). Furthermore, 9 reoperations for hepatic recurrence were performed, all of them in patients in the synchronous group (in one case two reoperations were carried out in the same patient).

Preoperative investigations included total body computed tomography (CT) scan, and carcinoembryonal antigen (CEA) blood analysis. In cases with an inconclusive CT scan, magnetic resonance imaging (MRI) of the liver, contrast-enhanced ultrasound (US), and 18F-fluorodeoxyglucose ^{18} (FDG)-positron emission tomography (PET)-CT scan were performed. All the patients gave their informed consent for the planned surgical procedures. All surgeries were performed by experienced surgeons or junior surgeons under the guidance of experienced colleagues. Follow-up after surgery included total body CT scans every three months for the first year, and every six months for the next four years thereafter. Blood level of CEA was determined every three months. The demographic, pathological and clinical data of the patients were retrieved from clinical records, death reports, and the local cancer registry. All the patients who resulted to be alive, were contacted by telephone in August 2014 in order to establish the exact mortality, recurrence and free of disease survival (FDS) rates.

Statistical analysis was performed using the STATA 13® statistical software (StataCorp, College Station, TX, USA). The Shapiro-Wilk test was used to verify the normality of the distribution of the variables. To describe normally distributed variables, means and standard deviations (SD) were used, while medians and interquartile ranges (IQR) were employed for non-normally distributed variables. The statistical differences between the groups A and B were evaluated with the student's t-test and the Wilcoxon test for quantitative variables, on the basis of their distribution; the chi-square test was employed for qualitative variables. Finally, survival was analyzed with the Kaplan-Meier method, and the differences in survival between the aforementioned groups with the log rank, the Wilcoxon-Breslow, and the Peto-Peto tests.

Results

Among the 77 patients examined 53 were males (69%); the mean age at diagnosis was 67 (IQR: 60-73) years. The mean weight of the patients was 71 kg, the mean height 165 cm, and the mean body mass index (BMI) 26. The American Society of Anesthesiologists (ASA) score was I in 12%, II in 54%, III in 30%, and IV in 4% of the patients. Furthermore, the 61% of them were active smokers. In 23 (30%) cases familiarity for cancer was found (colorectal cancer in 8 cases), while eleven patients (14%) had a previous tumor in another than the large intestine anatomical district, but none of them was under any oncological therapy at the time of diagnosis of the colorectal cancer. The anatomical localization of the primary tumors, the stage of the disease, and the comorbidities of the patients are depicted in Table I.

In group A, 43 initial operations have been performed (35 contemporaneously with the colic resection): five segmentectomies, seven bisegmentectomies, one trisegmentectomy, five hepatectomies, eight wedge resections, 17 metastasectomies. Six cases were submitted to neoadjuvant chemotherapy before surgery. Eight patients were reoperated on for a second time, and one patient for a third time. The median interval between the first and the second metastatic event was 19 months, while the third event occurred 12 months after the second surgery. In group B, 32 surgical interventions were carried out: seven segmentectomies, nine bisegmentectomies, three trisegmentectomies, seven hepatectomies, two wedge resections, and four metastasectomies. No substantial differences in the distribution of surgeries between the groups were found. The median number of lymph nodes removed was 13 (IQR: 10-18). The mean hospital stay was 29 days.

The mean number of the lesions removed per patient was two, and their mean diameter 3.33 cm. Among the 43 primitive operations in group A, 20 (46%) were for multiple metastases, greater than 3 cm in diameter, while

TABLE 1 - *Demographic, clinical and pathological data of our patients and statistical differences in univariate analysis.*

Variables		Total	Group A	Group B	p
Patients, n (%)		77 (100.00)	45 (58.44)	32 (41.56)	
Sex, n (%)	**Male**	53 (68.83)	30 (66.67)	23 (71.88)	0.627
	Female	24 (31.17)	15 (33.33)	9 (28.12)	
Age, median (IQR)		67 (60-73)	67 (61-72)	65 (57- 73)	0.566
Weight, mean (SD)		71.30 (14.55)	69.80 (14.76)	73.38 (14.25)	0.285
Height, mean (SD)		165.32 (8.31)	165.94 (8.40)	164.46 (8.26)	0.987
BMI, mean (SD)		26.23 (4.55)	25.37 (4.22)	27.40 (4.80)	0.074
ASA, n (%)	**1**	8 (11.59)	6 (15.38)	2 (6.67)	0.590
	2	37 (53.62)	21 (53.85)	16 (53.33)	
	3	21 (30.43)	11 (28.21)	10 (33.33)	
	4	3 (4.35	1 (2.56)	2 (6.67)	
Smoke, n (%)		45 (61.64)	23 (54.76)	22 (70.97)	0.159
Familiarity, n (%)		23 (29,87)	13 (29.00)	10 (31,25)	0.453
Other tumors, n (%)		11 (14.29)	6 (13.33)	5 (15.62)	0.777
Diabetes mellitus, n (%)		13 (16.88)	7 (15.56)	6 (18.75)	0.712
Dyslipidemia, n (%)		16 (20.78)	12 (26.67)	4 (12.50)	0.131
BPCO, n (%)		11 (14.29)	7 (15.56)	4 (12.50)	0.706
Arterial hypertension, n (%)		36 (46.75)	22 (48.89)	14 (43.75)	0.656
Cardiopathies, n (%)		8 (10.39)	3 (6.67)	5 (15.62)	0.204
Atrial fibrillation, n (%)		8 (10.39)	5 (11.11)	3 (9.38)	0.806
Comorbidity, n (%)		34 (44.16)	15 (33.33)	19 (59.38)	**0.023**
Primary tumor location, n (%) 0.489	**Right colon**	18 (23.38)	11 (24.44)	7 (21.88)	
	Left colon	23 (29.87)	13 (28.89)	10 (31.25)	
	Trasverse colon	3 (3.90)	3 (6.67)	0 (0.00)	
	Rectum	33 (42.86)	18 (40.00)	15 (46.88)	
Grade, n (%)	**G1**	4 (6.90)	1 (2.63)	3 (15.00)	**0.014**
	G2	44 (75.86)	27 (71.05)	17 (85.00)	
	G3	10 (17.24)	10 (26.32)	0 (0.00)	
pT Stage, n (%)	**T1 - T2**	9 (13.85)	5 (11.90)	4 (17.39)	0.540
	T3 - T4	56 (86.15)	37 (88.10)	19 (82.61)	
pN Stage, n (%)	**N0**	23 (35.38)	11 (26.19)	12 (52.17)	**0.036**
	N1 - N2	42 (64.62)	31 (73.81)	11 (47.83)	
CEA, median (IQR)		12.49 (4.90-39.46)	16.65 (8.81-55.58)	8.28 (2.84-16.85)	**0.028**
CA 19-9, median (IQR)		27.90 (8.56-115.2)	35.12 (8.83-145.35)	22.43 (6.18-115.20)	0.259
α-fetoprotein, median (IQR)		2.97 (2.12-4.15)	2.57 (2.21-3.45)	3.49 (1.9-4.5)	0.240
Total lymph nodes, median (IQR)		13 (10-18)	12 (10-18)	15 (12-23.5)	0.139
Neoadjuvant chemotherapy, n (%)		10 (13.16)	9 (20.00)	1 (3.23)	**0.034**
Adjuvant chemotherapy, n (%)		32 (45.07)	13 (32.50)	19 (61.29)	**0.016**
Metastases, n (%)	**1**	36 (46.75)	19 (42.22)	17 (53.12)	0.512
	2	19 (24.68)	11 (24.44)	8 (25.00)	
	Multiple	22 (28.57)	15 (33.33)	7 (21.88)	
Post-metastasectomy treatments, n (%)		47 (68.12)	31 (77.50)	16 (55.17)	**0.049**
Radicality, n (%)	**R0**	50 (74.63)	26 (68.42)	24 (82.76)	0.360
	R1	12 (17.91)	8 (21.05)	4 (13.79)	
	R2	5 (7.46)	4 (10.53)	1 (3.45)	
Other ablative treatments, n (%)		3 (3.90)	1 (2.22)	2 (6.25)	0.368
Extrahepatic metastases, n (%)		22 (30.14)	13 (30.23)	9 (30.00)	0.983

all the operations in group B (100%) were performed for multiple lesions lesser than 3 cm in diameter.

Two patients (2.4%), both in group A, died in the first 30 days after surgery. Postoperative morbidity was observed in 9 cases (11%); the most frequent complications were biliary fistulas and hepatic abscesses (Table II). Thirteen cases of recurrence occurred during the follow-up period, and nine re-operations were performed, as we mentioned before.

Thirteen cases (17%) of hepatic recurrence were observed in our series, twelve of them in the group of patients with synchronous tumors (one case was a second hepatic recurrence), and one in the metachronous group. Nevertheless, only nine patients were eligible for re-oper-

TABLE IA - *Univariate/multivariate logistic regression analysis*

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% IC)	p-value	OR (95% IC)	p-value
Sex	1.28 (0.47-3.43)	0.627	3.17 (0.65-15.46)	0.153
Age	1.02 (0.97-1.07)	0.472		
Weight	0.98 (0.95-1.02)	0.315		
Height	1.02 (0.96-1.08)	0.472		
ASA	0.65 (0.33-1.28)	0.212		
Smoke	0.49 (0.18-1.33)	0.162		
Alcohol	1.38 (0.54-3.53)	0.495		
Familiarity	0.49 (0.76-3.20)	0.460		
Other tumors	0.83 (0.23-3.00)	0.777		
Diabetes mellitus	0.82 (0.24-2.72)	0.741		
Dyslipidemia	2.54 (0.74-8.78)	0.139		
BPCO	1.29 (0.34-4.84)	0.706		
Arterial hypertension	1.23 (0.49-3.06)	0.656		
Cardiopathies	0.38 (0.85-1.75)	0.217		
Atrial fibrillation	1.21 (0.27-5.46)	0.806		
Comorbidity	0.34 (0.13-0.87)	0.025		
CEA	1.01 (1.00-1.03)	0.086		
Ca199	1.00 (1.00-1.00)	0.454		
Alfa fp	0.82 (0.61-1.11)	0.207		
Original tumor location	1.10 (0.83-1.44)	0.510		
Radicality	2.69 (1.42-5.09)	0.002		
Grade	11.52 (1.47-90.06)	0.020		
pT Stage	2.22 (0.96-5.12)	0.060	3.92 (1.07-14.33)	0.039
pN Stage	1.95 (0.91-4.18)	0.087		
Positive Nodes	1.00 (0.85-1.18)	0.972		
Total nodes	0.93 (0.84-1.02)	0.130		
Colon Neoadjuvant chemotherapy	7.50 (0.90-62.61)	0.063		
Colon Adjuvant chemotherapy	0.30 (0.11-0.81)	0.017	0.19 (0.04-0.81)	0.025
Number Metastases	1.41 (0.81-2.45)	0.218		
Hepati (neo)adjuvant chemotherapy	0.80 (0.29-2.17)	0.661		
Grade (mts)	0.84 (0.20-3.55)	0.812		
Radicality	1.89 (0.77-4.64)	0.165		
Margins of resection	1.92 (0.63-5.86)	0.254		
Hepatic chemotherapy	2.71 (0.95-7.69)	0.061	4.11 (1.01-16.72)	0.048
Other therapy (tarf)	0.34 (003-3.93)	0.388		
Metastases Recurrence	10.03 (1.22-82.24)	0.032		
Status	0.71 (0.27-1.87)	0.494		

ation. The mean survival time after the second operation was 19.7 (range 3-40) months. The four patients with hepatic recurrence not eligible for surgery died during the follow-up period at 4.18 and 30 months, respectively.

Table I depicts the results of the univariate analysis performed: statistically significant differences were found regarding the grade of the colonic tumor (p = 0.014), the pN stage (p = 0.036), and the serum concentration of the CEA, (p = 0.028). Also the use of neoadjuvant therapies was significantly higher in group A (p = 0.049). In multivariate logistic regression analysis (Odds Ratio –OR 95%IC) (Table 1A) the statistically significant parameters found were: the pT stage of the tumor (OR: 3.92, p = 0.039), the use of adjuvant chemotherapy for the colonic tumor (OR: 0.19, p = 0.025), and the adjuvant chemotherapy (OR: 4.11, p = 0.048). The global survival in our series was 32 patients (41.5%), 17 in

TABLE II - *Postoperative mortality and morbidity in the global cohort of patients under investigation.*

Postoperative complications	Number (%)
Biliary fistula	2 (2.4%)
Hepatic abscess	2 (2.4%)
Neurological deficiencies	2 (2.4%)
Urinary fistula	1 (1.2%)
Bronchopneumonia	1 (1.2%)
Anastomotic dehiscence	1 (1.2%)
Total	**9 (11%)**
Postoperative deaths	**2 (2.4%)**

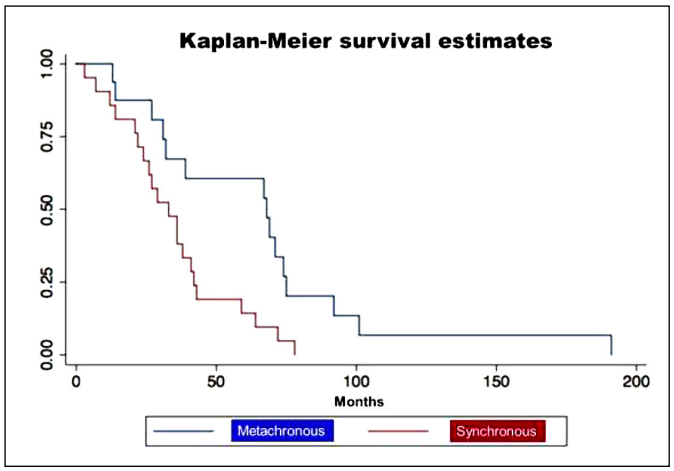

Fig. 1: Survival estimates in patients with synchronous and metachronous colorectal cancer metastases.

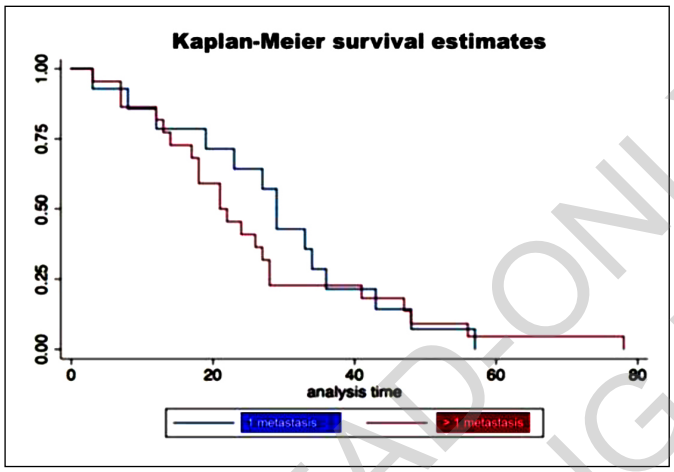

Fig. 2: Survival estimates in relation to the number of metastases resected.

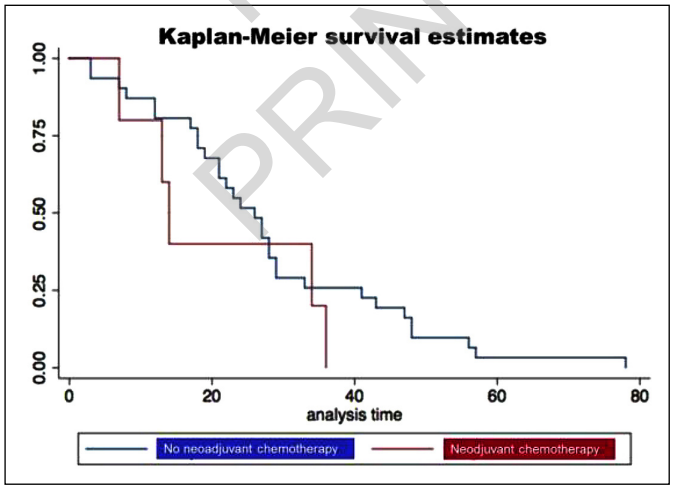

Fig. 3: Survival estimates and neoadjuvant chemotherapy.

group A and 15 patients in group B. Survival analysis with the Kaplan-Meier method and the Log Rank test evidenced a significant difference in long-term survival between the two groups (p = 0.008, Fig. 1): survival inferior to 25% within 50 months in group A, versus survival of the 60% of group B patients within 70-80 months (range 50-100). Figs. 2 and 3 depict the survival estimates in relation to the number of the metastases resected, and the use of neoadjuvant chemotherapy for the primary colonic cancer.

Discussion

Colorectal cancer (CRC) is a neoplastic disease with one of the highest incidence rates worldwide, and enormous efforts have been made in the last decades in all fields of preventive, clinical, surgical and molecular science in order to increase survival rates [1]. Great responses and results have been obtained in the management of non invasive and early stage disease, particularly with the improvements in multidisciplinary endoscopic, surgical, radiotherapeutic and medical oncology protocols [4]. Conversely, progress in the setting of advanced disease have been less consistent, and the relative survival remains relatively low [13]. Liver metastatic dissemination represents one of the leading causes of death in patients with colorectal cancer. In the past, non-treated patients with resectable disease had a 3-years survival rate of 12% [14]. To date, surgical resection of resectable hepatic CRC metastases represents a valid therapeutic option, which allows the 24-64% of the patients to be alive at 5 years from the treatment [4-8,10]. These figures are consistently lower (10-11%) in patients who underwent chemotherapy alone (10). Furthermore, perioperative mortality is relatively low, reaching excellent percentages in reference centers. In our series, the perioperative mortality was 2.4%, the postoperative morbidity 11%, while the 5-years survival rate was 41.5%, confirming the validity of surgery in the management of patients with CRCLM.
Nevertheless, not all patients are resectable at the time of diagnosis. Several factors, such as the number of the lesions, their dimensions, their anatomical localization, the functional status of the liver, and the global performance status of the patient influence the decision whether to operate on or not. Currently, the employment of recently neoadjuvant chemotherapies allows to downstage the metastatic disease, and brought the percentage of the resectable patients at 20-25% of the cases, improving the 10-15% of older reports [15,16]. Moreover, the selection criteria were widened in the last two decades, and this allowed to further increment the number of patients submitted to surgery.
The current aggressive approach, described by other authors and used by our team in the present series, includes the following criteria: a) no limit to the number of lesions to resect, b) multiple bilobar metastases,

c) no dimensional limits, d) extrahepatic lesions when resectable and limited in the lung, e) no limits regarding the margins of resection, f) radicality obtained with the aid of other ablative techniques when surgically impossible, g) invasion of the inta- or extrahepatic veins, h) use of portal embolization to improve hepatic volumes, l) resection of the hepatic pedicle in cases of regional lymph node involvement, m) synchronous or metachronous lesions [2,17,18].

This last issue has been poorly investigated in the past, especially in relation to the treatment adopted. Patients with synchronous metastases seem to have worst outcomes, under the pressure of unfavorable biological and clinical factors [12]. These patients can be treated in a single stage, carrying out a double resection of the primary and metastatic tumors, or in two stages, integrating chemotherapy and choosing a "colon-first" or, more recently, "liver first" approach. The latter option is based on the need to limit the systemic extension of the disease, which more rapidly leads to death, and then treat the primary tumor, which in the meanwhile can be managed with stents or other means if necessary [19]. On the other hand, the single stage approach has the advantage to limit the number of surgeries, but it can be applicable only in cases of limited metastatic dissemination, as evidenced in a recent meta-analysis [20]. This was the policy adopted also by our multidisciplinary team; in cases of extrahepatic disease, the approach was decided on the basis of the number of the lesions, the performance status of the patients, and the possibility to obtain negative resection margins [21]. We operated on all resectable cases, as encouraging 5-years survival rates have been reported, not only for lung but also for ovarian lesions [22-24]. Indeed, the indication to surgery was confirmed in 84 out of the 90 lesions (93%) observed in our 77 patients.

Thirteen cases (17%) of hepatic recurrence were observed in our series, twelve of them in the group of patients with synchronous tumors (one case was a second hepatic recurrence), and one in the metachronous group. Nevertheless, only nine patients were eligible for re-operation. The mean survival time after the second operation was 19.7 (range 3-40) months. The four patients with hepatic recurrence not eligible for surgery died during the follow-up period at 4.18 and 30 months, respectively. The FDS rate is extremely variable in literature, probably due to the biological features of the colorectal tumors, and numerous confounding factors. In the study of Tomlison et al., performed on 612 patients with a 10-years follow-up program, the proportion of patients with no evidence of disease (NED) was 22%, while the 72% of them died from disease; 214 patients lived at least five years, and among them 73 (34%) died from disease, 42 (58%) for a recurrence occurred before the five years, and 17 (23%) for a recurrence observed after the five years of follow-up [25]. Several authors advocate that recurrence depends primarily on the state of the resection margins. During the past decades 'the 1 cm rule' was recommended, often causing the rejection of many patients from surgery [11]. Recent publications evidenced that resection margins are less important as long as R0 status is obtained, and 2 mm and 5 mm have been suggested as sufficient [26-28]. Our policy is to justify intended R1 resection, given the current great progress in chemotherapy treatments and the encouraging outcomes, as well as the fact that the use of surgical devices removes a small rim of liver tissue during the transection, impeding the exact determination of surgical margins [29]. Our R0 and R1 resections rate were 75% and 18% respectively, which is consistent with previous reports.

A statistically significant difference was found in the survival of patients with synchronous and metachronous lesions, with a clear advantage for the patients of the latter group. This enforces previous evidences reported in literature [12]. Nevertheless, the number of the metastases, single or multiple had no impact on survival, as opposed to previous observations of other authors [30]. Also the use of neoadjuvant chemotherapy produced no statistically significant differences on survival, but it was significantly more employed in patients with synchronous disease, as confirmed in both univariate and multivariate analysis. This finding suggest that surgery should be performed when possible, while neoadjuvant treatment should be used only in cases of initially unresectable disease. These analyses evidenced also that the stage of the disease, the grade of the primary tumor, and the serum levels of CEA were higher in patients with synchronous disease. Such factors have been largely demonstrated in the past to have a negative impact on survival, as they reflect the most aggressive biological behavior and the advanced phase of the natural history of the disease, at the time of diagnosis [6,8,31].

Of the 43 patients with synchronous lesions, in this series, most went immediately to surgery. Only 6 were sent for neoadjuvant therapy. Often, when patients present with synchronous disease they are given 4-8 cycles of neoadjuvant chemotherapy just to ensure they do not have progressive disease. This is in large part because it is recognized that synchronous disease is a negative prognostic indicator, and about 20% of patients will be resistant to chemotherapy. With only 43 patients in our analysis (and only 6 patients having received chemotherapy), it may be difficult to apply these results/outcomes to the general population [32,33].

Conclusions

Our findings, despite the retrospective and small cohort design of the study, suggest that the most relevant prognostic factor in patients with colorectal cancer metastasis involving the liver is the timing of the metastatic event; synchronous lesions have a greater recurrence rate,

while the metachronous lesions present a better survival when surgically treated. Surgery should be performed when possible, while neoadjuvant treatments should be used in initially unresectable disease.

Riassunto

Nel seguente lavoro abbiamo valutato l'impatto di diversi fattori clinici e patologici nei pazienti affetti da tumore del colon-retto metastatico e sottoposti ad intervento chirurgico.
Nel nostro istituto, dal 2009 al 2014, sono stati eseguiti 84 interventi di metastasectomia epatica in 77 pazienti. 43 pazienti (Gruppo A) erano affetti da lesioni metastatiche sincrone mentre 32 (Gruppo B) da lesioni metacrone. Inoltre sono stati effettuati 9 reinterventi in pazienti con lesioni inizialmente sincrone. Il follow-up dopo l'intervento chirurgico è stato effettuato mediante TC total body ogni 3 mesi per il primo anno e ogni 6 mesi per i successivi 4 anni. I valori di CEA son stati dosati ogni 3 mesi.
L'analisi univariata ha evidenziato, in maniera statisticamente significativa, più recidive nei pazienti con lesioni sincrone (p = 0.011) ed alto grading, stadio pN e valori di CEA. Nell'analisi di regressione logistica multivariata i parametri statisticamente significativi sono stati: lo stadio pT (OR: 3.92, p = 0.039), l'uso di chemioterapia adiuvante per la neoplasia colica (OR: 0.19, p = 0.025) e la chemioterapia adiuvante (OR: 4.11, p = 0,048). La sopravvivenza globale è rappresentata da 32 pazienti (41.5%), 17 con lesioni sincrone e 15 con lesioni metacrone e vi è stata una differenza significativa nella sopravvivenza a lungo termine tra questi due gruppi (p = 0.008).
In conclusione il fattore prognostico più rilevante nei pazienti con metastasi epatiche da neoplasia colo-rettale è il timing della metastasi; i pazienti con le lesioni metacrone hanno una migliore sopravvivenza quando trattati chirurgicamente.

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