Metachronous colorectal liver metastases has better prognosis – is it true?

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ABSTRACT – **Background** – Liver metastases from colorectal cancer are an important public health problem due to the increasing incidence of colorectal cancer worldwide. Synchronous colorectal liver metastasis has been associated with worse survival, but this prognosis is controversial. **Objective** – The objective of this study was to evaluate the recurrence-free survival and overall survival between groups of patients with metachronous and synchronous colorectal hepatic metastasis. **Methods** – This was a retrospective analysis of medical records of patients with colorectal liver metastases seen from 2013 to 2016, divided into a metachronous and a synchronous group. The Cox regression model and the Kaplan-Meier method with log-rank test were used to compare survival between groups. **Results** – The mean recurrence-free survival was 9.75 months and 50% at 1 year in the metachronous group and 19.73 months and 63.3% at 1 year in the synchronous group. The mean overall survival was 20.00 months and 6.2% at 3 years in the metachronous group and 30.39 months and 31.6% at 3 years in the synchronous group. Patients with metachronous hepatic metastasis presented worse overall survival in multivariate analysis. The use of biological drugs combined with chemotherapy was related to the best overall survival prognosis. **Conclusion** – Metachronous colorectal hepatic metastasis was associated with a worse prognosis for overall survival. There was no difference in recurrence-free survival between metachronous and synchronous metastases.

HEADINGS – Colorectal neoplasms. Neoplastic metastasis. Liver. Prognosis. Survival.

INTRODUCTION

Hepatic metastases from colorectal cancer are an important public health problem due to the increasing incidence of colorectal cancer worldwide[1]. Hepatic metastases from colorectal cancer may be present in 15% to 20% of cases at diagnosis and in up to 60% of cases during the life of these patients[2]. The liver is the only site of metastasis in 20% to 50% of cases[3]. Hepatic metastases may be present from the diagnosis of primary colorectal neoplasia or even be diagnosed before it. In this case, they are called synchronous metastases when they occur in the first 6 months after diagnosis of primary colorectal neoplasia[4]. Metastases diagnosed after 6 months are called metachronous[4]. However, this definition is heterogeneous, since other time intervals are adopted between the diagnosis of the primary tumour and of the liver metastasis, ranging from 0 to 12 months[5].

Numerous therapeutic innovations have been developed in the last decade with the intention of improving the prognosis and increasing the survival of patients with hepatic metastasis[6-8]. Such advances in therapy were able to contribute to this goal, with new surgical techniques such as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), staged resections, selective ligation of the portal vein branch, use of intraoperative ultrasound, and modern chemotherapy regimens associated with biological agents[9-12].

Synchronous colorectal liver metastasis is classically associated with worse prognosis, being a component of several prognostic scores[13-17]. However, there are discordant studies showing that the survival of synchronous liver metastasis does not differ from metachronous metastasis[18-20]. In view of the divergent results, there is a need for a new approach on the subject, given the rapid evolution of systemic and surgical treatments for colorectal liver metastases.

The objective of this study was to evaluate the recurrence-free survival and overall survival between groups of patients with metachronous and synchronous colorectal hepatic metastasis.

METHODS

A retrospective analysis of the data of patients with colorectal liver metastases treated at the Clinical Hospital of the Federal University of Goias from 2013 to 2016 was performed. Patients were divided into two groups: metachronous group (time between diagnosis of primary tumour and liver metastasis greater than 6 months) and synchronous group (time less than or equal to 6 months). Patients with multiple primary neoplasms or unavailable data were excluded from the study.

Clinical, anatomical, and surgical characteristics and their distributions between the two groups were evaluated. The variables studied were age, gender, location of primary tumour, extrahepatic disease, carcinoembryonic antigen (CEA), *KRAS*/*NRAS* gene ex-

pression, degree of cell differentiation, number of liver metastases, number of hepatic segments affected, distribution of metastases, surgical treatment performed, chemotherapy scheme, biological drugs, use of intraoperative ultrasound, transfusion of blood products, surgical complications, size of the surgical margins of resected liver metastasis, and recurrence site.

Recurrence-free survival and overall survival were compared between the metachronous and synchronous groups. The follow-up period was at least 12 months in both groups, with periodic computer tomography (CT) and seric carcinoembryonic antigen (CEA) protocol. PET-SCAN was also used at the multidisciplinary team's discretion. The effect of all variables studied on survival in the total study population in univariate and multivariate analyses was also studied.

The chi-squared test was used to compare the clinical, anatomical, and surgical variables between the synchronous and metachronous groups. Survival curves were obtained using the Kaplan-Meier method, and the log-rank test was used to compare the groups. The Cox regression model was used in multivariate analysis to identify the variables associated with recurrence-free survival and overall survival; it included variables that presented P-values <0.1 in the univariate analysis. The risk prediction was exposed through the P-value, hazard ratio (HR), and 95% confidence interval (95% CI). The differences were considered statistically significant when $P<0.05$. Statistical analysis was performed using SPSS® for Windows®, version 16.0.

This study was approved by the Research Ethics Committee of the Clinical Hospital of Federal University of Goias (protocol number 1,595,740).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

RESULTS

A total of 59 records were analysed, of which 54 were included in the study. One patient had no diagnosis of liver metastasis confirmed on follow-up imaging and was excluded; three patients were excluded due to the absence of histological evidence of colorectal primary neoplasia; and one patient was excluded because of two primary neoplasms of different origins. Thus, the metachronous group consisted of 16 patients, and the synchronous group contained 38 patients.

Clinical aspects

The mean age of the patients was 58.6 years in the metachronous group and 57.1 years in the synchronous group. There was a predominance of males in both groups.

The median CEA value was 34.53 ng/mL in the metachronous group and 12.45 ng/mL in the synchronous group. The genetic study of the *KRAS/NRAS* family showed the prevalence of the wild type in both groups.

A moderate degree of cell differentiation predominated in both groups.

The use of biological therapy associated with the chemotherapy regimen (5-fluorouracil and/or capecitabine associated with oxaliplatin and/or irinotecan) was more frequent in the synchronous group, but without statistical significance. The biological agents used in the study were bevacizumab, cetuximab, and panitumumab.

Among the patients operated on for hepatic metastasis, the patients in the synchronous group underwent more preoperative chemotherapy treatments than the metachronous group, but without statistical significance. The comparison of clinical features between the groups is displayed in TABLE 1.

TABLE 1. Clinical features of patients in synchronous and metachronous groups.

	Synchronous		Metachronous		P-value
	n	%	n	%	
Age					
≤ 60 years	19	50.0	9	56.3	0.675
> 60 years	19	50.0	7	43.7	
Gender					
Male	20	52.6	10	62.5	0.505
Female	18	47.4	6	37.5	
CEA					
<50 ng/mL	26	68.4	10	66.7	0.902
≥50 ng/mL	12	31.6	5	33.3	
KRas/NRas					
Mutated	12	46.2	3	33.3	0.503
Wild-type	14	53.8	6	66.7	
Differentiation grade					
Well	3	9.7	1	6.7	
Moderate	23	74.2	13	86.7	0.606
Poor	5	16.1	1	6.7	
Biological drugs					
No	16	44.4	11	68.8	0.105
Yes	20	55.6	5	31.3	
Preoperative chemotherapy					
Yes	10	55.6	2	40.0	0.538
No	8	44.4	3	60.0	

Chi-squared test. CEA: carcinoembryonic antigen.

Anatomical aspects

Primary colorectal neoplasia occurred more frequently in the left colon in both groups. Metastatic disease occurred exclusively in the liver at higher frequency in both groups.

The metachronous group had up to three hepatic lesions in most of the cases, unlike the synchronous group, which presented more lesions, but without statistical significance. Both groups showed a predominance of up to four hepatic segments affected by metastases.

Hepatic metastatic disease was predominantly unilobar in the metachronous group, unlike the synchronous group, in which there was a predominance of bilobar metastasis, but without statistical significance. The comparison of the anatomical characteristics between the groups is displayed in TABLE 2.

TABLE 2. Anatomical characteristics of patients with synchronous and metachronous colorectal liver metastases.

	Synchronous		Metachronous		P-value
	n	%	n	%	
Location of primary tumour					
Rectum	12	31.6	5	31.3	0.981
Colon	26	68.4	11	68.8	
Colon affected					
Right	6	23.1	3	27.3	0.786
Left	20	76.9	8	72.7	
Extrahepatic disease					
No	22	57.9	9	56.3	0.911
Yes	16	42.1	7	43.8	
Number of liver metastases					
≤3	18	47.4	9	56.3	0.551
>3	20	52.6	7	43.8	
Number of hepatic segments affected					
≤4	21	55.3	10	66.7	0.448
>4	17	44.7	5	33.3	
Distribution of metastases					
Unilobar	14	36.8	9	56.3	0.188
Bilobar	24	63.2	7	43.8	
Hepatic lobe affected					
Right	10	71.4	4	50.0	0.315
Left	4	28.6	4	50.0	

Chi-squared test.

Surgical aspects

Approximately one-third of the patients in the metachronous group and almost half of the patients in the synchronous group underwent surgical treatment of hepatic metastasis. The most performed surgeries were non-anatomical surgeries in both groups.

Intraoperative hepatic ultrasound was used as an auxiliary diagnostic resource in the majority of cases, and in most cases, there was no need for intraoperative blood transfusion in both groups.

Postoperative surgical complications were more frequent in the metachronous group, but without statistical significance.

Among the liver resections, excluding laparotomies with findings of unresectable disease, R0 surgeries were performed in most surgeries in both groups. Surgical margins were disease free and ≥1 cm in both groups.

In the metachronous group, extrahepatic pulmonary recurrence was predominant, whereas in the synchronous group, hepatic recurrence was more frequent, but without statistical significance. The comparison of surgical features between the groups is displayed in **TABLE 3**.

TABLE 3. Surgical features of patients in synchronous and metachronous groups.

	Synchronous		Metachronous		P-value
	n	%	n	%	
Surgical treatment					
No	20	52.6	11	68.8	0.274
Yes	18	47.4	5	31.2	
Hepatic surgery					
Nodulectomy	7	38.9	2	40.0	
Segmentectomy	6	33.3	2	40.0	0.552
Right hepatectomy	1	5.6	1	20.0	
Laparotomy	4	22.2	0	0.0	
Colorectal neoplasms surgery					
Elective	21	61.8	9	60.0	0.907
Emergency	13	38.2	6	40.0	
Intraoperative ultrasound					
No	5	29.4	0	0.0	0.168
Yes	12	70.6	5	100.0	
Blood transfusion					
No	12	70.6	4	80.0	0.678
Yes	5	29.4	1	20.0	
Surgical complications					
No	14	77.8	3	60.0	0.423
Yes	4	22.2	2	40.0	
Hepatic resection					
R0	11	78.6	4	80.0	
R1	2	14.3	1	20.0	0.805
R2	1	7.1	0	0.0	
Surgical margins					
≥1cm	6	54.5	3	60.0	
<1cm	2	18.2	1	20.0	0.953
Positive	3	27.3	1	20.0	
Recurrence					
Yes	9	81.8	3	75.0	0.770
No	2	18.2	1	25.0	
Recurrence site					
Liver	5	55.6	1	33.3	
Lung	2	22.2	2	66.7	0.528
Liver and lung	1	11.1	0	0.0	
Lung and brain	1	11.1	0	0.0	

Chi-squared test.

Recurrence-free survival

The mean recurrence-free survival in the metachronous group was 9.75 months and 50% at 1 year, while in the synchronous group, the mean was 19.73 months and 63.3% at 1 year, as shown by the recurrence-free survival curves for the metachronous and synchronous groups (FIGURE 1).
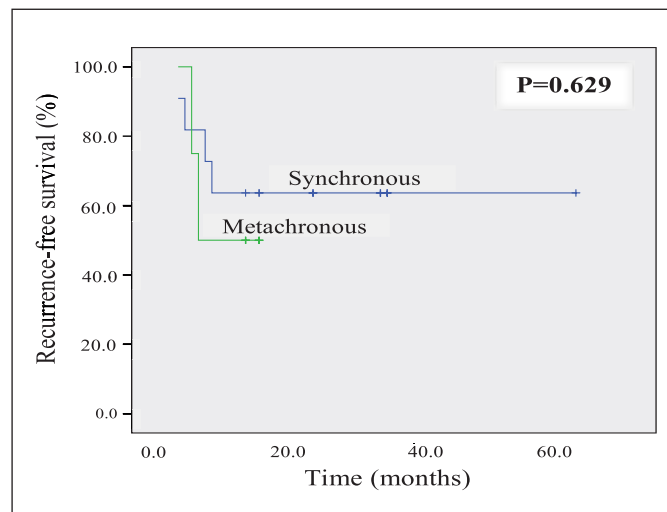

FIGURE 1. Recurrence-free survival curves in metachronous and synchronous groups.

Univariate analysis was performed using the Cox model of all patients undergoing potentially curative liver surgery. The variable surgical margins showed an association with recurrence-free survival in the univariate analysis, but it did not have statistical significance in the multivariate analysis.

Overall survival

The mean overall survival in the metachronous group was 20.00 months and 6.2% at 3 years, while in the synchronous group, the mean was 30.39 months and 31.6% at 3 years, as shown by the overall survival curve for the metachronous and synchronous groups (FIGURE 2).
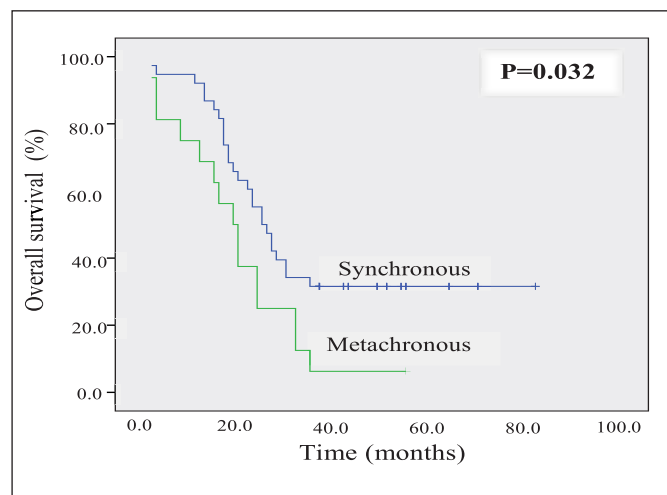

FIGURE 2. Overall survival curves in metachronous and synchronous groups.

A univariate analysis of the total study population was performed using the Cox model. For the multivariate analysis, we chose the variables age, metachronicity, extrahepatic disease, number of liver metastases, number of hepatic segments involved, distribution of liver metastases, use of biological drugs, and surgical treatment. The Cox multivariate analysis revealed metachronous hepatic metastasis as an independent variable related to worse overall survival (P=0.036) and chemotherapy treatment combined with biological drugs as an independent variable related to better overall survival (P=0.001). The multivariate analysis of overall survival is shown in TABLE 4.

TABLE 4. Multivariate analysis of prognostic factors of overall survival.

	Hazard Ratio	95% CI		P-value
Age ≤60 years	1.73	0.78	3.85	0.180
Metachronicity	2.66	1.06	6.63	0.036*
Extrahepatic disease	1.24	0.41	3.76	0.705
Liver metastasis >3	3.12	0.69	14.04	0.138
Hepatic segments involved >4	1.64	0.37	7.26	0.515
Bilobar metastasis	0.76	0.25	2.26	0.616
Biological drugs	0.21	0.08	0.50	0.001*
Surgical treatment	0.38	0.12	1.20	0.099

Cox regression model. * $P<0.05$.

DISCUSSION

Metachronous colorectal liver metastasis is associated with better survival, especially in studies of prognostic scores[13-17]. However, its actual influence on prognosis is controversial[18-20]. The present study evaluated the survival of patients with colorectal liver metastasis in the metachronous and synchronous groups and the clinical, anatomical, and surgical characteristics of each group. Metachronous colorectal liver metastasis was associated with worse overall survival, an association that contravenes evidence of a worse prognosis for synchronous hepatic metastasis[13-17,23]. Neo et al. conducted a database study and found a 3-year overall survival of 33% in metachronous metastases and 28% in synchronous metastases, with no significant difference[18]. Mekenkamp et al. also found no difference between the survival of patients with metachronous and synchronous metastasis[19]. Knopke et al. found worse survival in patients with synchronous colorectal liver metastasis, with a mean overall survival of 53 months for metachronous metastasis and 39 months for synchronous metastasis[16]. Kuo et al. also found an association between synchronous hepatic metastasis and worse prognosis, with lower overall survival (26.9% vs 48.1%) and recurrence-free survival (13.8% vs. 38.9%) rates[23].

In the present study, some factors could explain the worse prognosis of metachronous metastasis. First is the oligosymptomatic nature of colorectal liver metastasis, which can sometimes delay the performance of follow-up examinations and consequently delay the diagnosis of metachronous metastasis[24]. This does not usually occur in patients with synchronous metastasis, since staging examinations are performed routinely at the time of diagnosis of the primary tumour. Another important factor is the influence of the neoplastic tumour microenvironment, in which the association of

different molecular markers in metachronous and synchronous metastases is studied, which could be related to different carcinogenesis mechanisms, levels of tumour aggressiveness, and prognoses[25,26].

In this study, another variable was also related to prognosis: the use of biological drugs was associated with better overall survival. This result may be related to the inversion of the predicted prognosis for metachronous metastasis. In our service, patients with synchronous colorectal liver metastases are treated with high-dose chemotherapy regimens based on the association of 5-fluoracil with oxaliplatin or irinotecan, and nearly half of these patients also received biological agents such as bevacizumab, cetuximab, and panitumumab. The same type of chemotherapeutic treatment was performed in patients who developed metachronous metastases, but 70% of these patients were exposed to these drugs before the appearance of liver metastasis, which theoretically could generate some degree of resistance to the chemotherapeutic and biological agents in the microbiological environment of the metastatic tumour[3,19].

The metachronous and synchronous groups of this study were homogeneous in the characteristics analysed. Some studies have reported the association of unfavourable characteristics with synchronous hepatic metastases. For example, Tsai et al. found bilobular distribution, greater tumour number, and greater tumour diameter in synchronous metastases[21], and Mekenkamp et al. found greater tumour invasion of the primary neoplasia in the synchronous group[19]. Ng et al. had a more heterogeneous group, with a higher prevalence of women and a higher mean age in the metachronous group, as well as fewer curative surgeries and more complications in the synchronous group[22]. The present study found no significant difference between the groups in any of the analysed variables. The homogeneity of the metachronous and synchronous groups in this sample strengthens our results because it reduces the biases related to the unfavourable clinical characteristics that could unbalance the groups statistically.

The study has some limitations, mainly related to the retrospective model of data collection from medical records and to the short period of follow-up.

The association of the synchronicity of liver metastasis with prognosis is not an exhausted topic of discussion and remains controversial, with divergent results. Therefore, there is a need for prospective studies with longer follow-up to evaluate the prognosis of metachronous and synchronous liver metastases in the context of modern multimodal therapeutic strategies.

CONCLUSION

Metachronous colorectal hepatic metastasis was associated with a worse prognosis for overall survival. There was no difference in recurrence-free survival between groups with metachronous and synchronous metastases.

Authors' contributions

Quireze Junior C: study design, interpretation of data, preparation of manuscript, critical revision of manuscript. Brasil AMS: Study literature review, data collect, preparation of manuscript. Morais LK: Study material contribution, literature review, critical revision of manuscript. Campion ER: study material contribution, interpretation of data, critical revision of manuscript. Taveira EJF: study material contribution, critical revision of manuscript. Rassi MC: study material contribution, critical revision of manuscript. All authors read and approved the final manuscript.

Quireze Junior C, Brasil AMS, Morais LK, Campion ER, Taveira EJF, Rassi MC. Metástase hepática colorretal metacrônica tem melhor prognóstico – é verdade? Arq Gastroenterol. 2018,55(3):258-63.

RESUMO – Contexto – As metástases hepáticas de câncer colorretal representam um importante problema de saúde pública devido à incidência crescente de câncer colorretal pelo mundo. A metástase hepática colorretal sincrônica está associada a pior sobrevida, no entanto, o pior prognóstico é assunto controverso. Objetivo – O objetivo do estudo foi avaliar a sobrevida livre de recorrência e a sobrevida global entre os grupos de pacientes com metástase hepática colorretal metacrônica e sincrônica. Método – Análise retrospectiva através de revisão de prontuários de pacientes com metástase hepática colorretal atendidos no período de 2013 a 2016, divididos em grupos metacrônico e sincrônico. Foram utilizados o modelo de regressão de Cox e o método de Kaplan-Meier com teste de Log-rank para comparação de sobrevida entre os grupos. Resultados – A média de sobrevida livre de recorrência no grupo metacrônico foi de 9,75 meses e 50% em 1 ano, e no grupo sincrônico 19,73 meses e 63,3% em 1 ano. A média de sobrevida global no grupo metacrônico foi de 20,00 meses e 6,2% em 3 anos, e no grupo sincrônico 30,39 meses e 31,6% em 3 anos. Os pacientes com metástase hepática metacrônica apresentaram pior sobrevida global em análise multivariada. O uso de drogas biológicas associadas ao tratamento quimioterápico foi relacionado ao melhor prognóstico em sobrevida global. Conclusão – A metástase hepática colorretal metacrônica foi associada a pior prognóstico na sobrevida global. Não houve diferença na sobrevida livre de recorrência entre as metástases metacrônica e sincrônica.

DESCRITORES – Neoplasias colorretais. Metástase neoplásica. Fígado. Prognóstico. Sobrevida.

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