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Radioembolization in patients with colorectal cancer liver metastasis. A single centre 9-years retrospective study

Radioembolização de metástases hepáticas de carcinoma colorretal. Um estudo retrospetivo de 9 anos numa instituição oncológica

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Abstract

Introduction: The role of radioembolization (RE) in patients with liver metastatic colorectal cancer (mCRC) is still unclear. This research aims to assess the prognostic factors and outcomes of RE in these patients.
Methodology: A retrospective analysis of all patients with liver mCRC who underwent RE in a single-centre institution from January 2011 to March 2020, was performed. The one-year survival was evaluated with the Kaplan-Meier method and potential prognostic factors were analysed using the log-rank test, Mann-Whitney test, chi-square test, Fisher's test, and t-test for independent samples.
Results: Thirty patients were analysed. The median age was 61.5 years and most patients were male (63.3%). There was a low complication rate. Successful RE (defined by tomographic response, according to RECIST 1.1 criteria, as partial, complete or stable, at three months of follow-up) was observed in 50% of the cases. Cancer stage ≤ 3 (p<0,040), CEA levels at diagnosis lower than 20ng/mL(p=0,035) and after RE (p=0,023), more than one year between diagnosis of CRC and the emergence of liver metastases (p=0,036), absence of vascular (p=0,028) or lymphatic (p=0,020) invasion at the time of diagnosis were significantly associated with a successful. The one-year survival of patients with and without successful RE was 9.4 and 8.9 months, respectively.
Conclusion: RE is a well-tolerated therapy, with objective results in half of treated patients and a non-significant increase in patient survival. There are RE response prognostic factors that have been identified that may help to better select patients to treat.

Keywords

Radioembolization; Liver metastasis; Colorectal cancer.

Resumo

Introdução: O papel da radioembolização (RE) de metástases hepáticas de carcinoma colorretal (mhCCR) permanece indefinido. O presente estudo pretende avaliar os resultados e possíveis fatores de prognóstico da RE nestes pacientes.
Metodologia: Foi realizada uma análise retrospetiva de todos os doentes com mhCCR quimiorrefratárias e irressecáveis submetidos a RE numa instituição, desde janeiro de 2011 a março de 2020. A sobrevida a um ano foi determinada pelo método de Kaplan-Meier; para avaliação de fatores de prognóstico foram usados os testes log-Rank, Qui-quadrado, Fisher, Mann-Whitney e teste-t.
Resultados: Foram avaliados 30 pacientes. A idade média foi de 61,5 anos e a maioria dos doentes eram do sexo masculino (63,3%). A dor abdominal foi a complicação mais frequente (40%). O sucesso da RE (definido pela resposta tomográfica, segundo os critérios RECIST 1.1, como parcial, completa ou estável, aos três meses de seguimento) foi observado em 50% dos casos. Um estádio ≤ 3 (p<0,040), níveis de CEA < 20 ng/mL no momento do diagnóstico (p=0,035) e após a RE (p=0,023), e ausência de invasão vascular (p=0,028) ou linfática (p=0,020) na peça cirúrgica do tumor primário, bem como um tempo livre de metastização superior a um ano desde o diagnóstico (p=0,036) foram significativamente associados ao sucesso da RE. O tempo médio de sobrevivência de pacientes com e sem sucesso na RE foi de 9,4 e 8,9 meses, respetivamente.
Conclusão: A RE é uma terapêutica bem-tolerada, com resultados objetivos em metade dos pacientes tratados e com um aumento não significativo da sobrevivência dos doentes. Existem fatores de prognóstico de resposta à RE que foram identificados e que podem ajudar a selecionar melhor os doentes a tratar.

Palavras-chave

Radioembolização; Metástases hepáticas; Carcinoma colorretal.

Introduction

Colorectal carcinoma (CRC) is the third most diagnosed malignant neoplasm in Portugal and the second deadliest neoplasm in the country.[1]

The liver is the most frequent site of metastasis, with 20 to 30% of patients having liver metastases at the time of diagnosis and about 70% having documented metastatic disease at the time of death.[2–7,10–12] Surgical resection of liver metastases is considered the treatment of choice for these patients, but only 20% of them meet

the criteria for surgery;[9,14,15] for these, the therapeutic options to control local disease and increase survival are limited, being chemotherapy regimens the therapeutic pillar. However, one of the great challenges in managing the disease is the growing proportion of patients with liver involvement, preferentially a liver that maintains good functional capacity, having exhausted all therapeutic options.[4,16,19] In these chemo-refractory patients, the use of locoregional therapies such as RE with Yttrium-90 (90Y) becomes relevant to increase the time free from disease progression and survival.[7] RE consists of the release of radioactive microspheres (being the 90Y the most common source of radiation) in the hepatic arterial branches responsible for tumor irrigation or in the lobar hepatic arteries. The administration position and activity are previously calculated, aiming to optimize the tumor radiation dose and spare the liver tissue).[17,18] This radiation causes necrosis, fibrosis and a significant decrease in tumor vascularization, often culminating in non-viable lesions.[4,5] Several studies demonstrate that RE improves response to chemotherapy treatment, delaying liver disease progression and allowing overtreated patients to take a therapeutic break without compromising disease stability, with a safe and well-tolerated intervention.[14,18]

The role of 90Y RE in the treatment of patients with mCRC remains to be elucidated; for the proper selection of patients, it is imperative to define the place of this intervention in the sequence of therapeutic regimens and to establish the predictive factors for the success of the intervention.[2,4,12,19]

This study aims to assess the outcomes associated to 90Y RE in patients with unresectable and chemo-refractory mCRC and to determine which factors impact the success of this intervention.

Materials and Methods

• Study design

A populational, observational, retrospective, analytical-descriptive, hospital-based study was carried out.

After approval by the ethics committee, all patients with liver metastases from CRC treated with RE with 90Y microspheres (80% resin and 20% glass) in the Intervention Radiology department, in conjunction with the Nuclear Medicine Service at IPO-Porto, from January 2011 to March 2020, were selected and included in this study.

A unique code was assigned to each analyzed clinical file, in order to ensure patient privacy and confidentiality. Data were collected by consulting the computerized clinical file of each patient and the corresponding physical file. The information collected was registered and organized in digital format using the Statistical Package for the Social Sciences® (SPSS), version 25, for Microsoft® Windows.

Various retrospective information about the patients was collected, including demographic data (age and gender); disease characteristics, such as tumor extension, distribution and stability; therapeutic regimens prior to RE; and factors that may interfere with prognosis, such as lymphatic and vascular invasion in the surgical specimen of the primary tumor, presence of K-RAS mutation, synchronous or metachronous metastases (diagnosed after the primary neoplasm) and serum carcinoembryonic antigen (CEA) values at diagnosis, before and after RE. Information was also collected on post-intervention complications, which were categorized by the Common Terminology Criteria for Adverse Events (CTCAE) classification system, version 5.0.21

• Criteria for patients' eligibility

All patients aged ≥18 years; histologically proven adenocarcinoma of the colon or rectum; liver metastases histologically confirmed and considered unresectable; lack of response to previous treatments or no indication for other local therapies; good functional status (with a maximum Eastern Cooperative Oncology Group (ECOG) scale rating of two); admission and eligibility criteria to be subject to RE (renal, liver and hematological functions within the eligibility parameters to safely perform the procedure); one-year follow-up with control CT at three, six and twelve months or until the patient's death.

All patients with contraindications for RE were excluded: presence of documented liver disease, namely cirrhosis classified as Child-Pugh B or higher, portal hypertension, liver abscesses, sarcoidosis or liver tuberculosis; non-embolized hepatic collateral arteries that could allow extrahepatic distribution of microspheres; hepatopulmonary shunts exceeding 20%; severe ascites and pregnancy.[3,7–9,16]

• Pre-radioembolization clinical assessment

All patients were considered for RE by unanimous decision of a multidisciplinary team. Before the procedure, data regarding the clinical history, physical examination and laboratory analysis of the selected patients were collected (blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TB) and the tumor marker CEA). The approved patients were initially subjected to a work-up, consisting of an abdominal CT scan to assess the imaging findings related to the hepatic and vascular anatomy and characterization of the liver lesions for later comparison with the CT performed after the procedure. Hepatic angiography was also performed in order to assess the vascular anatomy of the liver and collaterals,[3,8–10,12,13,16,19] with administration of albumin macroaggregates with Technesium99 for further investigation of gastro-intestinal and hepato-pulmonary shunts through single photon emission CT (SPECT).[3,7–10,12,13,16,19]

• Procedure description

Patients approved for treatment, after work-up and adequate dosimetry, within one to three weeks, were submitted to treatment. RE consisted of obtaining selective hepatic arterial access using angiography techniques. All treatments were performed on an Integris V5000 angiograph, PHILIPS. Initially, a puncture of the femoral artery (60% of cases) or of the left radial artery (40% of cases) was performed, the aorta was catheterized and an abdominal aortography and an arteriography of the celiac trunk were always performed. Afterwards, after identifying the anatomical variants of the hepatic circulation, the selection of the hepatic artery (right and/or left) and/or its segmental branches was carried out, according to the distribution of the hepatic disease. The selection of the site for administration of the microspheres was achieved using a microcatheter. After angiographic confirmation of correct microcatheter position, administration of radioactive microspheres was performed using the suppliers' proper devices. The microspheres used were Sirtex Medical resin SIR-Spheres® Y-90 (80% of cases) and Boston Scientific's glass TheraSphereTM Y-90 (20% of cases). Confirmation

of the correct distribution of the activity was later evaluated by SPECT. All treatments were jointly planned by the Interventional Radiology and Nuclear Medicine Services. The Interventional Radiology physicians who performed the procedures had more than five years of experience in Angiography and locoregional treatment techniques for hepatic embolization, as well as specific training by certified centers. The Nuclear Medicine team consisted of two medical experts with skills in this technique after adequate training in the handling and calculation of dosimetry. The activity released ranged from 0.70 Gigabequerel GBq (in case of unilobar administration) to 2.90 GBq.

• Statistical analysis

Continuous variables were represented as mean and standard deviation (SD) when their distribution was normal and as median and interquartile range (IQR) when their distribution was not normal. Categorical variables were represented by relative (%) and absolute (n) frequency. The normality of the distribution of continuous variables was analyzed using the Shapiro-Wilk test. The success of RE was defined by the presence of partial response, complete response or stable disease, through computed tomography assessment at three, six and twelve months of follow-up, based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[20] criteria. Chi-square, Fisher's, t-test for independent samples and Mann-Whitney tests were used to establish significant associations between the collected variables and the success of the RE. Multivariate binary logistic regression was used to detect predictive factors of this technique's success. The Kaplan-Meier survival function allowed us to study the median survival after RE. The log-Rank test was used to study differences in the distribution of survival between successful and unsuccessful patients after RE. All statistical analysis was performed using SPSS, version 25, with a significance level of α set at 0.05.

Results

• Descriptive assessment

This study included a total of thirty-two patients diagnosed with mCRC with unresectable and chemo-refractory disease undergoing RE; two of them were excluded from the study because follow-up analysis data were not available. Thus, thirty patients were analyzed (n=30); their demographic and clinical characteristics at the time of diagnosis are shown in Table 1. Most patients were male (63.3%; n=19) and the mean age was 61.5 years (minimum 32 years and maximum 90 years). The most frequent origins of primary CRC tumor were the sigmoid colon (40.0%; n=12) and the rectum (33.3%; n=10). 73.3% (n=22) of patients had metastases at diagnosis (stage IV). The majority (76.7%; n=23) had bilobar liver metastases, having undergone bilobar RE; the remainder (23.3%, n=7) had unilobar metastases, having undergone unilobar RE. All patients underwent only one RE session. 20.0% (n=6) had extrahepatic metastases (pulmonary, retroperitoneal, supra- and infra-diaphragmatic lymph node and peritoneal carcinomatosis). Most patients were in ECOG stage 0 (56.7%; n=17).

The clinical characteristics of the patients before and after the RE are shown in Tables 1 and 2. All (n=30) patients underwent chemotherapy regimens (CT) prior to the RE, namely: 26.67% (n=8), 40% (n=12) and 33.33% (n=10)

Table 1 – Demographic, clinical and laboratorial characteristics at diagnosis and established therapies prior to radioembolization.

Characteristics	**N = 30**
Sex, % (n)	
Male	63,3 (19)
Female	36,7 (11)
Age (years), median +/- SD	61,5 +/- 13,5
Primary origin, % (n)	
Sigmoid colon	40,0 (12)
Rectum	33,3 (10)
Ascending colon	16,7 (5)
Descending colon	6,7 (2)
Transverse colon	3,3 (1)
Stage at diagnosis, % (n)	
I	0 (0)
II	10,0 (3)
III	16,7 (5)
IV	73,3 (22)
Liver metastases at diagnosis, % (n)	73,3 (22)
Extrahepatic metastases, % (n)	20,0 (6)
CEA levels at diagnosis, % (n)*	
< 20 ng/mL	48,1 (13)
≥ 20 ng/mL	51,9 (14)
K-RAS mutations, % (n)**	56,7 (17)
Time between diagnosis and metastization, % (n)	
< 1 year	73,3 (22)
1 – 2 years	13,3 (4)
> 2 years	13,3 (4)
Surgical resection of primary neoplasm, % (n)	80,0 (24)
Vascular invasion (surgical piece of the primary tumor), % (n)	53,3 (16)
Lymphatic invasion at diagnosis (surgical piece of the primary tumor), % (n)	66,7 (20)
ECOG, % (n)	
0	56,7 (17)
1	36,7 (11)
2	6,7 (2)
Previous percutaneous ablation, % (n)	16,7 (5)
Prior systemic chemotherapy (CT), % (n)	100 (30)
1 regimen	26,67 (8)
2 regimens	40,0 (12)
≥ regimens	33,33 (1)
Prior chemoembolization (CE), % (n)	6,7 (2)
Prior Bevacizumab, % (n)	56,7 (17)
Time between diagnosis and RE, % (n)	
< 1 year	13,3 (4)
1 – 2 years	16,7 (5)
> 2 years	70,0 (21)
Liver metastases, % (n)	
Unilobar	23,3 (7)
Bilobar	76,7 (23)
Disease stability, % (n)	
Stable	30,0 (9)
Progressing	70,0 (21)
Laboratorial values, median +/- IQR	
ALT (U/L)	27,0 +/- 36
AST (U/L)	30,0 +/- 24
ALP (U/L)	141,0 +/- 121
TB (µmol/L)	10,3 +/- 5
Pre-RE CEA levels, % (n)	
< 20 ng/mL	43,3 (13)
≥ 20 ng/mL	56,7 (17)

SD, standard deviation; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin; ECOG, Eastern Cooperative Oncology Group; CT, chemotherapy; CE, chemoembolization; RE, radioembolization; N, number of patients with available data; *N=28; **N=27; IQR, interquartile range.

underwent 1, 2 and 3 or more pre-RE CT regimens, respectively. After RE, two (6.7%) patients had resectable disease after the technique and three (10%) met criteria for percutaneous ablation; 70.0% (n=21) underwent chemotherapy.

Half (n=15) of the patients showed imaging progression of the disease at three months, 26.7% (n=8) at six months and 6.7% (n=2) at twelve months, and these values are shown in Table 3 and in Graph 1. Five patients (16.7%) did not show disease progression until the end of the follow-up. At six months after RE, the mortality rate was 10.0% (n=3) and 33.3% (n=10) at twelve months. No patient died three months after RE. Median survival time in the first year after RE was 9.0 months (95% CI, 8.2-9.8).

Table 2 – Clinical outcomes after radioembolization.

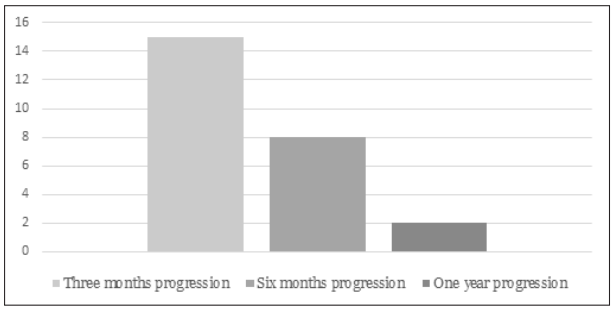
Characteristics	
Post-RE CEA levels, % (n)*	
< 20 ng/mL	50,0 (14)
≥ 20 ng/mL	50,0 (14)
Resection performed, % (n)	6,7 (2)
Post-RE procedure, % (n)	
Systemic chemotherapy	70,0 (21)
Percutaneous ablation	10,0 (3)
Bevacizumab	36,7 (11)
Chemoembolization	3,3 (1)

Table 3 – Descriptive analysis of the proportion of patients with progressing, stable disease, partial response or complete response after RE, based on tomographic response at three months of follow-up, according to RECIST 1.1 criteria.

CT evaluation	**At 3 months**	**At 6 months**	**at 1 year**
Progression	50,0 (15)	26,7 (8)	6,7 (2)
Stable disease	26,7 (8)	16,7 (5)	10,0 (3)
Partial response	20,0 (6)	6,7 (2)	3,3 (1)
Complete response	3,3 (1)	0,0 (0)	3,3 (1)

CEA, carcinoembryonic antigen; RE, radioembolization; *N (number of patients with available data) = 28.

Graph 1 – Disease progression based on computed tomography evaluation, according to RECIST 1.1 criteria.[20]



• Complications

Complications associated to RE were categorized according to the CTCAE v5.0 classification criteria as previously mentioned. The following were recorded: abdominal pain (40.0%; n=12), asthenia (36.7%; n=11), nausea and vomiting (30%; n=9), anorexia (20%; n=6), fever (13.3%; n=4), and changes in bowel habits (6.7%; n=2), these being mild complications which did not imply increased surveillance or altered the normal course of the post-intervention period, categorized as grade 1. Two cases (6.7%) of radiation-induced gastric ulcer were also reported: in one case the sequel was mild and did not interfere in the patient's daily activities, being categorized grade 2; in the other case, gastric antrectomy was necessary to correct the complication, resulting in a severe, permanent sequel that severely limited the patient's life (this being the first patient treated in the institution using this therapeutic technique), being categorized as grade 4. Regarding biochemical toxicity, hyperbilirubinemia was documented in 36.7% (n=11), assessed 1 month after RE, grade 1 in six cases, grade 2 in four cases and grade 3 in one case.

• Assessment of success predictive factors

Table 4 compares and associates the presence of certain clinical and laboratory characteristics, as well as the outcomes after RE, with the success of the technique based on the CT assessment. The presence of a stage equal to or less than 3 ($p<0.040$) and the absence of vascular ($p=0.028$) and lymphatic ($p=0.020$) invasion at the time of diagnosis, as well as a metastasis-free time of more than one year since diagnosis ($p=0.036$) were significantly associated to the RE's success. CEA values below 20 ng/mL at diagnosis ($p=0.035$) and after RE ($p=0.023$) were also significantly associated to RE success. To define the predictive factors for success after RE, we introduced the aforementioned variables (which reached statistical significance in the univariate comparative analysis) in a multivariate logistic regression model; however, the model was not statistically significant ($X2=0.001$; $p=1,000$) and did not allow establishing success predictors after RE.

The median survival time for successful patients after RE was 9.4 months (95% CI, 1.8-17.1) and for unsuccessful patients it was 8.9 months (95% CI, 7.5 -10.2). The distribution of survival (Graph 2) did not differ significantly between groups ($p=0.810$).

Discussion

Most patients with a long period between diagnosis and RE underwent multiple treatments before and after RE: all had chemotherapy regimens prior to RE, 70% of them with disease progression when they were selected for this intervention, due to failure of previously established

Graph 2 – Median survival time using the Kaplan-Meier function for successful and unsuccessful patients after radioembolization. The follow-up of patients was carried out over 12 months. The median survival time for successful patients after radioembolization was 9.4 months and for unsuccessful patients it was 8.9 months. The distribution of mean survival time did not differ significantly between groups (p=0.810). RE, radioembolization.

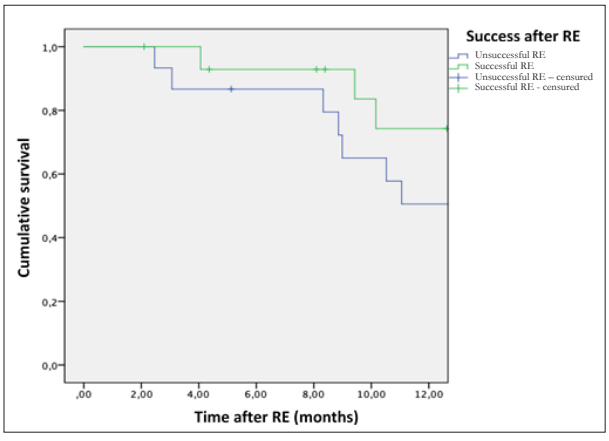


Table 4 – Comparative analysis of the sample characteristics with successful radioembolization.

Characteristics	**RE success**		
	Yes (n=15)	**No (n=15)**	*P Value*
Sex, % (n) Male Female	 66,7 (10) 33,3 (5)	 60,0 (9) 40,0 (6)	*0,705*
Age (years), median +/- SD	63,5 +/- 14,1	59,5 +/- 13,0	
Primary site, % (n) Sigmoid colon Rectum Ascending colon Descending colon Transverse colon	 26,7 (4) 40,0 (6) 20,0 (3) 6,7 (1) 6,7 (1)	 53,3 (8) 26,7 (4) 13,3 (2) 6,7 (1) 0,0 (0)	*0,569*
Stage at diagnosis, % (n) I II III IV	 0,0 (0) 20,0 (3) 26,7 (4) 53,3 (8)	 0,0(0) 0,0 (0) 6,7 (1) 93,3 (14)	*0,040**
Liver metastases at diagnosis, % (n)	53,3 (8)	93,3 (14)	*0,013**
Extrahepatic metastization, % (n)	20,0 (3)	20,0 (3)	*1,000*
K-RAS mutation, % (n)	57,1 (8)	64,3 (9)	*0,699*
Surgical resection of primary neoplasm, % (n)	80,0 (12)	80,0 (12)	*1,000*
Vascular invasion at diagnosis, % (n)	33,3 (5)	73,3 (11)	*0,028**
Lymphatic invasion at diagnosis, % (n)	46,7 (7)	86,7 (13)	*0,020**
Prior percutaneous ablation, % (n)	13,3 (2)	20,0 (3)	*0,624*
Prior systemic chemotherapy, % (n)	100 (15)	100 (15)	*1,000*
Prior chemoembolization, % (n)	6,7 (1)	6,7 (1)	*1,000*
Prior Bevacizumab, % (n)	53,3 (8)	60,0 (9)	*0,713*
ECOG, % (n) 0 1 2	 46,7 (7) 46,7 (7) 6,7 (1)	 66,7 (10) 26,7 (4) 6,7 (1)	*0,510*
Time between diagnosis and metastization, % (n) < 1 year 1 - 2 years > 2 years	 53,3 (8) 20,0 (3) 26,7 (4)	 93,3 (14) 6,7 (1) 0,0 (0)	*0,036**
Time between diagnosis and RE, % (n) < 1 year 1 - 2 years > 2 years	 20,0 (3) 13,3 (2) 66,7 (10)	 6,7 (1) 20,0 (3) 73,3 (11)	*0,536*
Disease stability, % (n) Stable Progressing	 33,3 (5) 66,7 (10)	 26,7 (4) 73,3 (11)	*0,690*
CEA levels at diagnosis, % (n) < 20 ng/mL ≥ 20 ng/mL	 60,0 (9) 26,7 (4)	 26,7 (4) 66,7 (10)	*0,035**
Pre-RE CEA levels, % (n) < 20 ng/mL ≥20 ng/mL	 53,3 (8) 46,7 (7)	 33,3 (5) 66,7 (10)	*0,269*
Post-RE CEA levels, % (n) < 20 ng/mL ≥20 ng/mL	 66,7 (10) 26,7 (4)	 26,7 (4) 66,7 (10)	*0,023**

RE, radioembolization; SD, standard deviation; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; *Value P≤0,05, indicating characteristics associated to RE's success.

regimes. After RE, 70% of patients were instructed to restart chemotherapy. Thus, as in other studies, RE did not contraindicate the use of subsequent therapies, namely the reinstitution of the chemotherapy regimen after the procedure.[4,7,8]

The dimensional reduction of liver metastases for subsequent percutaneous ablation or surgical resection was noted in three and two patients, respectively, comprising a percentage of 10 and 6.7%, respectively, and 16.7% in total procedures, similar to the one reported in other studies.[3,7]

Half of the patients in this study showed disease progression on control CT at three months. However, evaluating the success of the technique only by the behavior of the disease on CT may not be the most reliable method, given that the RECIST 1.1 scale used assesses disease progression only by the difference in the size of the lesions before and after

RE, not considering the fact that the presence of edema, necrosis or peritumoral hemorrhage is common.[3,8,16,18] Thus, the increase in the size of the lesions can distort the results and define a disease that is stable as progressing.[3,8,18] [16,18] Therefore, it is suggested that, in future studies, the definition of response to RE should include not only CT studies, but also studies evaluating the metabolic response, such as positron emission tomography (PET-CT), as suggested by several authors.[3,8,18]

The statistical analysis of the relationship between the various parameters and the success of RE (based on CT assessment, according to RECIST 1.1 criteria), allowed the identification of possible predictors of success of this therapy. Thus, in the sample under analysis, a stage less than or equal to three at diagnosis, the absence of vascular and lymphatic invasion, laboratory values of CEA less than 20 ng/mL and a time until metastasis equal to or greater than 1 year were clinical variables associated with the success of the intervention. It was also observed that patients with subsequent confirmation of RE success had CEA levels below 20 ng/mL. It should also be reported that other studies had already established a relationship between the effectiveness of RE and CEA levels, lymphatic invasion and the presence of metastases at diagnosis.[3,12,18,19] However, despite these promising results, when introduced in a multivariate logistic regression model, the variables were not statistically significant to be considered as predictors of RE success. The small number of patients evaluated and their early deaths had a great impact on the multivariate analysis of potential prognostic factors. It is intended, therefore, to update these data in larger cohorts, with longer follow-up periods, to assess the impact of these factors on population survival and the role they may play in helping to select patients for this intervention.

The median survival time for successful patients after radioembolization was 9.4 months and for unsuccessful patients it was 8.9 months. Although there were no statistically significant differences between the groups (p=0.810), the values obtained were similar to results from other published studies on RE in the studied population. In retrospective studies similar to this one, Kennedy et al.[14] described a median survival of 9.6 months in patients with multiple chemotherapy regimens; Jakobs et al.[10] 10.5 months; and Martin et al.[18] 8.9 months. In prospective studies, Hendlisz et al.[8] compared patients with RE regimens added to chemotherapy and patients with regimens consisting solely of chemotherapy and had a 10-month survival with RE vs. 7.3 months without RE. Bester et al.[7] and Seidensticker et al.[16] developed studies between patients who underwent RE and a control group managed with the best palliative care possible (BPC). In the first, a survival of 11.9 months with RE vs. 6.6 months for patients with BPC and, in the second, 8.3 months with RE vs. 3.5 months with BPC were described.

RE was generally well tolerated. The rate of complications and toxicity is consistent with other previously published studies and were mostly mild symptoms, easily managed and reversible with supportive care. There were no RE-associated deaths in the first three months after the intervention and deaths subsequently recorded until the end of follow-up were related to disease progression. Only two patients (6.7%) had a serious complication, RE-induced gastric ulcer; this incidence is also similar to that found in the literature.[7]

The limitations of this study are related to the number of patients treated for this type of tumor and its retrospective nature (since this population is very specific and small), as well as to the fact that only one year of follow-up was performed. The absence of control groups to compare the magnitude of the RE effect (vs absence of RE vs chemotherapy) is another limitation to be noted. The definition of several groups, with different therapeutic associations, could help to establish the possible role of RE in the therapeutic escalation of mCRC. However, due to the poor prognosis associated with this pathology, carrying out such studies becomes difficult.

In summary, RE is a well-tolerated therapy, with objective results in half of treated patients and with a non-significant increase in patient survival time. There are RE response prognostic factors that have been identified that may help to better select patients to be treated. The introduction of this technique at an earlier stage of cancer treatment on these patients could lead to more promising results, namely in the reduction of progression-free survival at the liver level.[5]

Divulgações Éticas / Ethical disclosures

Conflicts of interest: The authors have no conflicts of interest to declare.

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Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I BF. Global cancer observatory: cancer today. International Agency for Research on Cancer. ISBN-13 (Database). 2020.

2. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27:1386-422.

3. Sofocleous CT, Violari EG, Sotirchos VS, Shady W, Gonen M, Pandit-Taskar N, et al. Radioembolization as a salvage therapy for heavily pretreated patients with colorectal cancer liver metastases: factors that affect outcomes. Clin Colorectal Cancer. 2015;14:296-305.

4. Rohan Jeyarajah D, Majella Doyle MB, Joseph Espat N, Hansen PD, Iannitti DA, Kim J, et al. Role of yttrium-90 selective internal radiation therapy in the treatment of liver-dominant metastatic colorectal cancer: an evidence-based expert consensus algorithm. J Gastrointest Oncol. 2020;11:443-60.

5. Winter H, Rassam J, Virdee PS, Goldin R, Pitcheshwar P, Weaver K, et al. Hepatic resection following selective internal radiation therapy for colorectal cancer metastases in the foxfire clinical trial: clinical outcomes and distribution of microspheres. Cancers (Basel). 2019;11:1155.

6. Marsala A, Lee EW, Padia SA. Yttrium-90 radioembolization for metastatic colorectal cancer: outcomes by number of lines of therapy. Semin Intervent Radiol. 2017;34:116-20.

7. Bester L, Meteling B, Pocock N, Pavlakis N, Chua TC, Saxena A, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol. 2012;23:96-105.

8. Hendlisz A, Van Den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28:3687-94.
9. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, et al. Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010;103:324-31.
10. Jakobs TF, Hoffmann RT, Dehm K, Trumm C, Stemmler HJ, Tatsch K, et al. Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. J Vasc Interv Radiol. 2008;19:1187-95.
11. Gangi A, Lu SC. Chemotherapy-associated liver injury in colorectal cancer. Therap Adv Gastroenterol. 2020;13:1-9.
12. Weiner AA, Gui B, Newman NB, Nosher JL, Yousseff F, Lu SE, et al. Predictors of survival after yttrium-90 radioembolization for colorectal cancer liver metastases. J Vasc Interv Radiol. 2018;29:1094-100.
13. Dutton SJ, Kenealy N, Love SB, Wasan HS, Sharma RA. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional selective internal radiation therapy (SIRT) as first-line treatment for patients with unresectable liver-on. BMC Cancer. 2014;14:1-7.
14. Kennedy AS, Ball D, Cohen SJ, Cohn M, Coldwell DM, Drooz A, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for 90Y resin microspheres. J Gastrointest Oncol. 2015;6:134-42.
15. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer. 2018;18:1-11.
16. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2012;35:1066-73.
17. Braat MNGJA, Van Erpecum KJ, Zonnenberg BA, Van Den Bosch MAJ, Lam MGEH. Radioembolization-induced liver disease: a systematic review. Eur J Gastroenterol Hepatol. 2017;29:144-52.
18. Martin LK, Cucci A, Wei L, Rose J, Blazer M, Schmidt C, et al. Yttrium-90 radioembolization as salvage therapy for colorectal cancer with liver metastases. Clin Colorectal Cancer. 2012;11:195-9.
19. Damm R, Seidensticker R, Ulrich G, Breier L, Steffen IG, Seidensticker M, et al. Y90 Radioembolization in chemo-refractory metastastic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system. BMC Cancer. 2016;16:1-7.
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.
21. U.S. Department of Health and Human services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. NIH. 2017.