Original Article

Evaluation of response to neoadjuvant treatment, by nuclear magnetic resonance, as a predictor of oncologic results and survival of patients with rectal cancer

RODRIGO SOARES NAPOLEÃO DO RÊGO[1], FÁBIO LOPES DE QUEIROZ[2], BRENO XAIA MARTINS DA COSTA[1], FERNANDA ELIAS FERREIRA RABELO[1], PAULO CESAR DE CARVALHO LAMOUNIER[3], LUCIANA COSTA SILVA[5], VALDIVINO ALVES FILHO[4], MARIA ZULEIME CARMONA[4]

[1]Resident, Service of Coloproctology of the Hospital Felício Rocho – Belo Horizonte (MG), Brazil. [2]Coordinator of Residency, Service of Coloproctology of the Hospital Felício Rocho – Belo Horizonte (MG), Brazil. [3]Coordinator, Service of Coloproctology of the Hospital Felício Rocho – Belo Horizonte (MG), Brazil. [4]Preceptor, Service of Coloproctology of the Hospital Felício Rocho - Belo Horizonte (MG), Brazil. [5]Professor, Department of Propedeutics of the Medical School of the Universidade Federal de Minas Gerais – Belo Horizonte (MG), Brazil.

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ABSTRACT: Introduction: Neoadjuvant chemoradiation promotes tumor size reduction and staging before the surgery, reducing the risk of involving the circumferential resection margin and local recurrence. For patients who have been submitted to the neoadjuvant therapy, the usefulness of a second nuclear magnetic resonance (MRI) after chemoradiation has not been clearly explained. Objective: Assess the degree of tumor regression and downstaging after chemoradiation using MRI, compared with the pathology, and its correlation with surgical outcomes and patient prognosis. Methods: This study investigated 13 patients. Their mean age was 52.3 years and 69.23% were male. Results: The agreement in T and N staging was 30.76%, between the second MRI and pathology, overestimated in 55.55% of the remaining. T staging agreement was 53.84% and N staging agreement, 61.53%. The circumferential resection margin was free of cancer in 100%. The survival rate was 92%, with 75% disease-free in a mean follow-up of 1-2 years. Conclusion: A second MRI after chemoradiation can evaluate the degree of tumor regression, but with low compliance in relation to pathology, with tendency to overstaging. More studies are required to confirm these initial observations.

Keywords: magnetic resonance imaging; rectal cancer; neoadjuvant therapy.

INTRODUCTION

Rectal cancer corresponds to 30 to 50% of all colorectal tumors. Its prognosis is influenced by several factors, such as lateral extension of tumor, lymph node involvement and presence of distant metastases. The rate of local recurrence, after isolated surgical treatment, ranges from 3 to 32%, with the presence of tumor less than 1 mm from the circumferential resection margin (CRM) an important prognostic indicator of local recurrence, distant metastases and worsened survival[1,2]. Neoadjuvant chemoradiation (NACR) promotes tumor size reduction and staging before the surgery, reducing the risk of involving the CRM and local recurrence[3]. This procedure is indicated for tumors T3, T4 and/or with lymph node involvement[4]. Magnetic Resonance Imaging (MRI) can assess staging, involvement of radial circumference margin and the

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extramural venous invasion with high accuracy, identifying factors of difficult prognosis[1,5]. For patients with rectal cancer submitted to neoadjuvant therapy, the usefulness of a second MRI after chemoradiation to assess the response to the treatment, and performed just before the surgical procedure, has not been clearly explained. The potential benefits that have been reported are: accurate identification of tumor regression for an adequate CRM, after a standard surgery with total mesorectal excision, and warn for possible points requiring more careful dissection or wider resection. In addition, some studies relate the response to the NACR to the prognosis. Few studies have assessed the predictive value of MRI after NACR as a predictor of oncologic results and survival of patients with rectal cancer.

This study has the purpose of assessing the degree of tumor regression and downstaging obtained after chemoradiation through MRI, comparing it to the anatomopathological (AP) study and its correlation with the patients' surgical results and prognosis.

METHODS

This is a prospective observational study that included patients treated between August 2008 and December 2010. These patients were submitted to preoperative staging by thorax, abdomen and carcinoembryonic antigen (CEA) tomography, as well as a clinical evaluation. Locoregional staging was performed through pelvic MRI. The patients classified to MRI as T3/T4 and/or with affected lymph nodes were submitted to chemoradiation (radiotherapy of 4500 to 5040 cGy for 5 weeks, associated with chemoradiation with the combination of 5-fluorouracil 350 mg/m^2/day and folinic acid 20 mg/m^2/day for 5 days in weeks 1 and 5). The surgery was performed eight weeks after the neoadjuvant therapy, using the technique of total mesorectal excision. One week before the surgery, one more pelvic MRI was performed to assess the degree of tumor regression. Later, the preoperative MRI results were compared to the AP study of the surgical specimen. Then, the predictive value of MRI was evaluated in relation to the response to the neoadjuvant therapy, as well as the relation between the response to neoadjuvant therapy and the prognosis of these patients.

T and N staging used in the study followed the UICC (Union for International Cancer Control) classification. The degree of tumor regression was assessed following the modified Dworak classification, which is Degree 0: no regression, similar aspect to the original tumor; Degree 1: dominating tumor mass with small areas of fibrosis/mucin; Degree 2: predominance of fibrotic or mucin alterations and visible intermediate sign; Degree 3: dense fibrosis, with no obvious residual tumor; and Degree 4: no evidence of tumor (complete response).

This study was approved by the Research Ethics Committee of the Hospital Felício Rocho, under CAAE (*Certificado de Apresentação para Apreciação Ética*) protocol 0008.0.240.000-11.

RESULTS

This study analyzed 13 patients. Table 1 shows the patients' characteristics. Nine patients (69.23%) were male. Their mean age was 52.3 years old. All patients were submitted to the surgery of low anastomosis of colon with total mesorectal excision performed by the same surgeon. One patient presented hepatic metastases at the diagnosis, which was later resected.

All patients presented free circumferential resection margins.

The AP study showed compliance in relation to T staging of 53.84% (7/13) estimated in the post-neoadjuvant therapy MRI, with tendency to overstaging of 83.33% (5/6) in the others. Regarding the lymph node status, the AP study agreed with the post-NACR MRI in 61.53% (8/13). When assessing associated T and N staging, the compliance was 30.76% (4/13); also with tendency to overstaging of 55.55% (5/9) in the other patients (Table 2).

In the follow-up period of the 13 patients, one patient died due to postoperative complications (staged patient, T3N0 at the first examination, with tumor regression estimated as Degree 2 by MRI, remained T3N0 after the NACR and the AP study indicated T2N0), one patient had local recurrence and distant metastases one year and eight months after the surgery (a T3N2 patient, with tumor regression estimated as Degree 3, but with T3N0 staging after the NACR and the AP study indicating T3N0) and died six months after the recurrence; two resected he-

patic metastases (one patient with metastases at the diagnosis, T3N2, with tumor regression estimated as Degree 3, T3N0 at the second MRI and the AP study indicating TxN1; and another T3N2 patient, of tumor regression classified as Degree 1, who remained T3N2 at the post-NACR MRI and the AP study showing T2N2). The nine other patients (69.23%) have had the disease under control so far, without recurrence and/or metastases.

Regarding the two patients that presented local and/or distant recurrence, 1 (50%) showed tumor regression at the second MRI. And only one out of the nine patients showing tumor regression with reduction at staging presented recurrence (Table 3).

DISCUSSION

MRI with emphasis on the rectum can classify rectal tumors according to prognostic factors and assess T and N staging with 85-90% accuracy[3,6]. For this reason, it enables a better surgical planning, showing the points of high vulnerability during mesorectal dissection to the surgeon and leading to a lower rate of involvement of circumferential resection margins, which is an important prognostic factor of local recurrence and survival[1,5].

This study shows initial observations indicating that the post-neoadjuvant therapy MRI could not estimate the reduction at the post-neoadjuvant therapy staging, showing compliance in relation to the AP

Table 2. *Compliance index of the anatomopathological analysis in relation to the condition indicated in post-neoadjuvant therapy MRI.*

STAGING	POST-NACR MRI (n)	Confirmation – AP	%
T	13	7	53.84
N	13	8	61.53
TN	13	4	30.76

AP: anatomopathological study; MRI: magnetic resonance imaging; NACR: neoadjuvant chemoradiation.

Table 3. *Evaluation of recurrence in relation to tumor regression.*

		Recurrence	
		Yes	No
Tumor Regression	Yes	1	8
	No	1	1

Table 1. *Clinical characteristics of patients.*

	Patient	PRE-NACR MRI	POST-NACR MRI	DWORAKr	AP	CRM	Time to surgery	Clinical status
1	AFS	T2N2	T2N0	2	T2N0	Free	1-2 YEARS	No recurrence
2	AGF	T4bN2	T4bN1	3	T4N0	Free	1-2 YEARS	No recurrence
3	BNT	T3aN0	T2N0	2	T2N0	Free	1-2 YEARS	No recurrence
4	DT	T3bN0	T0N0	4	T0N1	Free	1-2 YEARS	No recurrence
5	DPC	T3dN1	T3dN0	1	T3N2	Free	>2 YEARS	No recurrence
6	KAS	T2N0	T2N0	1	T1N1	Free	>2 YEARS	No recurrence
7	MLD	T3N0	T3N0	2	T2N0	Free	1-2 YEARS	Death – surgical complications
8	OAS	T3N2	T3N2	1	T2N2	Free	1-2 YEARS	Resected hepatic Mtx
9	ORM	T3bN0	T0N0	2	T2N0	Free	<1 YEAR	No recurrence
10	PFM	T3aN0	T1N0	3	T1N0	Free	1-2 YEARS	No recurrence
11	SH	T3bN2	T3N0	3	T0N1	Free	<1 YEAR	Resected hepatic metastases
12	TJLJ	T3aN0	T3aN0	2	T0N0	Free	1-2 YEARS	No recurrence
13	VF	T3cN2	T3cN0	3	T3N0	Free	>2 YEARS	Recurrence + Lung and bone metastases – death

AP: anatomopathological study; CRM: circumferential resection margin; Mtx: metastases; MRI: magnetic resonance imaging; NACR: neoadjuvant chemoradiation.

study of 30.76%. The other patients presented tendency to overstaging. According to Barbaro et al., MRI sensitivity and specificity are approximately 80%, with tendency to overtsaging[6]. When MRI shows staging higher than the AP results, it does not affect the oncologic surgical quality, as the surgeon tends to consider a wider resection margin, for a free CRM. If, after the resection, the actual staging is lower than the value estimated in MRI, the non-involvement of margins is kept. This overstaging tendency occurs especially due to the difficult differentiation of initial T2 to T3, and the radiologist tends to classify as overstaging. In addition, post-neoadjuvant therapy fibrosis makes this differentiation between tumor and cicraticial tissue more difficult, which favors overstaging. When trying to avoid an undertreated patient, in an oncologic perspective, overstaging occurs in case of any doubt, leading to a more aggressive treatment, with higher morbidity, but oncologically adequate. In neoadjuvant NACR, precise staging to assess the response to treatment is very important, as it can guide through surgical approach optimization, such as sphincter preservation in low tumors, less aggressive resection of initially advanced tumors or intraoperative radiation therapy, according to the tumor response[6,7].

NACR results in reduced number and size of both benign and malign mesorectal lymph nodes. Dow Mu-Koh et al.[3] report that NACR is useful in the assessment of lymph node response to neoadjuvant treatment, with 88% accuracy, but it is uncertain in terms of how much this response can be translated into survival[3,8]. The compliance found in lymph node status after NACR was 61.53%. In the evaluation of mesorectal lymph nodes, the utilization of morphological criteria (outline irregularity and sign heterogeneity) offers improved accuracy than the size to distinguish malign from non-malign lymphatic ganglia.

Three patients (23.07%) presented complete pathological response, without evidence of tumor tissue in the specimen, only fibrosis and inflammatory alterations. Only 1 (33,33%) of them presented post-NACR MRI suggesting complete remission. In another case, MRI indicated complete remission, but the AP study showed neoplastic tissue. In the evaluation of complete pathological response, MRI presented the positive predictive value of 50.0% and the negative predictive value of 83.3%.

Pre-NACR MRI influenced the proper surgical planning, especially in larger tumors, resulting in 100% free CRM, which improves the prognosis, since a compromised CRM leads to local recurrence rate of 83.0%[6].

Regarding the prognosis, two deaths occurred. One patient died of postoperative complications and one patient after the disease recurrence. Survival in this mean follow-up period of 1 to 2 years was 91.7% and 75.0% are free from the disease. These are initial observations and require longer follow-up periods for a better survival evaluation.

The patients with worse response, who presented local recurrence or distant metastases, were those with tumors in advanced stage. At pre-NACR MRI, all patients were staged as T3N2, configuring a worsened prognosis, regardless of the response to NACR when evaluated through MRI or the AP study. The first, with tumor recurrence and distant metastases diagnosed after 20 months, was T3N2, with tumor regression classified as Degree 3, but with T3N0 staging after NACR and the AP study indicated T3N0, and died six months after the salvage surgery due to recurrence. The second, with hepatic metastasis diagnosed when the clinical condition appeared, was T3N2, with regression classified as Degree 3, post-NACR MRI indicating T3N0 and the AP study indicating TxN1, is now well, after metastasis resection, receiving clinical and oncologic follow-up care for seven months. The third, was T3N2, with regression Degree 1, post-NACR MRI still indicating T3N2 and the AP study showing T2N2, was submitted to hepatic metastasis resection and is receiving follow-up care. These patients, even after the lesion size reduction, with tumor regression after NACR, still showed advanced staging at the second MRI (all were T3 and one was N2). The AP study of two patients showed lymph node involvement despite the tumor regression and one showed no tumor regression at the degree of wall invasion, only tumor size reduction (leading to patient's death). The AP study confirmed T staging with poor response indicated at MRI in all these three patients.

It is important to point out that 7 (77.78%) out of total 9 patients that now have no locoregional or distant metastases presented good response as indicated at MRI, characterized by tumor regression of

Degrees 2, 3 and 4. Even a patient who was T4N2, presenting good response at NACR and whose MRI indicated Degree 3 regression, with the AP study showing T4N0, has the disease now under control, in 2-year follow-up. Although the second MRI tends to overstage the lesion, these patients who were good responders, according to the radiologic criteria, and later confirmed by the AP study, or the patients who presented better pathological response, are those without disease recurrence.

CONCLUSION

Our results indicate that the second MRI after the neoadjuvant therapy can show tumor regressions, if any, but it is of little use in the determination of downstaging, when compared to the AP study, tending to overstaging. Patients with tumors in advanced phases, lymph node involvement and poor response as evaluated through MRI, tend to show worsened prognosis. Further studies are required to confirm these first observations.

RESUMO: Introdução: A radioquimioterapia neoadjuvante promove redução do tamanho e do estadiamento dos tumores do reto antes da cirurgia, reduzindo o risco de acometimento de margem de ressecção circunferencial e da recorrência local. Para pacientes que se submeteram a neoadjuvância, a realização de uma segunda ressonância magnética (RNM) após a radioquimioterapia, para avaliação do resultado do tratamento, pode trazer dados relevantes para a programação cirúrgica e previsão do prognóstico, porém sua utilização ainda é controversa. Objetivo: Avaliar a capacidade da RNM prever o grau de regressão tumoral e o *downstaging* obtidos e a correlação entre o grau de regressão tumoral com o prognóstico dos pacientes. Métodos: Foram incluídos 13 pacientes até o momento; desses 69,23% eram do sexo masculino e a idade média foi de 52,3 anos. Resultados: O anatomopatológico (AP) mostrou conformidade em relação ao estadiamento T e N estimado pela RNM pós-neoadjuvância de 30,76%; nos demais pacientes, houve tendência ao superestadiamento em 55,55%. No estadiamento T houve concordância de 53,84% e quanto ao *status* linfonodal, concordância 61,53%. A margem de ressecção circunferencial foi livre de neoplasia em 100%. A sobrevida foi de 92%, com 75% de sobrevida livre de doença num seguimento médio de 1-2 anos. Conclusão: Uma segunda ressonância após neoadjuvância pode avaliar se houve regressão tumoral, porém com baixa conformidade em relação ao anatomopatológico, com tendência ao superestadiamento. Mais estudos são necessários para corroborar essas impressões iniciais.

Palavras-chave: imagem por ressonância magnética; câncer de reto; terapia neoadjuvante.

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Correspondence to:
Rodrigo Soares Napoleão do Rêgo
Serviço de Coloproctologia do Hospital Felício Rocho
Avenida do Contorno, 9530, Barro Preto
CEP 30110-068 – Belo Horizonte (MG), Brazil.
E-mail: rodrigo_snr@yahoo.com.br