Мак Мед Прегледˇ 2020; 74(2): 105-109

ММР

Original article

THE VALIDITY OF MAGNETIC RESONANCE IMAGING IN DETERMINING PREOPERATIVE NODAL STAGING IN RECTAL CANCER

ВАЛИДНОСТА НА МАГНЕТНАТА РЕЗОНАНЦА ВО ОДРЕДУВАЊЕ НА ПРЕДОПЕРАТИВНИОТ НОДАЛЕН СТЕЈЏИНГ КАЈ РЕКТАЛЕН КАРЦИНОМ

Ana Lazarova[1], Ljuben Arsenkov[2] and Stefan Arsenkov[2]

[1]Department of Radiology, [2]Department of Abdominal Surgery, University Clinic for Surgery "St. Naum Ohridski" in Skopje, Faculty of Medicine, Ss Cyril and Methodius University Skopje, Republic of North Macedonia

Abstract

Introduction. The basic diagnostic tool in preoperative staging of rectal cancer is magnetic resonance imaging (MRI), which allows the selection of patients who in addition to surgical treatment, are candidates for preoperative chemoradiotherapy (neoadjuvant treatment).
The aim of this study was to demonstrate the validity of magnetic resonance imaging in determining the nodal stage (stage N) of rectal cancer preoperatively.
Methods. In this study 82 patients with colonoscopy proven rectal cancer, aged 43 to 87 years (an average age of 66.65), were treated.
Magnetic resonance imaging (MRI) was performed preoperatively and the N stage of the disease was determined. The MRI was made with a 1.5T magnet in standard pulse sequences SAG T2, AX T1, AX T2, AX DWI.
Results. The results obtained for the N stage with magnetic resonance imaging were correlated with the pathohistology finding postoperatively taken as the gold standard in determining the sensitivity and specificity of magnetic resonance imaging. The sensitivity and specificity of MRI in determining the N0 stage of rectal carcinoma was 36.6% and 48.8%, respectively. The sensitivity and specificity of MR in determining the N1 stage of rectal carcinoma was 35% and 79%, respectively. The sensitivity and specificity of MR in determining the N2 stage of rectal carcinomas were 25% and 98.6%, respectively.
Conclusion. Magnetic resonance imaging is the basic and also most important diagnostic modality in preoperative staging of rectal cancer and provides a clear insight into nodal status, with an accuracy of 43% to 85%.

Keywords: MRI, rectal cancer, preoperative N staging

Correspondence to: Ana Lazarova, Department of Radiology, University Clinic for Surgery "St. Naum Ohridski" in Skopje, R. N. Macedonia; E-mail: anidinamita@gmail.com

Абстракт

Вовед. Основна дијагностичка алатка во предоперативниот стејџинг на ректален карцином е магнетната резонанца која овозможува селекција на пациенти кои покрај хируршкиот третман се кандидати за предоперативен неоадјувантен третман.
Целта на оваа студија е да ја прикаже валидноста на магнетната резонанца во одредување на предоперативниот нодален стадиумот (N стадиумот) на ректален карцином.
Методи. Обработени се 82 пациенти со колоноскопски докажан ректален карцином на возраст од 43 до 87 години, и на просечна возраст од 66.65± 9.8 години.
Кај кои предоперативно е направена магнетна резонанца (МР) и е одреден N стадиумот на болеста. МР беше правена со1.5T магнет во стандардни пулс секвенци SAG T2 , AX T1,AX T2,AX DWI.
Резултати. Добиените резултатиза N стадиумот со магнетна резонаца се корелирани со патохистолошкиот наод постоперативно кој е земен како златен стандард за одредување на сензитивноста и специфичноста на магнетната резонанца. Сензитивноста и специфичностана МР во одредувањена N0 стадиум на карцином и на ректум беше 36.6%, и 48.8% консеквентно. Сензитивноста и специфичностана МР во одредувањена N1 стадиум на карцином и на ректум беше 35% и 79% консеквентно. Сензитивноста и специфичностана МР воодредувањена N2 стадиум на карцином и на ректум беше 25% и 98.6% консеквентно.
Заклучок. Магнетната резонаца е златен стандард во предоперативниот стејџинг на ректален карцином и дава јасен увид во нодалниот статус ,со точноста на нодалниот стејџинг од 43% до 85%.

Клучни зборови: магнетнарезонаца, ректален карцином, предоперативен нодален стејџинг

Introduction

Rectal cancer is a malignant disease spread in the developed countries, and it is the third most common malignant disease worldwide. The prognosis for rectal cancer has improved over the past decade, largely owing to advances in preoperative staging, which has reflected a therapeutic approach where significant changes have been made from simple surgical treatment to multimodal treatment. This reduced the local recidivism rate by 11% and increased the 5-year survival rate by 58% [1]. The preoperative neoadjuvant therapy or chemoradiotherapy is required in advanced rectal cancer because of it effects to reduce the size and stage of the tumor, also to minimize the risk of distant metastases. Also chemoradiotherapy is important because it provides less extensive surgical treatmen and possibly sphincter reservation technique for tumors located in a low rectum [3]. The multimodal approach includes a short cycle of radiotherapy (5x5 Gray), combined with the chemotherapy needed for treatment [4].
The new strategies standardize approximately 6 weeks of chemoradiotherapy, 6 to 8 weeks of preoperative recovery, and an additional 4 weeks if additional adjuvant therapy is required. Initial chemotherapy provides a theoretical advantage in dealing with possible micrometastases and thus prevents the occurrence of detectable metastases [5].
It is important to know whether a patient with rectal cancer is a candidate for surgery only or for preoperative radiochemotherapy followed by surgery. MRI can allow this selection because it is the most important tool in the staging of rectal cancer. Magnetic resonance imaging method plays a crucial role in preoperative staging of rectal cancer [6].
All T4 stage tumors, T3 stage with involved resection margins, T3 stage with metastatic modified lymph nodes in the mesorectum close to resection margins, and T3 stage with positive extramural vascular invasion are candidates for preoperative neoadjuvant treatment [2].
Compared to other imaging methods, MRI is characterized by excellent resolution, multiplanar projection; it gives full insight into all organs in the small pelvis, thus showing the ratio of tumor and rectum to other organs; it is non-invasive and does not use ionizing radiation, which is why is most suitable in preoperative staging of rectal cancer [7].

Material and methods

This paper shows the results of 82 patients diagnosed with rectal cancer by colonoscopy. Magnetic resonance imaging was performed preoperatively to determine the stage of the disease that would further influence the decision on treatment of the disease, whether it would be only surgical or preoperative neoadjuvant treatment followed by surgery.
This paper demonstrates the sensitivity and specificity or validity, accuracy of magnetic resonance imaging in determining the preoperative nodal stages (N stage) of rectal cancer. A comparison was made between the results for the N-stage performed by magnetic resonance imaging preoperatively with the results obtained from the pathohistology operative finding, which was taken as the gold standard on the basis of which the correlation was made.
The examination was made on a 1.5 T magnet in the University Clinic for Surgical Diseases "St. Naum Ohridski" Skopje.
Inclusion criteria for participation in this series were: patients with colonoscopy proven rectal cancer in whom pre-operative staging with MRI was indicated.
Patients excluded from this study were those who, due to implanted metal parts, were contraindicated in performing the examination and those who could not with stand the examination due to claustrophobia.
The standard MR protocol included:
Sagittal T2 waited image, axial T1, T2 and DWI were performed. Pulls sequences after contrast administration were not done, due to partial volume effect given by the contrast medium.Tumor has localization in the low rectum when is localized up to 5 cm from the anorectal junction; in the middle rectum when tumor is localized from 5 to 10 cm from the anorectal junction; and 10 cm above the anorectal junction is a high rectal localization of the tumor.
The presence of lymph nodes and N staging is a significant prognostic indicator and determines the rate of recurrence. If the lymph nodes are larger than 5 mm in diameter, they have an irregular shape and heterosignal appearance, and the likelihood that they contain metastatic deposits is high [8].
Even in T1 and T2 stages of the disease, there is a risk of metastatic altered LN (lymph nodes) Mesorectal nodules are the first to be involved; metastatic modified nodules are usually up to 5 mm distance from the tumor [9].
Extra-mesorectal nodes are mainly involved in the advanced stage of rectal cancer. Inguinal metastatic LNs, which are characteristic of anal cancer, are uncommon in rectal cancer. Although metastatic altered LNs are larger than benign ones; metastatic deposits may also be present in small LNs. Most often the size of LN with metastatic deposits is 5-8 mm, but additional morphological criteria for irregular contours and mixed signal intensity should be included here. When evaluating mesorectal nodules, the distance to the mesorectal fascia should be taken into account [10].
It is important to look for extra-mesorectal lymph nodes because they can trigger a local tumor recurrence. Of great importance is the data on whether the tumor penetrates the presacral fascia. With standard total mesorectal excision these lymph nodes cannot be removed.

Detection of malignant extra-mesorectal lymph nodes indicates the need for a more extensive surgical approach, as well as the use of radiotherapy in high-risk areas [11].

Results

The study included 82 patients, 58.5% (48) of whom were male, and 41.5% (34) female (Table 1).
Patients' age ranged from 43 to 87 years, with a mean age of 66.65±9.8 years.

Table 1. Distribution of patients by gender

Gender	n (%)
male	48 (58.54)
female	34 (41.46)

Table 2. Distribution of patients in relation to the number of LN - MRI

MRINo.LN	n (%)
0	22 (26.83)
1	11 (13.41)
2	10 (12.19)
3	15 (18.29)
4	13 (15.85)
5	6 (7.32)
6	1 (1.22)
7	3 (3.66)
8	1 (1.22)

Pathohistology group: N0 was up to three metastatic (MS) changed LNs in the mesorectum; N1 was from 3-6 MS changed LNs in the mesorectum, and N2 was over 6 MS changed LNs in the mesorectum.

Table 3. LNs number in relation to stage

Pathohistology LN	n (%)
N0	41 (50)
N1	24 (29.27)
N2	10 (12.19)
N3	2 (2.44)
N2b(8)	1 (1.22)
N2b(6)	1 ((1.22)
N1(3)	1 (1.22)
0	2 (2.44)

In terms of lymphatic status, the pathohistology finding in 50% (41) of patients did not confirm the presence of lymph nodes. Among those with positive lymph nodes, N1 status dominated, confirmed pathohistology in 29.3%

Table 4. LN stage - MRI / pathohistology

MRI LN	Pathohistology LN 0	N0	N1	N2	LN 3	Total
0	2	20	0	0	0	22
Up to 3	0	15	15	5	1	36
4,5,6	0	6	10	4	0	20
7,8,9	0	0	0	3	1	4
Total	2	41	25	12	2	82

(24) of patients, and N2 lymphatic status, confirmed in 12.2% (10) of patients, while N3 in 2% of patients (Table 2 and 3).
A positive, direct correlation was found between the MRI finding and the pathohistology finding, with respect to N staging (R=0.548). The higher N stage determined by MRI corresponded to a higher N stage within the pathohistology finding, and vice versa. For a value of p <0.0001, this correlation was statistically significant (Table 4 and 5).

Table 5. Correlation in the LN stage between MRI and pathohistology

Variable	Correlation N	Spearman-R	p-level
MRI LN & pathohistology LN	80	0.548	p=0.000000 sig

MRI detected 36 tumors with 1, 2 or 3 lymph nodes, of which 15 were true positive, at stage N0 according to the pathohistology finding, and 21 findings were false positive. With MRI 46 tumors were not marked as N0 stage, of which 26 were true negative, and 20 results were false negative.
The sensitivity and specificity of MR in determining the N0 stage of rectal carcinoma was low, 36.6%, and 48.8%, consequently (Table 6).

Table 6. Validity of MR in determining N0 stage of rectal cancer

Estimate	95% CI	
Sensitivity	0.366	[0.236 to 0.519]
Specificity	0.488	[0.343 to 0.635]
LR+	0.715	[0.433 to 1.18]
LR-	1.299	[0.88 to 1.921]

MRI detected 20 tumors with 4, 5 or 6 lymph nodes, of which 7 were true positive, hence in stage N1 according to the pathohistology finding, and 13 findings were falsely positive. With MRI 62 tumors were not marked as stage N1, of which 13 were true negative, and 49 results were false negative.
The sensitivity and specificity of MRI in determining the N1 stage of rectal carcinomas was 35% and 79%, consequently (Table 7).

Table 7. Validity of MRI in determining stage N1 of rectal cancer

Estimate	95% CI	
Sensitivity	0.35	[0.181 to 0.567]
Specificity	0.79	[0.674 to 0.873]
PPV	0.35	[0.181 to 0.567]
NPV	0.79	[0.674 to 0.873]
LR+	1.667	[0.774 to 3.599]
LR-	0.823	[0.582 to 1.163]

MRI detected 4 tumors with 7, 8 or 9 lymph nodes, 3 of which were true positive, hence in stage N2 according to the pathohistology finding, and one result was false positive. With MRI 78 tumors were not marked as N2 stage, of which 9 true negative, and 69 results were falsely negative.

The sensitivity and specificity of MRI in determining the N2 stage of rectal carcinomas were 25% and 98.6%, respectively (Table 8).

Table 8. Validity of MRI in determining N2 stage of rectal cancer

Estimate	95% CI	
Sensitivity	0.25	[0.089 to 0.532]
Specificity	0.986	[0.923 to 0.997]
PPV	0.75	[0.301 to 0.954]
NPV	0.885	[0.795 to 0.938]
LR+	17.857	[1.981 to 154.61]
LR-	0.761	[0.548 to 1.056]

Discussion

MRI gives multiplanar projection, great resolution, and compared to other images modalities it is the best choice for rectal cancer staging. Also the anatomic position of the rectum with the fixation on the pelvic floor ,as well as the absence of peristalsis makes it perfect organ for MR examination [15].

Although rectal tumors can be diagnosed by digital examination, irigography, colonoscopy, or sigmoidoscopy, as well as endorectal ultrasound, these endoluminal techniques do not provide sufficient data on the extends of the tumor within the pelvis and the relation with other organs [13].

MRI provides much higher resolution and soft contrast compared to CT, which means that modality is widely accepted and recommended in the overall insight of tumor localization, growth pattern, ratio to surrounding structures, T stage, nodal stage, and gives great possibility of evaluating extramural vascular invasion [14].

Only regional lymph nodes are included in the TNM classification; mesorectal LNs and iliac LNs belong to nodal staging. The involvement of other LNs is considered a metastatic disease extension. Mesorectal nodules are often the first group of LNs to be involved and are usually up to 5 cm from the tumor [12].

Extra-mesorectal nodes are mainly involved in locally advanced tumor stage. Inguinal MS altered LNs that are more typical of anal cancer than rectal cancer are not as common even in low-rectal cancer, but are a poor prognostic indicator. Although metastatic-altered LNs are basically larger than benign, reactive LNs, malignant disease may be present in very small LNs. Their size from 5 to 8 mm is highly susceptible to malignant changes, but additional morphological features must be taken into account, such as irregular contours and mixed signal intensity.

The craniocaudal localization of suspected MS altered LNs in relation to the tumor should also be taken into account, as well as their distance to the circulatory resection margins [12].

In our results for N-staging, 36 tumors with 1, 2 or 3 lymph nodes were detected preoperatively with MRI, of which 15 were true positive, hence in stage N0 according to the pathohistology finding, and 21 findings were falsely positive. With MRI 46 tumors were not marked as N0 stage, of which 26 true negative, and 20 results were falsely negative.

The sensitivity and specificity of MRI in determining the N0 stage of rectal carcinoma was low, 36.6% and 48.8%, consequently. This is due to the fact that in N0 stage which covers up to 3 LNs the probability of MS being changed is lower, so there are also reactive LNs that can give false positive results, and to be interpreted as MS changed. MRI detected 20 tumors with 4, 5 or 6 lymph nodes, of which 7 were true positive, hence in stage N1 according to the pathohistology finding, and 13 findings were falsely positive. With MRI 62 tumors were not marked as stage N1, of which 13 were true negative, and 49 results were false negative.

The sensitivity and specificity of MRI in determining the N1 stage of rectal carcinomas were 35% and 79%, consequently.

MRI detected 4 tumors with 7, 8 or 9 lymph nodes, 3 of which were true positive, hence in stage N2 according to the pathohistology finding, one result was false positive. With MRI 78 tumors were not marked as stage N2, of which 9 were true negative, and 69 results were false negative.

The sensitivity and specificity of MRI in determining the N2 stage of rectal carcinomas was 25% and 98.6%, respectively.

These results are a direct indication that the sensitivity and specificity of MR in preoperative N staging is increasing at a more advanced stage-N1 and N2, which is in line with the results published in world literature where sensitivity varies from 35 to 70% and specificity from 67% to 95% depending on the stage N of the disease [16].

Of great importance is the positive, direct correlation found between the MR finding and the pathohistology finding in relation to N staging (R=0.548). The higher N stage determined by MR corresponded to a higher N stage than the pathohistology finding, and vice versa. For a value of $p<0.0001$, this correlation was statistically significant.

No intravenous contrast medium was used in our study, so DWI with T2 pulse sequences were used for nodal staging.

The literature has shown that using only the DWI pulse sequence for the more advanced nodal stage has moderate sensitivity (67%-78%) and specificity (60%-67%), but the combination with the T2 pulse sequence indicates an increase in sensitivity and specificity in the nodal staging [16].

The latest global trends are aimed at using lymph node-specific contrast agents: ultrasmall supermagnetic iron oxide (USPIO).

It is an iron nanoparticle that is taken from normal cells and reduces the signal intensity of normal cells to the T2 pulse sequence. Because MS modified LNs do not

take on these iron nanoparticles, they look brighter-more hypersensitive than benign non-metastatic LNs. Thus, the sensitivity and specificity of N-staging is increased to 60%-100% and 94%-99%, respectively [17]. Another intravenous contrast medium used recently in world centers is GADOFOSVESET, which is a form of gadolinium and is reversibly bound to albumin; it has a long intravascular half-life. Normal and reactive LNs take Gadofosvest and show hypersignal as well as blood vessels while malignant infiltrated LNs have hyposignal characteristics, thus differing from normal ones in favor of promising results [18].

Conclusion

Magnetic resonance imaging methods is a gold standard for preoperative rectal cancer staging because it is highly precise for detection of transmural tumor invasion, invasion of the mesorectal fascia, involvement of adjacent organs, insight into nodal status, and visualization of a positive extra mural vascular invasion. Nodal staging with MRI is important for the decision of further treatment of rectal cancer. Also, MRI shows a good accuracy (of 43% to 85%) for N staging.

Conflict of interest statement. None declared.

References

1. Kosinski L, Habr-Gama A, Ludwig K, Perez R. Shifting concepts in rectal cancer management: a review of contemporary primary rectal cancer treatment strategies. *CA Cancer J Clin* 2012; 62: 173-202.
2. Bipat S, Glas AS, Slors FJ, *et al*. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging-a meta-analysis. *Radiology* 2004; 232: 773-783.
3. Adam IJ, Mohamdee MO, Martin IG, *et al*. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994; 344: 707-711.
4. Intven M, Reerink O, Philippens ME. Dynamic contrast enhanced MR imaging for rectal cancer response assessment after neo-adjuvant chemoradiation. *J Magn Reson Imaging* 2014 Aug 14 [Epub ahead of print].
5. Gollub MJ, Gultekin DH, Akin O, *et al*. Dynamic contrast enhanced-MRI for the detection of pathological complete response to neoadjuvant chemotherapy for locally advanced rectal cancer. *Eur Radiol* 2012; 22: 821-831.
6. Suzuki C, Torkzad MR, Tanaka S, *et al*. The importance of rectal cancer MRI protocols on interpretation accuracy. *World J Surg Oncol* 2008; 6: 89.
7. Mannaerts GHH, Rutten HJT, Martijn H, Hanssens PEJ, Wiggers T. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. *Diseases of the Colon and Rectum* 2001; 44(12): 1749-1758.
8. Peschaud F, Cuenod CA, Benoist S, *et al*. Accuracy of magnetic resonance imaging in rectal cancer depends on location of the tumor. *Dis Colon Rectum* 2005; 48: 1603-1609.
9. Tang R, Wang JY, Chen JS, *et al*. Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. *J Am Coll Surg* 1995; 180: 705-712.
10. Suzuki K, Muto T, Sawada T. Prevention of local recurrence by extended lymph-adenectomy for rectal cancer. *Surg Today* 1995; 25: 795-801.
11. Engelen SM, Beets-Tan RG, Lahaye MJ, *et al*. Location of involved mesorectal and extramesorectal lymph nodes in patients with primary rectal cancer: preoperative assessment with MR imaging. *Eur J Surg Oncol* 2008; 34: 776-781.
12. Saha S, Monson KM, Bilchik A, *et al*. Comparative analysis of nodal upstaging between colon and rectal cancers by sentinel lymph node mapping: a prospective trial. *Dis Colon Rectum* 2004; 47: 1767-1772.
13. Kim NK, Kim MJ, Park JK, *et al*. Preoperative staging of rectal cancer with MRI: accuracy and clinical usefulness. *Ann Surg Oncol* 2000; 7: 732-737.
14. Sagar PM, Pemberton JH. Surgical management of locally recurrent rectal cancer. *Br J Surg* 1996; 83: 293-304.
15. Shepherd NA, Baxter KJ, Love SB. Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. *J Clin Pathol* 1995; 48: 849-855.
16. Kim DJ, Kim JH, Ryu YH, *et al*. Nodal staging of rectal cancer: high-resolution pelvic MRI versus ^{18}F-FDGPET/CT. *J Comput Assist Tomogr* 2011; 35: 531-534.
17. Zhou J, Zhan S, Zhu Q, *et al*. Prediction of nodal involvement in primary rectal carcinoma without invasion to pelvic structures: accuracy of preoperative CT, MR, and DWIBS assessments relative to histopathologic findings. *PLoS ONE* 2014; 9: e92779.
18. Brown G, Richards CJ, Bourne MW, *et al*. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. *Radiology* 2003; 227: 371-377.