MRI-Pathology Agreement in Rectal Cancer: Real-World Data from a Prospective Rectal Cancer Registry

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Rezumat

Concordanța dintre IRM și examenul histopatologic în cancerul rectal: studiu prospectiv pe baza Registrului pentru Cancer Rectal

Introducere: Imagistica prin rezonanță magnetică (IRM) este utilizată în mod obișnuit în stadializarea preoperatorie a cancerului rectal. Concordanța stadializării IRM cu examenul histopatologic final, deși îmbunătățită, nu a ajuns încă la perfecțiune. Scopul acestui studiu este de a analiza gradul de concordanță dintre IRM și examenul histopatologic la pacienții operați de cancer de rect mediu/inferior.


Rezultate: În general, concordanța dintre IRM și examenul histopatologic în ceea ce privește stadiul T și stadiul N a fost de 64,7%, respectiv, 69,2%. Concordanța dintre IRM și examenul histopatologic în ceea ce privește stadiul T a fost de 62,7% pentru...
Background

Diagnostic staging of mid-low rectal cancer has achieved high levels of accuracy in recent years (1). Magnetic resonance imaging (MRI) of the pelvis has especially gained a central role in rectal cancer staging (2). Its accuracy has been shown to be between 31% and 100% in reporting the T stage and between 39% and 95% for nodal involvement (3). Scientific literature agrees in entrusting MRI with the ability to study the stage rectal cancer up to the point of planning surgical and chemoradiotherapeutic treatment based on the information obtained (4,5). According to the European Society for Medical Oncology (ESMO) clinical practice guidelines on rectal cancer, nCRT is recommended if the CRM is involved/threatened at MRI (6). The accuracy of MRI in rectal cancer has reached increasingly high levels, but this data is limited by the fact that the majority comes from patients enrolled in clinical trials (7,8). Nevertheless, the reliability of MRI outside of these settings is still unclear (9). We are missing a part of the ‘real world scenario’, which is rarely included in studies on pelvic MRI and rectal cancer.

In particular, the concordance between MRI staging and the final pathologic exam lack precise and reliable data. In addition, the accuracy of MRI in describing rectal cancer patient's state is far from being able to correlate with the pathology findings which raises questions about the accuracy of the real-life decision-making process during cancer boards.

Abstract

Introduction: Magnetic Resonance Imaging (MRI) is routinely used in preoperative rectal cancer staging. The concordance of MRI staging with final pathologic exam, albeit improved, has not yet reached perfection. The aim of this study is to analyze the agreement between MRI and pathologic exam in patients operated on for mid-low rectal cancer.

Material and Method: Patients undergoing neoadjuvant chemoradiation therapy (nCRT) or upfront surgery were analyzed. Between January 2019 to December 2019, 140 patients enrolled in the AIMS Academy rectal cancer registry were analyzed. Sixty-two patients received nCRT and 78 underwent upfront surgery.

Results: Overall, the agreement between MRI and pathologic exam on T stage and N stage were 64.7% and 69.2%, respectively. The agreement between MRI and pathologic exam on T stage was 62.7% for patients who did not receive nCRT and 67.4% for patients who received nCRT (p = 0.62). The agreement on N stage was 76.3% for patients who did not receive nCRT and 60.0% for patients who received nCRT (p = 0.075).

Conclusions: Real-world data shows MRI is still far from being able to correlate with the pathology findings which raises questions about the accuracy of the real-life decision-making process during cancer boards.

Key words: Magnetic Resonance Imaging, rectal cancer, neoadjuvant chemoradiation therapy
after radiation therapy seems to decrease when inquired (10,11).

This study aims to analyze the concordance of MRI data with the pathology report of patients undergoing surgery for rectal cancer in a large multicenter population and to compare this concordance between patients who received nCRT and patients who underwent upfront surgery.

**Materials and Method**

After approval by the local ethic committees, patients enrolled in the AIMS Academy rectal cancer registry who underwent preoperative MRI were analyzed. All patients enrolled in the registry sign a written informed consent for trial participation. The Advanced International Mini-Invasive Surgery (AIMS) academy clinical research network was conceived to create a rectal cancer registry to prospectively collect data of consecutive patients operated on for rectal cancer in high volume colorectal surgical units in Northern Italy. Each of the six enrolling centers follows similar guidelines for the preoperative, intraoperative, and postoperative management of patients. Inclusion criteria for enrollment were: 1) histologically proved adenocarcinoma of the rectum; 2) patient aged > 18 years old; 3) indication for surgical resection with curative intent. Exclusion criteria were emergency surgery, palliative operation, metastatic disease at presentation, or inability to perform a MRI scan (13). To be included in the AIMS registry, each center must perform at least 30 rectal resections per year, must have dedicated radiologists for rectal MRI, and discuss every rectal cancer case within an ad hoc multidisciplinary cancer board.

The first aim of the study was to assess the concordance between MRI data and the pathology report. The second aim is to compare this concordance between patients who received a nCRT and patients who underwent upfront surgery. Matched MRI and microscopic pathological collected parameters are listed in Table 1.

Rectal cancer treatment was approached according to NCCN guidelines (13). Preoperative assessment consisted of colonoscopy, CT scan of chest, abdomen, and pelvis, endorectal ultrasound, and pelvic MRI. All patients performed MRI in the enrolling centers.

Indication for nCRT was given after a multidisciplinary board discussion at the local institutions according to the NCCN Guidelines, and it is not questioned in this study (14).

In patients who did not receive nCRT, preoperative MRI data were compared with the pathology report, while restaging MRI data were used in patients who received nCRT. MRI imaging was performed according to the indication provided by Institute of Cancer Research, Sutton, Surrey, UK (15). The pathological classification was assessed according to AJCC TNM stage (8th edition) (16). A pathological complete response (pCR) was defined as absence of adenocarcinoma cells in the surgical specimen (ypT0N0M0).

**Statistical Analysis**

Baseline patients’ characteristics are presented stratified by neo-adjuvant therapy status. Counts and percentages were used to summarize categorical variables, medians, and ranges to summarize continuous variables. Comparisons between the two independent strata were made through either a Chi-squared test for proportions or a Wilcoxon test for medians.

For categorical variables, the agreement between MRI and pathologic examination was evaluated through the percentage of agreement, defined as the sum of all valid concordant observations divided by the sum of

<table>
<thead>
<tr>
<th>MRI parameters</th>
<th>Pathological examination parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade of tumor response</td>
<td>Dworak grade</td>
</tr>
<tr>
<td>Involvement of the mesorectal fascia</td>
<td>Involvement of the mesorectal fascia</td>
</tr>
<tr>
<td>Involvement of small extramural veins</td>
<td>Infiltration: venous</td>
</tr>
<tr>
<td>T - MRI</td>
<td>T - Histology</td>
</tr>
<tr>
<td>N - MRI</td>
<td>N - Histology</td>
</tr>
<tr>
<td>Stage – MRI</td>
<td>Histology Stage</td>
</tr>
</tbody>
</table>
all valid observations. Differences between strata were evaluated by a Chi-square test. All the analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Of the 143 patients included from the AIMS Academy rectal cancer registry between January 1st and December 31st, 2019, three did not perform MRI due to claustrophobia and were excluded, sixty-two (44%) patients underwent nCRT, and seventy-eight (56%) underwent upfront surgery. Patients’ characteristics are described in Table 2. There was no statistically significant difference between the two groups in sex, age, BMI, ASA score, and tumor stage. The upper rectal cancers rate was higher in the upfront surgery group since upper rectal tumors are excluded from nCRT. 5 patients had undergone prior rectal surgery for hemorrhoids which did not change the clinical treatment for rectal cancer.

Overall, the agreement between MRI and pathologic exam on T stage and N stage were 64.7% (91/140) and 69.2% (97/140), respectively. In particular, the agreement rate between MRI and pathologic exam were 62.7% (37/59) for upfront surgery patients who did not receive nCRT and 67.4% (29/43) for patients who received nCRT (p = 0.62 for T stage), and 76.3% (45/49) and 60.0% (27/45) (p = 0.075) for N stage.

The T stage was understaged at MRI in the 23.7% (14/59) and overstaged in the 13.6% (8/59) of upfront surgery patients (no nCRT), while was understaged in the 9.3% (4/43) and overstaged in the 23.3% (10/43) of patients who receive nCRT.

The N stage was understaged at MRI in 10.2% (6/59) and overstaged in 13.6% (8/59) of upfront surgery patients (no nCRT), while was understaged in 8.9% (4/45) and overstaged in 31.1% (14/45) of patients who received nCRT.

The concordance between MRI tumor regression grade and Dworak tumor regression grade after nCRT was 74.3% (26/35), with 17.1% (6/35) underestimate and 8.6% (3/35) overestimate rates at the MRI. MRI-pathology concordance about the small extramural veins involvement was 77.8% (35/45) in upfront surgery patients (no nCRT) with 15.6% (7/45) underestimate and 8.6% (3/45) overestimate rates, and 59.1% (13/22) in patients who receive nCRT, with 36.3% (8/22) underestimate and 4.5% (1/22) overestimate rate (p=0.11).

There were no (0/35) MRI underestimation and 2.9% (1/35) overestimation of the free circumferential margin in upfront surgery patients (no nCRT), while there were no (0/20) underestimation and 25% (5/20) overestimation in patients who received nCRT. Results are reported in Table 3.

Discussion

The presented data show a concordance between MRI and pathologic exam lower than the one reported by clinical trials (17,18). Displaying a gap between a clinical trial and “real world setting” despite, the enrolling centers are participating in a rectal cancer registry with established and controlled qualitative criteria. The low concordance rate between MRI and pathologic examination is a
Table 3. Accuracy of MRI with respect to pathological examination

<table>
<thead>
<tr>
<th>Neo-adjuvant</th>
<th>MRI</th>
<th>Missing data</th>
<th>Histology</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 78)</td>
<td>MRI</td>
<td>Missing data</td>
<td>Tis-T1</td>
<td>T2</td>
</tr>
<tr>
<td>T1 SM 1-2-3</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>0</td>
<td>1</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>T3 a-b-c</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>T4a</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>T4b</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>12</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>Yes (n = 62)</td>
<td>MRI</td>
<td>Missing data</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>T1 SM 1-2-3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>T3 a-b-c</td>
<td>2</td>
<td>1</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>T4a</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>T4b</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>8</td>
<td>16</td>
<td>31</td>
</tr>
</tbody>
</table>

No neoadjuvant: understaged 14/59 (23.7%), overstaged 8/59 (13.6%)
Neoadjuvant: understaged 4/43 (9.3%), overstaged 10/43 (23.3%)

<table>
<thead>
<tr>
<th>N stage</th>
<th>Histology</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 78)</td>
<td>MRI</td>
<td>Missing data</td>
</tr>
<tr>
<td>N0</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>N+</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Yes (n = 62)</td>
<td>MRI</td>
<td>Missing data</td>
</tr>
<tr>
<td>N0</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>N+</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>42</td>
</tr>
</tbody>
</table>

No neoadjuvant: understaged 6/59 (10.2%), overstaged 8/59 (13.6%)
Neoadjuvant: understaged 4/45 (8.9%), overstaged 14/45 (31.1%)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 78)</td>
<td>MRI</td>
<td>Missing data</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Stage 2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Yes (n = 62)</td>
<td>MRI</td>
<td>Missing data</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>21</td>
</tr>
</tbody>
</table>

No neoadjuvant: understaged 11/58 (19.0%), overstaged 9/58 (15.5%)
Neoadjuvant: understaged 3/43 (7.0%), overstaged 17 (39.5%)
constant in all the parameters analyzed and raises serious interrogations regarding the value of MRI-based treatment decisions for patients with rectal cancer (19).

Our study reports an overall concordance of MRI preoperative findings and final pathology of 64.7% (66/102) for the T stage and 69.2% (72/104) for the N stage.

In 2017, Moreno et al. reported MRI to be 87% sensitive (95% CI: 81%-92%) and 75% specific (95% CI: 68%-80%) for T stage and 77% sensitive (95% CI: 69%-84%) and 71% specific (95% CI: 59%-81%) for lymph node involvement. With a 1-mm threshold, MRI can reach a sensitivity of 76% and a specificity of 88% in detecting the involvement of the
circumferential margin (20). Wei, Ming-Zhu et al. in a recent meta-analysis, reported MRI to have a global sensitivity of 81% (95% confidence interval (CI), 67%–90%), and a global specificity of 67% (95% CI, 51%–80%) in re-assessing T stage. Regarding re-assessing the N stage, the global sensitivity reported was 77% (95% CI, 65%–86%), and the global specificity was 77% (21). Our reported results do not compare favorably with the studies above, even if all participating centers have high-resolution MR scanners and a dedicated gastrointestinal MRI radiologist.

The agreement between MRI data and the final pathologic exam does not seem to significantly differ between patients receiving nCRT and patients undergoing upfront surgery for rectal cancer in our multicenter sample. Regarding the agreement in detecting lymph nodes metastasis, the concordance between the MRI and the pathology findings was better in the group of patients not receiving nCRT. This difference, although not significant, could be exacerbated by the increase in the enrolled cases. It is known in fact that MRI accuracy for irradiated tissues is more difficult and particularly affected by an alteration of the MRI signal. De Jong et al. concluded in a recent meta-analysis that MRI has a poor ability to truly exclude nodal involvement in case of negative test results in irradiated patients, adding that the false-negative rate is therefore too high to alter the operative approach (22). Low agreement level between the restaging MRI and pathologic exam regarding lymph node involvement should be taken into serious consideration given its importance in detecting possible complete response (23).

Analogous is the ability of MRI found to describe tumor involvement of extramural veins. Unfortunately, data on venous infiltration were not uniformly present in radiological reports. As stated by Chung et al., the MRI parameters might depend on the examiner, particularly in describing real-life data (24).

A recent study by Ang Z. et al. retrospectively compared MRI and pathologic data in 114 “real world” patients undergoing rectal surgery. The reported MRI accuracy was 56.6% for T stage and 55.8% for N stage (25). Prediction of extramural disease was reported as accurate in 51% of patients, while the negative circumferential resection margin was accurately predicted in 98.6% of patients. These results quite are in line with our finding, corroborating the hypothesis that the discrepancy in T and N staging between MRI and pathologic examination is an actual issue in real-world practice.

This study has several biases. The heterogeneity of the professional figures involved in radiological and pathologic reporting can certainly play a main role in determining the levels of accuracy here reported. Missing data is a clear source of concern, above all when data entry happened within a prospective registry. However, the problem of missing data must be emphasized. Speaking about real-world data and making them public can help us to realize how much the multidisciplinary and multicentric treatment of rectal cancer requires precision and dedication that is certainly not yet achieved. Excluding patients with incomplete data entry will certainly provide a more homogeneous sample, but it would not describe a real-world practice nor the enormous amount of work that still needs to be done, even within a rectal cancer registry. Updating and improving network experiences through continuous auditing will surely improve the level of diagnostic accuracy.

Another bias of this study is not to report the temporal distance between the end of nCRT, the restaging MRI and surgery. A tailored study on the timing of MRI and its accuracy in restaging rectal cancer should be performed.

Conclusion

In conclusion, our real-world data shows that, despite the known potentials, MRI is still far from being able to properly correlate with the pathologic findings, which raises questions about the accuracy of the real-life decision-making process during cancer boards.
Author’s Contributions
Mari G and Crippa J conceived the trial. Achilli P and Orig M. wrote the manuscript. Montroni I, Calini G and Maggioni D. revised the paper. Totis M, Tamini N, Oldani M, Cocozza E, Berselli M, Borroni G, Magistro C., Ferrari G., Petri R, Ziccarelli A, Crestale S, did the data collection. Bagnardi V.and Peveri G. did the statistical analysis. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest and Source of Funding
All authors declare that they have nothing to disclose. No funding was received for this trial. Because of the nature of the data collected, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Ethics of Approval
The trial was approved by the ethics committee of each hospital.

Data are Available

References