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REVIEW ARTICLE

# Non-Operative Management Versus Total Mesorectal Excision for Locally Advanced Rectal Cancer with Clinical Complete Response After Neoadjuvant Chemoradiotherapy: a GRADE Approach by the Rectal Cancer Guidelines Writing Group of the Italian Association of Medical Oncology (AIOM)

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## Abstract

**Background** The standard approach for locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME). After nCRT 20% of patients achieve a clinical complete response (pCR) and could be treated with a non-operative management (NOM).

**Methods** The panel of the Italian Association of Medical Oncology (AIOM) Guidelines on rectal cancer applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach addressing the following question: Should NOM vs. TME be used for patients with rectal cancer with clinical complete response after nCRT? Five outcomes were identified: disease-free survival (DFS), mortality, local recurrence, colostomy rate, and functional outcomes.

**Results** Nine studies were included in the analysis. A higher risk of disease recurrence was observed in the NOM group compared to the TME group (RR = 1.69, 95% CI 1.08, 2.64) on the other hand, we observed a slightly positive but not significant effect on mortality of NOM (RR = 0.82, 95% CI 0.46, 1.45). Patients in the NOM group were more likely to experience local recurrence (RR = 5.37, 95% CI 2.56, 11.27) and patients in the TME group were more likely to have a permanent colostomy (RR = 0.15, 95% CI 0.08, 0.29). Only one study evaluated functional outcomes. The overall certainty of evidence was rated as very low.

**Conclusions** NOM was found to correlate with a higher risk of local recurrence which did not translate in worse OS and a lower colostomy rate. Due to the paucity of evidences, no recommendations are possible. NOM remains an experimental treatment; thus, patients managed with NOM should be enrolled in clinical trials with a dedicated follow-up schedule.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s11605-020-04635-1) contains supplementary material, which is available to authorized users.

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**Keywords** GRADE · Rectal cancer · Metanalysis · Surgery · Neoadjuvant chemotherapy

## Introduction

Colorectal cancer (CRC) is the third leading cancer type and the third cause of cancer death worldwide. In the USA, 97,220 were diagnosed in 2018, with 50,630 estimated deaths.[1] In Italy, the incidence of CRC was 37,500 in 2017, with 13,210 estimated deaths.[2] About 35% of CRC are rectal tumors, and most of them are locally advanced at the time of diagnosis. The standard approach for locally advanced rectal cancer (LARC), defined as a lesion clinically staged as T3–4 or node positive, is neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME). The use of neoadjuvant therapy significantly reduces the rate of local recurrence compared to adjuvant therapy or optimal surgery alone.[3–5] After nCRT, up to 40% of patients show a poor pathological response, while about 20% achieve a pathological complete response (pCR). In the latest group, the TME surgery might represent an over-treatment, which is often associated with major postoperative complications and severe impairment of bowel function and quality of life.[6]

In 2004, Habr-Gama et al. proposed, for patients with a clinical complete response (cCR) after nCRT, a non-operative management (NOM), also named "watch-and-wait" approach.[7] With this approach, the survival outcomes were found to be comparable to radical surgery. Following this report, an increasing number of studies has been conducted to confirm the safety and feasibility of NOM. Current evidence suggests that patients treated with NOM are more likely to experience local recurrences (also named "tumor-regrowth"), but are successfully salvaged with radical surgery in approximately 90% of cases. Thus, NOM should include a strict follow-up with salvage surgery for patients who show a local regrowth. Overall, this approach seems to be associated with a disease-free and overall survival comparable to those of patients who receive a standard radical surgery and follow-up.[8–10] Despite these preliminary findings are encouraging, NOM is still considered an experimental approach. Concern about the watch and wait strategy relies on the lack of a clear definition of cCR, which is also inaccurately defined by the most used imaging techniques.[11] Further concerns rely on the wide discrepancy between the diagnosis of clinical and pathological response, on the yet non standardized follow-up schedule after NOM, and, finally, on the lack of randomized and multicenter controlled trials.[8]

The panel of the Italian Association of Medical Oncology (AIOM) guidelines on rectal cancer decided to address this relevant issue applying the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach[12] to summarize the evidence on NOM for patients with locally advanced rectal cancer who show a cCR after nCRT.

## Methods

### AIOM Clinical Practice Guideline Panel and Question Evaluated According to the GRADE Methodology

The panel of the AIOM clinical practice guideline on rectal cancer includes academic and community practitioners in medical oncology, radiation therapy, surgery, histopathology, and radiology. Every year, updated evidence-based guidelines are published on the AIOM website (www.aiom.it). Before that, guidelines are sent to external reviewers for further supervision. External reviewers for the AIOM clinical practice guideline on rectal cancer are physicians, chosen by the AIOM deputy members, from each of the following scientific organizations: AIOM, AIRO (Associazione Italiana di Radioterapia ed. Oncologia Clinica), SICCR (Società Italiana di Chirurgia Colo-Rettale), SIRM (Società Italiana di Radiologia Medica), SIMG (Società Italiana di Medicina Generale).

In this manuscript, we addressed the following question, formulated as PICO (population, intervention, comparator, important outcomes): Should NOM vs. TME be used for patients with rectal cancer with clinical complete response after nCRT?

To answer this question, five outcomes were identified. Four of them were considered as critical for decision-making: mortality, local recurrence, recurrences, and functional outcomes (i.e., incontinence); one outcome (i.e., colostomy rate) was considered to be important but not critical.

### Search Strategy and Selection of the Evidence

PubMed, Embase, and the Cochrane Library were searched up to March 29, 2018. The following keywords were considered: rectal neoplasm, chemoradiotherapy, surgery, organ sparing treatment, and TME. No date or language restriction was applied. Two reviewers independently evaluated titles and abstracts first, and then full text of all plausible studies retrieved in .pdf.

A cross-referencing from relevant studies and review articles on the topic was also conducted to confirm retrieval of all possible pertinent studies. The PRISMA flow-chart is reported in Fig. 1.

The included studies were required to compare NOM to TME for patients with LARC and cCR after nCRT. For each

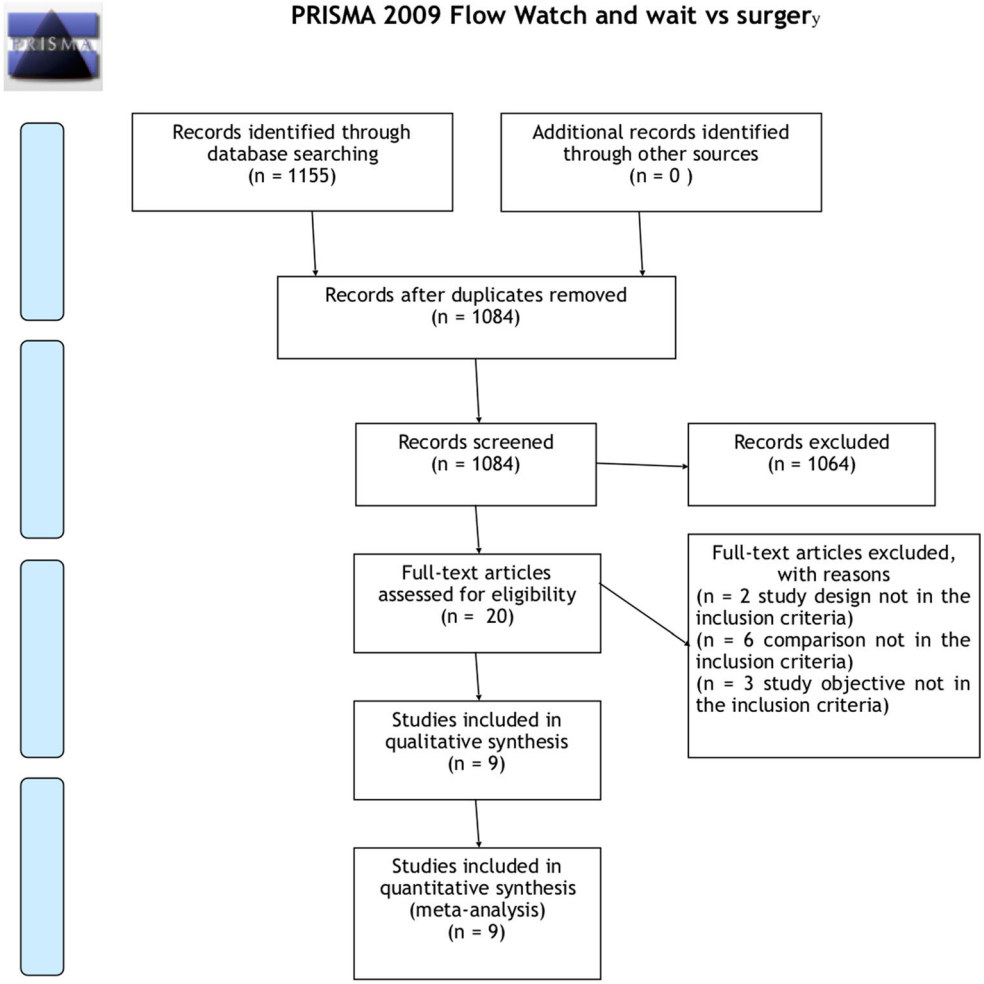



**Fig. 1** PRISMA flow diagram demonstrating results of literature search

eligible study, we collected information concerning study design, characteristics of included patients, and study results.

## Quality Evaluation of the Evidence

We used the GRADE approach to evaluate the quality of evidence.[13] Evidence concerning each considered outcome was thus judged based on its five specific domains: study limitations, inconsistency of results, indirectness of the evidence, imprecision, and publication bias. Evidence from randomized controlled trials started from a high quality and evidence that included observational data started from a low quality. The certainty of the evidence increased or decreased for the following reasons: study limitations of study methods and execution; inconsistency of results, when the body of evidence had inconsistent results but the reasons for the inconsistency could not be explained; indirectness, when indirect evidence was present, e.g., the population, interventions, or outcomes stated in the formulated question differed from the population, interventions, or outcomes found in the body of evidence; publication bias, when the body of evidence did not include all of the studies that should have been included (e.g., positive results only); imprecision, when the confidence intervals were sufficiently wide to consider an estimate consistent with either an important harm or an important benefit. Observational studies could be upgraded if a large magnitude of the treatment effect was present, if a dose response was present, or if the treatment effect persisted when plausible factors or biases working against the treatment were present.[13]

Overall, the certainty of evidence could be judged as high, moderate, low, or very low. Study limitations were assessed according to the Newcastle-Ottawa scale that included three items: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

The EtD framework (Supplementary Table) provided a transparent and structured approach to support the decision-making process.[14,15] It allowed to summarize the evidence in relation to the priority of the problem, the substantiality of the

desirable and undesirable effects, balance of the effects, certainty of evidence, patients' values and preferences, use of resources, equity, acceptability, and feasibility.

## Results

### Question: Should NOM vs. TME be Used for Patients with Rectal Cancer with cCR after Neo-adjuvant Chemoradiotherapy?

The search strategy returned 1084 records: 1064 were excluded by title and abstract, because they were not relevant for the purpose of the study. Twenty full-text articles were assessed for eligibility: 11 studies were excluded, leaving 9 studies that met the inclusion criteria and were included in the analysis (Fig. 1). The included studies were all observational cohort studies, comparing patients with rectal cancer achieving clinical complete response after nCRT, who underwent TME (control arm) or NOM (i.e., watch and wait) strategy (intervention or experimental arm). Patients in both the control and experimental arm were considered fit for surgery, and could then benefit of both types of treatment. The main characteristics of the included studies are summarized in Table 1. All of the included studies were set in high-volume, specialized centers; the number of participants ranged from 38[16] to 122.[8] The summary of our findings can be found in Fig. 2.

### Outcome of Benefit: Disease-Free Survival

Seven studies reported on DFS.[7–9,11,14,16,17] Overall, the rate of recurrence was 14.4% (32/222) in the NOM group, compared to 8.9% (28/314) in the TME group. One study showed that patients treated with NOM were approximately two times more likely to have a better DFS,[7] while six studies favored the TME group without reaching a statistical significance.[8,9,11,14,16,17] In the last study, DFS was reported to be statistically worse in the NOM compared to the surgery group.[9] Overall, a higher risk of disease recurrence was observed in patients who underwent NOM compared to those undergoing TME (RR = 1.69, 95% CI 1.08, 2.64) (Fig. 2a).

### Outcome of Harm: Mortality

Seven studies addressed mortality as an outcome.[7–10,14,16,17] Mortality was 5.17% (12/232 patients) in the NOM group and 7.27% (23/316 patients) in the TME group. Five studies reported a positive effect of NOM strategy with a RR ranging from 0.05 to 0.54,[7,8,10,14,17] while two reported a negative effect with a RR ranging from 1.31 to 7.13.[9, 16] Overall, NOM had a positive but not significant effect on mortality (RR = 0.82, 95% CI 0.46, 1.45) (Fig. 2b).

### Outcome of Harm: Local Recurrence

Nine studies reported on local recurrence.[7–11,14,16–18] A rate as high as 11.78% (31/263) of patients in the NOM group experienced a recurrence, compared to the 1.69% (6/354) of patients in the TME group. All the studies included in the analysis showed an advantage of TME over NOM with a RR ranging from 1.60 to 22.85. Overall, patients in the NOM group were more likely to experience local recurrence (RR = 5.37, 95% CI 2.56, 11.27) (Fig. 2c).

### Outcome of Harm: Definitive Colostomy

Six studies addressed colostomy rate as a negative outcome.[7,9,14,16–19] In the NOM group, the incidence of colostomy was 3.7% (7/190) compared to 28.08% (51/177) in the TME group. All studies favored the NOM over the TME group with a RR ranging from 0.02 to 0.38. Only 3 studies met statistical significance.[7,17,18] Overall, patients in the TME group were more likely to have a permanent colostomy compared to the NOM group (RR = 0.15, 95% CI 0.08, 0.29) (Fig. 2d).

### Functional Outcomes

The functional outcomes (fecal incontinence, bowel function, and sexual impotence) were evaluated only in one study which included 21 patients with cCR who underwent NOM.[17] Several items from the Memorial Sloan-Kettering Cancer Center bowel function questionnaire and the Wexner incontinence score were different between patients treated with TME and those who underwent NOM.[20,21] In particular, patients of the TME group showed impairment of bowel function after food intake, tended to use more often pads and colonic irrigation, to have less control over flatus and more changes in their bowel habits, compared to patients who underwent NOM

### Overall Quality of the Evidence

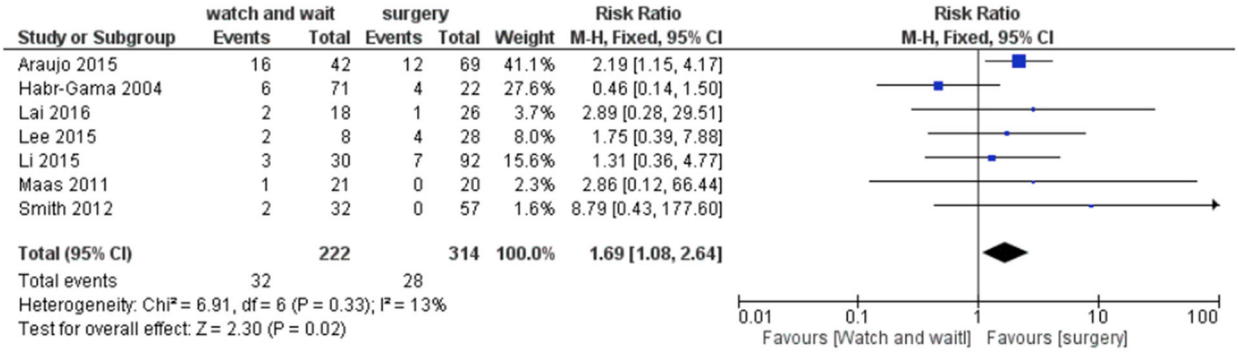
The overall certainty of evidence was rated as very low according to the GRADE approach. The risk of bias for the included studies was judged to be very serious due to the absence of a specific control of the confounding factors and to a not adequate follow-up period. Almost in all studies there was no description on the ascertainment of exposure and in the study by Maas et al. the control group was drawn from another cohort included in a previous prospective study of the same research group.[17] All studies, with the exception of Lai et al.,[14] received 0 stars for the comparability item: these studies were not controlled for any confounding factor. Almost in all studies the follow-up was short and there was no information on the lost to follow-up patients, which negatively impacted on

**Table 1** Main characteristics of the studies included in the analysis

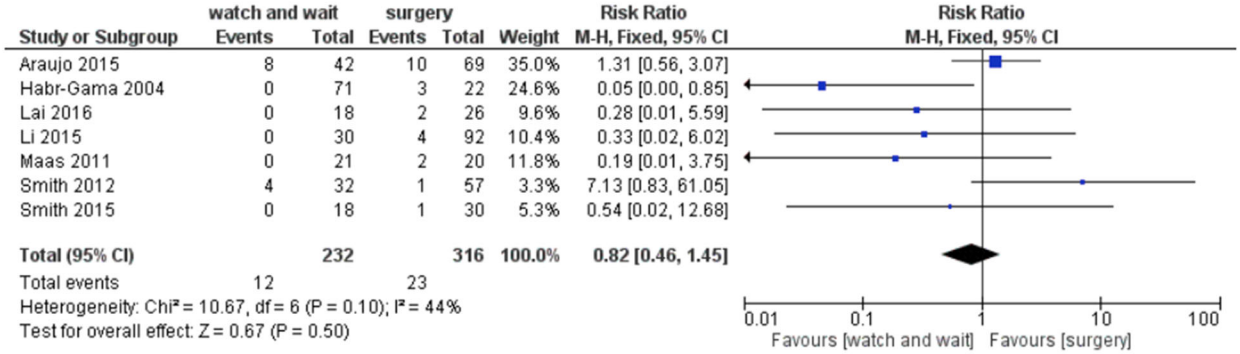
| Author, year | Study type | N. | | M:F | | Age (years) | | Distance from AV (mean, cm) | | cT (basal) | | cN (basal) | | Follow-up (months) | | CT regimen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | NOM | TME | NOM | TME | NOM | TME | NOM | TME | NOM | TME | NOM | TME | NOM | TME | |
| Araujo R.O. et a-l.,2015 | Retrospective | 42 | 69 | 17:25 | 34:35 | 60.1 | 63.6 | < 5(35) > 5 (7) | < 5 (41) > 5 (28) | N.R. | N.R. | N.R. | N.R. | 47.7 | 46.7 | Fluoropirymidine-based CT + local RT (45.0–50.4 Gy) |
| Li J. et a-l.,2015 | Prospective | 30 | 92 | 18:12 | 60:32 | 62 | 56 | 3.5 | 3.08 | T1 (3) T2 (5) T3 (15) T4 (7) | T1 (10) T2 (14) T3 (48) T4 (20) | N+ (16) | N+ (-5-3) | 58 | 58 | Not reported |
| Lee S.Y. et al., 2015 | Retrospective | 8 (NOM) + 16 (LE) | 28 | 7 + 11:1 + 5 | 21:7 | 70 | 64 | 4 + 2 (LE) | 4 | T2 (5 + 7) T3 (2 + 9) T4 (1 + 0) | T2 (6) T3 (21) T4 (1) | N+ (3 + 2) | N+ (-1-5) | 48 | 48 | Fluoropirymidine-based CT + local RT (50.4 Gy) |
| Seshadri R.A. et al., 2013 | Retrospective | 23 | 10 | 14:09 | 06:04 | 50 | 53 | 3 | 4 | T2 (9) T3 (14) | T2 (4) T3 (6) | N.R. | N.R. | 72 | 37 | Mitomycin C (6 mg/m$^2$) + 5FU (325 mg/m$^2$ × 5day) + local RT (50 Gy) |
| Smith J.D. et al., 2012 | Retrospective | 32 | 57 | 18:14 | 27:30 | 70 | 60 | 6 | 7 | T2 (10) T3 (22) | T2 (11) T3 (39) | N+ (18) | N+ (-3-1) | 28 | 42 | Systemic CT (non-specified) + local RT (45.0–56.0 Gy) |
| Smith R.K. et al., 2015 | Retrospective | 18 | 20 | 15:03 | 20:10 | 62.3 | 60.4 | 4.01 | 6 | T1 (1) T2 (1) T3 (16) | T2 (4) T3 (25) T4 (1) | N+ (7) | N+ (-1-2) | 68.4 | 46.3 | 5FU/capecitabine + local RT (dose non specified) |
| Maas M. et al., 2011 | Retrospective | 21 | 20 | 14:07 | 16:4 | 64.5 | 64.1 | 2.8 from ARJ | 3.4 from A-RJ | T1 (1) T2 (5) T3 (13) T4 (4) | T2 (1) T3 (17) T4 (2) | N0 (6) N1 (6) N2 (9) | N0 (-3) N1 (-6) N2 (-1-1) | 24.8 | 81.6 | Capecitabine 2 × 825 mg/mq + local RT (50.4 Gy) |
| Lai C.L. et al., 2016 | Retrospective | 18 | 26 | 15:03 | 12:14 | 67.6 | 63.8 | 3.35 from D.L. | 4.81 from D.-L. | N.R. | N.R. | N+ (7) | N+ (-1-8) | 49.9 | 42.3 | 5FU 350 mg/m$^2$/day × 1 day + leucovirin 10 mg/mq/day × 5 + 5 days + local RT (45 Gy or 54 Gy) |
| Habr-Gama A. et al., 2004 | Retrospective | 71 | 22 | 36:35 | 12:10 | 58.1 | 53.6 | 3.06 | 3.08 | T2 (14) T3 (49) T4 (8) | T2 (1) T3 | N+ (16) | N+ (-6) | 57.3 | 48 | 5FU 425 mg/mq/day and colonic acid 20 mg/mq/day × 3days + local |

**Table 1** (continued)

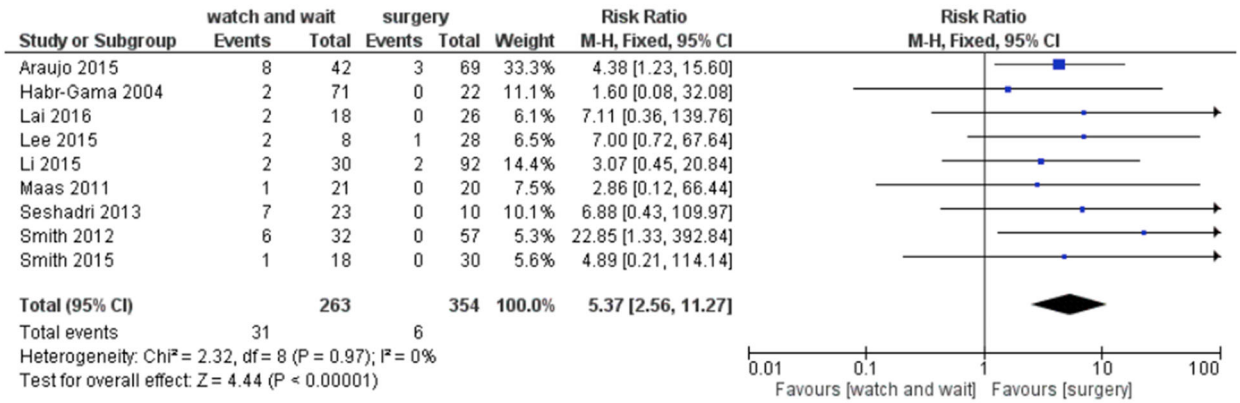
| Author, year | Study type | N. | | M:F | | Age (years) | | Distance from AV (mean, cm) | | cT (basal) | | cN (basal) | | Follow-up (months) | | CT regimen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | NOM | TME | NOM | TME | NOM | TME | NOM | TME | NOM | TME | NOM | TME | NOM | TME | |
| | | | | | | | | | | | (19)<br>T4 (2) | | | | | RT (50.4 Gy) |


watch and wait
surgery
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Araujo 2015 16 42 12 69 41.1% 2.19 [1.15, 4.17]
Habr-Gama 2004 6 71 4 22 27.6% 0.46 [0.14, 1.50]
Lai 2016 2 18 1 26 3.7% 2.89 [0.28, 29.51]
Lee 2015 2 8 4 28 8.0% 1.75 [0.39, 7.88]
Li 2015 3 30 7 92 15.6% 1.31 [0.36, 4.77]
Maas 2011 1 21 0 20 2.3% 2.86 [0.12, 66.44]
Smith 2012 2 32 0 57 1.6% 8.79 [0.43, 177.60]
Total (95% CI) 222 314 100.0% 1.69 [1.08, 2.64]
Total events 32 28
Heterogeneity: Chi² = 6.91, df = 6 (P = 0.33); I² = 13%
Test for overall effect: Z = 2.30 (P = 0.02)
0.01 0.1 1 10 100
Favours [Watch and wait] Favours [surgery]

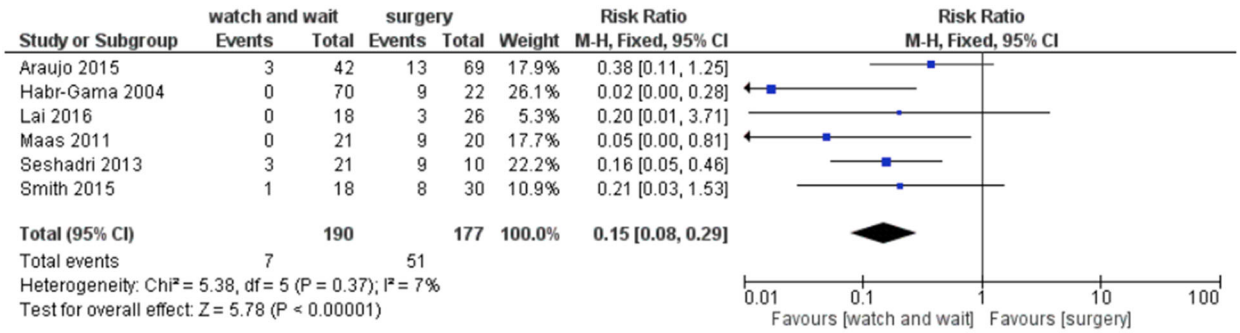
**a**


watch and wait
surgery
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Araujo 2015 8 42 10 69 35.0% 1.31 [0.56, 3.07]
Habr-Gama 2004 0 71 3 22 24.6% 0.05 [0.00, 0.85]
Lai 2016 0 18 2 26 9.6% 0.28 [0.01, 5.59]
Li 2015 0 30 4 92 10.4% 0.33 [0.02, 6.02]
Maas 2011 0 21 2 20 11.8% 0.19 [0.01, 3.75]
Smith 2012 4 32 1 57 3.3% 7.13 [0.83, 61.05]
Smith 2015 0 18 1 30 5.3% 0.54 [0.02, 12.68]
Total (95% CI) 232 316 100.0% 0.82 [0.46, 1.45]
Total events 12 23
Heterogeneity: Chi² = 10.67, df = 6 (P = 0.10); I² = 44%
Test for overall effect: Z = 0.67 (P = 0.50)
0.01 0.1 1 10 100
Favours [watch and wait] Favours [surgery]

**b**


watch and wait
surgery
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Araujo 2015 8 42 3 69 33.3% 4.38 [1.23, 15.60]
Habr-Gama 2004 2 71 0 22 11.1% 1.60 [0.08, 32.08]
Lai 2016 2 18 0 26 6.1% 7.11 [0.36, 139.76]
Lee 2015 2 8 1 28 6.5% 7.00 [0.72, 67.64]
Li 2015 2 30 2 92 14.4% 3.07 [0.45, 20.84]
Maas 2011 1 21 0 20 7.5% 2.86 [0.12, 66.44]
Seshadri 2013 7 23 0 10 10.1% 6.88 [0.43, 109.97]
Smith 2012 6 32 0 57 5.3% 22.85 [1.33, 392.84]
Smith 2015 1 18 0 30 5.6% 4.89 [0.21, 114.14]
Total (95% CI) 263 354 100.0% 5.37 [2.56, 11.27]
Total events 31 6
Heterogeneity: Chi² = 2.32, df = 8 (P = 0.97); I² = 0%
Test for overall effect: Z = 4.44 (P < 0.00001)
0.01 0.1 1 10 100
Favours [watch and wait] Favours [surgery]

**c**


watch and wait
surgery
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Araujo 2015 3 42 13 69 17.9% 0.38 [0.11, 1.25]
Habr-Gama 2004 0 70 9 22 26.1% 0.02 [0.00, 0.28]
Lai 2016 0 18 3 26 5.3% 0.20 [0.01, 3.71]
Maas 2011 0 21 9 20 17.7% 0.05 [0.00, 0.81]
Seshadri 2013 3 21 9 10 22.2% 0.16 [0.05, 0.46]
Smith 2015 1 18 8 30 10.9% 0.21 [0.03, 1.53]
Total (95% CI) 190 177 100.0% 0.15 [0.08, 0.29]
Total events 7 51
Heterogeneity: Chi² = 5.38, df = 5 (P = 0.37); I² = 7%
Test for overall effect: Z = 5.78 (P < 0.00001)
0.01 0.1 1 10 100
Favours [watch and wait] Favours [surgery]

**d**

◀ **Fig. 2** **a** Statistic analysis: disease-free survival (DFS). **b** Statistic analysis: mortality. **c** Statistic analysis: local recurrence. **d** Statistic analysis: colostomy rate

the ability to draw conclusion on the outcomes of interest. In general, as potential confounding biases, patients in the NOM group were older than patients in the TME group, presented with tumors in better stages, and with lower tumors. The quality of the evidence was also downgraded for inconsistency for the outcomes "mortality" ($I^2 = 64\%$) and "DFS" ($I^2 = 32\%$). Moreover, due to the heterogeneity of the population included in the studies (Caucasian, Asian), we decided to downgrade the quality of evidence of all outcomes by one level for indirectness. The imprecision dimension was judged to be serious for mortality and DFS, due to the low number of events.

## Discussion

The current study aimed to answer the following clinical question: "Should NOM vs. TME be used for patients with rectal cancer with cCR after nCT?" Using the GRADE approach, the panel of the AIOM guidelines on rectal cancer assessed the current available literature in order to define the safety of a non-operative approach to patients with LARC (Fig. 3). Compared with the surgery group, the evidences that NOM patients have a better overall and disease-free survival are very low and not powerful enough to be conclusive; on the opposite, there is strong evidence that NOM patients have a higher risk of local recurrence compared to patients treated with TME. Why a higher rate of local recurrence does not translate in worse OS may depend to the ability to perform a strict follow-up allowing an early diagnosis of regrowth and a consequent successful salvage surgery.

The analysis of the NOM strategy is challenging because many aspects of this approach are not standardized, making the comparisons between studies difficult. Candidate to NOM are patients with a cCR after neoadjuvant therapy; however, methods to define cCR and definition itself vary widely. Likely, cCR cannot be defined solely by a single diagnostic test[11] and, according to the most accredited definitions, digital rectal examination, proctoscopy, and pelvic MRI are widely recommended.[7,22,23] A further potentially confounding aspect is that cCR does not equal pCR. Up to 75% of patients considered to have a cCR show residual cancer in the surgical specimen,[24] and about one-third of patients with a cCR experiences recurrence (either local or distant) at 2 years.[25] Most of these considerations support the need of a wide and accepted standardized approach and suggest caution to extend NOM to low-volume or non-specialized centers, which could fail to guarantee adequate follow-up and salvage surgery. As expected, the percentage of definitive stoma was significantly higher in the surgery group, compared to the NOM group, either because a definitive stoma is part of standard surgical procedures (i.e., abdominoperineal resection) or because the number of patients whose protective stoma is never reversed is higher than expected. As concern as the functional and quality of life outcomes, only the study by Maas et al.[17] showed an advantage in the perceived quality of life for patients treated with a conservative approach. In particular, the authors reported significant difference in bowel function between the NOM and the surgery groups, qualified as symptoms triggered by food intake, need of pads and colonic irrigation, fecal incontinence, and higher defecation frequency. The scarcity of data related to the bowel function and quality of life does not allow drawing conclusions on this aspect. Finally, none of the

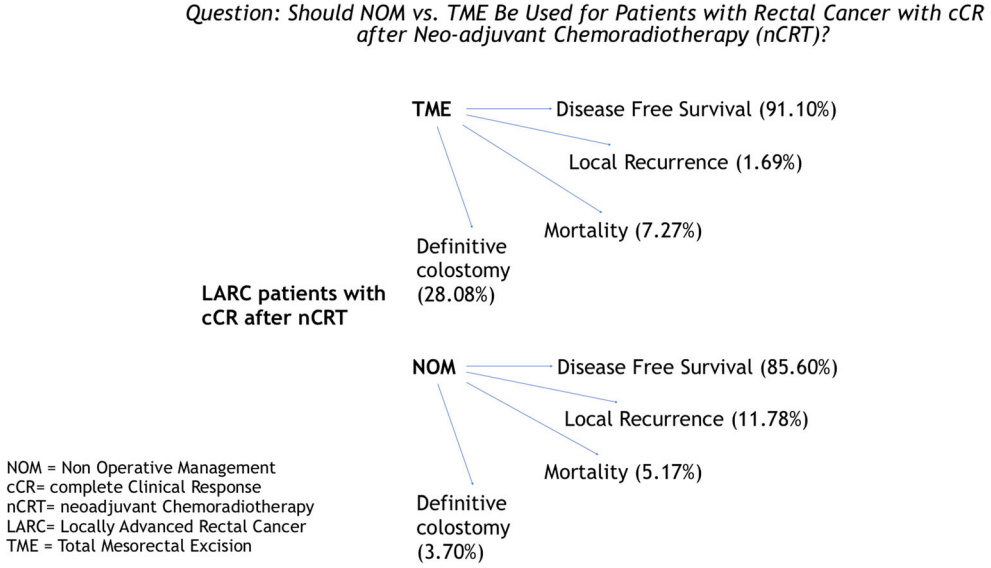



**Fig. 3** Summary of the findings: outcomes vs. complications

studies considered colostomy-free survival, which was chosen as a relevant outcome. To our knowledge, this is the first GRADE-based assessment of clinical studies on NOM. The GRADE approach represents a systematic method to determine the certainty of evidence and strength of recommendations, providing structured, transparent, and comprehensive criteria to judge the quality of available studies. This method guarantees impartial, reliable results, which can be confidently used to draw guidelines. Several limitations need to be considered when interpreting the results. The quality of evidence resulted to be very low, for the following reasons. First, the studies we considered were retrospective cohort studies, some with a low sample size. No data were available on preoperative treatment and postoperative follow-up, except for the study by Maas et al..[17] The study by Smith et al.[16] considered patients with stage I rectal cancer, who are not usually selected for nCT (i.e., indirectness). It should be noticed, moreover, that it is methodologically difficult to find a good comparative group of patients; in fact, patients with a regrowth cannot be considered equivalent to pCR patients after TME surgery. Finally, the definition of cCR and the follow-up strategies were highly heterogeneous, thus making comparison between the studies difficult; false-positive and false-negative pCR findings should also be taken into account. Due to the paucity of evidences, no recommendations are possible. NOM remains an experimental treatment; thus, patients managed with NOM should be enrolled in clinical trials with a dedicated follow-up schedule.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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