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ORIGINAL RESEARCH

Is It Possible a Conservative Approach After Radiochemotherapy in Locally Advanced Rectal Cancer (LARC)? A Systematic Review of the Literature and Meta-analysis

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Abstract

Background Locally advanced rectal cancer is usually treated with a preoperative approach with radiochemotherapy followed by surgery. Patients obtaining a pathologic complete response have a very favorable long-term prognosis. This study was intended to assess whether major surgery can reduce tumor recurrences and prolong survival of patients with a complete response after radiochemotherapy.

Methods Computerized literature search was performed to identify relevant articles. Comparative studies reporting the outcomes of non-operative and operative management in patients after neoadjuvant treatment were reviewed. Data synthesis was performed using Review Manager 5.0 software.

Results Twelve non-randomized comparative studies with a total of 1812 patients were suitable for analysis. There was no significant difference in overall survival at 3 and 5 years (odds ratio [OR] 1.31; 95% CI 0.64–2.69; $p = 0.46$ and 1.48; 95% CI 1.00–2.20; $p = 0.50$) and in disease-free survival at 3 and 5 years (odds ratio [OR] 1.20; 95% CI 0.68–2.14; $p = 0.53$ and 1.22; 95% CI 0.86–1.74; $p = 0.26$, respectively) between locally advanced rectal cancer patients treated with and without operative approach.

Conclusions Major surgery does not seem to improve prognosis in patients obtaining a complete response after radiochemotherapy. Clinical trials, using clear criteria to identify complete response patients, are needed to recommend non-operative approach.

Keywords Rectal cancer conservative approach · Conservative approach · Radiochemotherapy

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Introduction

Locally advanced rectal cancer (LARC) is usually treated with neoadjuvant treatment followed by surgery. Patients with an intermediate risk for local recurrence (mid-rectal T3N0 or high- to mid-rectal N1 tumors) receive short-term radiotherapy preoperatively. Instead, patients with a high risk for local recurrence (an involved circumferential margin, N2 disease, and distal tumors) are treated with a long-term radiotherapy. When chemotherapy is added preoperatively, an increase of effectiveness of radiotherapy has been observed to obtain down-staging and down-sizing [1]. Six to 8 weeks after radiochemotherapy, standard treatment entails definitive surgery by low anterior resection (LAR) with total mesorectal excision (TME) or by abdominoperineal resection (APR) for all acceptable-risk patients regardless of the tumor response.

Nevertheless, literature data show that tumor response is a predictor of outcome. A multicenter study, analyzing a very large number of patients achieving a pathological complete response (pCR) after neoadjuvant treatment, shows that these patients have improved long-term outcomes regardless of their initial clinical T and N stages [2]. These results are confirmed by a recent meta-analysis [3, 4] suggesting that pCR might be indicative of a prognostically favorable biological tumor profile with better long-term outcomes. On the other hand, major surgical treatment of rectal cancer entails surgical complications (morbidity and mortality); the average perioperative mortality rate is 4%, but in the elderly, this rate increases from 10% [5] to 30% [6]. Therefore, a conservative approach of patients with clinical complete response could be an engaging approach [7] in order to avoid the risks associated with surgery, especially in elderly patients [8–10].

Several recent studies addressed the role of a conservative approach in this subset of patients, and none of these studies are randomized controlled trials. These results remain inconsistent, and overall assessment of the treatment effect is difficult principally due to the small sample size of each study. A meta-analysis is therefore required to provide an improved level of evidence on this subject and whether or not to continue research in this sector.

Methods

Selection of Studies

A computerized search of the literature was performed by searching MEDLINE, EMBASE, OVID, and Cochrane database from the time of inception to 2016. The following medical search headings (MeSH) "rectal cancer," "chemo-radiotherapy," "rectal surgery," "comparative studies" or "chemo-radiotherapy and local excision," "comparative study," and combinations of these were used, as were the keywords "conservative approach rectal cancer," "local excision rectal cancer," "radiotherapy-chemo pathological response." The computer search was supplemented with hand searches of reference lists for all available review articles, primary studies, meetings, abstracts, and bibliographies of books in order to identify other studies not found in the computer search. Only comparative clinical studies were included. The final inclusion of articles was determined by consensus between three authors (MB, MT, and FF); discrepancies among reviewers were infrequent (overall inter-observer variations < 10%) and were solved by discussion. These studies were analyzed on an intention-to-treat basis. When not reported in the trial, the response rate according to intention-to-treat was calculated. The present meta-analysis was performed by following recommendations of the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) Statement [11].

Criteria for Inclusion and Exclusion

Only studies comparing the outcomes of patients with LARC after neoadjuvant radiochemotherapy between non-operative and operative management were taken into consideration. Abstracts, letters, proceedings from scientific meetings, editorials, expert opinions, reviews without original data, case reports, studies lacking control groups, repetitive data, non-English language papers, and animal studies were excluded.

Review of the Trials

The trials were first reviewed using a list of predefined, pertinent issues concerning the characteristics of patients and treatments. To assess the methodological quality of studies, the methodological index for non-randomized studies (MINORS) was applied [12]. The following 12 items were evaluated for each study: a clearly stated aim, consecutive patients, prospective data collection, reported endpoints, unbiased outcome evaluation, adequate length of follow-up, loss to follow-up < 5%, ≥ 20 patients in each arm, adequate control group, contemporary groups, controls equivalent to cases, and adequate statistical analyses.

Statistical Methods

The meta-analysis was performed using the Review Manager ver. 5.0 (The Cochrane Collaboration, Software Update, Oxford). To combine the results from individual trial, we used the proportion of events observed in the treated and control groups. With these observed proportions of events, the odds ratio (OR) was computed for each study. The Mantel–Haenszel method was used to combine odds ratio with 95% CI for the outcomes of interest.

The effect of treatment on the defined outcome measures was calculated from the study data using models based on both fixed and random effects assumptions. In addition to within-study variance, the random effects model was considered heterogeneity among studies. Because of the different clinical settings and groups of subjects analyzed and because the tests for heterogeneity lacked statistical power due to the few studies included in this meta-analysis, we have presented the results of random effects models. Statistical heterogeneity between studies was evaluated using the Mantel–Haenszel χ^2 test [13]. Statistical significance was defined as $p < 0.05$.

Results

Characteristics of the Studies

The search of the literature yielded 305 citations (Fig. 1). Of these, 12 studies [14–25] met the inclusion criteria. Studies were included in the meta-analysis if they evaluated comparatively a conservative approach versus major surgery after neoadjuvant radiochemotherapy, if they included patients with resectable histologically proven rectal cancer without metastatic disease, and if overall survival was assessed as an outcome measure of the effect of the treatment. Decisions on which studies to include were taken blindly by the two reviewers (F.F. and M.M.). Disagreements were resolved by discussion. Excluded studies were identified with the reason for exclusion. Studies were excluded if they were non-comparative or if they were published as a preliminary report and subsequently published as a final paper. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis. The main features of the trials included in the meta-analysis are shown in Table 1.

These studies were published between 2004 and 2016, in seven countries. Only four studies were prospective trials. The analyzed population of each study varied greatly, ranging from 8 [14] to 473 [21] patients. All were non-randomized trials. The median MINORS score was 17 (range 10–23) as shown in Table 2. The 12 comparative studies included 1812 patients treated with neoadjuvant radiochemotherapy, 509 of whom received the conservative approach. In all studies, a similar surveillance period was reported and the median follow-up period ranged from 25 to 72 months. The inclusion criteria were uniform in all studies; even surgical patients were treated according to total mesorectal excision criteria in all but three studies [16, 18, 22].

3- and 5-Year Overall Survival

The effect of surgical approach on the 3-year overall survival (ten studies: 1779 patients, 188 deaths) is shown in Fig. 2a. Pooled analyses estimated that surgery was not associated with significant improvement in the 3-year overall survival (odds ratio [OR] 1.31; 95% CI 0.64–2.69; $p = 0.46$). Same results were obtained when a fixed effects model was used. Robust analysis showed that nine studies remaining after exclusion of either the trial did not change for 3-year overall survival. We performed a subgroup analyses to evaluate whether there was evidence of a different effect of major surgery with the different conservative approach. Analysis showed that the pooled OR for 3-year overall survival were, respectively, 0.79 (95% CI 0.21–2.96; $p = 0.73$) in patients treated with local surgery [14, 16] and 1.53 (95% CI 0.64–3.61; $p = 0.34$) in patients with only follow-up [15, 17–24]. A separate subgroup analysis was performed in relation to the nature of retrospective [15–18, 20, 21, 23] and prospective [14, 19, 22, 24] studies. Pooled OR were, respectively, 1.14 (95% CI 0.40–3.31; $p = 0.80$) in retrospective studies and 2.40 (95% CI 0.81–7.10; $p = 0.11$) in prospective studies, in favor of a conservative approach. Pooling trials with rate ≥ 50 and < 50% of pathological complete response in surgery group, we obtained a OR 0.67 (95% CI 0.27–1.64; $p = 0.38$) and a OR 2.01 (95% CI 0.69–5.82; $p = 0.20$). Finally, using MINORS quality score, we examined the difference between trials ≥ 20 [14, 17, 19, 22, 23] and < 20 [15, 16, 20, 21, 24], and no difference was found with OR 1.69 (95% CI 0.65–4.44; $p = 0.28$) and OR 1.26 (95% CI 0.31–5.01; $p = 0.75$).

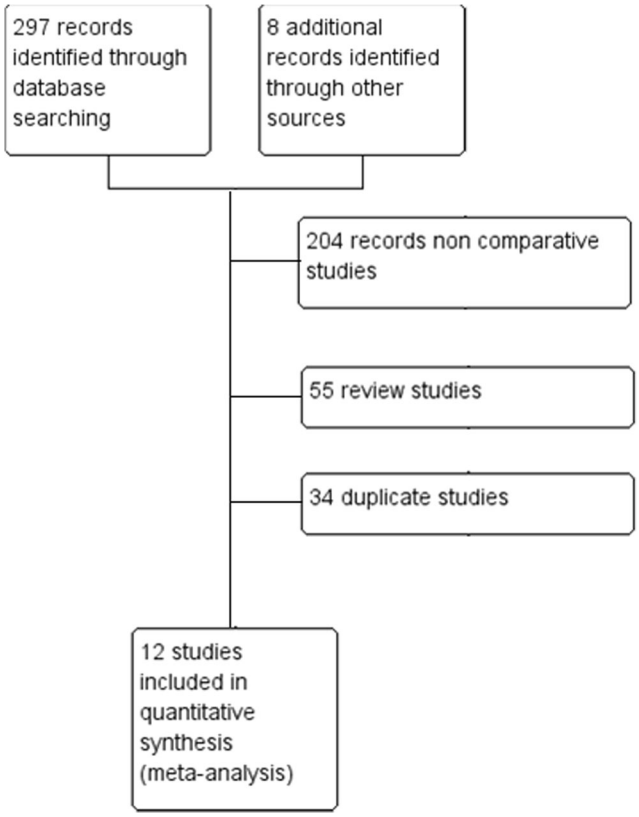


Fig. 1 Flowchart of the literature search and selection process

Five-year overall survival was reported in nine studies [14–17, 19–21, 23, 25] (1277 patients, 222 deaths). Major surgery was not associated with a significant improvement in 5-year overall survival (odds ratio [OR] 1.48; 95% CI 1.00–2.20; $p = 0.05$), as shown in Fig. 2b. In all the robust analyses, the pooled estimate of the treatment effect was not significant. The results of the 5-year overall survival did not differ according to different conservative approach, study design, MINORS quality score, rate of stage III disease in the study, and number of pathological response.

The funnel plots of the studies that reported 3- and 5-year OS analysis are shown in Fig. 3. Almost all studies lie inside

Table 1 Characteristics of clinical trials

First author	Country	Study period	Study design	Populations	Stage		Neoadjuvant therapy	cCR % in conservative approach	Median follow-up (months)		After RCT type of conservative approach (CA)	Type of surgery in c
					II	III			CA	S		
Araujo et al. [23]	Brazil	2002–2013	Retrospective	111	27	48	RT = 4500–5040 cGy 5FU or capecitabine +5FU	100	47.7	46.7	Observation	TME
Bonnen et al. [25]	USA	1990–2002	Retrospective	431	201 (46.6%)	230 (53%)	RT = 4500 + 750 cGy 5FU or capecitabine	89	42	32	Local excision	TME
Callender et al. [21]	USA	1990–2008	Retrospective	515	248 (48.2%)	267 (51.8%)	RT = 4500–5040 cGy 5FU	84	63	59	Observation	TME
Caricato et al. [14]	Italy	1997–2002	Prospective	30	5 (16.7%)	20 (67%)	RT = 5040 cGy 5FU and CDDP	37.5	37	48	Local excision	TME
Habr-Gama et al. [15]	Brazil	1991–2002	Retrospective	265	76%	24%	RT = 5040 cGy 5FU (425 mg/m^2)	100	57.3	48	Observation	TME
Habr-Gama et al. [20]	Brazil	2006–2010	Retrospective	68	43 (63%)	27 (39.7%)	RT = 5400 cGy 5FU	100	56	53	Observation	TME
Kundel et al. [16]	Israel	1997–2007	Retrospective	320	158 (53%)	100 (37.7%)	RT = 4500 cGy 5FU or capecitabine	100	48		Local excision	n.r.
Maas et al. [19]	Holland	2004–2010	Prospective	192	All patients locally advanced		RT = 5040 cGy capecitabine	100	25 ± 19		Observation	TME
Renehan et al. [22]	UK	2005–2013	Prospective-retrospective	357	92 (25.7%)	265 (74.2%)	RT = 4500 cGy 5FU or capecitabine	100	33		Observation	n.r.
Seshadri et al. [18]	India	1991–2008	Retrospective	291	All patients T3-T4 or N+		RT = 5040 cGy 5FU and MitoC	100	72		Observation	n.r.
Smith et al. [17]	USA	2006–2010	Prospective	89	All patients T3-T4 or N+		RT = 5040 cGy 5FU or capecitabine	100	42		Observation	TME
Smith et al. [24]	USA	2006–2014	Retrospective	145	Neoadjuvant therapy for stages I–III rectal cancer		n.r	100	39.6		Observation	TME

RT radiotherapy, *5FU* 5 fluorouracil, *cCR* clinical complete response, *TME* total mesorectal excision

Table 2 Scoring for the studies by the revised and validated version of MINORS

	Clearly stated aim	Consecutive patients	Prospective data collection	Reported endpoints	Unbiased outcome evaluation	Adequate length of follow-up	Loss to follow-up < 5%	≥ 20 patients in each arm	Adequate control group	Contemporary groups	Controls equivalent to cases	Adequate statistical analyses
Araujo et al. [23]	2	1	0	2	2	2	2	2	1	2	2	2
Bonnen et al. [25]	1	1	0	1	2	2	2	2	1	2	1	2
Callender et al. [21]	1	1	0	2	1	2	2	2	1	1	0	2
Caricato et al. [14]	2	1	2	2	2	2	2	0	1	2	2	2
Habr-Gama et al. [15]	2	1	0	2	1	2	2	2	2	1	1	1
Habr-Gama et al. [20]	1	1	0	2	1	2	2	2	1	2	1	1
Kundel et al. [16]	1	1	0	2	1	2	2	2	1	1	1	1
Maas et al. [19]	2	2	2	2	2	2	2	1	2	2	2	2
Renehan et al. [22]	2	2	2	2	2	2	2	2	1	2	1	2
Seshadri et al. [18]	0	1	0	1	1	2	1	0	1	1	1	1
Smith et al. [17]	2	2	2	2	2	1	2	2	1	2	1	1
Smith et al. [24]	0	1	0	1	0	1	2	2	2	2	2	0

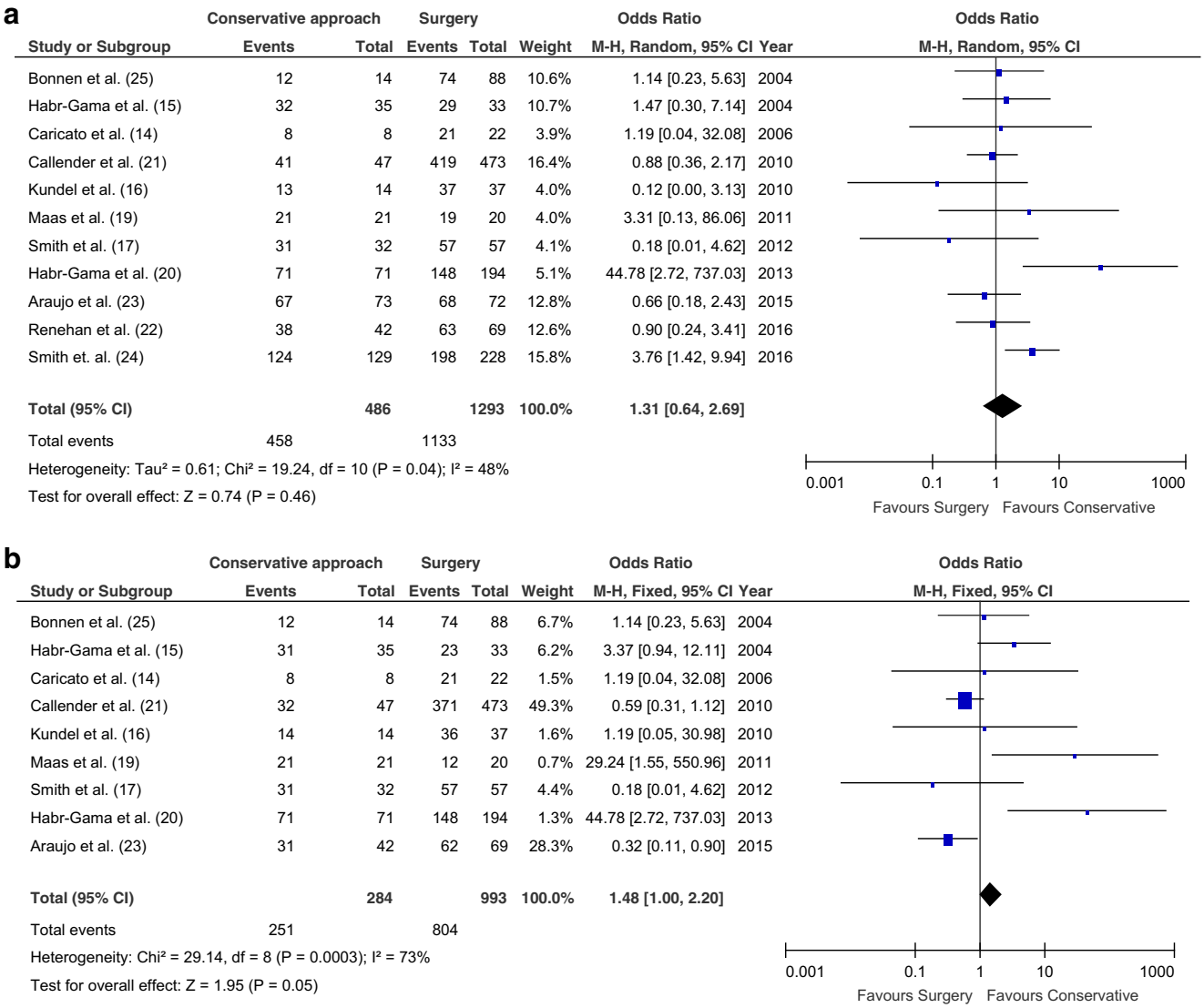


Fig. 2 Overall survival. **a** 3-year overall survival. Meta-analysis of 11 trials of conservative approach in LARC using a random effects model. **b** 5-year overall survival. Meta-analysis of nine trials of conservative approach in LARC using a random effects model. The odds ratio (OR) and 95% confidence interval (CI) for the effect of treatment on 3- and 5-year overall survival are shown on a logarithmic scale. Studies are arranged by publication year

the 95% CIs, with an even distribution around the vertical (Begg and Egger's test: $p = 0.869$ and 0.153, respectively), indicating no apparent publication bias. Under the random effects model for the 3- and 5-year OS analysis, using the trim-and-fill method and leave-one-out procedure, the results were unchanged.

3- and 5-Year Disease-Free Survival and Regrowth Rate

All studies reported on disease-free survival at 3 years (1812 patients, 1466 patients alive without disease). Pooled analyses showed that the difference was insignificant between the two groups OR 1.20; (95% CI 0.68–2.14; $p = 0.53$) as shown in Fig. 4a. Further, pooled analysis of studies provides information that OR of 5-year disease-free survival was also similar in the two groups (OR 1.22; 95% CI 0.86–1.74; $p = 0.26$) (Fig. 4b). In all the robust analyses, the pooled estimate of the treatment effect was not significant. The results of the 3- and 5-year disease-free survival did not differ according study design, rate of stage III disease in the study, and number of pathological response.

Globally, the mean regrowth rate in the patient with non-operative approach was 17.5%, as shown in Fig. 5. In all these patients, a definitive surgery was possible, allowing a similar long overall and disease-free survival rate. In Table 3, it is shown the used type of surgery for local re-growths. Most of these patients were treated with abdominoperineal resection (32.9%) or anterior resection (35.2%); however, no pelvic exenteration was described.

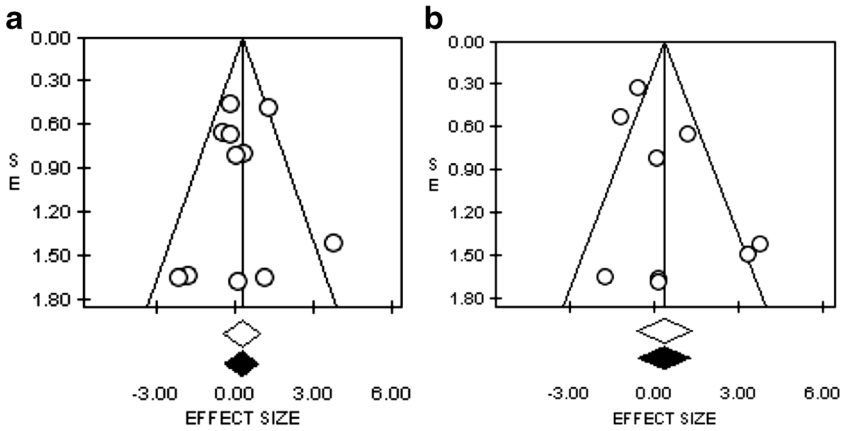


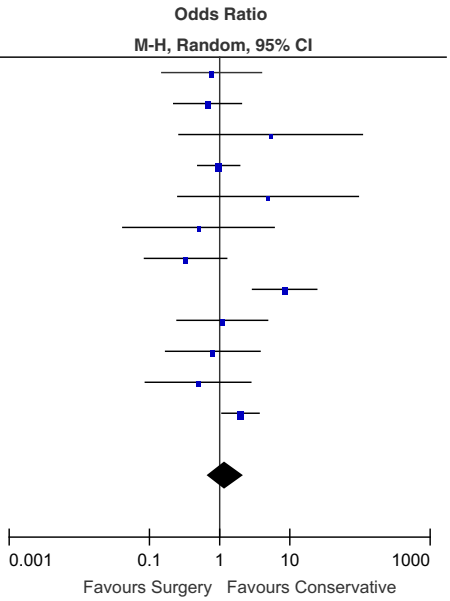
Fig. 3 Funnel plot for publication bias for 3- (**a**) and 5-year (**b**) overall survival

a

Study or Subgroup	Conservative approach Events	Total	Surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Bonnen et al. (25)	12	14	78	88	7.3%	0.77 [0.15, 3.95]	2004
Habr-Gama et al. (15)	25	35	26	33	10.7%	0.67 [0.22, 2.04]	2004
Caricato et al. (14)	8	8	17	22	3.0%	5.34 [0.26, 108.26]	2006
Callender et al. (21)	35	47	355	473	14.1%	0.97 [0.49, 1.93]	2010
Kundel et al. (16)	14	14	32	37	3.1%	4.91 [0.25, 94.75]	2010
Maas et al. (19)	19	21	19	20	4.1%	0.50 [0.04, 5.99]	2011
Smith et al. (17)	26	32	53	57	9.0%	0.33 [0.08, 1.26]	2012
Habr-Gama et al. (20)	67	71	129	194	11.1%	8.44 [2.95, 24.17]	2013
Seshadri et al. (18)	12	23	5	10	8.1%	1.09 [0.25, 4.82]	2013
Araujo et al. (23)	39	42	65	69	7.8%	0.80 [0.17, 3.76]	2015
Smith et. al. (24)	69	73	70	72	6.8%	0.49 [0.09, 2.78]	2016
Renehan et al. (22)	113	129	178	228	14.8%	1.98 [1.08, 3.65]	2016
Total (95% CI)		**509**		**1303**	**100.0%**	**1.20 [0.68, 2.14]**	
Total events	439		1027				

Heterogeneity: Tau² = 0.49; Chi² = 25.03, df = 11 (P = 0.009); I² = 56%

Test for overall effect: Z = 0.63 (P = 0.53)



b

Study or Subgroup	Conservative approach Events	Total	Surgery Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Habr-Gama et al. (15)	24	35	25	33	14.0%	0.70 [0.24, 2.03]	2004
Bonnen et al. (25)	10	14	73	88	9.9%	0.51 [0.14, 1.86]	2004
Caricato et al. (14)	8	8	17	22	0.9%	5.34 [0.26, 108.26]	2006
Callender et al. (21)	35	47	322	473	25.7%	1.37 [0.69, 2.71]	2010
Kundel et al. (16)	14	14	32	37	1.1%	4.91 [0.25, 94.75]	2010
Maas et al. (19)	19	21	13	20	2.2%	5.12 [0.91, 28.64]	2011
Smith et al. (17)	31	32	57	57	3.3%	0.18 [0.01, 4.62]	2012
Habr-Gama et al. (20)	54	71	129	194	28.7%	1.60 [0.86, 2.98]	2013
Araujo et al. (23)	35	42	65	69	14.2%	0.31 [0.08, 1.12]	2015
Total (95% CI)		**284**		**993**	**100.0%**	**1.22 [0.86, 1.74]**	
Total events	230		733				

Heterogeneity: Chi² = 13.74, df = 8 (P = 0.09); I² = 42%

Test for overall effect: Z = 1.13 (P = 0.26)

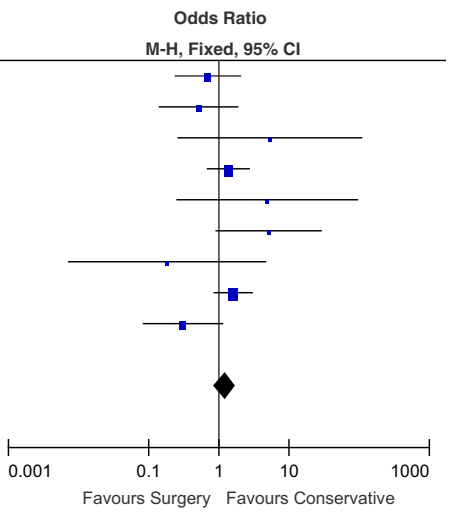


Fig. 4 Disease-free survival. **a** 3-year disease-free survival. Meta-analysis of 12 trials of conservative approach in LARC using a random effects model. **b** 5-year disease-free survival. Meta-analysis of nine trials of conservative approach in LARC using a random effects model. The odds ratio (OR) and 95% confidence interval (CI) for the effect of treatment on 3- and 5-year disease-free survival are shown on a logarithmic scale. Studies are arranged by publication year

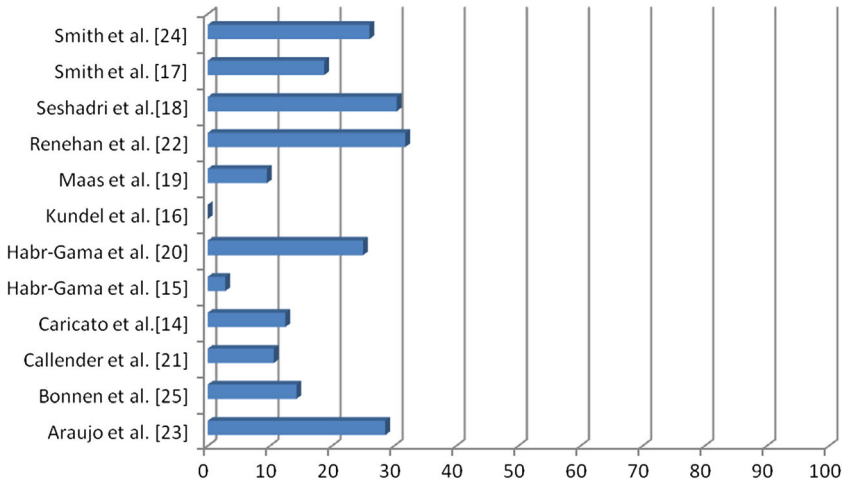


Fig. 5 Regrowth rate in patients treated conservatively

Discussion

In rectal cancer, current practice is to treat resectable patients with radical surgery regardless of the response to neoadjuvant therapy [26]. This study has investigated the key clinical question whether a clinical complete response after neoadjuvant treatment is sufficient to avoid a major surgery and to allow a conservative approach in locally advanced rectal cancer (LARC). In literature, it is clearly demonstrated that patients with complete response after neoadjuvant treatment have better long-term outcome than patients with little or no response [2, 3]. The pooled analysis by Maas et al. [3], on 3105 patients, shows an HR of 0.51 (0.38–0.67) and 0.44 (0.34–0.57) in favor of pathological complete response patients in overall survival and disease-free survival, respectively. The Italian multicenter study by Capirci et al. [2] analyzing 566 patients with a pathological complete response, identified in these patients a favorable group with 5-year rates of disease-free survival, overall survival, and cancer-specific survival of 85, 90, and 94%, respectively. From these studies, an important finding is that recurrences are in dependence on the postoperative ypT category; therefore, the prognosis of patients is related to radiation response and was independent of preradiation staging. Read et al. [27] have found that nodal metastases are rare in patients whose mural tumor burden shrinks to ypT0-1 after neoadjuvant radiotherapy. The same conclusions have been made in the study by Borschitz et al. [28] where the strongest prognostic factors are a complete response (ypT0) or responses on a submucosa level (ypT1). None of the ypT0 patients have had a local recurrence and only 4% developed metastases. A response at the submucosa level (ypT1) has been associated with local recurrence in 2% and with systemic progression in 7% of patients. Patients with residual tumor extending to the muscularis propria (ypT2) have shown a local recurrence and a systemic recurrence rate of 7% each, respectively. In view of these considerations, a non-operative approach in rectal cancer has a good rationale, avoiding morbidity associated with radical surgery in LARC patients after neoadjuvant treatment with a comparable oncological outcome.

This meta-analysis of studies provides a comprehensive aggregate analysis of this available evidence to date. Given that there are no randomized trials of conservative approach in LARC patients, the appropriate use of meta-analysis represents an important method to extract all possible information from existing data to examine the relative benefits and risks of conservative approach versus a major surgery [29].

Table 3 Patients with only local regrowth in non-operative arm and type of following surgery

First author	Patients with only local recurrence in conservative approach	Type of surgery in only local recurred patients
Araujo et al. [23]	5	3 APR 1AR 1 refused APR
Bonnen et al. [25]	2	2 LE
Callender et al. [21]	5	3 not specified surgery 2 refused surgery
Caricato et al. [14]	1	1 APR
Habr-Gama et al. [15]	2	1 LE 1 brachytherapy
Habr-Gama et al. [20]	4	2 AR 2 APR
Kundel et al. [16]	0	0
Maas et al. [19]	1	1 LE
Renehan et al. [22]	36	20 APR 8 AR 6 others
Seshadri et al. [18]	7	n.r.
Smith et al. [17]	6	3 AR 3 APR
Smith et al. [24]	19	16 AR 2 LE

AR anterior resection, *APR* abdominoperineal resection, *LE* local excision

Although results of a systematic review of observational studies cannot be considered definitive, taken together, these trials can help us to understand, whether or not, continuing the research in this area and can provide major information regarding safety and efficacy of the conservative approach.

In this meta-analysis on 1812 patients in 12 comparative studies, we found that major surgery may not positively impact on the 3- and 5-year outcomes in patients with a complete response after neoadjuvant treatment. About 17.5% of patients with clinical complete response treated conservatively experienced a regrowth of disease, treated surgically. In these sceneries, primary concern is that for patients with local regrowth, there is a bulky disease and a pelvic exenteration is required with a significant decline in quality of life. In all analyzed studies, no pelvic exenteration was described; probably, this is related to more intensive follow-up.

These positive results are an encouragement to continue along this path. Pooled data confirm the good prognosis of this subset of patients with complete response, identifying probably a different disease.

The main criticisms of conservative approach in patients with LARC are the correct identification of subset of patients with a clinical complete response after neoadjuvant therapy and its correlation with pathological complete response. Obviously, assessing a complete response is crucial in a non-operative approach. Despite many studies reporting some promising results, no clinical, radiological, or molecular features have demonstrated any ability to predict response with adequate sensitivity or specificity to guide management [30]. Histology and clinical evaluation are the most effective methods of assessment of complete response; histology is considered the gold standard. MRI and PET/CT demonstrate a great potential for this assessment, but both modalities have limited accuracy [30]. In view of this uncertainty and of inconsistency across studies to evaluate complete response, a subgroup analysis was performed in this meta-analysis. There are no differences in outcomes between patients treated with local surgery to obtain histology [14, 16, 25] and patients with only follow-up [15, 17–24].

It is plausible that clinical and radiological assessment is adequate to evaluate tumor response in order to choose a conservative approach. Without an evaluation of clinical response, oncological outcome obviously decreases. A recent SEER study [31] has evaluated more than 5900 rectal cancer patients treated with major surgery or non-operative approach after radiotherapy and regardless the results of neoadjuvant treatment. The 5-year overall survival has been significantly better in patient after surgery (80%) than in conservative approach (56%). Another criticism to conservative approach is the heterogeneity, across trials, in terms of co-morbidity and operability between treated patients. Conservative approach has been reserved for patients unfit for major surgery or with co-morbidities that would place them at a greater risk for complications with major surgery. Therefore, there could be a slight underestimation of the conservative approach in LARC patients with complete response, since enrolled patients are likely to have had worse overall survival than patients who have been originally scheduled to undergo major surgery. The recent study by Renhean et al. [22], matching treatment groups using propensity score to address imbalance of potential confounders, has demonstrated an advantage for the watch and wait approach respect to major surgery.

That being so, obtaining a complete response after neoadjuvant treatment could be a goal in order to allow a conservative approach in LARC patients. A conventional long-course radiotherapy is able to obtain down-staging and complete response in rectal cancer. To increase the rate of CR, there are two approaches: the use of drugs as radio-sensitizers to improve therapeutic ratio of radiotherapy and/or the use of a higher radiation dose. The possibility of a conservative approach could justify the overtreatment and additional morbidity due to chemotherapy or a more aggressive approach, considering the prognosis of patients with cCR without major surgery. Many studies are carried out to better evaluate these two approaches.

A randomized clinical trial of surgical resection versus conservative treatment in rectal patients achieving complete response 12 weeks after chemo-radiotherapy is conducted by Instituto Do Câncer Do Estado de São Paulo (NCT02052921). Conservative approach and major surgery are indirectly evaluated in another randomized clinical trial by Memorial Sloan Kettering Cancer Center, where investigators are studying the use of neoadjuvant chemotherapy before or after neoadjuvant radiochemotherapy (NCT02008656).

This meta-analysis of non-randomized studies has several obvious limitations, which must be taken into account when considering the results. All of the studies included are non-randomized and all but two are retrospective in nature. Hence, these results can only be an estimate of the true benefit of a conservative approach for LARC patients with a complete response after neoadjuvant treatment. Despite its limitations, this study makes a strong attempt to evaluate the best evidence available by selecting high-quality studies and pooling their findings. By acting this way, there is evidence that non-randomized studies may generally give valid results.

Conclusion

This meta-analysis represents the largest body of information currently available for assessing the role of conservative approach for LARC patients with complete response after neoadjuvant therapy. This study shows that major surgery does not seem to improve the prognosis and therefore non-operative approach could be used in complete response patients, waiting to have biological and clinical response markers [32] to drive and better justify the correct approach.

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Compliance with Ethical Standards

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

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