

RESEARCH ARTICLE

Intra-operative Rectal Washout with Saline Solution Can Effectively Prevent Anastomotic Recurrence: a Meta-analysis

Can Zhou^{1,2&}, Yu Ren^{2&}, Ke Wang², Jie Liu¹, Jian-Jun He², Pei-Jun Liu^{1*}

Abstract

Background and Objective: Rectal washout with saline solution may theoretically prevent anastomotic recurrence in patients with resectable rectal cancer, although exact clinical effects have not yet been determined. In order to derive a more precise estimation of the relationship, the present meta-analysis was performed. **Method:** Relevant studies were identified by a search of Medline, Embase and Google Website with no restrictions to September 1, 2013, and included in the systematic review and meta-analysis. **Results:** 5 trials (642 participants) were included to assess the association between rectal washout with saline solution and anastomotic recurrence. The rate of anastomotic recurrence (AR) was 6.23% (40/642), with the pooled OR derived from the five studies being 0.32 (95% CI=0.15–0.70, $P=0.004$). The pooled OR derived from the TME and radical resection subgroups were 0.72 (95% CI=0.16–3.12, $P=0.66$) and 0.51 (95% CI=0.13–1.96, $P=0.32$), respectively. **Conclusion:** Results from this analysis show that intra-operative rectal washout with mere saline solution largely reduces the risk of anastomotic recurrences in patients with resectable rectal cancer.

Keywords: Rectal cancer - rectal washout - anastomotic recurrence - prevention - meta-analysis

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Introduction

Improvements in surgery and the application of combined approaches to fight rectal cancer have succeeded in reducing the anastomotic recurrences (AR), which is relatively rare among pelvic recurrences of rectal cancer following surgical resection, ranging 2.4% from 12% of all patients who underwent colorectal anastomosis (Li Destri et al., 2011). Nevertheless, anastomotic recurrence of rectal cancer remains a significant clinical problem, yields fatal outcomes that associated with severe morbidity, low rates of success of salvage procedures, and eventual death in the majority of patients (Kaiser et al., 2006; Enríquez-Navascués et al., 2011).

One theory for AR is that viable tumor cells, which are shed from the surface of solid tumor tissue in the lumen of the rectum during anterior resection, may be responsible for some locoregional anastomotic recurrences (Tsunoda et al., 1997). It was hypothesized one hundred years ago that “liberated cancer cells” may cause recurrence after surgery for rectal cancer (Turner et al., 1948; Goligher et al., 1951) and most surgeons today continue to avoid touching or manipulating a tumor excessively, so as not to spread malignant cells inside or outside the bowel. The implantation of malignant cells tends to occur when the mucosal surface is damaged (Hubens et al., 1994). Braided sutures are also capable of entrapping and transferring large numbers of free intra-luminal tumor cells in vivo (Umpleby et al., 1984; Skipper et al., 1987; McGregor et

al., 1989). For this reason, a thorough mechanical rectal irrigation with normal saline will probably eliminate exfoliated malignant cells and prevent the implantation of these cells and the anastomotic recurrence of rectal cancer (Long et al., 1989; Juhl et al., 1990; Fukuda et al., 1991; Sayfan et al. 2000; Church et al., 2003; Agaba et al., 2004; Terzi et al., 2006). However, there is no conclusive evidence of a beneficial effect of intraoperative rectal washout on anastomotic recurrence after anterior resection of rectal cancer (Fukuda et al., 1991; Shinto et al., 1996; Kawahara et al., 1998; Nakano et al., 2004).

Thus, we are prompted to investigate, with greater precision, the effect of intra-operative rectal washout with normal saline on the prevention of anastomotic recurrence after anterior resection for rectal cancer. This systematic review and meta-analysis is conducted to comprehensively assess the overall evidence regarding anastomotic recurrence following rectal washout with normal saline, by scrutinizing pertinent original research articles and analyzing the pooled data, with the aim of to provide meaningful clues for prevention of anastomotic recurrence after anterior resection in patients with rectal cancer.

Materials and Methods

Literature search

Relevant articles published with no restrictions to September 1, 2013 were identified by searching Pubmed,

¹Department of Centre of Translational Medicine, ²Department of Surgical Oncology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China [&]Equal contributors *For correspondence: peijun1020@163.com

Embase, and Google Website. The following search terms were used: “rectal washout”, “saline solution”, “anterior resection”, “local recurrence” and “anastomotic recurrence”. Both free text search and MeSH search were employed. Both free text search and MeSH search were employed.

Two researchers, Can Zhou and Yu Ren, independently assessed the titles or abstracts of all identified articles in a standardised manner and excluded those deemed irrelevant for this review. Can Zhou retrieved data from the included articles and Yu Ren checked these data for their relevance. Disagreements on inclusion were discussed with the guidance of the corresponding author Peijun Liu, if necessary. The following information was extracted from each included article: the authors’ names, the year of publication, the characteristics of trial participants, the inclusion and exclusion criteria of the trial, the type of intervention, the type of outcome measured.

Inclusion and Exclusion criteria

A data extraction sheet was developed based on the data extraction template of the Cochrane Consumers and Communication Review Group. Eligible articles had to meet the following criteria: studies (1) comparing rectal washout with saline solution (WOS) with no washout with saline solution (NWOS) for patients undergoing rectal cancer resection; (2) characterizing the surgery for rectal cancers as anterior resection or sphincter-sparing surgery; (3) of laparoscopic or hand-assisted resections for rectal cancer; (4) in which the outcome was an anastomotic recurrence (AR) of rectal cancer, with AR diagnosed by imaging, endoscopy, or palpation, and anastomotic recurrence categorized as AR and defined as isolated failure in anastomosis; (5) of which the most recent publication was included when two studies were reported by the same institution. All eligible studies were assessed a second time for relevance to ensure the objectivity of the review.

Publications were excluded if the outcomes of interest were not reported or it was impossible to calculate the outcomes from the published results, or the studies did not contain a distinct group of patients with rectal cancer or compare the outcomes of interest between rectal washout with saline solution (WOS) with no washout (NWOS).

Statistical analysis

The statistical analysis was performed by using the statistical software Review Manager® Version 5.2.5 (the Cochrane Collaboration, Software Update, Oxford, United Kingdom) in accordance with the PRISMA statement (Liberati et al., 2009) and the Cochrane Handbook for systematic reviews and the Quality of Reporting of Meta-analyses. The OR represents the risk of an adverse event occurring in the rectal washout (WOS) with saline solution group compared with the no rectal washout (NWOS) group. Data were analysed by using random- and fixed-effects models. The results from the fixed-effect model were reported since the two models produced almost the same results.

Statistical heterogeneity was quantitatively tested in the random- and fixed-effect models by using Chi-squared

test and I² tests. The conventional 0.05 level of significance was employed. Analyses were performed to evaluate the recurrence of anastomotic site in the subgroup of patients with rectal washout by using saline solution only, and in the two subgroups of patients who (1) underwent total mesorectal excision (TME), and (2) received a locally radical resection of the neoplasm.

Publication bias was evaluated by using graphic exploration with funnel plots (Egger et al., 1997; Higgins et al., 2011). In funnel plots, individual studies were plotted on the horizontal axis (HR) to create scatter plots for estimation of treatment effects (Higgins et al., 2011). If a study appeared to be an outlier, with the scatter plot obviously deviated from the HR, the following things may be conducted as sensitivity analyses: (1) fixed- and random-effects meta-analyses were undertaken to assess the robustness of the results to the method used to obtain these results; (2) the meta-analysis was repeated excluding a particular trial to determine whether the meta-analysis result was heavily determined by that trial (Higgins et al., 2011).

Results

Literature Search

The steps of our literature search are shown in Figure 1. The electronic literature search yielded 659 relevant articles published with no restrictions to September 1, 2013. Of these articles, 631 were excluded for meeting the exclusion criteria. The remaining 28 studies compared the outcomes of WOS versus NWOS during resection of rectal cancer, 8 excluded for meta-analyses, 10 excluded for duplication. Of the 10 articles, 2 retrieved from the same registry, and were excluded for not mentioned the irrigation fluid types (Jörgren et al.2010; Kodeda et al., 2010), 3 excluded for using 5% povidone-iodine (Long et al., 1989), 1% formaline (Church et al., 2003) or 1% cetrimide (Agaba et al., 2004). Thus, 5 more articles were subsequently excluded from this review. Overall, 5 studies published comparing the outcomes of washout versus no washout of the rectum during anterior resection for rectal cancer were included in this meta-analysis.

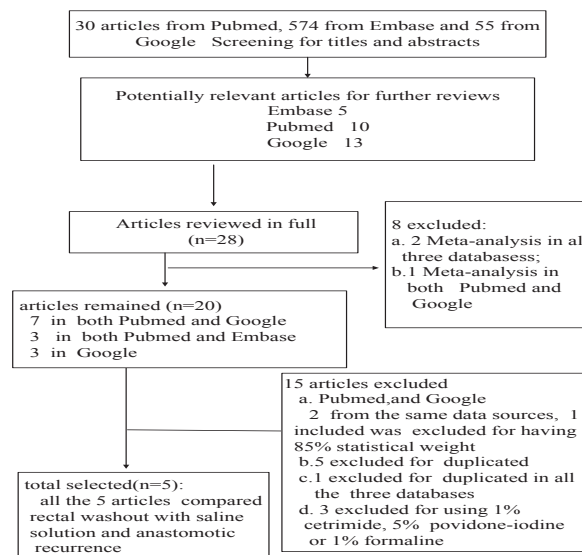
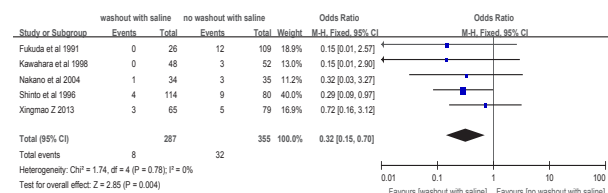
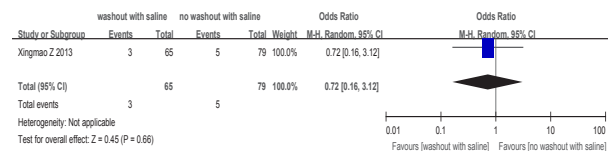
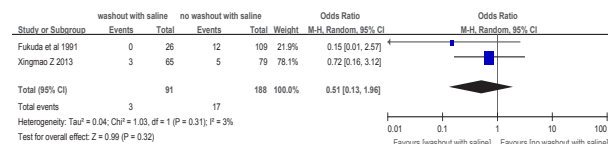


Figure 1. Flow Chart of Article Selection

Table 1. Characteristics and Demographics of Included Studies

Study	Year	Type	Group	N	n of LR	Mean Age	Women (%)	Washout		DFU (months)	Use of TME	End-points only
								Type	Volume(ml)			
Fukuda et al.	1991	P	WOS	26	0	NS	42.3	saline solution	600	48	No	AR
			NOWS	109	12	NS	40.4					
Kawahara et al.	1998	P	WOS	48	0	60.3	25	saline solution	2000	48	No	AR
			NOWS	52	3	60.2	40.4					
Nakano et al	2004	P	WOS	34	1	63.3	32.4	saline solution	2000	NS	No	AR
			NOWS	35	3	64.2	28.6					
Shinto et al	1996	R	WOS	114	4	59.6	46.5	saline solution	2000	48	No	AR
			NOWS	80	9	61.8	52.5					
Xingmao Z.	2013	P	WOS	69	3	56.3	58	saline solution	1500	48	Yes	AR
			NOWS	75	5	59	56					

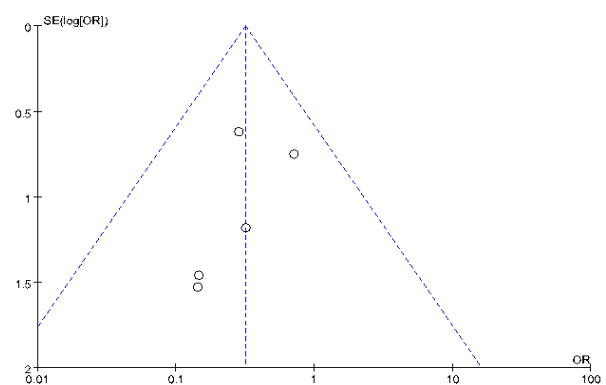
R, retrospective; P, prospective nonrandomized; WO, washout group with saline solution; NWO, no washout group with saline solution; TME, total mesorectal excision; NS, not stated; DFU, duration of follow-up; LR, local recurrence; AR, anastomotic recurrence

**Figure 2. Effect of Intra-operative Rectal Washout with Saline Solution on AR****Figure 3. Effect of Intra-operative Rectal Washout with Saline Solution on AR after TME****Figure 4. Effect of Intra-operative Rectal Washout with Saline Solution on LR after Radical Resection**

Studies included in the meta-analysis were performed in separate research centers. A total of 642 patients were included in the meta-analysis, of whom 287 (44.7%) underwent rectal washout and 355 (55.6%) did not have rectal washout during anterior resection for rectal cancer. Of the 5 studies, 4 were prospective studies, 1 was retrospective one, and none of them were randomized control trials (RCT). Four studies were conducted in Japan, one in China. One study was published in English, and four in Japanese. The Japanese papers were analyzed with the help of a Japanese translator. The two researchers, Can Zhou and Yu Ren, reached a consensus to the studies included in this review.

Characteristics of Included Studies

The characteristics of the 5 included studies are shown in Table 1. The patients reported in the 5 studies were fully matched with respect to age, sex, and Dukes or TNM stage. The occurrence of anastomotic recurrence was reported in all five studies. Only one study clearly mentioned the employment of TME; two studies included resections

**Figure 5. Funnel Plot of Intra-operative Rectal Washout with Saline Solution and Anastomotic Recurrence**

performed for radical resection.

Meta-Analysis of Outcomes

Effect of Intra-operative Rectal Washout with Saline Solution on Anastomotic Recurrence (AR): All five studies contributed to the meta-analysis investigating the effect of saline solution washout on anastomotic recurrence (AR) in patients. 287 patients underwent rectal washout during the rectal cancer resection and 355 did not, with an overall AR rate of 6.23% (40/642), as shown in Figure 2, The WOS group showed a significantly reduced AR rate, when compared with the NWOS group (2.79%, 8/287 vs 9.01%, 32/355; OR=0.32, 95% CI=0.15-0.70, $P=0.004$).

Effect of Intra-operative Rectal Washout with Saline Solution on Anastomotic Recurrence (AR) after TME: Only 1 study investigated the effect of saline solution washout on anastomotic recurrence (AR) in patients with TME. As shown in Figure 3, the AR rate in patients with rectal washout during TME was 4.61% (3/65), compared with 6.33% (5/79) in those with no rectal washout with Saline Solution. Nevertheless, the difference in AR between the WOS and NWOS groups was not statistically significant (OR=0.72, 95%CI = 0.16-3.12, $P=0.66$).

Effect of Intra-operative Rectal Washout on with Saline Solution on Anastomotic Recurrence (AR) after Radical Resection: Two of the five studies reported the number of

Table 2. Results of Meta-analysis and Sensitivity Analysis

Subgroup	SN	Group	PN	AR	Heterogeneity			Outcomes					
								Rate (%)			Fix-effect model		
					χ^2	I ² (%)	P	OR	95% CI	P	OR	95% CI	P
WOS for AR	5	WOS	287	2.79	1.74	0	0.78	0.32	0.15-0.70	0.004	0.34	0.15-0.77	0.009
		NWOS	355	9.01									
WOS for AR with TME	1	WOS	65	4.61	NA	NA	NA	0.36	0.16-0.77	0.008	0.72	0.16	3.12
		NWOS	79	6.33									
WOS for LR with RR	2	WOS	91	3.29	1.03	3	0.31	0.42	0.12-1.44	0.17	0.51	0.13-1.96	0.32
		NWOS	188	9.04									

SN, Study Number; WOS, Washout with Saline Solution Group; NWOS, No Washout Group with Saline Solution; PN, Patient Number; AR, Anastomotic Recurrence; NA, Not Applicable; RR, Radical Resection; LR, Local Recurrence; OR, Odds Ratio

patients with local recurrence after radical resection. As shown in Figure 4, the pooled OR derived from the two studies indicated that the risk of AR was not significantly reduced by rectal washout with saline solution during radical resection (OR=0.51, 95%CI=0.13–1.96, P=0.32). The AR rate was 3.29% (3/91) for the WOS group and 9.04% (17/188) for the NWOS group.

Publication Bias and Sensitivity Analysis

We can see, as shown in Figure 5, that scatter plots deviated from 5 studies were distributed around the horizontal axis, and none of the scatter plot exceeded the 95% CI limits, with no difference in heterogeneity was observed among the 5 studies ($\chi^2=1.74$, $p=0.78$ >0.05, $I^2=0\%$). Meanwhile, the data were analyzed by using the random- and fixed-effects models and similar results were obtained (as shown in Table 2). Thus, the sensitivity analysis of local recurrence shows no variation in statistical heterogeneity.

Discussion

This systematic review and meta-analysis of five studies evaluated the impact of intra-operative rectal washout on anastomotic recurrence in patients undergoing anterior resection of rectal cancer. The overall LR rate of 6.23% (40/642) in our study, which is lower than 8% documented by Jörgren (Jörgren et al.2010), suggested that rectal washout during anterior resection of cancer significantly reduced local recurrence. The pooled OR (0.32) derived from the 5 studies, which is lower than those (0.57–0.64) reported by Constantinides et al. (2008), Rondelli et al. (2012) and Matsuda et al. (2013), indicates that rectal washout significantly reduced the risk of local recurrence of rectal cancer by 68%. These differences may be due to the fact that none of these previous meta-analyses used different types of washout solutions, such as povidone-iodine (Long et al., 1989), cetrimide (Agaba et al., 2004) 0.9% NaCl (Fukuda et al., 1991; Shinto et al., 1996; Kawahara et al., 1998; Nakano et al., 2004) and formalin (Terzi et al., 2006), which had varied effects on cancer cells. The reason for the low overall AR rate may be that most rectal cancer cells are extra-luminal and out of the reach of rectal washout (Agaba et al., 2004).

It has been reported that TME for rectal cancer was

associated with a reduced local recurrence rate, when compared with conventional radical surgery (Heald et al., 1986; Scott et al., 1995; Arbman et al., 1996 ; Liang et al., 2007). Nevertheless, our meta-analysis of 1 studies revealed a pooled OR of 0.7 (95%CI = 0.16–3.12, P=0.66), which suggested that the application of rectal washout with saline solution provided no favorable influence on AR. This result revealed the confounding effect of TME and agreed well with what was reported by Constantinides (Constantinides et al., 2008).

In our meta-analysis, the pooled OR after radical resection were 0.46, demonstrating a trend in lowering local recurrence with the use of curative resection or radical resection. However, these data reached no statistical significance (95%CI=0.13–1.96, P=0.32). Therefore, we cannot draw the conclusion that radical resection confers a beneficial effect in reducing local recurrence.

Consequently, we may draw the conclusion that rectal washout with saline solution should be a routine practice during anterior resection. In addition to its effectiveness in preventing local recurrence, rectal washout with saline solution is easy and quick to perform and does not result in complications or significant costs. However, there is no conclusive evidence that saline solution is the preferred type of rectal washout for preventing anastomotic recurrence after anterior resection of rectal cancer.

The following limitations should be taken into consideration when the results of this study are interpreted. First of all, the 5 studies included in our meta-analysis used different washout volumes, ranging from 600 ml to 2000ml, which might have influenced the results of the present study.

Secondly, none of the 5 studies specifically addressed prognostic data, such as tumor size, degree of cellular differentiation, distal resection margin status, lymph node metastasis status. For this reason, we could not draw the conclusion that intra-operative rectal washout with saline solution was an independent prognostic factor for LR of rectal cancer.

Finally, and most importantly, the 5 included studies did not conduct randomized controlled trials (RCTs). Most of the studies were prospective non-randomized case-control studies. The reason for the absence of RCTs in these studies is unknown.

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