The American Journal of Surgery 220 (2020) 300–308

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Review Article

# Predictors for complete pathological response for stage II and III rectal cancer following neoadjuvant therapy - A systematic review and meta-analysis

Yeqian Huang, BMed, MD [a, b], Daniel Lee, BSc (Hons), MBBS [a, b], Christopher Young, MBBS, MS, FRACS, FACS [a, b, *]

[a] Department of Colorectal Surgery, Royal Prince Alfred Hospital, Camperdown, NSW, Australia, 2050
[b] Discipline of Surgery, The University of Sydney, Sydney, NSW, Australia

ARTICLE INFO

*Article history:*
Received 4 November 2019
Received in revised form
22 December 2019
Accepted 1 January 2020

*Keywords:*
Rectal cancer
Complete pathological response
Neoadjuvant therapy
Watch and wait approach

ABSTRACT

*Background:* There has been an increasing interest in the complete pathological response (pCR) in rectal cancers following neoadjuvant therapy. The aim of this study was to identify predictive factors of pCR in locally advanced rectal cancer following neoadjuvant therapy.
*Methods:* The studies identified were appraised with standard selection criteria. The selection criteria included studies on patients with stage II or III rectal cancer who underwent neoadjuvant therapy.
*Results:* Patients with pCR are more likely to be older ($p = 0.0002$), have cancers closer distance to the anal verge ($p < 0.00001$), smaller tumors ($P < 0.0001$), no clinical lymph nodes involvement ($p=<0.00001$) and waited more than eight weeks until definitive surgery ($p = 0.002$). There was no difference in gender ($p = 0.15$) and tumor differentiation ($p = 0.21$).
*Conclusions:* The 'Watch and Wait' approach may be appropriate for selected patients. Patients with lower rectal cancers, smaller tumors, and negative clinical lymph node involvement may be more likely to achieve pCR following neoadjuvant therapy.



## Introduction

Colorectal cancer is one of the most common cancers in Western society, with rectal cancer, accounting for 28% of cases. Over the past decade, an increasing understanding of the pathophysiology of rectal cancer progression and development of a multimodality approach has contributed to improved survival of patients. Long-course chemoradiotherapy followed by total mesorectal excision has been the gold standard approach for stage II and III rectal cancers.[1] In some centers, short-course radiotherapy has been used as an alternative to long-course chemoradiotherapy to reduce costs, reduce acute radiation toxicity, and for patients' convenience.[2] Recent randomized controlled trials and a recent meta-analysis demonstrated no difference in short-term disease outcomes between long-course chemoradiotherapy and short-course radiotherapy.[3–6] Most patients show substantial downsizing of the tumor, and 15–27% of patients did not have any residual tumor cells in the resected specimen.[7] This raises interest in whether a complete pathological response (pCR) is associated with improved outcomes in rectal cancer following neoadjuvant therapy and the possibility of a non-operative treatment strategy, the 'Watch and Wait' approach.[7,8] A meta-analysis published by Maas et al. (2010) suggested the patients with pCR after CRT have improved long-term outcomes compared with those without pCR which could reflect a favorable biological tumor profile associated with less propensity for local or distant recurrences and subsequently a better survival.[7]

Therefore, pCR may become clinically relevant and important in clinical decision-making and potentially allowing the development of risk-adapted treatment strategies. In patients without pCR or with partial response, more aggressive preoperative regimens may be considered.[9] For the patients who are more likely to have pCR, a less invasive approach including a tumor-localized resection or nonoperative management with intensive follow-up, could be considered.[7,9] The challenge remains in identifying those who will likely obtain a pCR after neoadjuvant CRT. There are several studies that have investigated potential factors that are associated with

* Corresponding author. RPAH Medical Centre, Suite G07/100 Carillon Ave, Newton, 2042, NSW, Australia.
*E-mail address:* yeqian.huang@hotmail.com (Y. Huang), christopher.young@sydney.edu.au (C. Young).

https://doi.org/10.1016/j.amjsurg.2020.01.001
0002-9610/

pCR. Thus the aim of this systematic review and meta-analysis was to identify potential predictive factors for pCR in patients with locally advanced rectal cancer following neoadjuvant therapy.

## Materials and methods

### *Search strategy*

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was conducted in the MEDLINE, EMBASE and PubMed databases (January 1990–November 2018). The search was limited to English language articles and to humans. The search terms used were "rectal cancer" or "rectal adenocarcinoma" or "rectal tumor" AND "complete response".

### *Selection criteria*

The selection criteria included studies on patients with stage II or III rectal cancer who underwent neoadjuvant therapy and subsequently underwent surgery. pCR was confirmed on the histological report. Studies that included patients with rectal cancers at all stages were excluded.

### *Data extraction and critical appraisal*

The studies were independently and critically assessed by two authors (YH and DL) according to the Methodological Index for Non-Randomized Studies (MINORS) tool.[10] Data extracted include the methodology, quality criteria, and endpoints addressed in the study. Factors investigated in this study include age, gender, clinical lymph node status, tumor distance from anal verge, waiting time to operation, tumor size and differentiation.

### *Statistical analysis*

Descriptive analysis was performed to provide summative figures. A meta-analysis of the perioperative outcomes from comparative studies was undertaken with Review Manager (RevMan) v.5.3 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, 2014) and Comprehensive Meta-analysis version 2.0 for Windows (Biostat, Englewood, New Jersey, USA). For continuous data, mean and standard deviation (SD) were estimated from the available median and range using the method described by Hozo et al. when they were not available.[11] The mean differences (MD) of the continuous data were calculated. Dichotomous data were pooled for events. The sample size of comparative groups, odds ratio (OR) and 95% confidence intervals (CI) were calculated. *A* random-effects model was used to control for heterogeneity among studies.[12] Heterogeneity among studies was assessed by I2 statistics, including I2 values up to 30%, to 60% and above 60% indicating low, moderate, and high levels of heterogeneity. Its significance was evaluated by Cochran's Q-test. Publication bias was assessed visually by funnel plots and statistically with the Egger regression

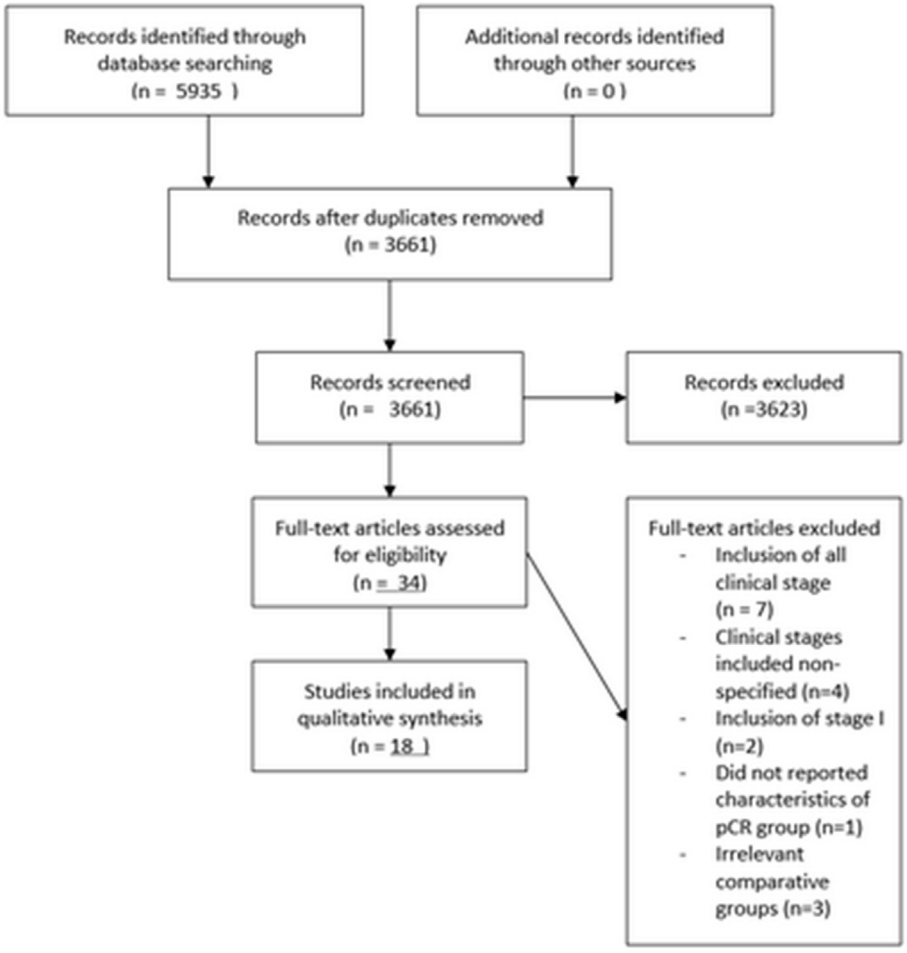


**Fig. 1.** PRISMA diagram of literature review.

**Table 1**
Background characteristics of included studies.

| Author, Year | Country of Origin | City | MINORS score | Study Period | Study type | PCR (n) | Non-PCR (n) | Total (n) | Definition of pCR | Neoadjuvant therapy | Type of surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bozkaya et al. (2018)[25] | Turkey | Ankara | 5 | Jan 2009–Dec 2015 | Retro | 46 | 157 | 203 | Surgical specimen and lymph nodes without viable tumor cells | CRT | LAR, APR, Hartmann's procedure |
| Letaief et al. (2017)[24] | Tunisia | Tunis | 3 | Jan 2006–Dec 2011 | Pros | 12 | 52 | 64 | Dworak Classification grade 4 | CRT | LAR, APR |
| Kuan et al. (2017)[18] | Taiwan | Taiwan | 5 | Jan 2007–Dec 2013 | Retro | 259 (**n = 259) | 1655 (**n = 1654) | 1914 (**n = 1913) | NR | CRT | LAR, APR, Others |
| Landi et al. (2017)[19] | Spain | Barcelona | 8 | 2004–2014 | Retro | 50 | 141 | 191 | The absence of gross and microscopic tumor cells in the specimen and in accordance with the nodal status (ypT0N0) | CRT | L-TME with loop ileostomy; L-TME without loop ileostomy; APR, Hartmann's with TME |
| Peng et al. (2016)[26] | China | Guangzhou | 6 | Dec 2003–Jun 2014 | Retro | 126 | 418 | 544 | The absence of viable tumor cells, with only fibrotic masses or acellular mucin pools present in proximity to the primary tumor and lymph nodes | CRT | AR, APR, Hartmanns procedure, Palliative colostomy |
| Wilkins et al. (2016)[28] | Australia | Malvern | 5 | Jan 2010–Jun 2014 | Retro | 26 (**n = 24) | 92 (**n = 86) | 118 (**n = 110) | The absence of detectable viable tumor cells in the specimen | CRT | APR, CA anas, proctocolectomy, ULAR, LAR, other |
| Zeng et al. (2015)[21] | China | Beijing | 8 | Jan 2005–Dec 2013 | Retro | 75 | 248 | 323 | Absence of viable tumor cells in the surgical specimen, including lymph nodes | CRT | LAR, APR, Hartmann operation |
| Han et al. (2015)[15] | South Korea | Seoul | 7 | Jan 2004–Dec 2012 | Retro | 91 | 241 | 332 | Based on tumor regression and fibrotic changes of pathologic specimen after CRT followed by surgery, using grading system adapted from Mandard et al.[36] | CRT | LAR, LAR with CA Anas anastomosis, APR |
| Bitterman et al. (2015)[8] | U.S. | New York | 8 | Aug 2004–Feb 2015 | Retro | 36 (**n = 36; ***n = 26) | 102 (**n = 101; ***n = 83) | 138 (**n = 137; ***n = 109) | ypT0N0M0 | CRT | LAR, APR, Transanal excision, Proctectomy |
| Wasmuth et al. (2015)[27] | Norway | Trondheim | 3 | 2000–2009 | Retro | 147 | 1237 | 1384 | NR | RT ± CTx | LAR, APR, Hartmann's procedure |
| Huh et al. (2013)[16] | Korea | Seoul | 8 | Dec 2000–Sep 2011 | Retro | 57 | 334 | 391 | Absence of viable adenocarcinoma cells in the surgical specimen | CRT | LAR with CR anas or CA anas; APR |
| Duldulao et al. (2011)[20] | U.S. | Duarte | 8 | NR | Pros | 28 | 99 | 127 | Absence of cancer cells in the rectal wall and regional lymph nodes on haemotoxylin and eosin staining | CRT | LAR, APR |
| Belluco et al. (2011)[22] | Italy | Aviano | 10 | Jan 1996–Sep 2008 | Retro | 42 | 97 | 139 | No residual cancer cells in the surgical specimen | CRT | APR, LAR, Full thickness transanal LE |
| De Campos-Lobato et al. (2011)[14] | Brazil | Rio de Janeiro | 8 | Jan 1997–Dec 2007 | Prosp | 58 (*n = 50) | 180 (*n = 169) | 238 (*n = 219) | Absence of viable adenocarcinoma cells in the surgical specimen | CRT | TME |
| Moureau-Zabotto et al. (2011)[9] | France | Marseilles | 6 | Jan 1998–Jan 2008 | Retro | 31 | 127 | 158 | The absence of any tumor cells in the operative pathology specimen defined by ypT0 | CRT | Proctectomy with TME with or without sphincter preservation |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kalady et al. (2009)[17] | U.S. | Cleveland | 6 | Jan 1997–Dec 2007 | Retro | 58 (**n = 56) | 184 (**N = 175) | 242 (**n = 231) | Absence of viable adenocarcinoma cells in the surgical specimen including lymph nodes | CRT | NR | |
| Hughes et al. (2006)[23] | UK | Harrow | 5 | Nov 1993–Aug 2003 | Pros | 23 | 107 | 130 | Unable to demonstrate any intact viable cancer cells within the operative specimen | CRT | APR, AR | |
| Brown et al. (2003)[13] | U.S. | Omaha | 6 | 1990–2001 | Retro | 21 | 68 | 89 | NR | CRT | LAR, LAR with CA Anas anastomosis, APR | |
| Total | – | – | – | – | – | 1186 | 5539 | 6725 | – | | – | |

Retro-Retrospective study; Prosp- Prospective Study; *N- the number of patients for distance from anal verge in that particular study); **- the number of patients for positive clinical N stage in that particular study; *** N- the number of patients with a known differentiation in that particular study; NR- Not reported; LAR with CA anas-low anterior resection with coloanal anastomosis; LAR with CR anas-low anterior resection with colorectal anastomosis; LE-local excision; AR- Anterior resection; ULAR-ultralow anterior resection; L-TME- laparoscopic TME; CRT- Chemoradiotherapy; RT-Radiotherapy; CTx- Chemotherapy; MINORS-methodological index for non-randomised studies.

model. The level of heterogeneity indicates the variability among the included studies. Publication bias occurs when the outcome of the study influences the decision of whether to publish the study. When it is present, the studies may not be representative of available evidence. It is important to consider the level of heterogeneity and publication bias when interpreting and applying our results. A p-value of <0.05 was considered significant.

## Results

### *Literature search*

The systematic search identified 34 potential articles. Fig. 1 shows the review process that led to the final inclusion of 18 studies for review following exclusion of articles that did not meet inclusion criteria.[8,9,13–28] Table 1 summaries the characteristics of studies.

A total of 1186 patients had pCR. Fourteen papers were retrospective[8,9,13,15–19,21,22,25–28] whereas others were prospective studies.[14,20,23,24] Seventeen studies included patients who underwent neoadjuvant chemoradiation,[8,9,13–26,28] whereas one study included patients who underwent neoadjuvant radiotherapy with or without neoadjuvant chemotherapy.[27]

### *Patients factors*

Table 2 summarizes the potential factors that affect the pCR rate. The median age was 59.7 years old (range = 54.0–70.0, mean = 60.4, standard deviation (SD) = 4.1) and 60.8 years old (range = 55.0–68.0, mean = 61.4, SD = 3.8) in the pCR and non-pCR groups respectively. Patients in the non-pCR group were significantly older than those in the pCR group (mean difference = −0.84, 95%CI = −1.29 to −0.39, Z = 3.66, p = 0.0002) with a significant high level of statistical heterogeneity ($I^2$ = 90%, Cochran Q = 143.498, P < 0.00001) but without significant publication bias (Egger test = −0.003, 95%CI = −4.871-4.865, P = 0.50) (Fig. 2). There were a similar number of male patients in both groups (median = 65.1%, range = 54.0–77.2, mean = 65.3%, SD = 6.3 for pCR group; median = 67.3%, range = 52.4–76.6, mean = 66.1%, SD = 7.2, Odds ratio (OR) = 0.91, 95%CI = 0.79–1.04, Z = 1.44, P = 0.15) with minimal statistical heterogeneity ($I^2$ = 0%, Cochran Q = 14.83, P = 0.61) and without significant publication bias (Egger test = −0.566, 95%CI = −0.587-1.719, P = 0.16) (Fig. 3).

### *Tumor factors*

The median distance of the tumor from anal verge was 5.0 cm (range = 4.3–7.2, mean = 5.3 cm, SD = 0.9) and 6.0 cm (range = 5.0–7.1, mean = 6.0 cm, SD = 0.6) in the pCR and non-pCR group respectively. The difference in distance of the tumor from anal verge was significant (MD = −0.43, 95%CI = −0.56 to −0.30, Z = 6.31, P < 0.00001) with significant high level of statistical heterogeneity ($I^2$ = 84%, Cochran Q = 49.79, P < 0.00001) but without significant publication bias (Egger test = -4.91, 95% CI = −16.80-6.98, P = 0.18) (Fig. 4).

Furthermore, patients with pCR had a significantly smaller tumors as compared to the non-pCR group (mean size: pCR: 4.8 cm (SD = 0.4) vs. non-pCR 5.4 cm (SD = 1.5); MD = −0.57, 95% CI = −0.86,-0.29, Z = 3.97, P < 0.00001) (Fig. 5). However there was a high level of heterogeneity ($I^2$ = 82%, Cochran Q = 27.95, P < 0.00001) but without significant publication bias (Egger test = 0.15, 95% CI = −7.10-7.40, P = 0.48). The median rate of positive lymph node was 47.6% in pCR group and 72.5% in non-pCR group. This was significantly higher in the non-pCR group (OR = 0.67, 95%CI = 0.57–0.78, Z = 5.18, P < 0.00001) with low level

**Table 2**
Outcomes.

| Author, Year | | Age | Gender (male %) (N) | Distance from anal verge (cm) | Positive lymph node (clinical) | Tumor size (cm) | Differentiation (well/mod %) | Interval to OT ≥ 8 weeks |
|---|---|---|---|---|---|---|---|---|
| Bozkaya et al. (2018)[25] | pCR | 70.0 (15.5) | 76.1 (35) | 5.0 (3.5) | 26.1 (12) | 5.0 (1.8) | 83.7 (170) | NR |
| | No pCR | 58.0 (10.5) | 63.7 (100) | 6.0 (2.3) | 55.4 (87) | 5.2 (1.8) | 86.0 (135) | NR |
| Letaief et al. (2017)[24] | pCR | NR | 66.7 (8) | NR | 41.7 (5) | NR | 100.0 (12) | NR |
| | No pCR | NR | 53.8 (28) | NR | 80.8 (42) | NR | 48.1 (25) | NR |
| Kuan et al. (2017)[18] | pCR | 59.6 (12.4) | 63.3 (164) | NR | 66.9 (172) | NR | NR | NR |
| | No pCR | 60.0 (12.1) | 68.6 (1294) | NR | 73.5 (1217) | NR | NR | NR |
| Landi et al. (2017)[19] | pCR | 63.0 (12.8) | 54.0 (27) | NR | 74.0 (37) | NR | NR | 100.0 (50) |
| | No pCR | 68.0 (10.0) | 60.3 (85) | NR | 85.1 (120) | NR | NR | 100.0 (141) |
| Peng et al. (2016)[26] | pCR | 55 (7.5) | 65.9 (83) | NR | 29.4 (37) | NR | 79.4 (100) | NR |
| | No pCR | 55 (11.5) | 66.5 (278) | NR | 44.0 (184) | NR | 76.6 (320) | NR |
| Wilkins et al. (2016)[28] | pCR | 62.1 (2.2) | 57.7 (15) | 7.2 (0.6) | 42.3 (11) | 4.4 (2.8) | NR | NR |
| | No pCR | 61.6 (1.4) | 69.6 (64) | 7.1 (0.3) | 61.9 (57) | 8.7 (4.8) | NR | NR |
| Zeng et al. (2015)[21] | pCR | 58.5 (10) | 58.7 (44) | 6.0 (2.0) | 72.0 (54) | NR | 88.0 (66) | NR |
| | No pCR | 57.0 (7.7) | 52.4 (130) | 6.0 (1.7) | 73.0 (181) | NR | 83.9 (208) | NR |
| Han et al. (2015)[15] | pCR | 58 (10.58) | 65.9 (60) | NR | 70.3 (64) | NR | 93.4 (85) | NR |
| | No pCR | 65.8 (11.74) | 69.7 (168) | NR | 73.5 (177) | NR | 89.2 (215) | NR |
| Bitterman et al. (2015)[8] | pCR | 59.3 (12.3) | 66.7 (24) | 4.5 (3.6) | 52.8 (19) | 5.0 (3.9) | 61.2 (22) | 70.0 (21) |
| | No pCR | 57.4 (13.8) | 60.8 (62) | 6.3 (3.5) | 72.5 (74) | 5.6 (2.7) | 69.6 (71) | 49.5 (46) |
| Wasmuth et al. (2015)[27] | pCR | 63.0 (8.8) | 59.2 (87) | NR | NR | NR | NR | NR |
| | No pCR | 65.3 (12.0) | 61.0 (754) | NR | NR | NR | NR | NR |
| Huh et al. (2013)[16] | pCR | 63 (10.3) | 77.2 (44) | 5.0 (2.5) | 63.2 (36) | 4.0 (1.5) | 93.0 (53) | NR |
| | No pCR | 63 (9.8) | 72.8 (243) | 5.0 (2.0) | 75.4 (252) | 4.5 (1.7) | 90.7 (303) | NR |
| Duldulao et al. (2011)[20] | pCR | NR | 61 (17) | NR | 83.0 (23) | NR | NR | NR |
| | No pCR | NR | 58 (57) | NR | 73.0 (72) | NR | NR | NR |
| Belluco et al. (2011)[22] | pCR | 60.3 (13.1) | 64.3 (27) | NR | 47.6 (20) | NR | NR | NR |
| | No pCR | 65.0 (15.5) | 68.0 (66) | | 48.4 (47) | NR | NR | NR |
| De Campos-Lobato et al. (2011)[14] | pCR | 54.0 (4.3) | 65 (38) | 5.0 (1.0) | 3.6 (2) | NR | NR | 65.9 (27) |
| | No pCR | 59.0 (2.8) | 75 (20) | 6.0 (0.5) | 2.9 (5) | NR | NR | 46.2 (61) |
| Moureau-Zabotto et al. (2011)[9] | pCR | 58.9 (10.4) | 64.5 (20) | NR | NR | 4.7 (2.4) | NR | 19.4 (6) |
| | No pCR | 59.4 (10.8) | 72.4 (92) | NR | NR | 4.8 (2.1) | NR | 16.5 (21) |
| Kalady et al. (2009)[17] | pCR | 55.5 (13.8) | 67.2 (39) | 5.0 (2.6) | 34.0 (19) | NR | 19.6 (9) | 48.3 (28) |
| | No pCR | 58.5 (11.2) | 74.9 (137) | 6.0 (2.5) | 37.8 (66) | NR | 20.5 (54) | 34.2 (63) |
| Hughes et al. (2006)[23] | pCR | 59.8 (12.8) | 65.2 (15) | 4.3 (2.0) | 30.4 (7) | 4.9 (1.5) | NR | NR |
| | No pCR | 64.0 (9.8) | 76.6 (82) | 5.3 (1.7) | 38.3 (41) | 5.6 (1.8) | NR | NR |
| Brown et al. (2003)[13] | pCR | 66 (2) | 76 (16) | 5.5 (0.6) | NR | NR | 95.0 (20) | NR |
| | No pCR | 65 (2) | 65 (44) | 6.0 (0.3) | NR | NR | 84.0 (57) | NR |

NR- Not reported.

of statistical heterogeneity ($I^2$ = 19%, Cochran Q = 17.35, P = 0.24) and without significant publication bias (Egger test = −0.006, 95% CI = −1.518-1.506, P = 0.50) (Fig. 6).

More patients in pCR group had well-differentiated or moderately differentiated tumors (median = 88.0%, range = 19.6–100.0, mean = 79.3%, SD = 25.1 in pCR group; median = 83.9%, range = 20.5–90.7, mean = 72.1%, SD = 23.4 in non-pCR group). However there was no statistical difference between two groups (OR = 1.18, 95%CI = 0.91–1.53, Z = 1.26, P = 0.21). There was a moderate level of statistical heterogeneity ($I^2$ = 31%, Cochran Q = 11.58, P = 0.17) and significant publication bias (Egger test = 1.597, 95%CI = −0.293-3.487, P = 0.04) (Fig. 7).

### *Operative timing*

There were more patients with pCR who waited for at least 8

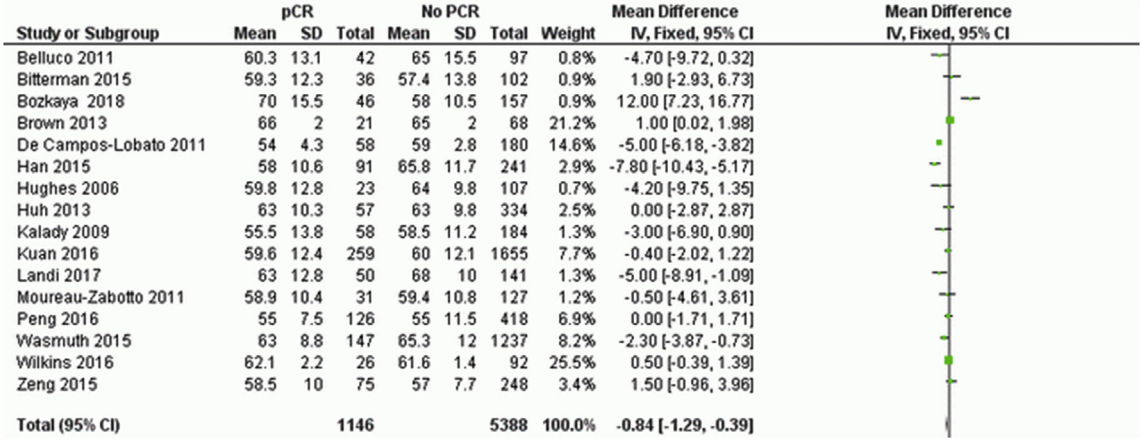


**Fig. 2.** Age.

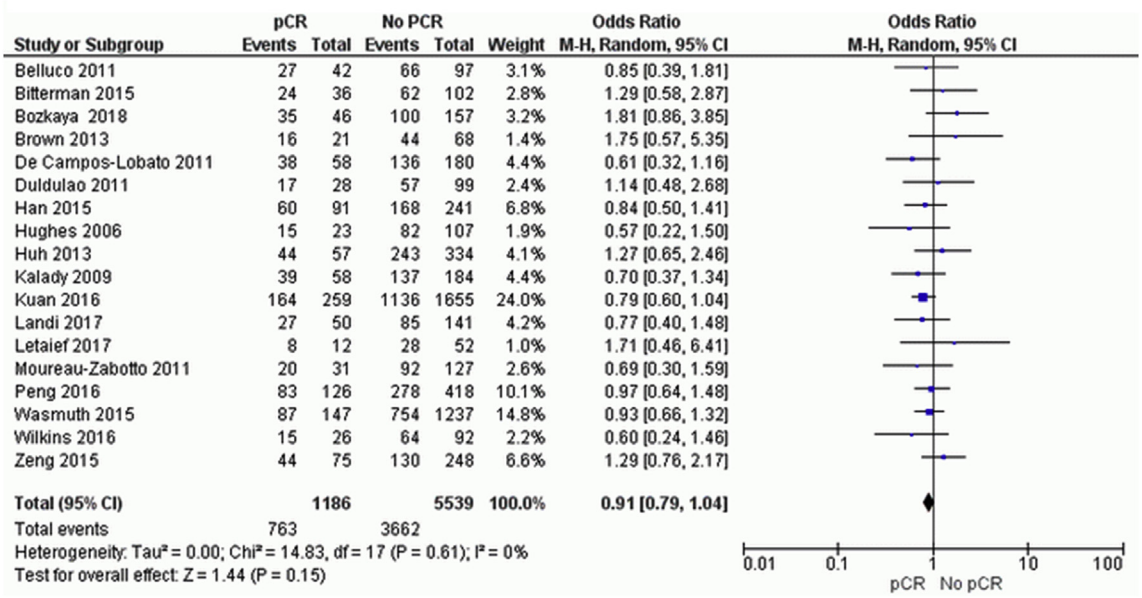


**Fig. 3.** Male gender.

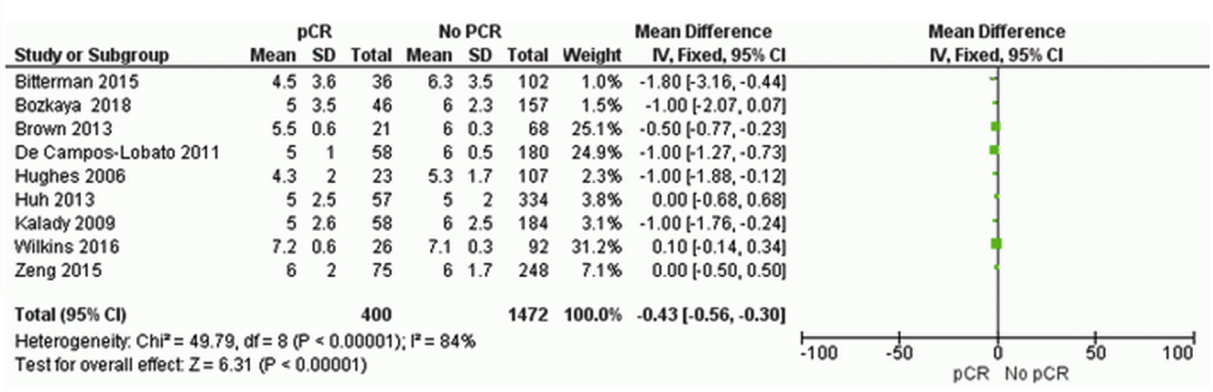


**Fig. 4.** Distance from anal verge (cm).

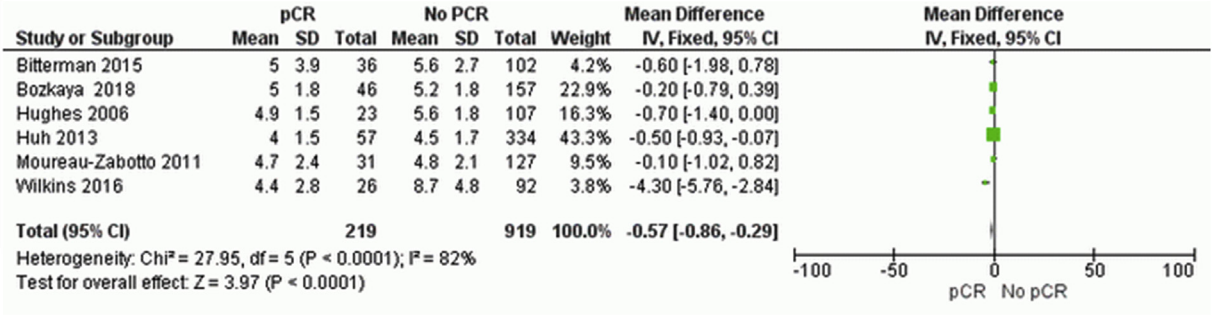


**Fig. 5.** Tumor size (cm).

weeks prior to operation (median = 65.9%, range = 19.4–100.0, mean = 60.7%, SD = 29.7). This was statistically significant between two groups (OR = 1.75, 95%CI = 1.24–2.51, Z = 3.13, P = 0.002) with a low level of statistical heterogeneity ($I^2$ = 0%, Cochran Q = 1.00, P = 0.80) and without significant publication bias (Egger test = −0.391, 95%CI = −7.266-6.483, P = 0.41) (Fig. 8).

## Discussion

Radical resection combined with neoadjuvant chemotherapy is the standard in the treatment of resectable mid and low T3 and T4 rectal cancer. However, it does have a significant morbidity rate and 90-day mortality of approximately 4%. This cause long-term

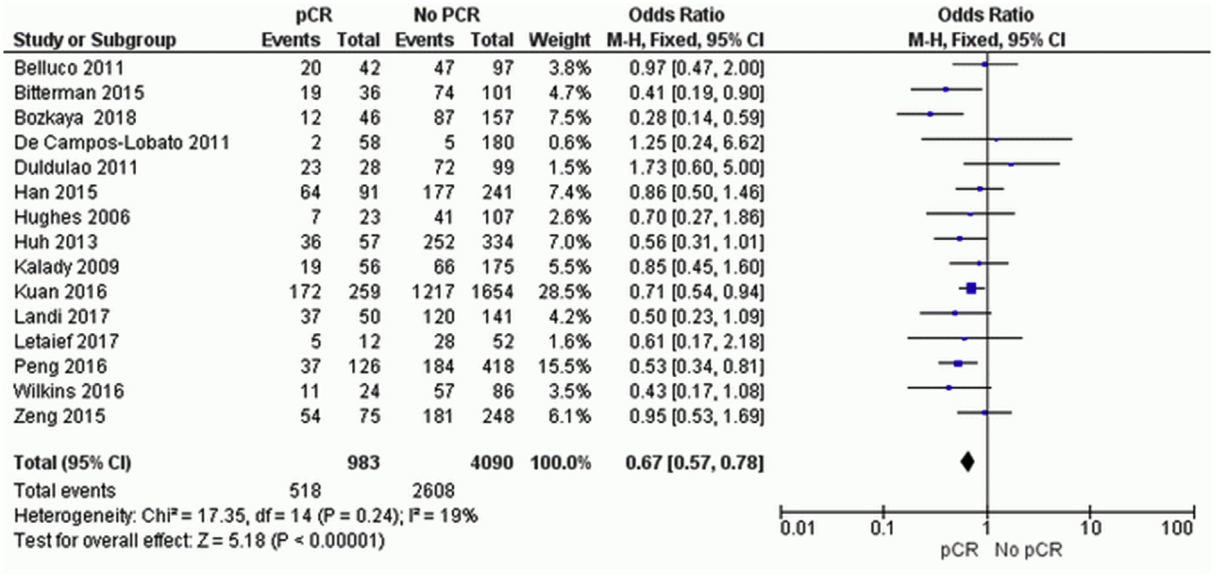


**Fig. 6.** Positive lymph node clinically.

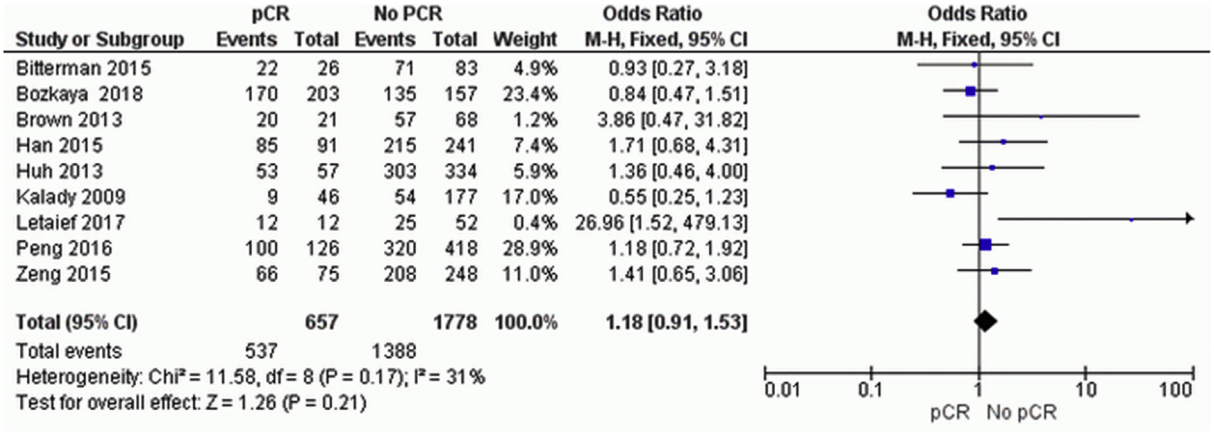


**Fig. 7.** Well or moderate differentiation.

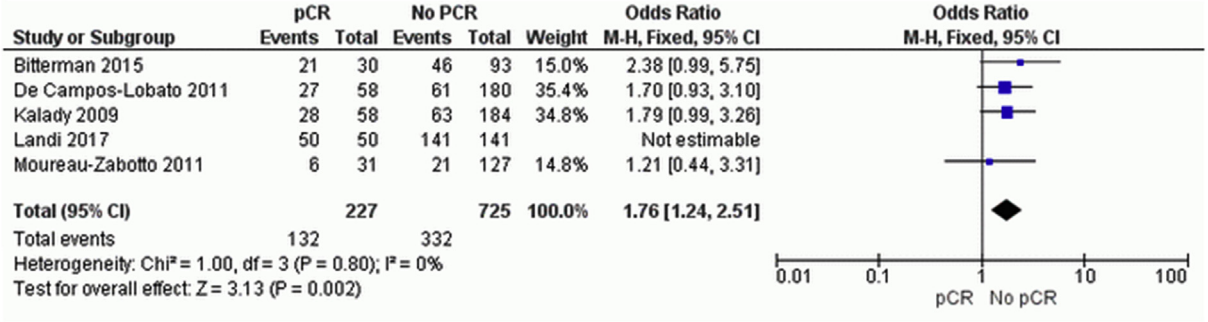


**Fig. 8.** Interval to operation.

functional bowel and urinary dysfunction.[29] Therefore, an organ-preserving option for rectal cancer is attractive. A non-operative approach would likely include intensive surveillance for those with rectal cancer who achieved clinical pCR. Dattani et al. (2018) performed a systematic review on oncological outcomes of patients with rectal cancer who underwent the 'Watch and Wait' approach. They identified a 3-year overall survival rate of 93.5%, a 3-year cumulative risk of local regrowth of 21.6%, and pooled 3-year cumulative rate of distant metastases of 6.8%.[29] pCR after neoadjuvant therapy could indicate a prognostically favorable biological tumor profile, resulting in less recurrence and distant metastases and improved survival.[7] Therefore, identifying the group of patients with rectal cancer who are more likely to have pCR after neoadjuvant therapy is valuable.

Our results demonstrated that patients who had a pCR are more likely to be older ($p = 0.0002$), have cancers closer to anal verge ($p < 0.00001$), have smaller tumors ($p < 0.0001$), have no clinical lymph nodes involvement ($p=<0.00001$) and have waited more than 8 weeks until definitive surgery ($p = 0.002$). Several factors need to be considered when interpreting the difference in age between the two groups. A watch and wait approach, as a potential alternative to the standard approach, is a relatively new concept. Furthermore, the decision for the watch and wait treatment can be influenced by the patient's age, baseline function, and medical comorbidities, especially in early studies.[1] Older patients are more likely to have medical comorbidities that increase their surgical risks significantly and require preoperative optimization. Therefore, it is possible that older patients were more likely to be elected for the watch and wait approach due to personal circumstances are more likely to be older, skewing the analysis. Therefore, the age difference, as shown in our result, may not truly reflect the patients' characteristics for the pCR group.

There were more patients with pCR that had smaller tumors in included studies (mean size in pCR group 4.8 cm vs. 5.4 cm in non-pCR). This is consistent with the current literature. Pretreatment tumor size (<5 cm) is an important factor that affects downstaging and complete response rates.[30] Furthermore, Ryan et al. (2015) performed a systematic review on pathological factors, imaging modalities, and molecular factors that predict pCR to neoadjuvant chemoradiotherapy in locally advanced rectal cancer. One of the predictors mentioned was good tumor differentiation.[31] This is also consistent with our results. Better tumor differentiation can present a more favorable biological tumor profile, which could be more responsive to neoadjuvant therapy.[7] Our results also indicate that patients who did not have pCR were more likely to have positive lymph node involvement then not. This may also reflect more aggressive tumors that are less likely to respond to neoadjuvant therapy.

In our study, it was demonstrated that more patients with pCR had waited more than 8 weeks prior to surgery. This finding is consistent with the literature. Petrelli et al. (2016) conducted a meta-analysis on the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer. It was suggested that a longer waiting interval more than the classical 6–8 weeks after completing neoadjuvant CRT increases the pathological downstaging and subsequently improves the pCR rate.[32] This, however, needs to be balanced against the risks of incomplete response while waiting. A recent review that has suggested patients who were observed but failed to sustain a complete response, may actually perform worse than those who underwent immediate surgery.[33]

There are several factors that need to be considered when interpreting the results of this review. The variations in diagnostic modality, the surgical technique, and neoadjuvant therapy between centers at different time points should be considered.[29] Local experience with comprehensive care of patients with rectal cancer is also crucial in achieving pCR.[34] There is still conflicting evidence on the long-term survival outcomes of patients with rectal cancer who underwent wait and watch approach.[29,35] Potential risks of watch and wait approach need to be balanced against the benefits of organ preservation.[35] Furthermore, the appropriate intensity and duration of follow-up to allow for the early detection of recurrence remains unclear. The costs and resources for intense surveillance should also be analyzed. Lastly, this study only reviewed English studies.

## Conclusions

Identifying the group of patients who most likely will respond to neoadjuvant therapy to achieve pCR is valuable. The 'watch and wait' approach may be appropriate for selected patients to avoid the morbidity and mortality associated with radical surgery. Patients who have lower rectal cancer, smaller tumors and negative lymph node involvement on clinical diagnosis may be more likely to achieve pCR following neoadjuvant therapy. However, it is difficult to draw a conclusion based on current evidence. Better designed prospective studies with standardized regimens are warranted. Also, more evidence is required to establish the long-term outcomes associated with pCR before advocating organ preservation therapy.

## Funding

Nil.

## Declaration of competing interest

The authors declare no conflicts of interest, and no support from any organization for the submitted work.

## References

1. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg*. 2012 Dec;256(6):965–972. PubMed PMID: 23154394. Epub 2012/11/17. eng.
2. Raldow AC, Chen AB, Russell M, et al. Cost-effectiveness of short-course radiation therapy vs long-course chemoradiation for locally advanced rectal cancer. *JAMA Netw Open*. 2019 Apr 5;2(4), e192249. PubMed PMID: 30977859. Pubmed Central PMCID: PMC6481445. Epub 2019/04/13. eng.
3. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol : Off J Am Soc Clin Oncol*. 2012 Nov 1;30(31):3827–3833. PubMed PMID: 23008301. Epub 2012/09/26. eng.
4. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiotherapy and oncology. *J Eur Soc Ther Radiol Oncol*. 2004 Jul;72(1):15–24. PubMed PMID: 15236870. Epub 2004/07/09. eng.
5. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*. 2006 Oct;93(10):1215–1223. PubMed PMID: 16983741. Epub 2006/09/20. eng.
6. Ma B, Gao P, Song Y, et al. Short-course radiotherapy in neoadjuvant treatment for rectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer*. 2018 Dec;17(4):320–330. e5. PubMed PMID: 30243484. Epub 2018/09/24. eng.
7. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2010;11(9):835–844.
8. Bitterman DS, Resende Salgado L, Moore HG, et al. Predictors of complete response and disease recurrence following chemoradiation for rectal cancer. *Front Oncol*. 2015;5:286.
9. Moureau-Zabotto L, Farnault B, de Chaisemartin C, et al. Predictive factors of tumor response after neoadjuvant chemoradiation for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2011;80(2):483–491.
10. Slim K, Nini E, Forestier D, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003 Sep;73(9):712–716. PubMed PMID: 12956787. Epub 2003/09/06. eng.
11. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(1):13.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials*. 1986;7(3):177–188.
13. Brown CL, Ternent CA, Thorson AG, et al. Response to preoperative chemoradiation in stage II and III rectal cancer. 2003;46(9):1189–1193.
14. de Campos-Lobato LF, Stocchi L, da Luz Moreira A, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. 2011;18(6):1590–1598.
15. Han YD, Kim WR, Park SW, et al. Predictors of pathologic complete response in rectal cancer patients undergoing total mesorectal excision after preoperative chemoradiation. 2015;94(45).
16. Huh JW, Kim HR, Kim YJ, Rectum. Clinical prediction of pathological complete response after preoperative chemoradiotherapy for rectal cancer. 2013;56(6):698–703.
17. Kalady MF, de Campos-Lobato LF, Stocchi L, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg*. 2009 Oct;250(4):582–589. PubMed PMID: 19710605. Epub 2009/08/

28. eng.
18. Kuan FC, Lai CH, Ku HY, et al. The survival impact of delayed surgery and adjuvant chemotherapy on stage II/III rectal cancer with pathological complete response after neoadjuvant chemoradiation. *Int J Cancer*. 2017 Apr 1;140(7):1662–1669. PubMed PMID: 27935051. Epub 2016/12/10. eng.
19. Landi F, Espin E, Rodrigues V, et al. Pathologic response grade after long-course neoadjuvant chemoradiation does not influence morbidity in locally advanced mid-low rectal cancer resected by laparoscopy. *Int J Colorectal Dis*. 2017 Feb;32(2):255–264. PubMed PMID: 27757541. Epub 2016/10/21. eng.
20. Duldulao MP, Lee W, Le M, et al. Surgical complications and pathologic complete response after neoadjuvant chemoradiation in locally advanced rectal cancer. *Am Surg*. 2011 Oct;77(10):1281–1285. PubMed PMID: 22127070. Epub 2011/12/01. eng.
21. Zeng WG, Liang JW, Wang Z, et al. Clinical parameters predicting pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Chin J Canc*. 2015 Aug 13;34(10):468–474. PubMed PMID: 26268466. Pubmed Central PMCID: PMC4593378. Epub 2015/08/14. eng.
22. Belluco C, De Paoli A, Canzonieri V, et al. Long-term outcome of patients with complete pathologic response after neoadjuvant chemoradiation for cT3 rectal cancer: implications for local excision surgical strategies. *Ann Surg Oncol*. 2011 Dec;18(13):3686–3693. PubMed PMID: 21691880. Pubmed Central PMCID: PMC3222828. Epub 2011/06/22. eng.
23. Hughes R, Glynne-Jones R, Grainger J, et al. Can pathological complete response in the primary tumour following pre-operative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for sterilisation of pelvic lymph nodes, a low risk of local recurrence and the appropriateness of local excision? *Int J Colorectal Dis*. 2006 Jan;21(1):11–17. PubMed PMID: 15864605. Epub 2005/05/03. eng.
24. Letaief F, Nasri M, Ayadi M, et al. Potential predictive factors for pathologic complete response after the neoadjuvant treatment of rectal adenocarcinoma: a single center experience. *Cancer Biol Med*. 2017 Aug;14(3):327–334. PubMed PMID: 28884049. Pubmed Central PMCID: PMC5570609. Epub 2017/09/09. eng.
25. Bozkaya Y, Özdemir NY, Erdem GU, et al. Clinical predictive factors associated with pathologic complete response in locally advanced rectal cancer. 2018;4(1):5–10.
26. Peng J, Lin J, Qiu M, et al. Clinical factors of post-chemoradiotherapy as valuable indicators for pathological complete response in locally advanced rectal cancer. *Clinics*. 2016 Aug;71(8):449–454. PubMed PMID: 27626475. Pubmed Central PMCID: PMC4975783. Epub 2016/09/15. eng.
27. Wasmuth H, Rekstad L, Tranø GJCD. The outcome and the frequency of pathological complete response after neoadjuvant radiotherapy in curative resections for advanced rectal cancer: a population-based study. 2016;18(1):67–72.
28. Wilkins S, Haydon A, Porter I, et al. Complete pathological response after neoadjuvant long-course chemoradiotherapy for rectal cancer and its relationship to the degree of T3 mesorectal invasion. *Dis Colon Rectum*. 2016 May;59(5):361–368. PubMed PMID: 27050597. Epub 2016/04/07. eng.
29. Dattani M, Heald RJ, Goussous G, et al. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. *Ann Surg*. 2018 Dec;268(6):955–967. PubMed PMID: 29746338. Epub 2018/05/11. eng.
30. Janjan NA, Khoo VS, Abbruzzese J, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M. D. Anderson Cancer Center experience. *Int J Radiat Oncol Biol Phys*. 1999 Jul 15;44(5):1027–1038. PubMed PMID: 10421535. Epub 1999/07/27. eng.
31. Ryan JE, Warrier SK, Lynch AC, et al. Predicting pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. *Colorectal Dis : Off J Assoc Coloproctol G B Irel*. 2016 Mar;18(3):234–246. PubMed PMID: 26531759. Epub 2015/11/05. eng.
32. Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. *Ann Surg*. 2016 Mar;263(3):458–464. PubMed PMID: 24263329. Epub 2013/11/23. eng.
33. Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. *Br J Surg*. 2012 Jul;99(7):897–909. PubMed PMID: 22539154. Epub 2012/04/28. eng.
34. Lorimer PD, Motz BM, Kirks RC, et al. Pathologic complete response rates after neoadjuvant treatment in rectal cancer: an analysis of the national cancer database. *Ann Surg Oncol*. 2017 Aug;24(8):2095–2103. PubMed PMID: 28534080. Epub 2017/05/24. eng.
35. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. 2019 Jan 10, e185896. PubMed PMID: 30629084. Pubmed Central PMCID: PMC6459120. Epub 2019/01/11. eng.
36. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma clinicopathologic correlations. *Cancer*. 1994;73(11):2680–2686.