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Prognostic Value of Tumour Regression Grade in Locally Advanced Rectal Cancer: A Systematic Review and Meta-analysis

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Abstract

Background

The current standard of care for locally advanced rectal cancer involves neo-adjuvant chemo-radiotherapy followed by total mesorectal excision. There is a spectrum of response to neo-adjuvant therapy, however the prognostic value of tumour regression grade(TRG) in predicting disease-free survival (DFS) or overall survival (OS) is inconsistent in the literature.

Methods

This study was performed in accordance with the PRISMA guidelines. A systematic search was undertaken using Ovid Medline, Embase and Google Scholar. Inclusion criteria were Stage II and III LARC receiving long course chemo-radiotherapy followed by radical surgery.

The aim of the meta-analysis was to assess the prognostic implication of each tumour regression grade for rectal cancer following neo-adjuvant chemo-radiotherapy. Long term prognosis was assessed. The main outcome measures were DFS and OS. A random effect model was performed to pool hazard ratio from each study.

Results

There were 4875 patients from 17 studies, with 775 (15.9%) attaining a pathological complete response and 719 (29.9%) no response. A significant association with OS was identified from a pooled estimated HR for pCR (HR 0.47, p-value=0.002) and non-responding tumours (HR 2.97, p-value <0.001). Previously known tumour characteristics such as ypN, lymphovascular and perineural invasion were also significantly associated with DFS and OS, with an estimated pooled HR of 2.2, 1.4 and 2.3 respectively.

Conclusion

In conclusion, the degree of TRG was of prognostic value in predicting long-term outcomes. The current challenge is the development of high validity tests to predict pathological complete response.

What does this paper add to the literature?

This study demonstrates the significant poorer prognosis for no response compared to partial and pathological complete response for locally advanced rectal cancer after neo-adjuvant chemo-radiotherapy. This provides an impetus for research to improve tumour response in those that has not responded to long course chemo-radiation.

Key words: Rectal cancer, neoadjuvant therapy, tumour response

Background

Colorectal cancer (CRC) is the fourth leading cause of cancer-related death worldwide, with a third of these tumours located in the rectum.[1] The current standard of care for locally advanced rectal cancer (LARC) is preoperative chemo-radiotherapy followed by total mesorectal excision (TME), particularly where the fascia propria is threatened.[2] The benefits of preoperative chemo-radiotherapy are well described, including an increase in the radiation effect. This is due to preservation of the local blood supply resulting in improved tissue oxygenation, thereby increasing radiation sensitivity, whilst minimising toxicity. The impact of this approach is tumour down-staging and to reduce the local recurrence rate. A pathological complete response (pCR), is confirmed where no residual tumour is identified in previously irradiated tumour bed.[3]

It is well documented that there is a spectrum of response to neoadjuvant chemo-radiotherapy (CRT); 10-25% will have a pCR, and an estimated 20% will have no response or tumour progression during treatment.[4-6] Consequently, there has been a significant shift in focus towards predicting and improving the rate of attaining a pCR, given this subset have a better 5-year disease-free survival (DFS) and overall survival (OS) compared to non-pCR tumours.[7] This subset of patients may also potentially avoid radical surgery ("watch and wait" approach), and the safe adoption of this management algorithm has been of great research interest.[8, 9]

There is an ongoing debate and conflicting data regarding the significance of pCR when compared to partial and non-responding tumours.[10-12] The limitations of these studies include their small sample size and absence of a standardized definition for TRG.[6, 13, 14] Moreover the majority of studies compare pCR to non-pCR (grouping partial and no

response together).[4, 15, 16] To date, there has only been one systematic review assessing specifically partial response tumours and its effect on outcome, published in 2012.[17] Included in that study were 1521 patients from 11 studies, and since then there has been eight new publications. Given the increasing body of evidence since this review, there is a genuine need to evaluate the prognostic significance of not only partial response but also complete and non-responding tumours.

For this reason, a meta-analysis was undertaken to determine the correlation of different levels of tumour regression grade (pCR, partial and non-response tumours) with long-term survival outcomes. Simultaneously the prognostic significance of other tumour reporting characteristics; such as ypN, lymphovascular invasion (LVI) or perineural invasion (PNI) after neoadjuvant CRT were assessed.

Methods

Search strategy and selection criteria

A systematic review and meta-analysis was performed in accordance with the PRISMA guidelines. The first step involved a comprehensive English literature search of all relevant studies in Ovid Medline, Embase and Google Scholar from January 1990 to December 2016. Two reviewers (JCK and GRG) performed the search and data extraction independently. Any discrepancy in the inclusion of a study or in data collection was independently reviewed by AGH. The search strategy can be found in Appendix A (for Ovid Medline and Embase) and the following keywords were used in combination; rectal cancer, neoplasm, complete response, tumour regression grade, neo-adjuvant therapy, and chemo-radiotherapy.

The inclusion criteria were pCR confirmed through histological examination of the resected specimen and comparison of pCR with partial and/or non-responding tumours. Studies were excluded if; there were less than 30 participants; authors included Stage IV patients; the study's main aim was to assess new neo-adjuvant agents without relevant comparisons required for this study; short course radiotherapy (5x5 Gy); long course radiotherapy alone and those without long-term outcomes or an estimated risk ratio over time.

Data extraction

A dataset consisting of agreed criteria was used in an electronic format to ensure all pertinent information was collected. This included author, year of publication, study period, number of centres, country of recruitment, study design, multivariate analysis adjustments, definition of each tumour regression grade, comparison undertaken in each study, number of participants, neo-adjuvant and adjuvant treatment, pathology after treatment (ypN, LVI and PNI), time interval from cessation of chemo-radiotherapy to surgery, covariates and time-to-event outcomes associated with survival data and long-term outcomes (DFS and OS).

Data analysis

In each study, time-to-event DFS and OS were extracted as hazard ratios (HR) with a 95% confidence interval.[18] Local tumour response was categorised as; 1) pCR; defined as no viable tumour identified in the resected specimen, 2) partial response; defined as Dworak TRG 1-3, Mandard TRG 2-4, and institution based partial response [19] and 3) no response; Dworak TRG 0, Mandard's TRG5 and institution based no response.

Multivariate regression hazard ratios were obtained if reported by the authors, otherwise univariate results were used; in which one study correlated pCR with DFS[6], and two studies correlated tumour distance from anal verge with outcomes. [11, 15, 20] Cox regression analysis for ypN, LVI and PNI were analysed as binary variables in all the included studies.

A pooled hazard ratio was calculated using a random-effect model because of study heterogeneity observed in some of the key covariates.[21] This model is an extension of a Bayesian meta-analysis, with the addition of a model fit using importance sampling and a likelihood-based approach.[21] Inter-study heterogeneity assessment was performed using I^2 statistic and can be interpreted as; 0-30% – minimal, 30-60% – moderate, 60-90% – substantial and 90-100% – considerable heterogeneity. The Newcastle-Ottawa scale was used to assess the quality of each study and a score of ≥6 represents good quality.

All statistical analyses were performed on IBM SPSS version 22 and RStudio version 0.99.486. A p-value <0.05 was considered significant.

Results

A total of 579 titles and abstracts were screened, with 58 studies selected for full text review, and a further 9 added after scanning the associated reference lists. Seventeen studies met the inclusion and exclusion criteria, with an overall patient number of 4785, in which 15.9% had pCR and 84.1% non-pCR (shown in Table 1). [4-6, 11-13, 15, 16, 20, 22-29] There were twelve retrospective studies[4, 11-13, 16, 20, 22, 24-28] four prospective observational studies[5, 6, 15, 29] and one randomised controlled trial[23] comparing pre- against post-operative chemo-radiotherapy.

All study participants had long-course neo-adjuvant CRT, which included radiotherapy (45-50.4 Gy) and 5-fluorouracil (5-FU) as a radiosensitising agent (as shown in Table 2). The interval time to surgery was >4 weeks, with the majority of surgeons performing a TME between 6-8 weeks post-neoadjuvant CRT. The shortest median follow-up was reported by Losi et al, at 35.3 months.[28] The use of adjuvant chemotherapy was another confounding factor identified in 12 studies. However, it did not affect DFS and/or OS in univariate or multivariate analysis across all studies.[5, 6, 12, 13, 15, 20, 23, 24, 27-30]

The overall local recurrence rate was 6.3% (285 patients) and distant recurrence was 20.7% (943 patients). In studies that reported on baseline characteristics between pCR and non-pCR, differences were seen in clinical T stage but not clinical N stage or tumour height from the anal verge. Local and distant recurrence was significantly higher in tumours which did not achieve pCR compared to those that did; 6.4% vs 1.8% and 25.3% vs 6.8% (p-value<0.001) respectively (see Table 3).

The degree of pathological response (pCR, partial, no response) showed significant prognostic power with an estimated pooled HR of 0.47 (95%CI 0.18-0.76, I^2 – 91.3%), 0.56 (95%CI 0.27-0.85, I^2 – 13.6%) and 2.97 (95%CI 1.6-4.34, I^2 – 0%; p-value=0.002, <0.001 and <0.001) for DFS respectively. However for OS, only pCR and partial response showed

significance with an estimated pooled HR of 0.43 (95%CI 0.17-0.69, I^2 – 35.3%) and 0.58 (95%CI 0.04-1.11, I^2 – 0%; p-value=0.001 and 0.035) respectively. The positive prognostic association of pathological response in 5-year DFS were 90.3%, 76.4% and 60.4%; and 5-year OS of 91.9%, 86.1% and 77.3%, for pCR, partial and no response respectively.

Three covariates, ypN, LVI and PNI were added into the analysis, and all had statistically significant association as a predictor for long-term outcomes; with estimated pooled HR for DFS of 2.2 (95%CI 1.76-2.64, I^2 – 0%), 1.5 (95%CI 1-1.75, I^2 – 0%) and 2.3 (95%CI 0.82-3.76, I^2 – 54.6%) respectively. All studies were assessed for quality and had scored > 6 using the Newcastle-Ottawa Scale, and consequently were deemed good quality studies.

Discussion

Amidst the rapid progression in research to develop reliable methods to identify pCR, this meta-analysis affirms that the degree of tumour response correlates with DFS and OS. This is clinically relevant, given the ever increasing interest in the “watch and wait” approach for those with a complete clinical response (cCR),[31] and the intensive search for new therapies to improve tumour response rates.[32] This question is particularly important if tumour regression is to be relied upon as a prognostic marker to direct clinical management away from the currently accepted doctrine in LARC.

One of the confounding factors that will affect rectal tumour response rate is the waiting time from cessation of neo-adjuvant CRT to surgery. The supporting evidence was reported in two recent meta-analyses, in which longer interval time to surgery (ideally 6 to 8 weeks) will yield higher pCR rates, than those who had surgery at 4 to 6 weeks with no added response rate beyond 9 weeks.[33, 34] This is not an issue in the current study as majority reported interval times of 6 to 8 weeks after neo-adjuvant CRT, with the exception of four studies, which reported minimum time to surgery of four weeks.[6, 11, 16, 26] Because it is reported as minimum interval time, it did not significantly impact the overall response rate in the individual results.

In this study, a reduced tumour response correlated in a stepwise manner to worsening DFS and a similar trend in OS. However only one study was identified for non-responding tumours, in which the HR was 4.43 but not statistically significant (p-value=0.19) for OS. Other commonly reported tumour characteristics were also negatively associated with long-term outcomes; including positive ypN, LVI and PNI. Prognostic markers such as ypN, LVI and PNI are commonly used to assess patient's risk of recurrence and therefore negate recommendation for adjuvant chemotherapy. However inconsistent reports on the significance of these markers to predict patient's prognosis is a concern.[11-13, 15, 22, 23, 29] By comparing the pooled HR results for each covariate, no response has the highest HR of 2.97, compared to LVI HR of 1.4, ypN HR of 2.2 and PNI HR of 2.3. Therefore this suggests that the worse tumour regression had the strongest predictive power, with clear demarcation between pCR, partial and no response.

In modern medicine, there has been a shift towards tailoring treatment to the individual, and this is gaining relevance in LARC where there is a heterogeneous response to neo-adjuvant CRT. There has been renewed interest in advocating the "watch and wait" approach in a subset of patients with pCR.[31] The idea of a rectal conserving approach was first popularised by Habr-Gama et al,[8] to avoid the associated morbidity related to surgery, which is in the order of 18-35%,[35-37] and mortality rate of 4-8%.[38]

On the premise of avoiding risk related to surgery, the Oncology Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe), prospective observational trial of real-world clinical practice in cancer treatment centres across the United Kingdom demonstrated no compromise in 3-year OS and DFS. This was reported as 96% and 88% ("watch and wait" group; HR 0.497, 95%CI 0.25-0.98, p-value=0.043) respectively in comparison to 87% and 78% in the immediate surgery group.[39] Similar findings were identified by Maas et al and Smith et al, reporting no significant difference in 2-year OS (100% and 97%) and DFS (89% and 88) between "watch and wait" and immediate surgery.[9, 40] These were however not prospective randomised trial, so can be biased.

Despite no difference in long-term outcomes between a "watch and wait" and immediate surgery approach, reservation in the adoption of this method remains. As reported in a systematic review of nine studies assessing the rate of salvage surgery for tumour regrowth after "watch and wait", salvage surgery was possible in 83.8% of patients. Furthermore, three patients went on to have local recurrences after salvage surgery, which was

statistically significant when compared to the immediate surgery group (no patients had local recurrence).[31] Consequently, the “watch and wait” approach is associated with a real risk of tumour regrowth within the previously treated tumour bed compared to the oncological certainty of surgery. Hence clinical complete response, a surrogate marker used to advocate for “watch and wait” approach does not always correlate with pCR.

The current challenge is to predict pCR accurately to allow change of management plan before radical surgery. Assessment of response to neo-adjuvant CRT has gained increasing research interest, but without much success. In the “watch and wait” approach, patients deemed to have achieved cCR must meet strict inclusion criteria. This includes digital rectal examination (DRE), and direct visualisation via endoscopy with biopsy of any suspicious lesion in irradiated tumour bed. [41] Poor correlation with this method was related to difficulty in distinguishing between fibrosis and microscopic tumour bed on palpation and the distribution of residual rectal cancer within different layers of bowel wall after neoadjuvnt CRT. [42]

Another method of increasing research traction is the utility of restaging magnetic resonance imaging (MRI) or positron emission tomography (PET). However this is not part of routine clinical practice. [43] Estimating pCR by PET relies on the degree of metabolic activity reduction after neoadjuvant CRT, with a baseline PET performed before treatment. Although this method has not been practice changing as yet due to poor specificity, [43] further refinement in a small prospective trial have noted measuring metabolic activity during neo-adjuvant CRT increased the sensitivity and specificity to 100% and 94% respectively. Another refinement was to use PET as an adjunct to clinical assessment of cCR, improving the overall accuracy from 91% to 96%. [44]

Championing the usage of restaging MRI is the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) group, whose main focus was to assess the accuracy of MRI in determining multiple facets of tumour response after neo-adjuvant CRT in relation to short-term (tumour regression) and long-term outcomes (DFS and OS). [45-47] In the process, the authors have developed MRI tumour regression grade (MR-TRG), to stratify good and poor responders.[47] From the study, they discovered extra-mural venous invasion was significantly predictive of poor responders in their updated series, when added to MR-TRG.[48] In their multivariate Cox-regression analysis, MR-vTRG grade 4-5 increases the risk of disease recurrence with an estimated HR of 5.75, and they concluded that it can

be used to identify high risk patients for more intensive therapy. Because patients were stratified as good versus poor responders, the accuracy to predict pCR using re-staging MRI cannot be determined.

Nonetheless in a meta-analysis (of 1,566 patients from 33 studies) performed by van der Paardt assessing the accuracy of re-staging MRI in predicting pCR, the pooled sensitivity and specificity were 19% and 94% respectively. This result was enhanced by applying diffusion weighted imaging (DWI), with significant increase in sensitivity to 84% but a lower specificity of 85%.[49] As there is currently only low quality studies with no convincing evidence favouring restaging MRI as a predictor of pCR, the TRIGGER trial, a multicentre randomised control trial assessing the utility of mrTRG may give clarity to the predictive accuracy of restaging MRI.

Many authors have attempted to predict response to neo-adjuvant CRT using various biomarkers including topoisomerase I, microsatellite instability, VEGF, EGFR and Ki-67.[50] These have all been shown to correlate with response but are not accurate to a level where they can be used as predictive markers to dictate clinical decision making. Similarly, gene expression profiling studies have failed to provide reliable prediction of pCR.[51, 52] A promising biomarker is tumour infiltrating lymphocytes which was reported to have significant discriminatory power in determining outcome compared to the traditional AJCC TNM staging.[53, 54] A large international consortium is currently underway to validate the utility of “Immunoscore” in routine clinical practice for colorectal cancer.[55]

As we wait for accurate prognostic tools, there is value in optimising neo-adjuvant therapy. Although “watch and wait” is relevant in a subset of patients, it is not the primary goal as multidisciplinary care with all modalities including surgery has demonstrated excellent results. Quantification of the potential benefit of tumour response to long term survival supports the concept of developing and improving the current neoadjuvant regimen to improve response rate. Recent trials have attempted to improve tumour response rate by adding oxaliplatin to flurouracil and/or combination with bevacizumab.[56, 57] So far this has not been shown to make any difference.

There are some limitations to our review. First data extracted was predominantly from retrospective studies (twelve out of seventeen), with half derived from prospectively

maintained databases. Second is the simplification of combining Dworak's and Mandard's classification into partial and no response to reduce the variability and subsets of partial response. The assessment of TRG is subjective, and classification can vary between pathologist, therefore may not be representation of partial/no response. Third is the potential for publication bias, as negative results are less likely to be published and abstracts from podium presentations are not included in this review. Fourth, some of the pooled HR's are from a small number of studies, such as the partial response pooled HR for OS, in which there were only two studies, with some results not necessarily representative of the true effect. Fifth inter-study heterogeneity was present in some of the subgroup analyses, compounded by differences between studies in grading tumour response rate.

In conclusion, this study substantiates the clinical importance of tumour regression grade as a prognostic factor for long-term outcome in patients with locally advanced rectal cancer. As research progresses, robust methods to predict pCR and the development of novel neo-adjuvant therapies to improve response rate has the potential to improve long-term outcome for these patients.

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Tables

Author and Year	Study Period	No. of centres and country	Study Design	Multivariate adjustments	Definition pCR	Comparison
De Felice 2016[15]	2007 to 2014	1, Italy	Prospective observational study	Age, sex, tumour; diameter, distant from AV, stage; ITS, NACRT and interruption of Rx	Absence of residual tumour in the operative specimen, including mesorectal fat and LNs	non-pCR
Wilkins 2016[16]	2010 to 2014	2, Australia	Retrospective study from prospectively maintained database	Age, sex, tumour; distance from AV, depth of invasion, stage, neoadjuvant Rx	Absence of detectable viable tumour cells in the specimen	non-pCR
McCoy 2015[22]	2006 to 2013	1, Australia	Retrospective study from prospectively maintained dtabase	Age, sex, tumour; stage, LVI, PNI, EMVI, type of operation	Dworak System Grade 4	Dworak
Wasmuth 2015[4]	2000 to 2009	36-56, Norwegian	Retrospective study from prospectively maintained database	Age, tumour; stage, operative procedure	No viable tumour identified	non-pCR
Fokas 2014[23]	1995 to 2002	26, Germany	Randomised control trial	Age, sex, tumour; height, stage,	Dworak System Grade 4	Dworak
Abdul-Jalil 2013[12]	2000 to 2010	1, Ireland	Retrospective observational study	Age, sex, tumour; stage, height, operative procedure, NACRT	RCPath	RCPath
Agarwal 2013[20]	2000 to 2008	1, USA	Retrospective observational study	Age, sex, tumour; distance from AV, stage, PNI, LVI, adjuvant chemotherapy, surgical margin	No residual cancer cells	Institution based TRG
Santos 2013[24]	2003 to 2011	1, Portugal	Retrospective study from prospectively maintained database	Age, sex, tumour; stage, distance from AV, surgical procedure	Mandard 1	Poor response (Mandard 3-5)
Park 2012[25]	1993 to 2008	1, USA	Retrospective observational study	Age, sex, tumour; distance from AV, stage, PNI, LVI, adjuvant chemotherapy,	Specimens with acellular mucin pools without viable tumour cells	Institution based TRG

De Campos-Lobato 2011[26]	1997 to 2007	1, USA	Retrospective study from prospectively maintained database	Age, sex, BMI, ASA, tumour; differentiation, distance from AV, margins, stage, neoadjuvant and adjuvant Rx	Absence of viable adenocarcinoma cells in the surgical specimen	non-pCR
Topova 2011[13]	1997 to 2009	1, Germany	Retrospective study from prospectively maintained database	Tumour; stage, LVI, venous invasion, neoadjuvant and adjuvant Rx	Dworak System Grade 4	Dworak
Hong 2010[5]	2004 to 2005	1, Korea	Prospective observational study	Tumour stage	Dworak Grade 4	Dworak
Kim 2010[30]	2001 to 2006	1, Korea	Retrospective observational study	Age, sex, tumour; stage, distance from AV, CEA, CRM, neoadjuvant and adjuvant Rx	Dworak Grade 4	Dworak
Losi 2006[28]	1998 to 2004	1, Italy	Retrospective observational study	Tumour; stage, down staging, adjuvant Rx	Dworak Grade 4	Poor response (Dworak 0-2)
Shivnani 2007[11]	1992 to 2002	1, USA	Retrospective observational study	Age, tumour;stage, location	No residual tumour identified (ypT0)	non-pCR
Chan 2005[29]	1993 to 2000	1, Canada	Prospective observational study	Tumour stage, fixed or tethered, LNI	No viable tumour identified	non-pCR
Ruo 2002[6]	1987 to 1983	1, USA	Prospective observational study	Age, sex, tumour stage	No viable tumour identified	Institution based TRG

Table 1: Study design, number of centres, country, multivariate adjustments and definitions of pCR

AV – anal verge, ITS – interval time to surgery, NACRT – neoadjuvant chemoradiotherapy, Rx – treatment, LVI – lymphovascular invasion, PNI – perineural invasion, EMVI – extramural venous invasion, CRM – circumferential resection margin, LN – lymph node

Author and Year	Total patients	Median age	95%CI	NRT (Gy)	NCT	ITS (weeks)	Adjuvant Rx	No. adj Rx	Median f/u	pCR (%)	PR (%)	No response (%)	non-pCR	LR (%)	DR (%)

De Felice 2016[15]	100	64	38-76	50.4/54	5-FU and OX	7-9	Yes, NR	NA	60 §	24 (24)	NA	NA	76 (76)	9	23
Wilkins 2016[16]	108	61.2ł	NA	NA	NA	4-14	NA	NA	36.9	26 (24.1)	NA	NA	92 (75.9)	1	23
McCoy 2015[22]	205	62ł	NA	50.4	5-FU or CP	6-8	NA	NA	60.2	46 (22.4)	159 (77.6)	0	159 (77.6)	6	33
Wasmuth 2015[4]	1531	63ł	31-84	50	5-FU	6-8	NA	NA	60	147 (9.6)	NA	NA	1384 (90.4)	86	340
Fokas 2014[23]	385	NA	NA	50.4	5-FU	6	5-FU	NA	132	40 (10.4)	254 (66)	91 (23.6)	345 (89.6)	22	119
Abdul-Jalil 2013[12]	153	64ł	24-79	45/50.4	5-FU	6-8	5-FU	122	36	36 (23.5)	NA	NA	117 (76.5)	4	30
Agarwal 2013[20]	251	55	NA	50.4	5-FU or CP	6-8	5-FU or CP/OX/IT/ bevacizumab	222	65-76	53 (21.1)	143 (57)	55 (21.9)	198 (78.9)	NA	NA
Santos 2013[24]	139	NA	NA	50.4	5-FU	8	5-FU+/-OX	NA	56 §	25 (18)	NA	NA	114 (82)	6	22
Park 2012[25]	725	57	48-66	50.4	5-FU or CP	6-8	5-FU or CP/OX bevacizumab	611	65	131 (18.1)	211 (29.1)	384 (52.7)	595 (81.9)	39	133
De Campos-Lobato 2011[26]	238	54ł	45-62	50.4	5-FU or CP	4-8	NA	107	55	58 (24.4)	NA	NA	180 (75.6)	39	24
Topova 2011[13]	174	65	37-84	50.4	5-FU or CP +/- OX	6	5-FU or CP +/- OX	81	45	37 (21.3)	134 (77)	3 (1.7)	137 (78.7)	9	27
Hong 2010[5]	44	59	32-72	50.4	CP and IT	6-8	CP	NA	59	11 (25)	30 (68.2)	3 (6.8)	33 (75)	1	12
Kim 2010[30]	420	58	27-83	50.4	5-FU and LEU or CP +/- IT	6	5-FU and LEU or CP +/- IT	406	50.5	58 (13.8)	289 (68.8)	73 (17.4)	362 (96.2)	43	90
Losi 2006[28]	106	64	29-80	50	5-FU	6-8	5-FU and FA	106	35.3	16 (15.1)	87 (82.1)	3 (2.8)	90 (84.9)	7	17
Shivnani 2007[11]	100	61	24-86	50.4	5-FU	4-8	NA	NA	52.4	25 (25)	15 (15)	60 (60)	75 (75)	5	17
Chan	127	62	30-79	50	5-FU, LEU	9	5-U and LEU	99	60	32	48	47 (37)	95 (74.8)	8	33

2005[29]					and MMC					(25.2)	(37.8)			
Ruo 2002[6]	69	57	24-79	50.4	5-FU and LEU	4-7	5-FU	NA	NA	10 (14.5)	59 (85.5)	0	59 (85.5)	NA	NA
Total	4875									775 (15.9)	1429	719 (29.9)	4111 (84.1)	285 (6.3)	943 (20.7)

Table 2: Patient neoadjuvant and adjuvant treatment regimens, treatment response and number of patients with local and distant recurrence

ł mean follow-up for pCR only

NA – not available, NRT – neoadjuvant radiotherapy, NCT – neoadjuvant chemotherapy, ITS – interval time from completion of treatment to surgery, adj – adjuvant, pCR – pathological complete response, PR – partial response, LR – local recurrence, DR – distant recurrence, OX –oxaliplatin, CP – capecitabine, 5-FU – 5-fluorouracil, IT – irinotecan, LEU – leucovorin, MMC – mytomycin, FA – folinic acid

Variable (No. of study)	pCR	non-pCR	p-value
Sex (8)[4, 12, 16, 20, 22, 23, 25, 26]			
Male	334 (15)	1894 (85)	
Female	203 (16.5)	1028 (83.5)	0.244
Stage			
T (7)[4, 12, 16, 20, 22, 23, 26]			
2	26 (41.3)	37 (58.7)	
3	267 (17.7)	1242 (82.3)	
4	45 (10)	407 (90)	<0.001
N (6)[12, 16, 20, 22, 23, 26]			
Negative	106 (20.2)	419 (79.8)	
Positive	146 (19)	621 (81)	0.607
Tumour height (5)[12, 16, 20, 22, 25]			
Low (<5)	127 (21.3)	468 (78.6)	
Mid (5-10)	108 (18.4)	481 (81.6)	
High (>10)	52 (22.2)	182 (77.8)	0.31

Local recurrence[4, 11, 16, 22, 23, 26, 28, 30]			
Yes	8 (1.8)	181 (6.4)	
No	450 (98.2)	2633 (93.6)	<0.001
Distant recurrence[4, 11, 16, 23, 28, 30]			
Yes	26 (6.8)	618 (25.3)	
No	359 (93.2)	1826 (74.7)	<0.001

Table 3: Clinical staging tumour characteristics

Pearson chi-square or Fisher's exact test was performed

Variable (No. of studies)	Author	Pooled HR	95%CI	p-value	I^2 statistics (%)	p-value
Disease Free Survival						
Pathological complete response (10)	Wilkins 2016, McCoy 2015, Fokas 2014, Santos 2013, De-Campos Lobato 2013, Topova 2011, Losi 2006, Chan 2005, Ruo 2005	0.47	0.18-0.76	0.002	91.3	<0.0001
Partial response (6)	McCoy 2015, Agarwal 2013, Park 2012, Topova 2011, Hong 2010, Kim 2010	0.56	0.27-0.85	<0.001	13.6	0.312
Poor response (5)	Abdul-Jalil 2013, Agarwal 2013, Park 2012, Hong 2010, Kim 2010	2.97	1.6-4.34	<0.001	0	0.92
ypN - positive vs negative (9)	McCoy 2015, Fokas 2014, Abdul-Jalil 2013, Argawal 2013, Topova 2011, Hong 2010, Shivnani 2007, Chan 2005, Ruo 2002	2.2	1.76-2.64	<0.001	0	0.469

LVI (5)	McCoy 2015, Fokas 2014, Agarwal 2013, Park 2012, Chan 2005	1.4	1-1.75	<0.001	0	0.63
PNI (3)	McCoy 2015, Agarwal 2013, Park 2012	2.3	0.82-3.76	0.002	54.6	0.111
Overall Survival						
Pathological complete response (5)	De Felice 2016, McCoy 2015, Wasmuth, 2015, Santos 2013, Topova 2011	0.43	0.17-0.69	0.001	35.3	0.186
Partial response (2)	McCoy 2015, Topova 2011	0.58	0.04-1.11	0.035	0	0.961
Poor response (1)	De Felice 2016	4.43	0.02-2.07	0.19		
ypN - positive vs negative (3)	De Felice 2016, McCoy 2015, Topova 2011	1.62	1.14-2.1	<0.001	0	0.72

Table 4: Pooled estimated hazard ratio for different tumour response category.

Author and Year	**pCR**		**Partial responders**		**Poor Responders**	
	DFS (%)	**OS (%)**	**DFS (%)**	**OS (%)**	**DFS (%)**	**OS (%)**
De Felice 2016[15]	95.7	95.7				70.4
McCoy 2015[22]	88.8	97.5			70	80
Wasmuth 2015[4]	81	87				67
Fokas 2014[23]	86		75			
Abdul-Jalil 2013[12]	100	88	86		67	
Agarwal 2013[20]	95.5		87.3-69.1		61.8	
Park 2012[25]	90.5	93.4	78.7	87	58.5	77.3

Topova 2011[13]	96.6	100	72.2-64.7	83-80.1	33.3	33.3
Hong 2010[5]	90.9		87.5-62.5			
Kim 2010[27]	92.5		91-78		56	
Losi 2006[28]	100					
Shivnani 2007[11]	89	91.3	77	79.5	75	79.5
Chan 2005[29]	97				60	
	90.3	91.9	76.4	86.1	60.4	77.3

Table 5: 5-year DFS and OS from each study

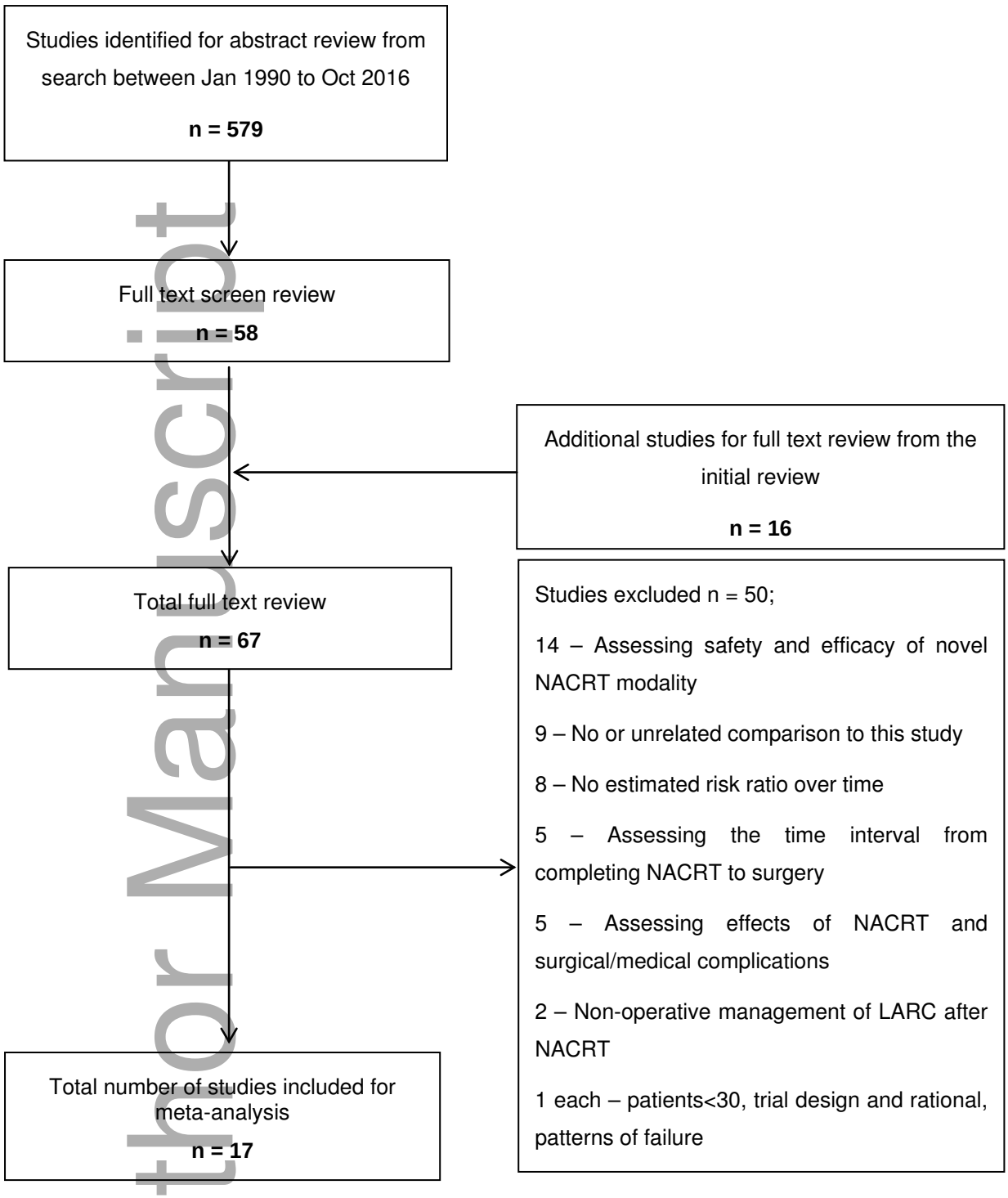

Figure 1: Flow diagram of search strategy

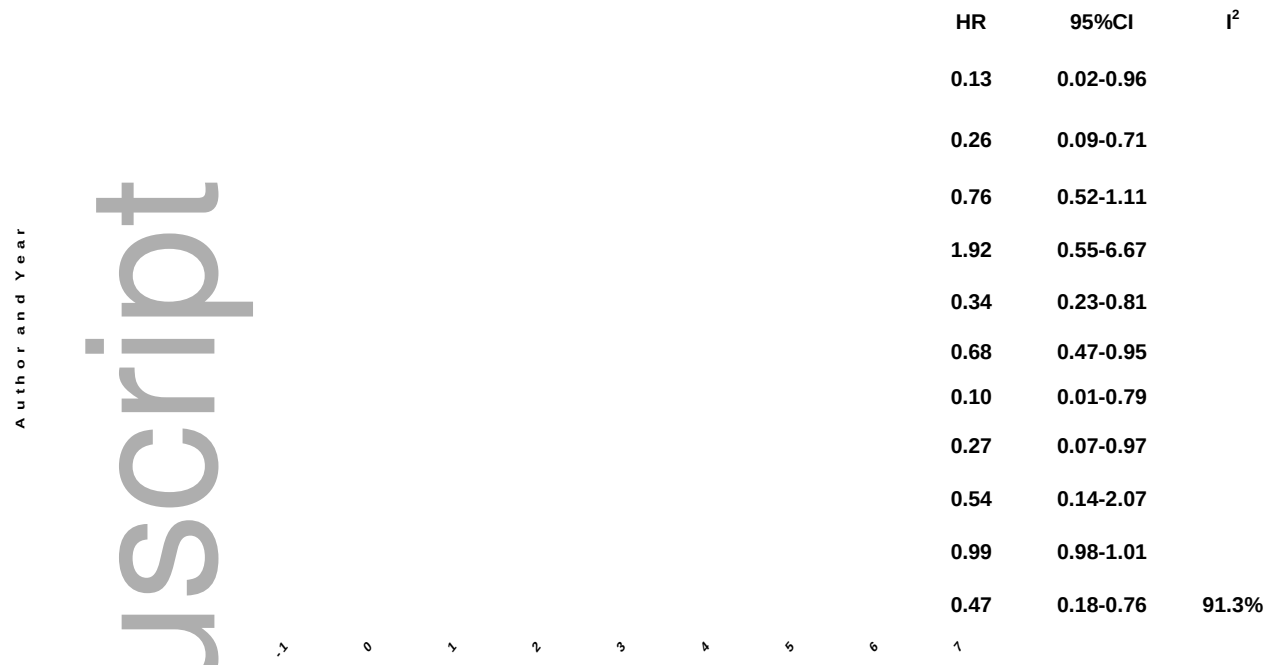

Figure 2: Forrest plot showing hazard ratio for pCR and DFS for each study, and total effect size for pooled HR

Figure 3: Forrest plot showing hazard ratio for pCR and OS for each study, and total effect size for pooled HR

Conflicts of Interest

No financial disclosures or conflicts of interest.