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Defining response to radiotherapy in rectal cancer using magnetic resonance imaging and histopathological scales

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Abstract

AIM

To define good and poor regression using pathology and magnetic resonance imaging (MRI) regression scales after neo-adjuvant chemotherapy for rectal cancer.

METHODS

A systematic review was performed on all studies up to December 2015, without language restriction, that were identified from MEDLINE, Cochrane Controlled Trials Register (1960-2015), and EMBASE (1991-2015). Searches were performed of article bibliographies and conference abstracts. MeSH and text words used included "tumour regression", "mrTRG", "poor response" and "colorectal cancers". Clinical studies using either MRI or histopathological tumour regression grade (TRG) scales to define good and poor responders were included in relation to outcomes [local recurrence (LR), distant recurrence (DR), disease-free survival (DFS), and overall survival (OS)]. There was no age restriction or stage of cancer restriction for patient inclusion. Data were extracted by two authors working independently and using pre-defined outcome measures.

RESULTS

Quantitative data (prevalence) were extracted and analysed according to meta-analytical techniques using comprehensive meta-analysis. Qualitative data (LR, DR, DFS and OS) were presented as ranges. The overall proportion of poor responders after neo-adjuvant chemo-radiotherapy (CRT) was 37.7% (95%CI: 30.1-45.8). There were 19 different reported histopathological scales and one MRI regression scale (mrTRG). Clinical studies used nine and six histopathological scales for poor and good responders, respectively. All studies using MRI to define good and poor response used one scale. The most common histopathological definition for good response was the Mandard grades 1 and 2 or Dworak grades 3 and 4; Mandard 3, 4 and 5 and Dworak 0, 1 and 2 were used for poor response. For histopathological grades, the 5-year outcomes for poor responders were LR 3.4%-4.3%, DR 14.3%-20.3%, DFS 61.7%-68.1% and OS 60.7-69.1. Good pathological response 5-year outcomes were LR 0%-1.8%, DR 0%-11.6%, DFS 78.4%-86.7%, and OS 77.4%-88.2%. A poor response on MRI (mrTRG 4,5) resulted in 5-year LR 4%-29%, DR 9%, DFS 31%-59% and OS 27%-68%. The 5-year outcomes with a good response on MRI (mrTRG 1,2 and 3) were LR 1%-14%, DR 3%, DFS 64%-83% and OS 72%-90%.

CONCLUSION

For histopathology regression assessment, Mandard 1, 2/Dworak 3, 4 should be used for good response and Mandard 3, 4, 5/Dworak 0, 1, 2 for poor response. MRI indicates good and poor response by mrTRG1-3 and mrTRG4-5, respectively.

Key words: Tumour regression; mrTRG; Poor response; Neo-adjuvant therapy; Rectal cancer

Core tip: The degree of primary tumour regression following neo-adjuvant therapy identified on final histopathological specimens is a prognostic factor and response variation has allowed risk stratification, aiding in post-surgical treatment and follow-up decisions. To do this effectively, we need to have a common language for defining good and poor response. Definitions of response using histopathology scales are heterogenous with 19 different scales. There is one pre-operative magnetic resonance imaging (MRI) scale. Outcomes of recurrence and survival histopathology regression assessments should use Mandard 1, 2/Dworak 3, 4 for good response and Mandard 3, 4, 5/Dworak 0, 1, 2 for poor response. MRI indicates good and poor response by mrTRG1-3 and mrTRG4-5, respectively.

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INTRODUCTION

Rationale

The multidisciplinary treatment of rectal cancer has markedly improved and led to better patient outcomes over the last three decades[1]. The reasons for this are multifactorial, but one important factor is the use of neo-adjuvant or adjuvant therapies[2].

The degree of primary tumour regression following neo-adjuvant therapy, identified on final histopathological specimens, has been shown to be a prognostic factor[3,4]. The variation in response allows clinicians to risk-stratify patients after surgery, which may help in post-operative decisions, such as who to treat with adjuvant chemotherapy and the intensity of follow-up.

Clinical studies use a number of different tumour regression grade (pTRG) scales to classify the degree of tumour response to neo-adjuvant chemo-radiotherapy (CRT). This often results in confusion as to whether a good or poor response has been achieved, with subsequent uncertainty regarding treatment and prognostic implications. This problem was highlighted by MacGregor *et al*[1] who stressed the importance of a universally accepted standard.

There has been no review of the reported pTRG scales to date. It is necessary to highlight the heterogeneity in these scales, in order to consolidate the current definitions with the purpose of converging towards a set of consensus definitions.

A newer method of assessing tumour regression relies on MRI (mrTRG), which has been validated as a prognostic tool. This may supercede pTRG, as it has the advantage of assessing tumour response before surgery. As such, it has the potential for enabling response-orientated tailored treatment, including alteration of the surgical planes, additional use of chemotherapy, or deferral of surgery[5-7].

Objective

This article investigates all the pathology tumour regression scales used to define good and poor response after neo-adjuvant chemotherapy for rectal cancer, to establish the true prevalence of poor responders and to identify the best scales to use in relation to outcomes.

MATERIALS AND METHODS

Protocol and registration

The title, methods and outcome measures were stipulated in advance and the protocol is available in the PROSPERO database[8].

Types of studies

All clinical, histopathological and imaging studies that define or attempt to define good and poor responders after neo-adjuvant therapy for colorectal cancers were identified. Included studies were those investigating rectal cancer response to neo-adjuvant therapy incorporating chemotherapy, radiotherapy or chemo-radiotherapy with different protocols. All clinical studies were chosen that defined good and poor response in relation to TRG or degree of response according to histopathology using terms such as "poor response", "minor response", "less response", "good response", "major response" or "more response".

Types of participants

All rectal cancer patients treated with long course radiotherapy or an interval period to surgery were selected for this review. All sensitizing chemotherapy protocols were included. Any surgical resection was included. Studies were also included with any post-operative adjuvant practice.

Exclusion criteria

Excluded studies were those that did not specifically state whether a response was good or poor, or that qualify it with some form of inference in the paper. Further exclusions were for: non-conventional deliveries of neo-adjuvant therapy, such as endo-rectal brachytherapy; trans-anal endoscopic microsurgery (commonly known as TEMS) and local excisions; and, when the reporting scale was in obvious contradiction with the order given in the original studies[9].

Types of variable of interest

The original papers reporting the various pTRG scales were identified and articles that used the scales in clinical, pathological and MRI studies were used in the current study.

Hypotheses and types of outcome measures

The primary hypothesis was that there is an optimal histopathological TRG scale that appropriately distinguishes between good and poor response. The secondary hypothesis was that the mrTRG scale differentiates between good and poor response. This was investigated by first reviewing the clinical studies examining the response of rectal cancer to neo-adjuvant therapy. These studies were used to show the range of definitions of good and poor response according to histopathology and MRI. This was then utilised to identify the optimal scale for identifying good and poor response after neo-adjuvant therapy for rectal cancer based on recurrence and survival outcomes.

Information sources

The Cochrane library, CENTRAL, EMBASE, CINAHL and PubMed databases were searched between January 1935 and December 2015. Relevant articles referenced in these publications were obtained and the "related article" function was used to widen the results. This was complemented by hand searches and cross-references from papers identified during the initial search. No language restriction was applied.

Searches

The text words "preoperative", "neo-adjuvant", "tumour regression", "poor responder", "good responder", "regression grading", "regression grade" and "rectal cancer" were used in combination with the medical subject headings "adjuvant combined modality therapy" and "rectal cancer". Irrelevant articles not fulfilling the inclusion criteria were excluded.

Study selection and data collection process

Each included article according to our review criteria was reviewed by two researchers (MRSS and JB). Where more specific data or missing data was required, the authors of the manuscripts were contacted. Data was entered onto an Excel worksheet and compared between authors. Any disagreements that arose between the reviewers were resolved through discussion, and if no consensus could be reached a third author (GB) would decide.

Data items

Data were extracted that related to the definition of good and poor response according to the TRG scales reported in clinical, histopathological and imaging studies. The ranges of permutations of each TRG scale to define good or poor response were also documented and the most commonly used definitions identified. The primary hypothesis was proven by examining all of the studies on response to neo-adjuvant therapy and there is a single definition (which may include other scales) that consistently differentiates between good and poor responses as defined by local recurrence (LR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS).

Risk of bias and quality assessment

Quality assessment and risk of bias was not formally assessed due to the exploratory nature of this review. Validity of other studies was benchmarked to studies that identified a significant difference. Clinical heterogeneity can be seen in the table of characteristics presented as Table 1.

Summary measures and data synthesis for summative and comparative meta-analyses

As part of assessing overall prevalence of poor responders, cumulative meta-analytical techniques were used. Analyses were performed using Comprehensive Meta-Analysis 2006 (Version 2, Biostat, Englewood, NJ, United States) for Windows 10[10]. In a sensitivity analysis, 0.5 was added to each cell frequency for

Table 1 Characteristics of studies reporting on good or poor response based upon histopathology

Ref.	Year	Chemotherapy protocol with radiotherapy	Radiotherapy protocol (Gy)	Surgical procedures	TME	Time to surgery (wk)	Cancer stage pre neo-adjuvant therapy	Adjuvant therapy
Gambacorta *et al*[21]	2004	Ralitrexed	50.4	APR/AR/Col-Anal resection/ Stoma	Y	6-8	Stage 2 or 3	Y
Pucciarelli *et al*[28]	2004	Fluorouracil, leucovorin carboplatin, oxaliplatin	45-50.4	APR/AR/ Hartmann's	Y	2-8	T2/3/4, N0/1/2	Y
Beddy *et al*[17]	2008	Fluorouracil	45-50	APR/AR	Y		T3/4, N1/2	
Giralt *et al*[22]	2008	Tegafir uracil, leucovorin	45 + 9 boost	APR/AR	Y	4-6	T3/4, N0/1/2	Y
Horisberger *et al*[24]	2008	Capecitabine, irinotecan	50.4	APR/AR/stoma	Y	4-7	T2/3/4, N+	
Suárez *et al*[31]	2008	Fluoropyridine-based	50.4	APR/AR/ Hartmann's	Y	6	Stage 2 or 3	Y
Bujko *et al*[18]	2010	Fluorouracil, leucovorin	50.4	APR/AR/ Hartmann's	Y	4-6	Stage 2 or 3	Y
Avallone *et al*[13]	2011	Fluorouracil, levo-folinic acid, ralitrexed, oxaliplatin	45.0	APR/AR/Stoma	Y	< 8	T3/4, N0/1/2	Y
Eich *et al*[19]	2011	Fluorouracil	50.4	APR/AR/TEMS/ Intersphincteric Surgery	Y	4-6	Stage 1,2 or 3	Y
Min *et al*[27]	2011	Fluorouracil, leucovorin	50.4	APR/AR	Y	6	T3/4, N0/1/2	
Shin *et al*[30]	2011	Fluorouracil	25-50.4	APR/AR/Pan		4-6	T3/4	
Huebner *et al*[25]	2012	Fluorouracil		APR/AR			T1/2/3/4, N0/1/2	Y
Lim *et al*[26]	2012	Capecitabine, fluorouracil, leucovorin	44-46+4.6 boost	Radical Proctectomy	Y		T3/4, N+	Y
Roy *et al*[29]	2012	Capecitabine, fluorouracil	45-50		Y	4-6	T1/2/3/4, N0/1/2	Y
Vallböhmer *et al*[32]	2012	Fluorouracil	50.4	APR/AR	Y		T3/4, N0/1/2	
Winkler *et al*[33]	2012	Capecitabine, oxaliplatin	45-50.4		Y	4-6	Stage 2 or 3	Y
Elezkurtaj *et al*[20]	2013	Fluorouracil	50.4		Y	4-6		
Hermanek *et al*[23]	2013			APR/AR/ Hartmann's	Y			Y
Fokas *et al*[14]	2014	Fluorouracil	50.4	APR/AR	Y	4-6	T3/4 or any T and N+	Y
Santos *et al*[16]	2014	Fluorouracil	50.4	APR/AR	Y	< 8	T2N+ or T3/4	Y
Hav *et al*[15]	2015	Fluorouracil, cetuximab, oxaliplatin	25-45	AR/Hartmann's	Y	6-8	T3/4 or any T and N+	

APR: Abdominoperineal resection; AR: Anterior resection; Pan: Panproctocolectomy; Col-Anal: Colorectal and anal resection; TME: Total mesorectal excision; Gy: Gray.

trials in which no event occurred, according to the method recommended by Deeks *et al*[11] and was not considered to affect the overall result necessitating the Peto method[12]. Where only a single patient was present in any of the groups, this was excluded due to the excessive effect of zero cell correction. Outcomes were reported as event rates. Forest plots were used for the graphical display.

Publication bias

For the outcome of prevalence, publication bias was assessed using funnel plots. We used the plots to subjectively assess asymmetry and conducted an Egger test for quantitative assessment.

RESULTS

Study selection and characteristics

There were 328 references. Full texts of 85 papers were reviewed. Overall, 21 articles were of relevance and reported 25 definitions for poor response in accordance with the TRG[13-33]. Of these, 16 articles also defined good response. Table 1 shows the characteristics of individual studies.

Qualitative and quantitative syntheses

Histopathological methods of classifying regression: There were 19 TRG scales reported across the studies[18,25,34-51] (Table 2). Only one TRG system incorporated whether a response was poor or good[36] and used a categorical TRG scale based on the one described by Dworak *et al*[35].

Which scales are used to define poor response using histopathological methods?

From the search, nine scales[18,25,34-36,38,40,43,44,46] were used in 25 reports (21 articles) to define poor response[13-33]. From these 25 reports, the nine scales were used in different combinations to produce 16 individual definitions of poor response (Table 3).

Table 2 Summary of histopathological tumour regression grade scales available in the literature for rectal cancer after neo-adjuvant treatment

TRG scale	Mandard (Low no. - More regression)[43]
0	
1	Complete regression - absence of residual cancer and fibrosis
2	Presence of rare residual cancer
3	An increase in the number of residual cancer cells, but predominantly fibrosis
4	Residual cancer outgrowing fibrosis
5	Absence of regressive changes
TRG scale	Modified Mandard (Ryan) (Low no. - More regression)[37]
0	
1	TRG 1 and 2 of the Mandard scale
2	TRG 3 of the Mandard scale
3	TRG 4 and 5 of the Mandard scale
4	
5	
TRG scale	Werner and Hoffler (Low no. - More regression)[41]
0	
1	0% viable tumour cells
2	< 10% viable tumour cells
3	10%-50% viable tumour cells
4	> 50% viable tumour cells
5	No regression
TRG scale	Dworak (Low no. - Less regression)[35]
0	No regression
1	Dominant tumour mass with obvious fibrosis and/or vasculopathy
2	Dominant fibrotic change with few tumour cells or groups(easy to find)
3	Very few tumour cells in fibrotic tissue with or without mucous substance
4	No tumour cells, only fibrotic mass (total regression or response)
5	
TRG scale	Modified Dworak (Low no. - Less regression)[38]
0	No regression
1	Regression ⩽ 25% of tumour mass (dominant tumour mass with obvious fibrosis and/or vasculopathy)
2	Regression > 25%-50% of tumour mass (dominantly fibrotic changes with few tumour cells of groups, easy to find)
3	Regression > 50% of tumour mass (very few tumour cells in fibrotic tissue with or without mucous substance)
4	Complete (total) regression (or response): no vital tumour cells
5	
TRG scale	AJCC 7th Edition[48]
0	Complete-no viable cells present
1	Moderate-single cells/small groups of cancer cells
2	Minimal-residual cancer outgrown by fibrosis
3	Poor-minimal or no tumour kill, extensive residual cancer
4	
5	
TRG scale	Memorial Sloan-Kettering (Low no. - Less regression)[47]
0	0%-85% regression
1	86-99% regression
2	100% regression
3	
4	
5	
TRG scale	Cologne (Low no. - Less regression)[40]
0	
1	> 50 % Viable rectal tumour cells
2	10%-50% Viable rectal tumour cells
3	Near complete regression with < 10% Viable rectal tumour cells
4	Complete regression (pathologic complete remission and ypT0)
TRG scale	Bujko/Glynne Jones (Low no. - More regression)[18,44]
0	No cancer cells
1	A few cancer foci in less than 10% of tumour mass
2	Cancer seen in 10%-50% of tumour mass
3	Cancer cells seen in more than 50% of tumour mass
4	
TRG scale	College of American Pathologists[50]
0	Complete response: No residual tumour
1	Marked response: Minimal residual cancer
2	Moderate response: Residual cancer outgrown by fibrosis
3	Poor or no response: Minimal or no tumour kill; extensive residual cancer
4	
TRG scale	RCPath system (Low no. - More regression)[42]
0	
1	No residual cells and/or mucus lakes only
2	Minimal residual tumour *i.e.*, microscopic residual tumour foci only
3	No marked regression
4	
TRG scale	RCRG system (Low no. - More regression)[34]
0	
1	Sterilisation or only microscopic foci of adenocarcinoma with marked fibrosis
2	Marked fibrosis but macroscopic disease present
3	Little or no fibrosis with abundant macroscopic disease
4	
TRG scale	Mod RCRG system (Low no. - More regression)[45]
0	
1	Macroscopic features may be varied. Microscopy reveals no tumour or < 5% of area of abnormality
2	Macroscopic features may be varied. Microscopy reveals combination of viable tumour and fibrosis. Tumour comprises 5%-50% of overall area of abnormality
3	Macroscopic or microscopic features may not be significantly different. Over 50% comprises tumour. Some fibrosis may be present but no more than untreated cases
4	
TRG scale	Japanese (Low no. - Less regression)[25]
0	No regression
1a	Minimal effect (necrosis less than 1/3)
1b	Mild effect (necrosis less than 2/3 but more than 1/3)
2	Moderate effect (necrosis more than 2/3 of the lesion)
3	No tumour cells
TRG scale	Ruo (Low no. - Less regression)[39]
0	No evidence of response
1	1% to 33% response
2	34% to 66% response
3a	67% to 95% response
3b	96% to 99% response
4	100% response (no viable tumour identified)
TRG scale	Junker and Muller (Low no. - Less regression)[46]

1	No regression
2a	> 10% residual tumour cells
2b	< 10% residual tumour cells
3	Total regression (no viable tumour cells)
TRG scale	Rodel (Low no. - Less regression)[36]
Poor	TRG 1 and 0 of the Dworak scale
Intermediate	TRG 2 and 3 of the Dworak scale
Complete	TRG 4 of the Dworak scale
TRG scale	Four point scale Swellengrebel *et al*[49]
pCR	Pathological complete response without residual primary tumour
Near pCR	Isolated residual tumour cells/small groups of residual tumour cells
Response	Stromal fibrosis outgrowing tumour
No response	No regression or those with stromal fibrosis outgrown by tumour
TRG scale	Modified Mandard TRGN by Dhadda *et al*[51]
TRGN 1	Complete regression with absence of residual cancer and fibrosis extending through the wall
TRGN 2	Presence of rare residual cancer cells scattered through the fibrosis
TRGN 3	An increased number of residual cancer cells, but fibrosis is still predominant

The overall proportion of poor responders after neo-adjuvant CRT was 37.7% (95%CI: 30.1-45.8) (Table 4, Figure 1). Study characteristics can be seen in Table 1. Table 5 shows the scales that define poor response with their permutations. Most studies used the Mandard or Dworak TRG scales. The studies using the Mandard scale[13,16,21,22,28-31] defined poor response as Mandard TRG 3 to 5, 4 or 4 to 5. The Dworak scale uses a similar numerical scale in the opposite direction to the Mandard system. From the articles that use the Dworak classification for their definitions[14-16,20,25,26,29,33], a poor response was defined as Dworak 0 to 1, 1, 1 to 2 or 0 to 2.

Outcomes of poor response defined by histopathological scales

Fourteen studies that defined poor response reported on outcomes (Table 5). LR at 5 years ranged from 2% to 26%[17,18,23,26,27,31], DR was 14.3% to 47%[18,23,26,27,31]. One study reported 10-year LR and DR of 3.6% and 39.6%, respectively[14]. Two-year DFS was 60.3% to 83.6%[19,29,31], 3-year DFS was 72.6% to 73.8%[30,31], 4-year DFS was reported by a single study as 47%[18], 5-year DFS was reported as 56% to 71%[13,16,17,23,26], and 10-year DFS was documented as 63%[14]. OS at 2 years was 87.3% to 92.6%[29] and at 5 years was 60.7% to 75.8%[16,23,26].

Which scales are used to define good response?

Six scales[18,25,35,40,43,44,46] were used in 20 reports (16 articles) to define good response[13-16,18,20,21,24-26,28-33]. These six scales produced 12 different definitions of good response (Table 2). The characteristics of these studies are shown in Table 1. Table 6 shows the scales defining good response along with their permutations.

Table 3 Permutations of regression scales to define poor and good response

Poor response		Good response	
TRG grading system	**Studies that used the scale**	**TRG grading system**	**Studies that used the scale**
Mandard TRG 3,4,5	Suárez *et al*[31] Santos *et al*[16]	Mandard TRG 1,2	Suárez *et al*[31] Gambacorta *et al*[21] Santos *et al*[16]
Mandard TRG 4	Gambacorta *et al*[21] Giralt *et al*[22]	Mandard TRG 2,3	Avallone *et al*[13]
Mandard TRG 4,5	Avallone *et al*[13] Roy *et al*[29] Pucciarelli *et al*[28] Shin *et al*[30]	Mandard TRG 1,2,3	Roy *et al*[29] Pucciarelli *et al*[28] Shin *et al*[30]
Dworak 1	Winkler *et al*[33]	Dworak TRG 2,3,4	Huebner *et al*[25] Roy *et al*[29]
Dworak TRG 0,1	Huebner *et al*[25] Roy *et al*[29] Fokas *et al*[14]	Dworak TRG 2,3	Fokas *et al*[14]
Dworak TRG 1,2	Lim *et al*[26]	Dworak TRG 3,4	Lim *et al*[26] Elezkurtaj *et al*[20] Santos *et al*[16] Hav *et al*[15]
Dworak TRG 0,1,2	Elezkurtaj *et al*[20] Hav *et al*[15] Santos *et al*[16]	Dworak TRG 3	Winkler *et al*[33]
Rodel TRG 3 [Dworak 0,1]	Min *et al*[27]	Japanese TRG 2,3	Horisberger *et al*[24]
Rodel TRG 3 [Wittekind (mod Dworak 0,1)]	Hermanek *et al*[23]	Japanese TRG 3	Vallböhmer *et al*[32]
Japanese TRG 0,1a,1b	Horisberger *et al*[24]	Miller Junker TRG 2a and 2b	Vallböhmer *et al*[32]
Japanese TRG 1	Vallböhmer *et al*[32]	Cologne TRG 3 and 4	Vallböhmer *et al*[32]
Miller Junker TRG 1	Vallböhmer *et al*[32]	Glynne Jones TRG 1	Bujko *et al*[18]
Miller Junker TRG 1,2a	Eich *et al*[19]		
Cologne TRG 1,2	Vallböhmer *et al*[32]		
Glynne Jones TRG 3	Bujko *et al*[18]		
Wheeler RCRG TRG 2	Beddy *et al*[17]		

Outcomes of good response defined by pathological scales

Ten studies reported on outcomes (Table 6). Most studies defined good response as Mandard 1 to 2, 1 to 3, 2 to 3 or Dworak 2 to 4, 3 to 4 or 2 to 3. LR at 5 years after a good response ranged from 0% to 9%[16,18,26,31] and DR was reported as 0% to 34%[16,18,26,31]. One study reported 10-year LR and DR of 8.0% and 29.3%, respectively[14]. Two-year DFS was 86.1% to 91.7%[29], 3-year DFS was 74.1%[30], 4-year DFS was 67%[18], 5-year DFS was 78.4% to > 90%[13,16,26], and 10-year DFS was 73.6%[14]. OS at 2 years was 89.2% to 92.2%[29], and at 5 years OS was

Table 4 Proportion of poor responders in the literature according to regression grades

TRG grading system	No. of reports (total 25 reports from 21 studies)	Proportion of poor responders	Lower limit of confidence Interval	Upper limit of confidence Interval
Mandard	8	34.9	22.8	49.4
Dworak	8	47.4	32.5	62.7
Junker/Muller	2	50.8	28.8	72.5
Japanese	2	35.0	20.4	52.9
Wheeler	1	38.9	30.8	47.7
Bujko/Glynne-Jones	1	22.1	15.8	30.0
Rodel based on Dworak	1	52.2	44.9	59.5
Rodel based on Wittekind (modified Dworak)	1	14.7	10.6	19.9
Cologne	1	7.1	3.2	14.8

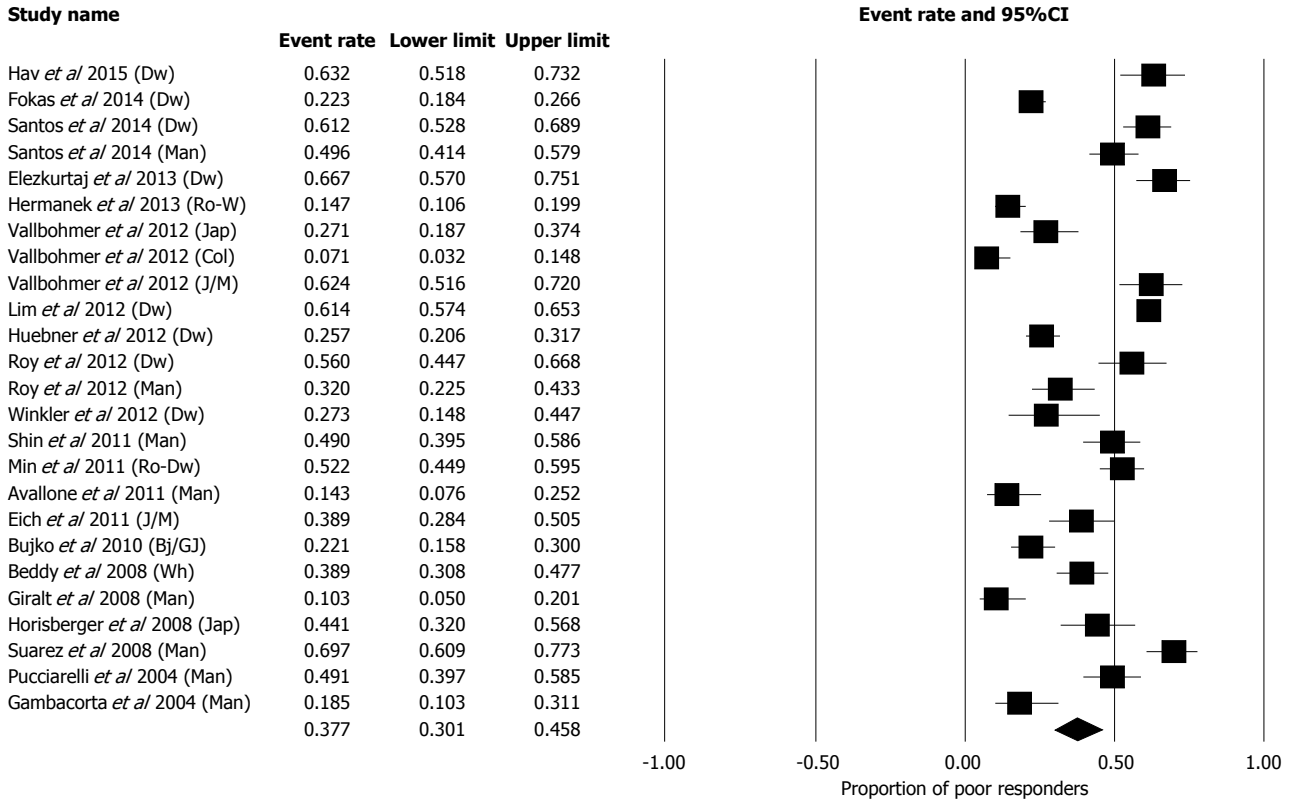


Figure 1 Proportion of patients who responded poorly to neo-adjuvant therapy.

77.4% to 88.2%[16,26].

Considerations and comparison between good and poor responders

A range of survival outcomes existed for good and poor response (Table 7). There were 15 reports (11 articles) comparing outcomes from good and poor response[13-16,18,26,28-32]. Four outcome measures were examined in detail: LR, DR, DFS and OS.

Studies differentiating between good and poor responders for LR

Six reports from five studies[14,16,18,26,31] compared good and poor response in relation to LR (Figure 2). Of these, one study reported a non-significantly higher LR in good responders compared with poor responders[14]. Five reports[16,18,26,31] showed LR was higher in poor responders, of which only one study showed a significant difference[26]. Using the definition given by Lim *et al*[26] there were three other studies with similar definitions[16,31]. The reported LR for good response ranged from 0% to 1.8%[16,26,31]. There were no studies that agreed with Lim *et al*[26] for the definition of poor response. Three studies[16,31] agreed with each other for poor response and reported LR of 3.4% to 4.3%. Lim *et al*[26] (which showed a significant difference between good and poor) gave LR rate in poor responders of 9.5%. This indicates that either Mandard 1 to 2 or Dworak 3 to 4 should be used to define good response for LR and Mandard 3 to 5 or Dworak 0 to 2 or 1 to 2 should be

Table 5 Study definitions of poor response according to histopathological tumour regression grade scales

Ref.	Year	TRG scale used (original disease application)	Are the scales reported accurately?	Poor response definition	Total (*n*)	Poor responders (*n*)	Average F/up in months	LR (%) 5 yr	DR (%) 5 yr	DFS (%)	OS (%)
Gambacorta *et al*[21]	2004	Mandard (oesophagus)	Yes	TRG 4	54	10	25				
Pucciarelli *et al*[28]	2004	Mandard (oesophagus)	Yes	TRG 4 and 5	106	52	42				
Beddy *et al*[17]	2008	Wheeler (rectal)	Yes	TRG 2	126	49	37	2[1]		Yr. 5: 71	
Giralt *et al*[22]	2008	Mandard (oesophagus)	No	TRG 4	68	7					
Horisberger *et al*[24]	2008	Japanese Society for Cancer of the Colon and Rectum (rectal)	Yes	TRG 0 and 1a and 1b	59	26					
Suárez *et al*[31]	2008	Mandard (oesophagus)	Yes	TRG 3 and 4 and 5	119	83	33	3.4[1]	14.3[1]	Yr. 2: 83.6 Yr. 3: 73.8	
Bujko *et al*[18]	2010	Glynne Jones/Bujko (rectal)	Yes	TRG 3	131	29	48	26	47	Yr. 4: 47	
Avallone *et al*[13]	2011	Mandard (oesophagus)	Yes	TRG 4 and 5	63	9	60			Yr. 5: Prob free of recurrence 56[2]	
Eich *et al*[19]	2011	Müller and Junker (lung)	Yes	TRG 1 and 2a	72	28	28			Yr. 2: 76 ± 14.8	
Min *et al*[27]	2011	Rodel (rectal based on Dworak)	Yes	Categorised as poor according to Rodel and based on TRG 0 and 1 on Dworak scale	178	93	43	21	31		
Shin *et al*[30]	2011	Mandard (oesophagus)	Yes	TRG 4 and 5	102	50	40.3			Yr. 3: 72.6	
Huebner *et al*[25]	2012	Dworak (rectal)	Yes	TRG 0+1	237	61					
Lim *et al*[26]	2012	Dworak (rectal)	Yes	TRG 1+2	581	357	61	9.5	27.2	Yr. 5: 63.6	Yr. 5: 71.3
Roy *et al*[29]	2012	Dworak (rectal)	Yes	TRG 0 and 1	75	42				Yr. 2: 68.9	Yr. 2: 92.6
Roy *et al*[29]	2012	Mandard (oesophagus)	Yes	TRG 4 and 5	75	24				Yr. 2: 60.3	Yr. 2: 87.3
Vallböhmer *et al*[32]	2012	Japanese Society for Cancer of the Colon and Rectum (rectal)	Yes	TRG 1	85	23					
Vallböhmer *et al*[32]	2012	Junker Miller (lung)	Yes	TRG 1	85	6					DNE
Vallböhmer *et al*[32]	2012	Cologne (oesophageal)	Yes	TRG 1 and 2	85	53					DNE
Winkler *et al*[33]	2012	Dworak (rectal)	No	TRG 1	33	9					DNE
Elezkurtaj *et al*[20]	2013	Dworak (rectal)	Yes	TRG 0,1 and 2	102	68					
Hermanek *et al*[23]	2013	Rodel (rectal based on Wittekind and Tannapfel (rectal based on Dworak)	Yes	Categorised as poor according to Rodel and based on TRG 0and1 on Wittekind and Tannapfel (a modified Dworak scale)	225	33	92	15.9	27.9	Yr. 5: 63.6	Yr. 5: 75.8
Fokas *et al*[14]	2014	Dworak (rectal)	Yes	TRG 0+1	386	90	132	Yr. 10: 3.6	Yr. 10: 39.6	Yr. 10: 63%	
Santos *et al*[16]	2014	Dworak (rectal)	Yes	TRG 0,1 and 2	144	85	56	3.5	16.4	Yr. 5: 68.1	Yr. 5: 69.1
Santos *et al*[16]	2014	Mandard (oesophagus)	Yes	TRG 3 and 4 and 5	144	69	56	4.3	20.3	Yr. 5: 61.7	Yr. 5: 60.7
Hav *et al*[15]	2015	Dworak (rectal)	Yes	TRG 0,1 and 2	76	48	20			No specific data but no correlation with DFS	

[1]Overall rate for total follow-up time; [2]Probability of being free from recurrence (DFS rate not given). LR: Local recurrence; DR: Distant recurrence.

Table 6 Study definitions of good response according to histopathological tumour regression grade scales

Ref.	Year	TRG scale used (original disease application)	Are the scales reported accurately?	Good response definition	Total (*n*)	Good responders (*n*)	Average F/up in months	LR (%) 5 yr	DR (%) 5 yr	DFS (%)	OS (%)
Gambacorta *et al*[21]	2004	Mandard (oesophagus)	Yes	TRG 1 and 2	54	24	25				
Pucciarelli *et al*[28]	2004	Mandard (oesophagus)	Yes	TRG 1 and 2 and 3	104	52	42			DNE	DNE
Horisberger *et al*[24]	2008	Japanese Society for Cancer of the Colon and Rectum (rectal)	Yes	TRG 2 and 3	59	33					
Suárez *et al*[31]	2008	Mandard (oesophagus)	Yes	TRG 1 and 2	119	36	33	0	0	DNE	
Bujko *et al*[18]	2010	Glynne Jones/ Bujko (rectal)	Yes	TRG 1	131	40	48	9	34	Yr. 4: 67	
Avallone *et al*[13]	2011	Mandard (oesophagus)	Yes	TRG 2 and 3	63	20	60			Yr. 5: Prob free of recurrence > 90%	
Shin *et al*[30]	2011	Mandard (oesophagus)	Yes	TRG 1 and 2 and 3	102	52	40.3			Yr. 3: 74.1	
Huebner *et al*[25]	2012	Dworak (rectal)	Yes	TRG 2 and 3 and 4	237	176					
Lim *et al*[26]	2012	Dworak (rectal)	Yes	TRG 3 and 4	581	224	61	1.3	11.6	Yr. 5: 86.7	Yr. 5: 88.2
Roy *et al*[29]	2012	Dworak (rectal)	Yes	TRG 2 and 3 and 4	75	33				Yr. 2: 91.7	Yr. 2: 89.2
Roy *et al*[29]	2012	Mandard (oesophagus)	Yes	TRG 1 and 2 and 3	75	51				Yr. 2: 86.1	Yr. 2: 92.2
Vallböhmer *et al*[32]	2012	Japanese Society for Cancer of the Colon and Rectum (rectal)	Yes	TRG 3	85	23					DNE
Vallböhmer *et al*[32]	2012	Junker Miller (lung)	Yes	TRG 2aand2b	85	65					DNE
Vallböhmer *et al*[32]	2012	Cologne (oesophageal)	Yes	TRG 3 and 4	85	26					DNE
Winkler *et al*[33]	2012	Dworak (rectal)	No	TRG 3	33	6					
Elezkurtaj *et al*[20]	2013	Dworak (rectal)	Yes	TRG 3 and 4	102	34					
Fokas *et al*[14]	2014	Dworak (rectal)	Yes	TRG 2 and 3	386	256	132	Yr. 10: 8.0	Yr. 10: 29.3	Yr. 10: 73.6%	
Santos *et al*[16]	2014	Dworak (rectal)	Yes	TRG 3 and 4	144	54	56	1.8	11.1	Yr. 5: 78.4	Yr. 5: 77.4
Santos *et al*[16]	2014	Mandard (oesophagus)	Yes	TRG 1 and 2	144	70	56	1.4	8.6	Yr. 5: 81.7	Yr. 5: 79.4
Hav *et al*[15]	2015	Dworak (rectal)	Yes	TRG 3 and 4	76	28	20			No specific data but no correlation with DFS	

Overall rate for total follow-up time. LR: Local recurrence; DR: Distant recurrence; DNE: Data given but not extractable; DFS: Disease-free survival.

used for poor response.

Studies differentiating between good and poor response for DR

Six reports from five studies[14,16,18,26,31] compared good and poor response in relation to DR (Figure 3). Of these, all showed DR was higher in poor responders, of which two studies (Lim *et al*[26] and Fokas *et al*[14]) showed a significant difference; although, they used different definitions. Using the definition given by Lim *et al*[26], there were three other studies with similar definitions[16,31]; the reported 5-year DR for good response was 0% to 11.6%. Using the definition given by Fokas *et al*[14], there was one other study with a similar definition[18]; the reported 5- and 10-year DR for good response was 34% and 29%, respectively. Poor response was defined by three studies[16,31], with similar definitions reporting DR of 14.3% to 20.3%. Poor response was 47% and 39.6% for 5- and 10-year DR, respectively, by two other studies[14,18] with similar

Table 7 Comparison of outcomes between good and poor responders

Ref.	Year	Good response defn.	Poor response defn.	LR %		*P* < 0.05	DR %		*P* < 0.05	DFS %		*P* < 0.05	OS %		*P* < 0.05	DSS		*P* < 0.05	Conclusion
				GR	PR		GR	PR		GR	PR		GR	PR		GR	PR		
Pucciarelli *et al*[28]	2004	TRG 1 and 2 and 3	TRG 4 and 5							Better in GR		No	Better in GR		No				Good responders have better, non-statistically significant outcomes for DFS and OS
Suárez *et al*[31]	2008	TRG 1 and 2	TRG 3 and 4 and 5	0	3.4	NC	0	14.3	NC	Better in GR		Yes				Better in GR		No	Good responders have better, statistically significant DFS but have better, non significant LR, DR and DSS
Bujko *et al*[18]	2010	TRG 1	TRG 3	9	26	No	34	47	No	67	47	No							Good responders have better, non-statistically significant outcomes for LR, DR and DFS
Avallone *et al*[13]	2011	TRG 2 and 3	TRG 4 and 5							Prob > 90%	Prob 56%	Yes							Good responders have better, statistically significant DFS
Shin *et al*[30]	2011	TRG 1 and 2 and 3	TRG 4 and 5							74.1	72.6	No							Good responders have better, non-statistically significant outcomes for DFS
Lim *et al*[26]	2012	TRG 3 and 4	TRG 1 and 2	1.3	9.5	Yes	11.6	27.2	Yes	86.7	63.6	Yes	88.2	71.3	Yes				Good responders have better, statistically significant outcomes for LR, DR, DFS and OS
Roy *et al*[29]	2012	TRG 1 and 2 and 3	TRG 4 and 5							86.1	60.3	Yes	92.2	87.3	No				Good responders have better, statistically significant DFS but have better, non significant OS
Roy *et al*[29]	2012	TRG 2 and 3 and 4	TRG 0 and 1							91.7	68.9	No	89.2	92.6	No				Good responders had better, non-statistically significant outcomes for DFS. Good responders had poorer, non-statistically significant outcomes for OS
Vallböhmer *et al*[32]	2012	TRG 3	TRG 1										Better in GR		No				Good responders have better, non-statistically significant outcomes for OS
Vallböhmer *et al*[32]	2012	TRG 2a and 2b	TRG 1										Better in GR		No				Good responders have better, non-statistically significant outcomes for OS
Vallböhmer *et al*[32]	2012	TRG 3 and 4	TRG 1 and 2										Better in GR		No				There was no statistically significant difference for OS between good and poor responders
Fokas *et al*[14]	2014	TRG 2 and 3	TRG 0 and 1	8	3.6	No	29.3	39.6	Yes	73.6	63	Yes							Good responders have better, statistically significant outcomes for DR and DFS. Good responders had poorer, non-statistically significant outcomes for LR
Santos *et al*[16]	2014	TRG 1 and 2	TRG 3 and 4 and 5	1.4	4.3	NC	8.6	20.3	NC	81.7	61.7	Yes	79.4	60.7	Yes				Good responders have better, statistically significant outcomes for DFS and OS
Santos *et al*[16]	2014	TRG 3 and 4	TRG 0 and 1 and 2	1.8	3.5	NC	11.1	16.4	NC	78.4	68.1	No	77.4	69.1	No				Good responders have better, non-statistically significant outcomes for DFS and OS
Hav *et al*[15]	2015	TRG 3 and 4	TRG 0 and 1 and 2							Better in GR		No							Good responders have better, non-statistically significant outcomes for DFS

Where data is not given the overall result is stated. LR: Local recurrence; DR: Distant recurrence; GR: Good responders; PR: Poor responders; NC: No statistical comparison made.

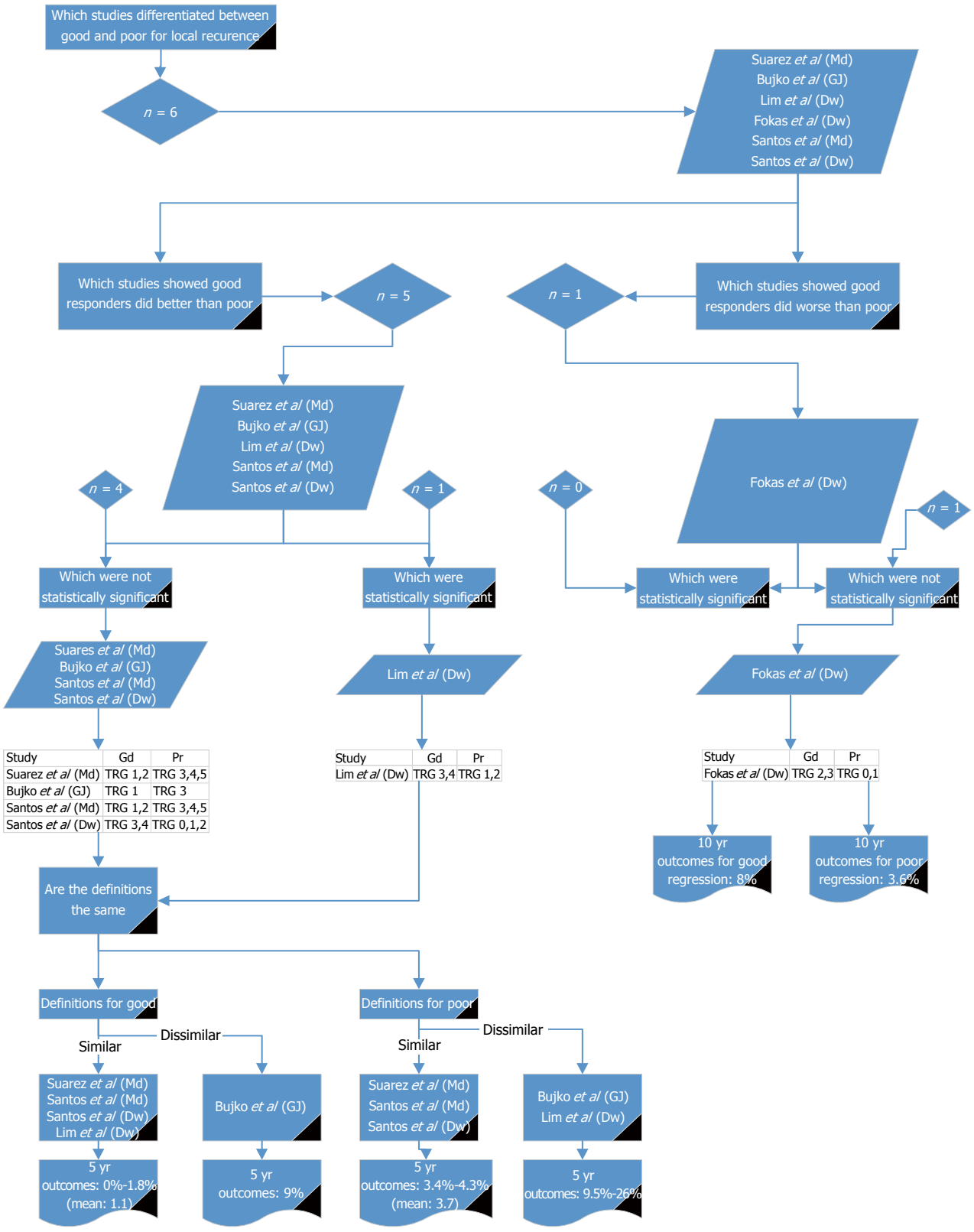


Figure 2 Studies reporting on local recurrence in good and poor responders.

definitions. Lim *et al*[26] reported 5-year DR as 27.2% for poor responders. The values reported by Fokas *et al*[14] and Bujko *et al*[18] are much higher than the other reports and do not reflect the body of literature. It would, therefore, be preferable to use either Mandard 1 to 2 or Dworak 3 to 4 for defining good response for DR and Mandard 3 to 5 or Dworak 0 to 2 or 1 to 2 for poor response.

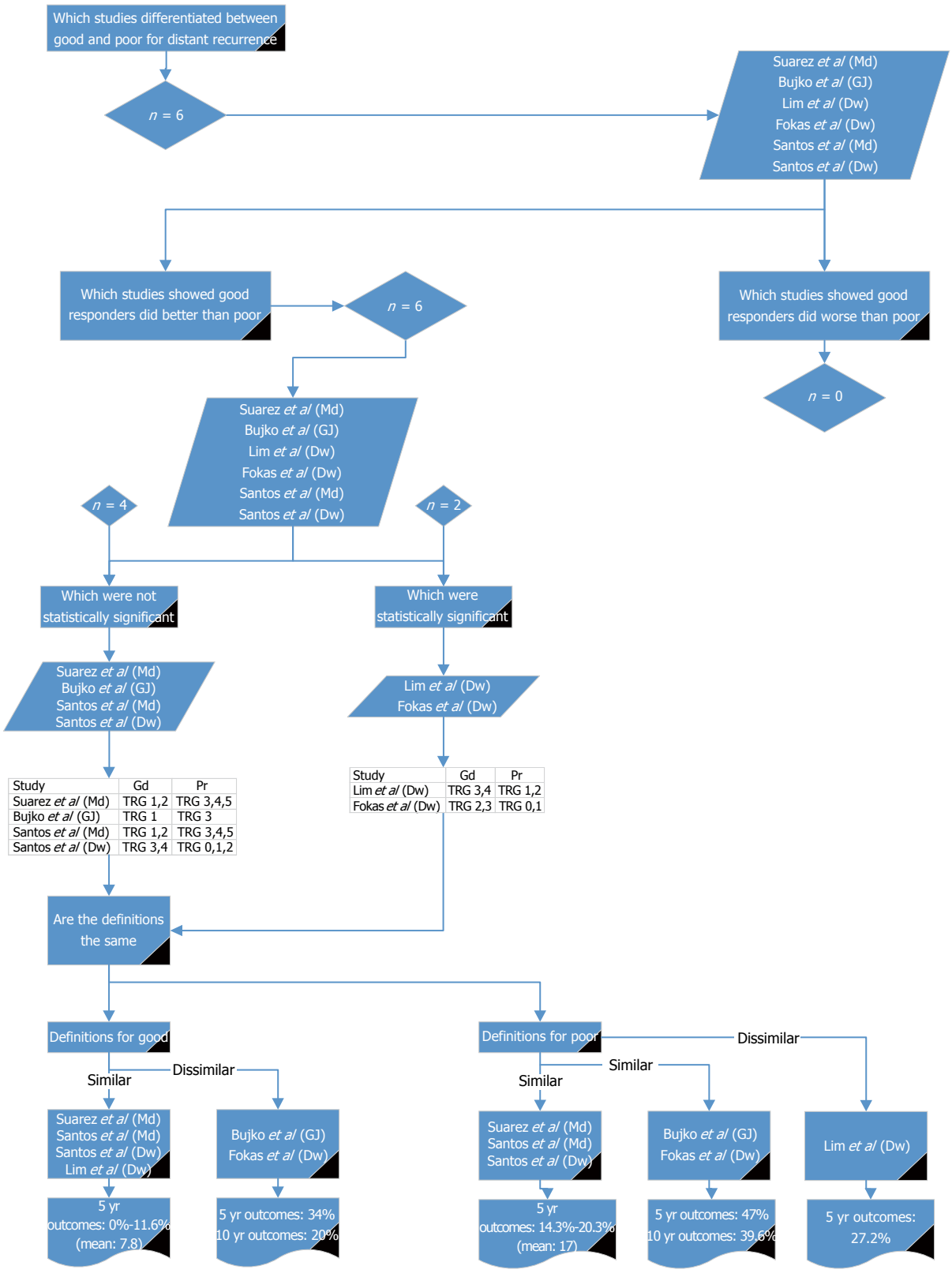


Figure 3 Studies reporting on distant recurrence in good and poor responders.

Studies differentiating between good and poor response for DFS

Twelve reports[13-16,18,26,28-31] compared good and poor response in relation to DFS (Figure 4). All of the studies showed DFS to be worse in poor responders. Six studies showed a significant difference between good and poor response[13,14,16,26,29,31]. For the definition of good response, three of the papers[16,26,31] showing a statistical significance used a similar definition to each other; two[13,14] used different definitions but were

similar to each other and one used a different definition to the other significant studies[29]. Using the definition given by Lim *et al*[26] and comparing it to studies with similar definitions[15,16,30,31], the reported DFS for good response at 5 years was 78.4% to 86.7%. Using the definition given by Fokas *et al*[14] and comparing it with the other reports with similar definitions[13], the reported 5- and 10-year DFS for good response was > 90% and 73.6%, respectively. Using the definition by Roy *et al*[29] and comparing it with the other studies with similar definitions[28-30], 2-year DFS was 86.1% to 91.7% and 3-year DFS was 74.1%.

For the definition of poor response, three of the papers[13,14,29] showing a statistical significance used a similar definition to each other, two[16,31] used different definitions but were similar to each other and one study was different in its definition of poor response[26]. Using the definition given by Avallone *et al*[13] and comparing it to the other studies with similar definitions[14,18,28-30], the reported DFS for poor response at 2 years was 60.3% to 68.9%, at 3 years was 72.6%, at 4 years was 47%, and at 5 years was 56%. Using the definition given by Suárez *et al*[31] and comparing it with the other studies with similar definitions[15,16], the reported DFS for poor response at 2 years was 83.6%, at 3 years was 73.8%, and at 5 years was 61.7% to 68.1%. Lim *et al*[26] reports a 5-year DFS of 63.6%. From these results it may be appropriate to use Mandard 1 to 2, 1 to 3 or 2 to 3 or Dworak 3 to 4, 2 to 4 or 2 to 3 for defining good response and Mandard 4 to 5, 3 to 5 or Dworak 0 to 1, 0 to 2 or Bujko 3 to define poor response.

Studies differentiating between good and poor response for OS

Nine reports[16,26,28,29,32] compared good and poor response in relation to OS (Figure 5). Of these, all but one[29] showed OS was non-significantly worse in poor responders. Six reports from four papers showed a significant difference[16,28,29,32]. For the definition of good response, two of the papers[16,32] showing a statistical significance used a similar definition to each other; two reports from one paper[32] used different definitions but were similar to each other, and a further two used similar definitions to each other but were different from the other papers[28,29]. Using the definition given by Pucciarelli *et al*[28] and comparing it with the other studies with similar definitions[29], the reported OS for good response at 2 years was 92.2%. Using the definition given by Lim *et al*[26] and comparing it with the other studies with similar definitions[16,26,32], the reported OS for good response at 5 years was 77.4% to 88.2%.

For the definition of poor response, two of the papers[28,29] showing a statistical significance used a similar definition to each other and a further two studies had similar definitions to each other[16,32]. Two reports from one study were different in their definitions of poor response[32]. Using the definition given by Pucciarelli *et al*[28] and comparing it with other reports with similar definitions[29], the reported OS for poor response was 87.3% at 2 years. Using the definition given by Vallböhmer *et al*[32] and comparing it with the studies with similar definitions[26], the reported OS for poor response was 71.3% at 5 years. Using the next definition given by Vallböhmer *et al*[32] and comparing it with studies with similar definitions[16], the reported OS for poor response was 60.7% to 69.1% at 5 years. From these results it may be appropriate to use Mandard 1 to 2, 1 to 3 or Dworak 3 to 4 or Cologne 3 to 4 for defining good response and Mandard 4 to 5, 3 to 5 or Dworak 0 to 2, 1 to 2 or Japanese 1a to 1b or Cologne 1 to 2 to define poor response.

Consensus histopathological definition of good and poor response

These results show that across the outcomes of LR, DR, DFS and OS, Mandard 1 to 2 and Dworak 3 to 4 could be used for defining good response and Mandard 3 to 5 and Dworak 0 to 2 for poor response.

MRI method of classifying regression

There was one mrTRG system using a 5-point scale[52] (Table 8). Lower mrTRG refers to greater regression and the system also divides the categories into type of response (complete, good, moderate, slight and none).

There were five papers on five studies reporting on poor response[5-7,52,53]. Characteristics of these studies can be seen in Table 9. Overall, the reported proportion of poor responders after neo-adjuvant CRT was 38.6% (95%CI: 34.5%-42.8%) and there was only moderate heterogeneity that was still significant (Q = 10.7, df = 4, I^2 = 63, P = 0.03) (Figure 6).

Definition of poor response as defined by MRI

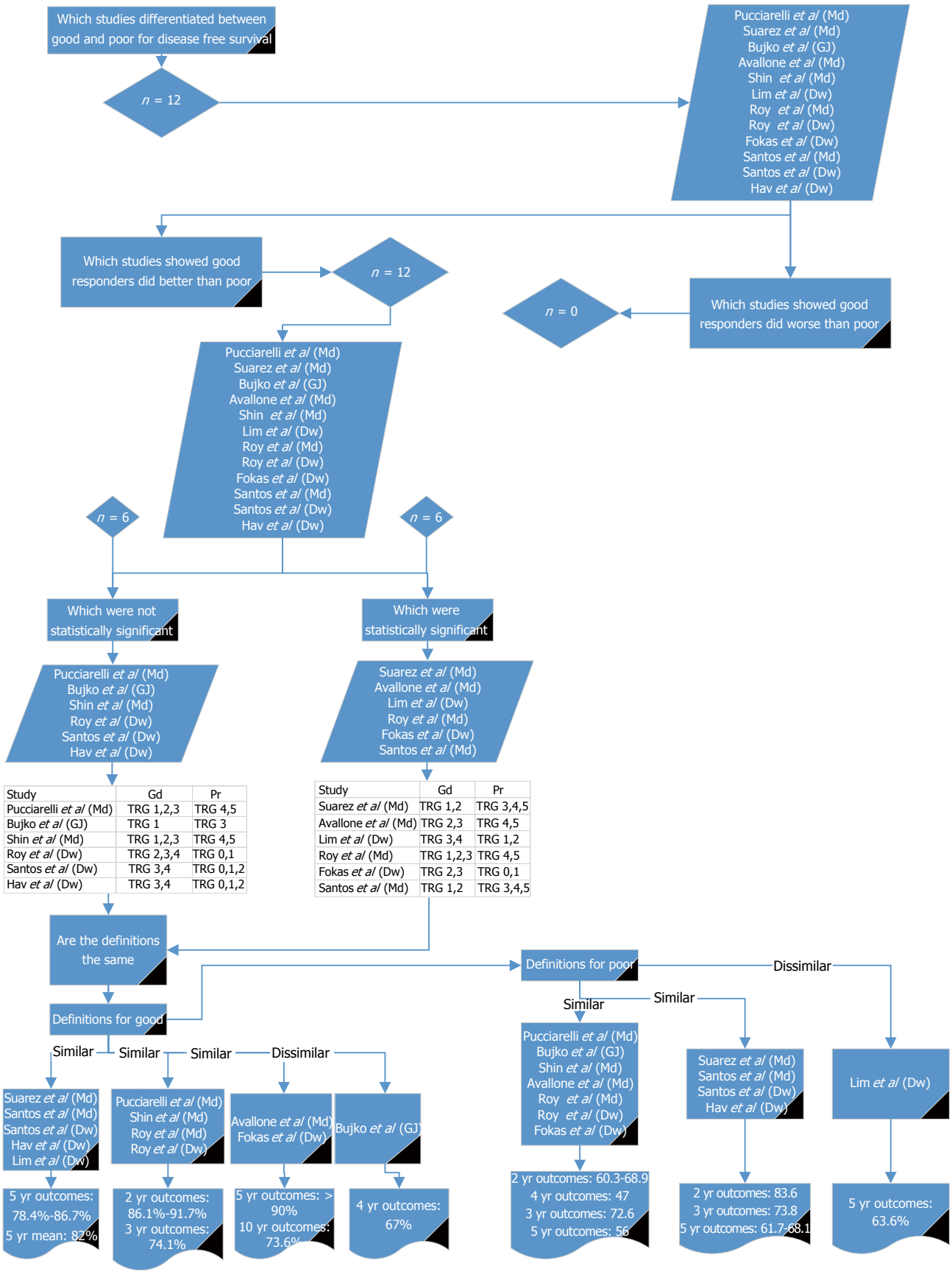
Two studies[5-7] stated that mrTRG was based on the Dworak scale, but the hierarchy actually follows that of the Mandard scale (Table 10). Three studies stated that it was based on the Mandard scale[52,53]. Poor response was defined as mrTRG 4 and mrTRG 5 by all of the papers. LR for poor responders at 5 years ranged from 4% to 29%[6,52]. Five year DR was 9%[52]. From our centres, unpublished data for 3-year DFS was 52%[53] and 5-year DFS was 31% to 68%[6,53]. OS at 3 years from this centre was 74%[53] and at 5 years was 27% to 68%[6,53].

Outcomes of good response defined by MRI TRG scales

LR rates for good responders at 5 years ranged from 1% to 14%[6,52]. Five-year DR was 3%[52] and DFS was 64% to 83%[6,53]. OS at 5 years was 72% to 90%[6,53] (Table 11).

Considerations and comparison between good and poor responders

mrTRG is a relatively new scale and the studies



Study	Gd	Pr
Pucciarelli *et al* (Md)	TRG 1,2,3	TRG 4,5
Bujko *et al* (GJ)	TRG 1	TRG 3
Shin *et al* (Md)	TRG 1,2,3	TRG 4,5
Roy *et al* (Dw)	TRG 2,3,4	TRG 0,1
Santos *et al* (Dw)	TRG 3,4	TRG 0,1,2
Hav *et al* (Dw)	TRG 3,4	TRG 0,1,2

Study	Gd	Pr
Suarez *et al* (Md)	TRG 1,2	TRG 3,4,5
Avallone *et al* (Md)	TRG 2,3	TRG 4,5
Lim *et al* (Dw)	TRG 3,4	TRG 1,2
Roy *et al* (Md)	TRG 1,2,3	TRG 4,5
Fokas *et al* (Dw)	TRG 2,3	TRG 0,1
Santos *et al* (Md)	TRG 1,2	TRG 3,4,5

Figure 4 Studies reporting on disease- free survival in good and poor responders.

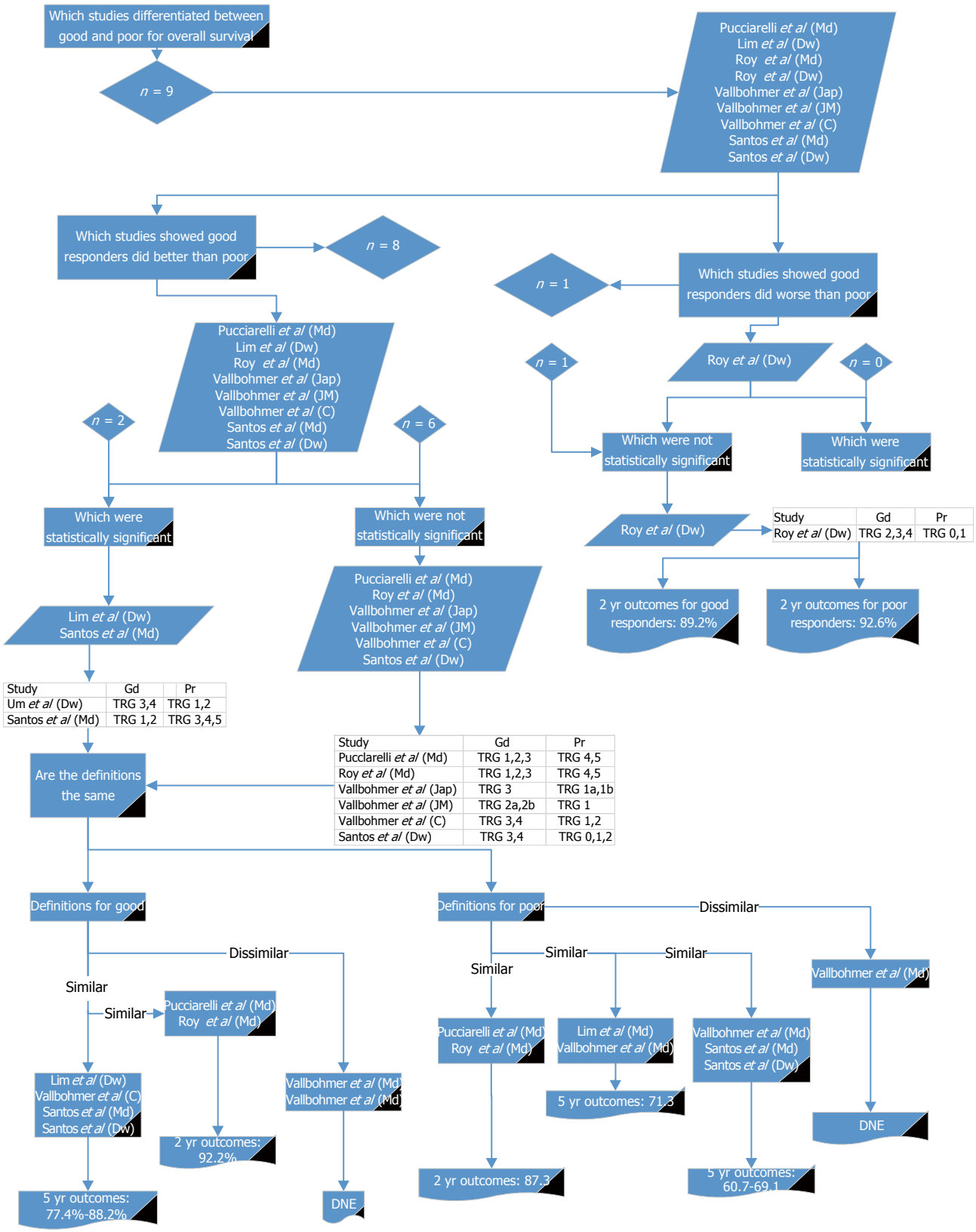


Figure 5 Studies reporting on overall survival in good and poor responders.

reporting it are from one centre; hence, consistency would be expected. Good responders were defined as mrTRG 1 to 3 or 1 to 2 and poor responders were defined as mrTRG 4 to 5 (Table 12).

Studies differentiating between good and poor responders for LR, DR, DFS and OS

There are three articles with available data comparing outcomes for good and poor responders (Table 11). In

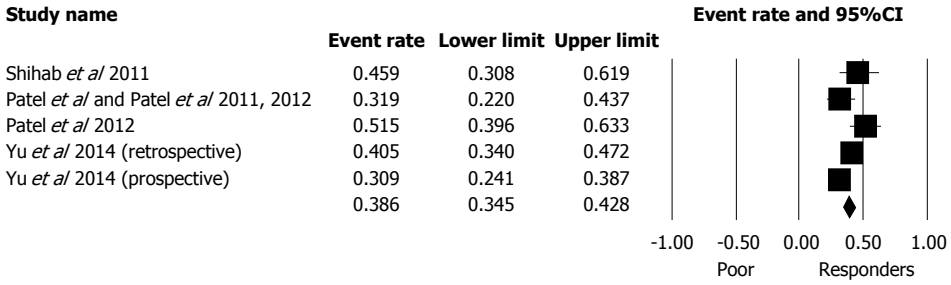


Figure 6 Proportion of patients who responded poorly to neo-adjuvant therapy according to magnetic resonance imaging.

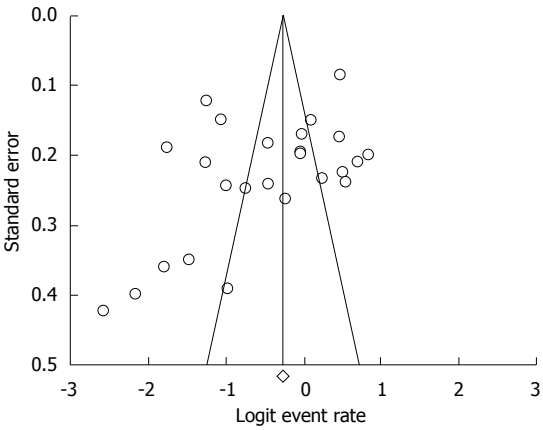


Figure 7 Funnel plot for studies reporting on the prevalence of poor response according to histology.

all three reports, good responders had better outcomes compared with poor responders in relation to LR, DR, DFS and OS. Furthermore in all but LR there was a statistically significant difference in outcomes.

Although there was a range of survival outcomes, the overall rates for survival are lower in poor responders, distinguishing them clearly from the survival figures and rates of those with good response.

Consensus mrTRG definition of good and poor response

From these results, good response may be defined as mrTRG 1 to 3 or 1 to 2 (with mrTRG3 as a separate, independent group) and poor responders as mrTRG 4 to 5. This consistency of results, therefore, indicates the secondary hypothesis is likely to be true.

Publication bias for prevalence

Publication bias for prevalence from histology was initially assessed using a funnel plot (Figure 7). There appeared to be some asymmetry on the plot and so Eggers test was used. There was statistically significant asymmetry seen (Intercept: -4.30, SE: 2.23, 95%CI:-8.90-0.31, t = 1.93, P = 0.07), indicating there is unlikely to be significant publication bias.

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Table 8 Summary of magnetic resonance imaging regression scale available in the literature

mrTRG scale	mrTRG (Low no. - More regression)[47]
1	Radiological complete response: no evidence of ever treated tumour
2	Good response (dense fibrosis; no obvious residual tumour, signifying minimal residual disease or no tumour)
3	Moderate response (50% fibrosis or mucin, and visible intermediate signal)
4	Slight response (little areas of fibrosis or mucin but mostly tumour)
5	No response (intermediate signal intensity, same appearances as original tumour)

DISCUSSION

The aim of this review was to investigate the range and method of how poor response to neo-adjuvant therapy for rectal cancer is defined in order to see which scale best distinguishes between the two groups in relation to outcomes.

Main findings

In summary, this paper has shown that across the outcomes of LR, DR, DFS and OS, Mandard 1, 2 and Dworak 3, 4 could be used for defining good response and Mandard 3, 4, 5 and Dworak 0, 1, 2 for defining poor response. There are other definitions shown above which may also differentiate good and poor response. The analysis has shown differences in the reliability of these scales in consistently identifying good and poor responders.

Summary and appraisal of evidence

Our results have shown that there are three major

Table 9 Characteristics of studies reporting on poor response based upon magnetic resonance imaging

Ref.	Year	Chemotherapy protocol	Radiotherapy protocol (Gy)	Surgical procedures	TME	Time to surgery (wk)	Cancer stage Pre neo-adjuvant therapy	Adjuvant therapy
Shihab *et al*[52]	2011			APR/AR	Y			
Patel *et al*[7] and Siddiqui *et al*[8]	2011 and 2012			APR/AR	Y			
Patel *et al*[6]	2012			APR/AR	Y		T1/2/3/4, N0/1/2	Y
Yu[53]	2014 (unpublished data from our centre)	Capecitabine, oxaliplatin ± cetuximab	50.4-54		Y		T2/3/4	Y
Yu[53]	2014 (unpublished data from our centre)	Capecitabine, oxaliplatin ± cetuximab	50.4-54		Y		T2/3/4	Y

Table 10 Study definitions of poor response according to magnetic resonance imaging tumour regression grade scales

Ref.	Year	TRG scale used (histological stage based upon)	Scales accurate?	Poor response definition	Total (*n*)	Poor responders (*n*)	Average F/up in months	LR (%) 5 yr	DR (%) 5 yr	DFS (%)	OS (%)
Shihab *et al*[52]	2011	MRI TRG (based on Mandard)	Yes	TRG 4,5	37	17		4	9		
Patel *et al*[5,7]	2012	MRI TRG (based on Dworak)	Yes	TRG 4,5	69	22					
Patel *et al*[6] and Patel *et al*[7]	2011 and 2012	MRI TRG (based on Dworak)	Yes	TRG 4,5	66	34	60	29		Yr. 5: 31	Yr. 5: 27
Yu[53]	2014 (unpublished data from our centre)	MRI TRG (based on Mandard and Dworak)	Yes	TRG 4,5	210	85				Yr. 3: 52%	Yr. 3: 74%
Yu[53]	2014 (unpublished data from our centre)	MRI TRG (based on Mandard and Dworak)	Yes	TRG 4,5	152	47				Yr. 5: 59%	Yr. 5: 68%

LR: Local recurrence; DR: Distant recurrence; DFS: Disease-free survival; OS: Overall survival; TRG: Tumour regression grade.

Table 11 Study definitions of good response according to magnetic resonance imaging tumour regression grade scales

Ref.	Year	TRG scale used (histological stage based upon)	Scales accurate?	Good response definition	Total (*n*)	Good responders (*n*)	Average F/up in months	LR (%) 5 yr	DR (%) 5 yr	DFS (%)	OS (%)
Shihab *et al*[52]	2011	MRI TRG (based on Mandard)	Yes	TRG 1,2,3	37	20		1	3		
Patel *et al*[6]	2012	MRI TRG (based on Dworak)	Yes	TRG 1,2,3	69	47					
Patel *et al*[5] and Patel *et al*[7]	2011 and 2012	MRI TRG (based on Dworak)	Yes	TRG 1,2,3	66	32	60	14		Yr. 5: 64	Yr. 5: 72
Yu[53]	2014 (unpublished data from our centre)	MRI TRG (based on Mandard and Dworak)	Yes	TRG 1,2	152	61				DFS, Yr. 5: 83%	DFS, Yr. 5: 90%

LR: Local recurrence; DR: Distant recurrence; DFS: Disease- free survival; OS: Overall survival; TRG: Tumour regression grade.

challenges when it comes to the standardization of tumour regression for rectal cancer. The first is the vast choice of regression scales available to histopathologists. The second is that studies use these varied scales to define poor response without consistency. The third is that there are marked differences between the scales. Therefore, trying to merge these systems into one, universally acceptable

Table 12 Comparison of outcomes between good and poor responders

Ref.	Year	Local recurrence (LR)	$P < 0.05$	Distant recurrence (DR)	$P < 0.05$	Progression disease-free survival (DFS)	$P < 0.05$	Disease-free survival (DFS)	$P < 0.05$	Overall survival (OS)	$P < 0.05$	Conclusion
Shihab *et al*[52]	2011	Better in GR	No	Better in GR	Yes							Good responders have better, statistically significant outcomes for DR but have better, non significant LR
Patel *et al*[5] and Patel *et al*[7]	2011 and 2012	Better in GR	No					Better in GR	Yes	Better in GR	Yes	Good responders have better, statistically significant outcomes for DFS and OS but have better, non significant outcomes for LR
Yu[53]	2014					Better in GR	Yes			Better in GR	Yes	Good responders have better, statistically significant outcomes for DFS and OS

GR: Good responders; NC: No statistical comparison made; DNI: Data not interpretable.

scale becomes unrealistic. Furthermore, studies have shown that inter-observer agreement amongst histopathologists using the existing scales is low[54]. The scales themselves do not advise on whether histopathologists should use a single worst slide for assessment or a composite assessment and adds to the challenge of defining good and poor response. This was highlighted by a study which showed poor inter-observer agreement between histopathologists assessing regression using different regression scales[54].

Some of the scales use qualitative estimates[25,39,46] for levels of fibrosis, but these overlap with regression grades in alternative scales given in other studies[35,43]. Even by trying to examine the correlation between two systems, two grades may be grouped into one grade on a different scale.

Both MRI and histopathological grading systems are open for misinterpretation if standard methods of preparation and interpretation are not employed; there has been a focused attempt to do this in relation to histopathological assessment[54,55] and mrTRG is a novel scale requiring appropriate training to ensure consistency when utilised in other centres.

Differences in the definitions of poor response are highlighted by the number of poor responders identified in each of the studies (Figures 1 and 6). This review concentrated on studies using specific terms stating what they believed to be poor response; however, there were studies that divided TRG into two groups but did not specifically state them as good and poor responders; their results are consistent with the range that is reported in this paper but differ in that they show a good correlation to outcomes for their presumed good and poor responders[56].

In relation to the original definitions, one study showed that poor responders could be either those with predominant fibrosis or patients with tumour outgrowing fibrosis[31] compared with other studies using the same Mandard scale which only defined poor responders as those with tumour outgrowing fibrosis[22]. This is then compounded by the fact that more than one grade on other scales could be combined together on an alternative system.

Importance and implications for practice

Historically, the histopathological TRG systems were developed without validation of the grading in relation to outcomes, and evolution of these scales has occurred with the presence of long-term prognostic information. Histopathological TRG is also dependent on thorough pathological sampling and comparisons are not made to the pre-treatment biopsy; therefore, high stromal content tumours are often given a better regression grade, even though the high stroma may not be due to regression. mrTRG may be one way to respond to this, as it compares and examines the whole tumour and because of the presence of one-scale heterogeneity is reduced. mrTRG also better distinguishes between good and poor response in relation to survival. LR appears to be reported with a large range using both histopathological and mrTRG and may relate to surgical factors being the most important issue in relation to this outcome.

Implications for research and further studies

Recent data from our centre would suggest that mrTRG3, whilst traditionally considered a good response, behaves more like the poor responder group[57] and could be considered as a separate group[58].

In summary, this paper has shown that across the outcomes of LR, DR, DFS and OS, Mandard 1 to 2 and Dworak 3 to 4 could be used for defining good

response and Mandard 3 to 5 and Dworak 0 to 2 for poor response. These definitions may help in achieving consensus in histopathological reporting. However, these definitions do not always produce a significant difference in the outcomes from the different studies utilizing these definitions. Furthermore, there are other definitions shown above which may also differentiate good and poor response. This casts doubt on the reliability of these scales in consistently identifying good and poor responders. A preoperative grading system, such as mrTRG, may be useful to appropriately differentiate good and poor response, thus guiding management decisions, and images attained could effectively be attained by high resolution MRI imaging.

A range of histopathological TRG scales is used in clinical studies. Good and poor response are heterogeneously described, even when using the same histopathological regression scales. Across the outcomes of LR, DR, DFS and OS, Mandard 1 to 2 and Dworak 3 to 4 could be used for defining good response and Mandard 3 to 5 and Dworak 0 to 2 for poor response. These definitions may help in achieving consensus in histopathological reporting. Preoperative mrTRG is similarly able to differentiate between good and poor response based on outcomes.

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COMMENTS

Background

Clinical studies use a number of different tumour regression grade (pTRG) scales to classify the degree of tumour response to neo-adjuvant chemo-radiotherapy (CRT). This often results in confusion as to whether a good or poor response has been achieved, with subsequent uncertainty regarding treatment and prognostic implications. This problem was highlighted by studies that stress the importance of a universally accepted standard. There has been no review of the reported pTRG scales to date. It is necessary to highlight the heterogeneity in these scales, consolidate the current definitions with the purpose of converging towards a set of consensus definitions. This article investigates all the pathology tumour regression scales used to define good and poor response after neo-adjuvant chemotherapy for rectal cancer, to establish the true prevalence of poor responders and to identify the best scales to use in relation to outcomes.

Research frontiers

A newer method of assessing tumour regression relies on MRI (mrTRG), which has been validated as a prognostic tool. This may supercede pTRG, as it has the advantage of assessing tumour response before surgery. Potential enabling response-orientated tailored treatment, including alteration of the surgical planes, additional use of chemotherapy or deferral of surgery.

Innovations and breakthroughs

The authors have found the best classification of good and poor response for rectal cancer response to neoadjuvant chemo-radiotherapy.

Applications

This systematic review has immediate application to rectal cancer care by identifying how to classify good and poor response in the context of outcomes of local recurrence, metastases, disease-free survival and overall survival

Peer-review

This is an interesting review about neoadjuvant therapy for postoperative outcome in rectal cancer.

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