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Review

Meta-analysis of oncological outcomes of sigmoid cancers: A hidden epidemic of R1 "palliative" resections

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ABSTRACT

Background: Colon cancer outcomes are now inferior to rectal cancer outcomes. The sigmoid colon is the most common site of colonic cancer. The aim of this review was to investigate the oncological outcomes for sigmoid cancer.

Methods: A systematic review and meta-analysis was performed. We included any study of the oncological outcomes for sigmoid cancer such as local recurrence, distant recurrence and disease free survival. A systematic search was conducted in Medline from inception to November 2016. Study quality was evaluated with the Newcastle-Ottawa Scale. The study was registered on PROSPERO (CRD42017069326).

Results: The search terms returned 1323 results. We identified a total of 17 eligible studies including 5953 patients. The pooled local recurrence rate was 10.5% in 15 studies with 5148 patients (95% CI 0.07–0.14) and heterogeneity measured by I^2 was 94%. The pooled distant recurrence rate was 19.5% (7 studies, 2040 patients, 95% CI (0.14–0.25), I^2 90%). The pooled disease free survival at 5 years was 80.4% (5 studies, 2336 patients, 95% CI 78.6%–82.1%, I^2 11.5%.). The median Newcastle-Ottawa score was 4 out of 9. R1 and R2 resections were excluded or not described in 16/17 studies. Two studies described R1 and R2 rates of 15–20%.

Conclusion: The pooled local recurrence rate of sigmoid cancer of 10.5% is higher than contemporary rates of local recurrence of rectal cancer. A large number of papers fail to describe or include R1 resections of sigmoid cancer, which are frequently described as palliative.

Introduction

Colon cancer outcomes are now worse than rectal cancer [1–5]. The reduction in local recurrence rates following surgical treatment of rectal cancer have been driven by improvements in staging, the development of surgical techniques such as total mesorectal excision (TME), pathological quality control/feedback and improvements in neoadjuvant and adjuvant therapy [2,6–9]. In colon cancer, the survival benefits of adjuvant chemotherapy are well established [10,11]. Research is ongoing into the benefits of neoadjuvant chemotherapy [12] and complete mesocolic excision [13]. But otherwise there have not been any significant innovations in the management of colon cancer adopted by the wider surgical community. Consequently, data from Denmark [1,2], Sweden [3], Scotland [4], and the USA [5] have shown that rectal cancer outcomes now surpass those of colon cancer.

The sigmoid is the most common site (25–33% [14]) of colon cancer, and will therefore have a significant impact on overall colon cancer outcomes. If oncological outcomes from sigmoid cancer treatment are poor, it will be due to a high local or distant cancer recurrence rate. However the recurrence rates for sigmoid cancer shows a significant variation in recent studies from Sweden [15] and the USA [16].

This study aimed to investigate the local recurrence rate of sigmoid cancer, as well as distant recurrence and disease free survival, and explore reasons for the variation in these rates.

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Methods

A systematic review and meta-analysis was planned and conducted according to PRISMA guidelines [17]. The review was prospectively registered on the PROSPERO database (CRD42017069326).

Primary outcomes

Local recurrence after surgical treatment of sigmoid or rectosigmoid cancer.

Secondary outcomes

Distant recurrence or disease free survival after surgical treatment of sigmoid or rectosigmoid cancer.

Inclusion criteria

Studies were eligible if they described the primary or secondary outcomes.

Exclusion criteria

Studies were excluded if they included less than 50 cases, did not describe the primary or secondary outcomes for sigmoid cancer, or grouped sigmoid cancer with other sites (eg sigmoid and rectal cancer, or left sided colon cancer). Studies published in a language none of the authors or their colleagues could translate were excluded.

Information sources

A literature search in Pubmed was performed on the 4th of February 2017 since inception. A combination of search terms (see appendix 1) was created by the lead author (ND'S), who has previously authored meta-analyses including Cochrane Reviews, after discussion with research librarians. When studies were not available through online journal access, the study authors were contacted by e-mail directly. We supplemented the search results by checking the reference lists of relevant and included studies.

Data extraction and management

Data was extracted independently by 2 authors (ND'S, AL) and disagreements resolved by consensus. Data was extracted on the following fields following a pilot: first author, year of publication, study design, number of participants, number of males and females, mean age of participants, local recurrence rate and sites, distant recurrence rate and sites, disease free survival (median and 5 year), TNM stage, grade of differentiation, lymphatic or venous invasion, emergency presentation. Individual patient level data was not sought since most studies were over 10 years old.

Assessment of methodological quality

Study quality was assessed by the Newcastle Ottawa Score [18] (see appendix 2). Studies with scores of less than 4 were at high risk of bias, 4–6 of moderate risk of bias, and over 7 at low risk.

Data synthesis

Meta-analysis using the random effects model was performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). The weighted summary proportions for local and distant recurrence, and disease free survival were calculated under the random effects model. Categorical variables for local and distant recurrence were analysed using ANOVA. Study heterogeneity was assessed by I^2 [19].

Results

Description of studies

The search terms identified 1323 studies (Fig. 1). Studies were filtered by title and abstract to exclude irrelevant publications. Full texts were retrieved for 87 articles, of which 75 were excluded. The reference lists of included studies were searched to identify a further 5 eligible studies that were included in the analysis. In the final analysis, 17 eligible papers were included with 5953 patients (see Table 1). The data for sigmoid cancers was frequently present as a subgroup for overall colon cancer. Consequently characteristics of patients with sigmoid cancer were not described in all studies and therefore not reported here.

Primary outcomes

1. The pooled local recurrence rate was 11% in 15 studies with 5148 patients (95% CI 0.08–0.14, Fig. 2). Heterogeneity measured by *I* [2] was 94%.

Secondary outcomes

The pooled distant recurrence rate was 19.5% in 7 studies with 2040 patients (95% CI 0.14–0.25, Fig. 3). Heterogeneity measured by *I* [2] was 90%.

The pooled 5 year disease free survival was 80.4% in 5 studies with 2336 patients (95% CI 0.79-0.82, Fig. 4). Heterogeneity measured by *I* [2] was 11.5%.

Subgroup analysis for study date showed a downwards trend for local recurrence with later studies, that was statistically significant after logistic regression analysis ($p = 0.03$). No significant change in distant recurrence was found in relation to study date ($p = 0.86$, Fig. 5).

Studies in which patients were given adjuvant therapy had lower rates of local recurrence ($p = 0.017$), but not distant recurrence ($p = 0.89$) on meta-regression.

No significant difference for local recurrence was found on metaregression by country/continent (USA, Europe, Asia) (see appendix 2). No further subgroup analysis could be carried out due to the paucity of data on other prognostic features in the included studies: data was not available on stage, TNM breakdown, tumour differentiation, EMVI or hazard ratios in more than 1–2 studies.

Assessment of methodological quality

The median Newcastle Ottawa Score of the included studies was 4 (range 2–7) out of a maximum possible score of 9, and therefore rated as moderate. Details of the quality assessment can be seen in Appendix 2.

Data on R1 resections was only given in three papers (see Table 2). R1 or non-curative operations were described in the study flow of 13 studies, but only included in the analysis of one study [16]. R1 rates varied from 15 to 20%. Studies excluded up to 54% of patients, with R1 resections amongst the exclusion criteria. We wrote to the corresponding authors for papers written since 2005 for further data on their R1/R2 resection rates.

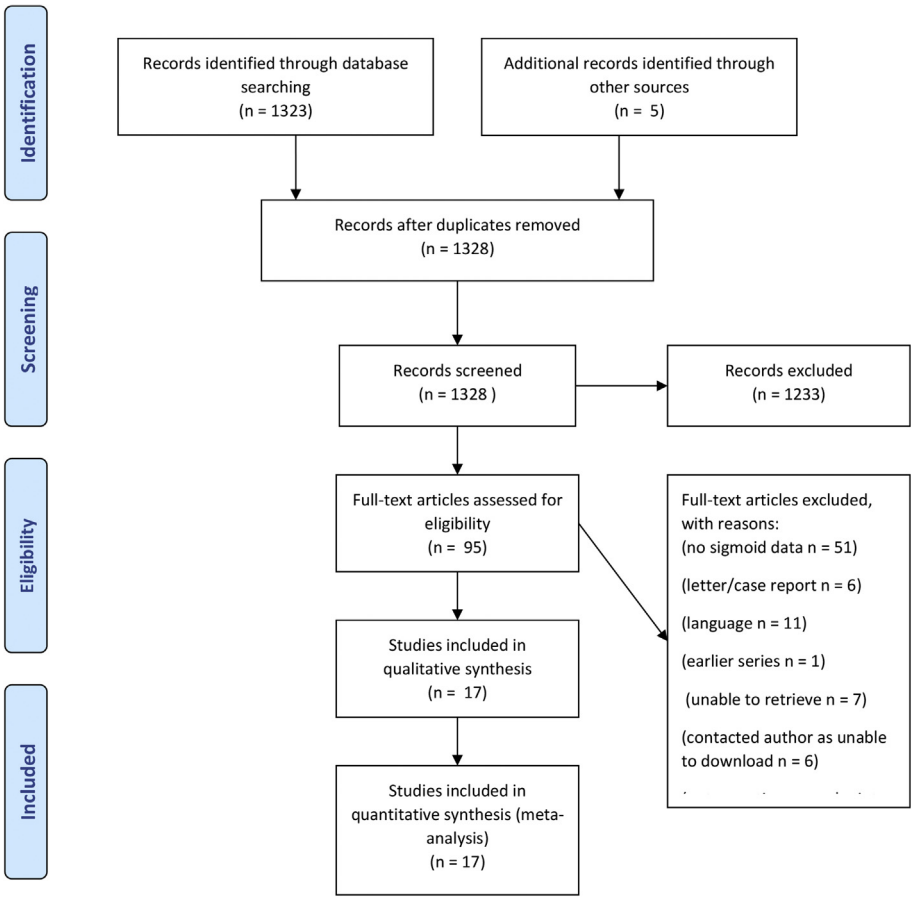

Fig. 1. PRISMA flowchart.

Table 1
Study characteristics.

Author	Country	Study period	Study design	No pts	Adjuvant therapy	Median follow up in months (range)	No. local recurrences (%)	No. distant recurrences (%)	5 year DFS
Amri et al. (2015) [20]	USA	2004–2011	retrospective	238	unclear	45	32 (13%)	45 (19%)	
Di Cataldo et al. (2007) [21]	Italy	1992–2001	retrospective	102	unclear	60	14 (14%)		87%
Harris et al. (2002) [22]	USA	1980–1993	retrospective	397	yes	69 (2–212)	14 (4%)		
Jagoditsch et al. (2000) [23]	Austria	1984–1997	retrospective	270	unclear	unclear			83%
Kraemer et al. (2001) [24]	Singapore	1989–1999	retrospective	422	yes	55 (3–119)	25 (6%)	74 (18%)	
Lautenbach et al. (1994) [25]	US	1967–1991	retrospective	136	unclear	48	17 (13%)		
Leung et al. (2004) [26]	Hong Kong	1993–2002	randomised	403	yes	51	18 (4%)	56 (14%)	77%
Liska et al. (2016) [16]	USA	1994–2008	retrospective	433	yes	93 (IQR 45–135)	15 (3.5%)		
Manfredi et al. (2006) [27]	France	1976–2000	retrospective	566	yes	60	109 (19%)	152 (27%)	
Marinello et al. (2015) [28]	Spain	1992–2010	retrospective	450	yes	60 (6–236)	32 (7%)		81%
Michelassi et al. (1991) [29]	USA	1965–1981	retrospective	230	no	60	21 (9%)		
Minsky et al. (1988) [30]	USA	1965–1978	retrospective	115	no	96 (60–240)	24 (21%)	9 (8%)	
Olson et al. (1980) [31]	USA	1960–1970	retrospective	85	no	unclear	17 (20%)	17 (20%)	56%
Park et al. (2016) [32]	International	2004–2008	retrospective	678	yes	73	17 (2.5%)		81%
Radespiel Troger et al. (2004) [33]	Germany	1984–1996	retrospective	535	no	68.5			80%
Sjovall et al. (2006) [15]	Sweden	1996–2000	retrospective	682	unclear	60 (1–100)	79 (12%)		
Willett et al. (1987) [34]	USA	1970–1977	retrospective	211	no	39 (12–100)	55 (26%)	70 (33%)	

Discussion

This systematic review found the local recurrence rate of sigmoid cancer ranged from 2.5% to 26% in the 17 included studies. The pooled rate of 10.5% is higher than the contemporary local recurrence rates in rectal cancer between 3% and 5% [35,36] described in randomised trials.

Is the local recurrence rate for sigmoid cancers higher than rectal cancers? A variety of methodological and clinical issues suggested the true local recurrence rate could be even higher than 10.5%.

Surgery for sigmoid cancer can be challenging. A sigmoid cancer at the apex of the sigmoid mesentery may be treated with a simple sigmoid colectomy. However, sigmoid cancers located at the pelvic inlet are prone to invasion of other pelvic organs and can be technically difficult to dissect, potentially leading to an R1

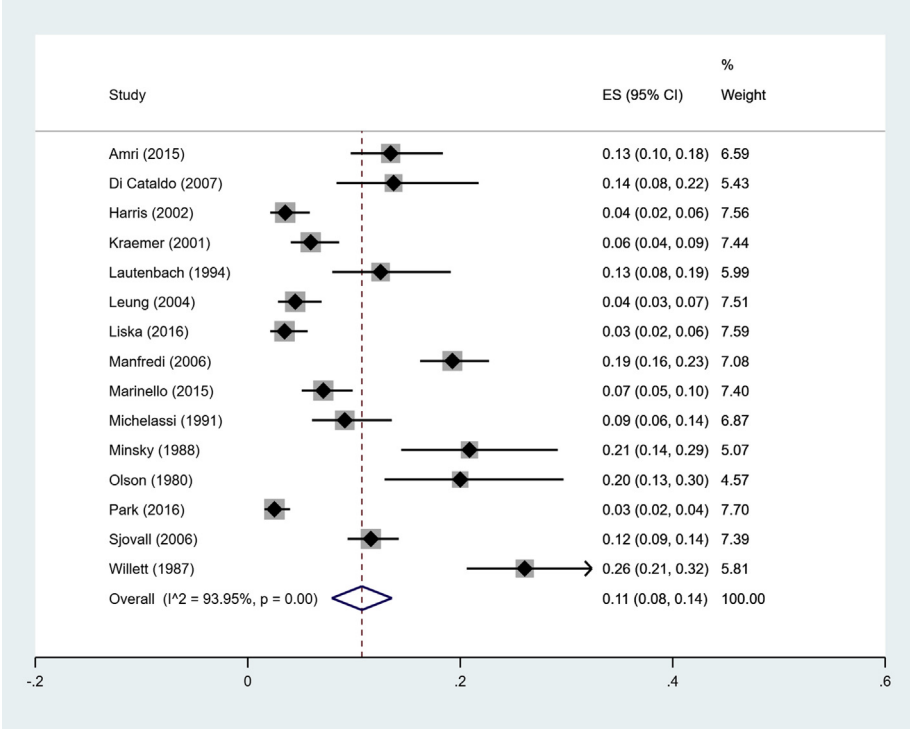

Fig. 2. Forest plot of 11% pooled local recurrence.

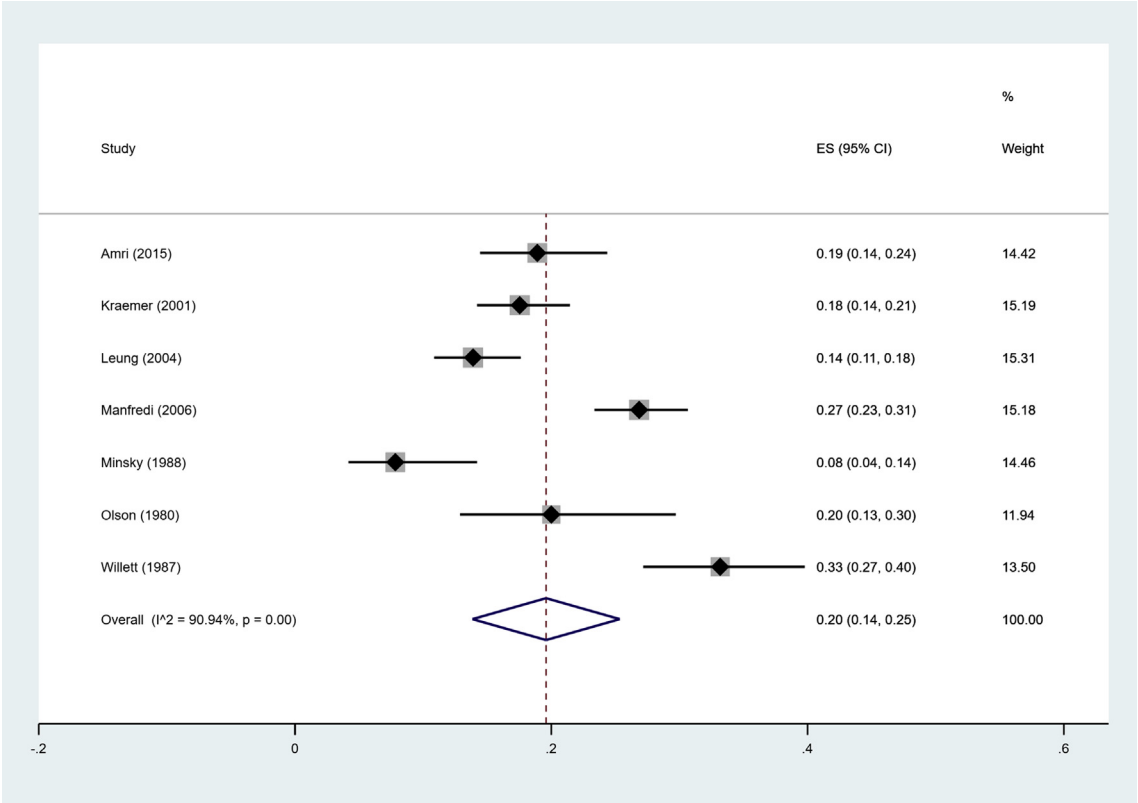

Fig. 3. Forest plot of 19.5% pooled distant recurrence.

resection.

One study reported R1-2 resections in 20% of patients and classified these cases as "palliative" [27]. Another study excluded "palliative" cases (28% overall) and consequently had a 100% R0 rate [22]. Other studies excluded "palliative" operations, but it is unclear whether the pre-operative intent of surgery was curative.

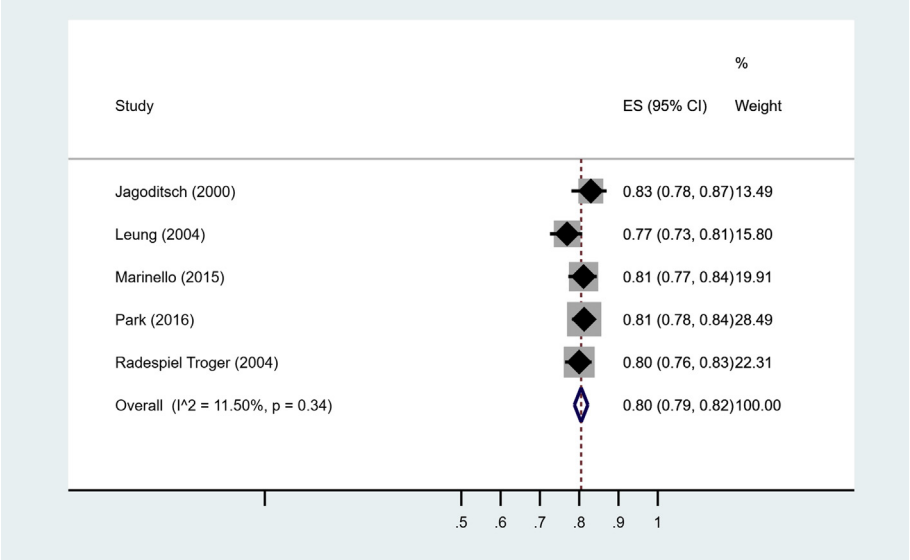

Fig. 4. Forest plot of pooled 80.2% 5 year disease free survival.

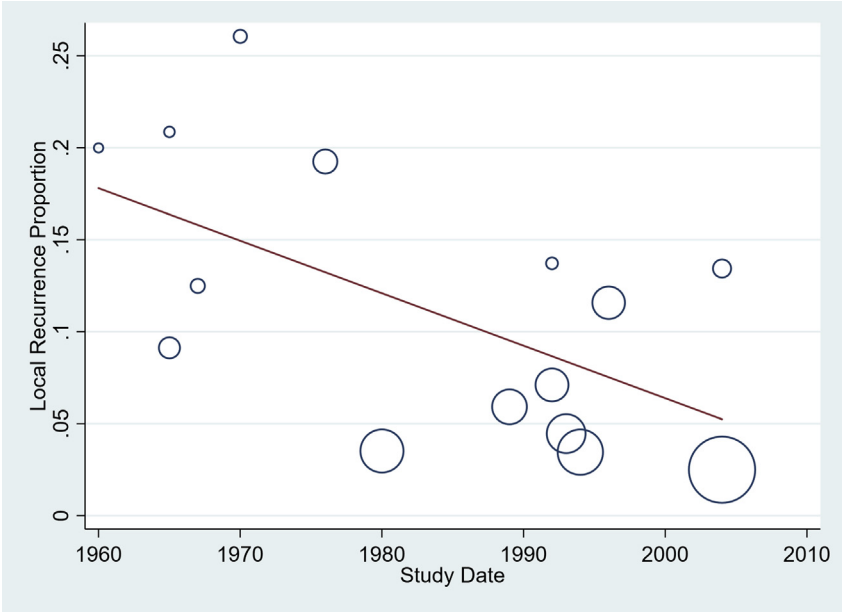

Fig. 5. Local Recurrence Rates vs Study Start Date.

Correspondence with one study author [15] confirmed that despite detailed breakdown of the "radicality" of surgery (ie whether margins were clear) by surgeon and pathologist in a national registry, the intent of surgery is not captured.

The practice of labelling R1 resections as palliative was commonplace in rectal cancer surgery 30 years ago [37]. Radical surgery in rectal cancer is rarely performed with palliative intent. The practice of deeming an operation as "palliative" after surgery or histology has revealed involved margins is no longer acceptable. That practice is no longer continued in part because better pre-operative staging in rectal cancer has enabled both patient selection and the optimal approach for curative surgery. This may involve referral for specialist surgery (exenterative, multivisceral, low rectal) in combination with pre-operative therapy. A similar approach has not been adopted in colon or sigmoid cancer. Perhaps consequently, we found that most studies (14/17) in this review excluded or did not describe R1-2 resections for sigmoid cancer in their analysis.

Because of a lack of documentation and reporting of a pre-operative strategy, we have seen that local recurrence rates for essentially R0 resections are considerably higher in sigmoid cancer than rectal cancer. If studies had included their R1-R2 resections, that were estimated at 15–20%, the local recurrence rate will be even higher.

Other patients at high risk of recurrence were excluded in some studies. This includes patients who had undergone emergency surgery [26,32], or who had neoadjuvant or adjuvant treatment [32,33]. Other studies only analysed results from sigmoid colectomies not anterior resections for sigmoid cancer [20], potentially excluding distal sigmoid cancers at the pelvic brim which are at

Table 2
Description of R1 resection rates and non-curative surgery.

Author	Were R1/R2s described in the study flow?	If described, were R1s/R2s included	What were R1/non-curative rates
Amri et al. (2015) [20]	no		4.3% R1/R2[b]
Di Cataldo et al. (2007) [21]	no		unable to retrieve data[b]
Harris et al. (2002) [22]	yes	no	28% max[a]
Jagoditsch et al. (2000) [23]	yes	no	15%
Kraemer et al. (2001) [24]	yes	no	
Lautenbach et al. (1994) [25]	yes	no	
Leung et al. (2004) [26]	no		
Liska et al. (2016) [16]	yes	yes (R1 included, R2 excluded)	R1 4% (author unable to retrieve R2 data[b])
Manfredi et al. (2006) [27]	yes	no	19.7%
Marinello et al. (2015) [28]	yes	no	no response[b]
Michelassi et al. (1991) [29]	no		
Minsky et al. (1988) [30]	yes	no	37% max[a]
Olson et al. (1980) [31]	yes	no	54% max[a]
Park et al. (2016) [32]	yes	no	unable to retrieve data[b]
Radespiel Troger et al. (2004) [33]	yes	no	
Sjovall et al. (2006) [15]	yes	no	4.5%–12.8%[b]
Willett et al. (1987) [34]	yes	no	no

[a] Total number of excluded patients when subset of patients with R1 resections not quantified.
[b] Data or response from personal correspondence with study author.

higher risk of recurrence.

Variation in the definition of local recurrence may lead to an underestimate of its incidence. One study did not classify peritoneal, mesenteric/retroperitoneal and omental disease within the category of local recurrence [20]. When those sites were included, the local recurrence rate increased from 1.9% to 13%.

Study and methodology quality issues

Many studies had either a high loss to follow up, or did not describe loss to follow up. Some international referral centres for cancer would use telephone follow up if record linkage was not possible. This less rigorous form of follow up permits the possibility of undetected recurrent cancer.

As nearly all studies were retrospective, institutions may have only submitted their data for publication if it showed a low local recurrence rate.

Clinical practice issues

The introduction of adjuvant and neoadjuvant therapies in later study periods may have reduced the number of recurrences. The distant recurrence rate was not lower in studies with adjuvant therapy; but these studies began recruitment in 1976, 1989 and 1993. Distant recurrence rates were not described in more contemporary studies that employed adjuvant therapy.

The different guidelines used to classify cancers as rectal or sigmoid may have led to their misclassification. Only 41% (7/17) of the studies described their criteria for localising cancer to the sigmoid. Some studies may have classified distal sigmoid tumours as rectal tumours, therefore excluding a subset of sigmoid tumour that would have a high recurrence rate. This could certainly be true in studies that classified all cancers below 18cm[28] or 15cm[15, 16, 32] as rectal and excluded them. "Rectosigmoid" tumours (ICD-10 C19) were excluded in 3 studies [20,31,33], again potentially removing a subset of sigmoid cancers that may have a high recurrence rate.

Patients that develop unresectable distant recurrence may have synchronous local recurrence, which may be missed by radiologists, or not recorded by their clinical team.

Low quality of included studies

The median Newcastle-Ottawa Score of 4 indicated that study quality was moderate. Only one study employed a randomised methodology [26], while the other studies were retrospective observational studies. The most frequent quality issues were the exclusion or failure to describe R1 resections (15/17), the omission of TNM staging data for sigmoid cancers (13/17) and the high or unclear loss to follow up (12/17).

Strengths and weaknesses

This systematic review was conducted according to recommended guidelines, and has revealed that sigmoid cancer outcomes are worse than previously thought. The poor methodological quality of the studies yields useful insights into conduct of future research, but led to heterogeneity which means the exact scale of the problem remains unknown. No staff in the author's institutions were found that spoke the languages of the studies that were excluded. None of the studies excluded on the basis of language were cited in any included study.

Guidelines for future research

Future research should not exclude patients with R1 resections, or adverse pre-operative prognostic factors. Studies should describe the modality and landmarks used to localise the tumour. The ICD "rectosigmoid" location should not be employed. Tumour stage should be given. Follow-up techniques and losses should be described in order to determine whether recurrent disease may have been missed. Local recurrences should be classified as to the anatomical area (eg anastomosis, mesentery, peritoneum, retroperitoneum, nodes, sacrum). The outcomes and treatment of patients with local recurrence should also be described. Treatment outcomes for sigmoid cancer should be held to the same standard as those of rectal cancer.

Conclusion

Sigmoid cancer has a high pooled local recurrence rate of 10.5%, which is significantly higher than contemporary local recurrence rates of rectal cancer. A large number of papers fail to describe or include R1 resections of sigmoid cancer, which are frequently described as palliative. The variation in sigmoid cancer local recurrence rates is due to a lack of quality in study methodology and reporting standards. High quality studies that include R1

resections are needed to determine the actual recurrence rate of sigmoid cancer.

Declaration of interests

None.

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Lieve Leijssen, Dave Berger and Annika Sjovall kindly retrieved additional data on R1 resection rates at their institutions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.09.028.

Appendix 1

Pubmed search terms.
Any field contains: neoplasm recurrence.
Or any field contains: disease free survival.
Or any field contains: disease-free survival.
Or any field contains: local recurrence.
Or any field contains: locoregional recurrence.
And any field contains: Colonic Neoplasms/surgery*

Appendix 2

Modified Newcastle-Ottawa scale

Selection.

1) Representativeness of patients with sigmoid cancer
   a) resectable, non-metastatic disease with no exclusion factors*
   b) somewhat representative of resectable, non-metastatic disease, but some acceptable exclusion factors*
   c) significant, unacceptable exclusion factors or unexplained stage variation within the data
   d) no description of the derivation of the cohort
2) Non-exposed cohort: do these contain some sigmoid cancers that have been classified as rectosigmoid?
   a) no rectosigmoid category
   b) rectosigmoid category
   c) no description
3) Verification of sigmoid cancer
   a) biopsy proven colorectal cancer*
   b) imaging proven cancer
   c) no description
4) Demonstration that outcome of interest (recurrence) was not present following surgery
   a) R1 data given*
   b) R1 resections excluded
   c) R0

Comparability.

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for disease stage using TNM classification *
   b) study describes criteria for localising sigmoid cancer*

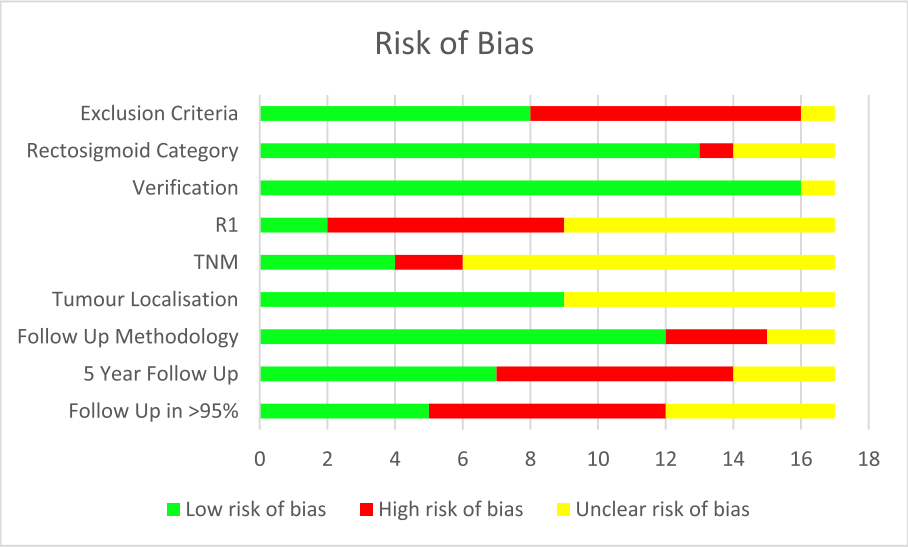
Outcome.

1) Assessment of outcome
   a) independent blind assessment by CT and colonoscopy*
   b) record linkage*
   c) questionnaire/interview
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (median follow up over 5 years)*
   b) no
   c) unclear
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for*
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 5% (select an adequate %) follow up, or description provided of those lost)*
   c) follow up rate < 95% (select an adequate %) and no description of those lost
   d) no statement

Newcastle-Ottawa Score by study.

Author	Exclusion Criteria	Rectosigmoid Category	Verification	R1	TNM	Tumour Localisation	Follow Up Methodology	5 Year Follow Up	Follow Up in >95%	Total Score
Amri [20]	0	0	1	0	1	0	0	0	0	2
Di Cataldo [21]	1	1	0	0	0	0	0	0	0	2
Harris [22]	0	1	1	0	0	1	0	1	1	5
Jagoditsch [23]	0	1	1	1	0	0	1	0	0	4
Kraemer [24]	1	1	1	0	0	0	1	0	0	4
Lautenbach [25]	0	1	1	0	1	0	1	0	0	4
Leung [26]	1	1	1	0	1	0	1	0	1	6
Liska [16]	1	1	1	1	0	1	0	1	1	7
Manfredi [27]	0	1	1	1	0	0	1	1	1	6
Marinello [28]	1	0	1	0	1	1	1	1	0	6
Michelassi [29]	0	1	1	0	0	0	1	0	0	3
Minsky [30]	0	1	1	0	0	1	0	1	0	4
Olson [31]	0	0	1	0	0	0	1	0	1	3
Park [32]	1	1	1	0	0	1	1	1	0	6
Radespiel Troger [33]	0	0	1	0	0	0	1	0	0	2
Sjovall [15]	1	1	1	0	0	1	1	1	0	6
Willett [34]	1	1	1	0	0	1	1	0	0	5
	8	13	16	3	4	7	12	7	5	

Risk of bias overall.



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