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REVIEW ARTICLE

Systematic review and meta-analysis of the outcomes following neoadjuvant therapy in upfront resectable gastric cancers compared to surgery alone in phase III randomised controlled trials

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Abstract

Background Gastric cancer is the fifth most common malignancy and the fourth most common cause of cancer mortality globally. The role of neoadjuvant chemotherapy in upfront resectable gastric cancer is a subject of ongoing research. In recent meta-analyses, R0 resection rate and superior outcomes were not consistently observed in such regimens.

Aim To describe the outcomes following phase III randomised control trials; comparing neoadjuvant therapy followed by surgery against upfront surgery with and without adjuvant therapy in resectable gastric cancers.

Methods The Cochrane Library, CINAHL, EMBASE, PubMed, SCOPUS and Web of Science was searched from January 2002 to September 2022.

Results 13 studies were included (3280 participants). R0 resection rates were in neoadjuvant therapy arms as compared to adjuvant therapy with odds ratio (OR) 1.55[95% CI: 1.13, 2.13](p=0.007) and compared to surgery alone OR 2.49[95% CI: 1.56, 3.96](p=0.0001). 3-year and 5-year progression-, event- and disease-free survival in neoadjuvant therapy as compared to adjuvant therapy were not significantly increased, 3-year OR 0.87[0.71, 1.07](p=0.19). Meanwhile, comparing neoadjuvant therapy to adjuvant therapy, 3-year overall survival (OS) hazard ratio was 0.88[95% CI: 0.70, 1.11](p=0.71) while 3- and 5-year OS OR was 1.18[95% CI: 0.90, 1.55], p=0.22 and 1.27[95% CI: 0.67, 2.42](p=0.47) respectively. Surgical complications were also more common with neoadjuvant therapy.

Conclusion Neoadjuvant therapy yields higher rates of R0 resection. However, improved long-term survival was not seen as compared to adjuvant therapy. Large multi-centred randomised control trials with D2 lymphadenectomy should be performed to better evaluate the treatment modalities.

Keywords Neoadjuvant therapy · Gastric cancer · Stomach neoplasms · Complications · Outcomes

Background

Gastric cancer remains one of the most common malignancies globally according to GLOBOCAN data 2020 and is the fourth most common cause of cancer mortality. Gastric cancers are mostly detected in the advanced stages when they have become symptomatic,[1,2] and prognosis remains poor. Radical oncological surgery namely gastrectomy with adequate lymphadenectomy remains as the only curative option in the management of advanced gastric cancer[3,4] however recurrence even with R0 resection still occurs frequently.[5] To further improve outcomes, multimodality treatments have been suggested for the management of gastric cancer.

The efficacy of neoadjuvant chemotherapy and/or radiotherapy has since been explored as a possible method to improve the outcomes of patients suffering from this malady.[6] Several chemotherapy regimens have been trialled thus far. Most notably, the success of the regimen of epirubicin, cisplatin and infused fluorouracil (ECF) in the management of locally advanced gastric cancers[7] led to the landmark

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United Kingdom Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) trial demonstrating the decreased tumour size and stage and improved progression-free and overall survival rates following a perioperative regimen of ECF in the management of resectable gastric cancers, including GEJ tumours.[8] Other multimodality management for upper gastrointestinal cancers have been trialled such as in the ChemoRadiotherapy for Esophageal cancer followed by Surgery Study (CROSS) where neoadjuvant chemoradiotherapy versus surgery alone was studied demonstrating survival benefits.[9] Arguments have been put forth to consider surgical resection alone, surgery with adjuvant therapy or surgery with neoadjuvant therapy and they are recognised as standard treatments for gastric cancer. In a recent meta-analysis by Yu J,[10] neoadjuvant therapy was compared against surgery alone in randomised trials and retrospective studies; despite longer operative times, R0 resection rate was higher in the neoadjuvant therapy groups. However, no significant differences were showed in long-term overall survival, post-operative complications and short-term mortality in the meta-analysis, which was discordant to the findings in the MAGIC trial. Furthermore, in comparison to adjuvant therapy, neoadjuvant therapy may not have improved outcomes as well. In a meta-analysis by Yu X,[11] short-term benefits were seen in neoadjuvant chemotherapy as compared to adjuvant therapy, as seen by improved 3-year survival odds. Unfortunately, 5-year survival rates do not enjoy the same improvements with neoadjuvant therapy as compared to their adjuvant counterparts. However, in opposition to the benefits of neoadjuvant therapy, the papers selected for meta-analysis demonstrated significant (>50%) heterogeneity in the analysis of 3-year survival. This was not present for the analysis of 5-year survival; hence this raises some doubts towards the benefits of neoadjuvant therapy. Therefore, the benefits of neoadjuvant chemotherapy in the management of locally advanced gastric cancers remain in question.

Internationally, there are varying recommendations for the management of gastric cancer,[12] ranging from neoadjuvant therapy being the ideal treatment in western countries to adjuvant being the main treatment in eastern countries. There is an accompanying gradual shift in the perceptions of neoadjuvant therapy in eastern countries as well,[13] however the consensus remains that neoadjuvant therapy is not the routine standard in the region.[14,15] Adjuvant chemotherapy following gastrectomy remains the gold standard along with D2 gastrectomy.[16,17] The need to clarify the utility of neoadjuvant therapy remains given the differences in outcomes noted between large scale trials and meta-analyses.

As more clinical trials are held, more phase II and III trials have begun to report their results. Unfortunately, phase II trials tend to overestimate the intervention effect,[18] and statistical analysis of the success of intervention may not be as robust as compared to those in phase III trials.[19] Given that the landmark trials are in earlier phases, the benefits of neoadjuvant therapy could have been overestimated.

The purpose of this systematic review is to further describe the outcomes following phase III and randomised control trials; comparing neoadjuvant therapy with surgery against surgery alone or upfront surgery followed by adjuvant therapy in upfront resectable gastric cancers. The gastric cancers are defined as T1-4aN0-3M0, corresponding to stages Ib to IIIc based on the AJCC or type IV linitis plastica tumours.[20] The review aims to detail the characteristics of the patients, tumours, interventions, and the associated outcomes to best inform clinicians on the utility of this treatment modality.

Methods

Search Strategy and information sources

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search of the Cochrane Library, CINAHL, EMBASE, PubMed, SCOPUS and Web of Science was carried out to identify articles published between January 2002 and September 2022. The search terms and results are available in the appendix.

Selection process and eligibility criteria

Three reviewers (Adelina, Alva, Sarah) independently reviewed the studies for inclusion. Studies were considered in the review if they met the following criteria: (1) phase III randomised control trials (RCT); (2) interventions compared neoadjuvant chemotherapy versus surgery alone or versus adjuvant chemotherapy. Studies were excluded if the following were met: (1) articles were not in English; (2) articles were case reports, guidelines, letters, non-comparative studies, protocols; (3) trial was ongoing; (4) patients had metastatic disease preoperatively.

Data collection and analysis

Two reviewers selected and extracted the data from the included studies:

1. Authors, year of publication
2. Patients' and tumour characteristics
3. Outcomes related to neoadjuvant therapy: patient drop out, pathological response, complications and morbidity, oncological stage pre- and post-neoadjuvant therapy.
4. Outcomes following surgery with or without neoadjuvant therapy: R0 resection, lymph nodes harvested,

patient survival, disease progression, and 3-year and 5-year in progression-free survival (PFS), disease-free survival (DFS) or event-free survival (EFS) and overall survival (OS)

The reviewers discussed any differences or omissions in data collection and a third party (TKV, CY) assisted in reaching a consensus.

Meta-analysis for the primary outcomes of 3-year and 5-year PFS, DFS, EFS and OS were conducted in Revman, Version 5.4 (Nordic Cochrane Centre) to obtain the hazard ratio (HR) where possible to determine the likelihood of the outcomes at the 3- or 5-year mark. However, if information provided does not allow for HR to be calculated, odds ratios (OR) would be used instead.[21] Secondary outcome for meta-analysis was the incidence of R0 resection. Comparisons and meta-analysis were conducted if 4 or more studies were available, while for comparisons with 3 or less studies, if there was low heterogeneity, analysis would be conducted.

Heterogeneity using I2 was utilized where 25%, 50% and 75% respectively were low, moderate, and high levels of heterogeneity. For low heterogeneity, analysis would be conducted using a fixed effects model, otherwise, a random effects model would be utilized.

Publication bias was assessed using the Egger's and Begg's test in MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium), in the events of significant publication bias, the trim and fill method was utilized.[22,23]

The Cochrane risk-of-bias tool for randomized trials version 2 tool (RoB 2) was utilized for quality and risk-of-bias assessment.[24] The tool evaluates biases in randomisation process, deviations from interventions, missing outcome data, measurement of the outcome and selection of the reported result. Two authors (Alva and Adelina) assessed bias within the studies independently and discordance was resolved with third party review.

Results

Study Selection

Figure 1 shows the flow chart for the article selection process. A total of thirteen randomised controlled trials (RCTs) were included. A summary of the trial's patient demographic (table 1), tumour characteristics (table 2), surgery characteristics (table 3), neoadjuvant therapy characteristics (table 4) and outcome parameters (table 5) are included below. RoB 2 analysis results can be found in the appendix.

Study Characteristics

A total of 3280 patients with ages ranging from 25 to 76, excluding the participants from Xue,[25] and Zhao[26] (due to unreported age ranges), were involved in the studies. Male patients accounted for the majority of participants at 74.7% of the total while females constituted the remaining 25.3%. In the neoadjuvant chemotherapy compared to surgery alone group, 5-fluorouracil and cisplatin were used in all neoadjuvant regimens, with docetaxel included in the studies by Basi,[27] and Hashemzadeh.[28] Folinic acid was included in the study by Schuhmacher.[29]

Comparing adjuvant therapy with surgery to neoadjuvant chemotherapy with surgery, varying combinations of docetaxel, cisplatin, 5-fluorouracil, S-1, oxaliplatin and capecitabine were used in adjuvant therapy. Similar combinations including the same agents were also used in neoadjuvant therapy.

A total of 1534 patients underwent neoadjuvant therapy, 291 underwent surgery alone and 1455 underwent adjuvant therapy only.

Tumour characteristics

In the neoadjuvant therapy compared to surgery alone analysis, 372 patients (66.9% of 556 patients) were diagnosed at T3 or T4 stage, 99 (17.8%) at T2 or T1 stage, and 8 (1.4%) at T0 stage. Nodal metastases (N1-3) were detected in 360 (64.7%) patients and no nodal metastases (N0) were detected in 93 (16.7%) patients.

In the adjuvant compared to neoadjuvant group, 1402 patients (51.46% of 2724) were diagnosed at T4 stage, 393 (14.4%) at T3, 80 (2.9%) at T2, 0 (0%) at T1 and 0 (0%) at T0. Nodal metastases (N1-3) were detected in 1722 (63.2%) patients and no nodal metastases (N0) were detected in 180 (6.6%) patients. Raw values for TMN staging were not reported in the papers by Fazio,[30] Biffi,[31] and Zhao.[26]

Surgery characteristics and outcomes

Among the patients who underwent surgery in the neoadjuvant compared to the surgery alone group, a majority of them underwent D2 lymphadenectomy. In the surgery alone group, the rate of D2 lymphadenectomy ranged from 11.5% to 100% in the neoadjuvant group (Table 3). Additionally, the rate of D1 lymphadenectomy ranged from 7.4% to 48.1% in the surgery only group and 2.9% to 86.4% in the neoadjuvant group. This does not include patients reported by Basi,[27] and Ychou,[32] as the degree of lymphadenectomy was unreported. The number of lymph nodes removed by Ramachandra,[33] Schuhmacher,[29] and Ychou,[32] ranged from 2 to 88 in the surgery alone group and 1 to 80 in the neoadjuvant group. Meta-analysis of rates of R0 in the neoadjuvant

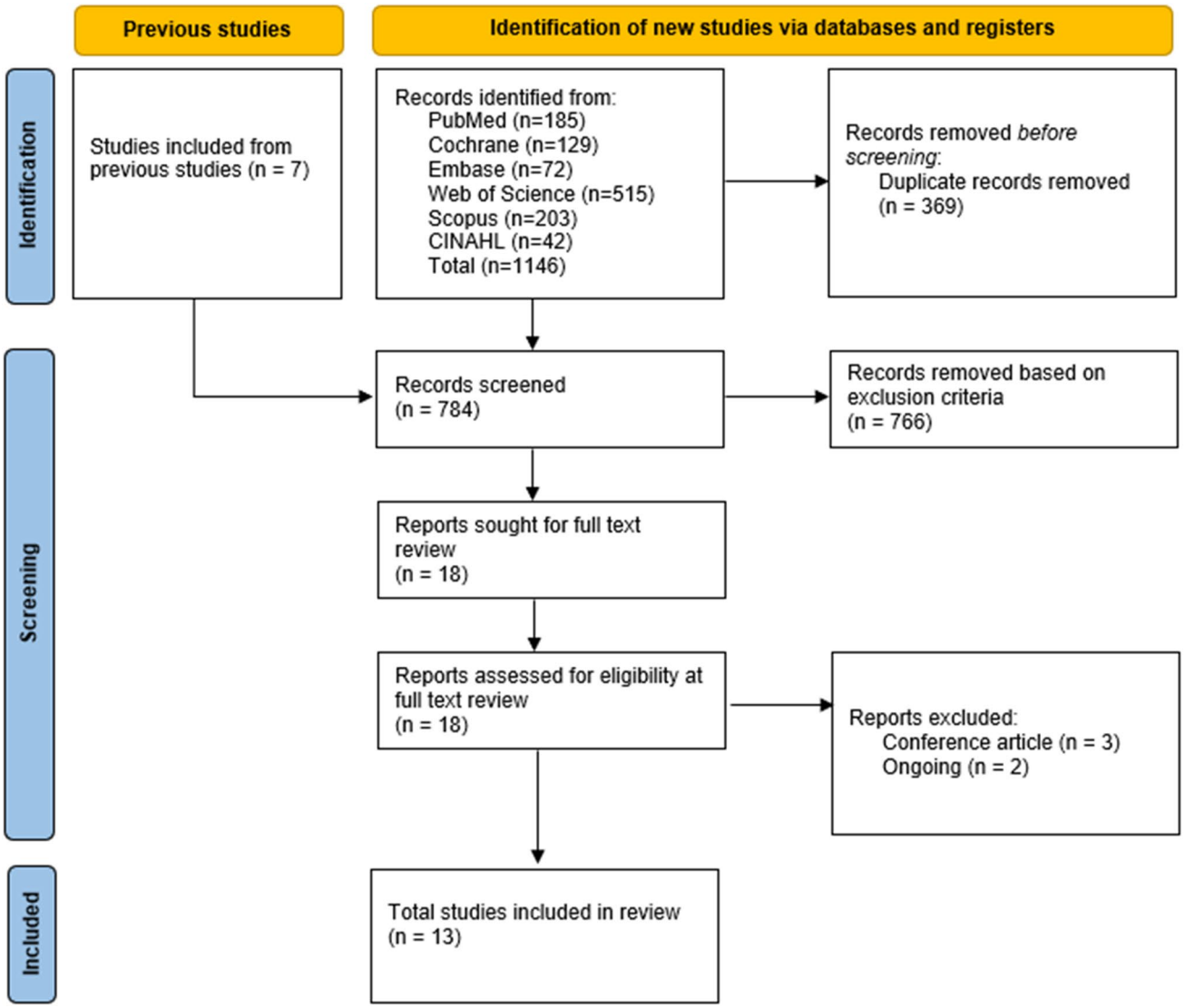

Figure 1 Flowchart for the selection of articles in this systematic review

versus adjuvant comparisons shows that the OR of R0 resection was 1.55 [1.13, 2.13], p=0.007, with neoadjuvant chemotherapy resulting in higher rates of R0 (Fig. 2). Comparing neoadjuvant therapy to surgery alone, the OR of R0 resection was 2.49 [1.56, 3.96], p=0.0001, with higher rates of R0 resection attained in neoadjuvant therapy groups (Fig. 3).

Among the patients who underwent surgery in the adjuvant compared to neoadjuvant group, almost all of them underwent D2 lymphadenectomy, with D2 rates ranging from 91% to 100% in the adjuvant group and 90.6% to 100% in the neoadjuvant group. Fazio,[30] Biffi,[31] Kang,[34] and Xue,[25] reported a range of 9 to 69 nodes removed in the adjuvant group and 13 to 76 in the neoadjuvant group. Rate of R0 resection averaged at 85.6% in the adjuvant group and 92.3% in the neoadjuvant group. Iwasaki,[35] and Terashima[36] did not report the degree of lymphadenectomy performed, number of nodes resected or rate of R0 resection (Fig. 4).

In neoadjuvant therapy patient arms, a total of 325 surgical complications were observed as compared to 69 in patients treated with surgery alone and 324 in patients treated with adjuvant chemotherapy and surgery. However, there was significant heterogeneity seen in reporting of adverse events, ranging from naming conventions of events to grouping of complications in intervention and control arms, hence meta-analysis was not conducted.

Disease free progression was reported in the trials by Ychou[32] and Zhao.[26] In Ychou's study,[32] neoadjuvant therapy sees better 5-year DFS as compared to surgery alone (34% vs 19%). In Zhao's study,[26] 2-year DFS was greater in neoadjuvant arms as compared to adjuvant therapy arms,

Table 1 Patient Characteristics from included studies

	Study arms	No. of participants	Age distribution (years)	Gender distribution (M:F)
Compared to surgery alone				
Basi, 2013[27]	Surgery alone	26	61.22 ± 6.26	22:4
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	28	62.63 ± 7.5	23:5	
	Total n=54			
Hashemzadeh 2014[28]	Surgery alone	52	59.7 ± 8.7	41:11
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	22	58.3 ± 9.1	15:7	
	Total n=74			
Ramachandra, 2019[33]	Surgery alone	30	51.83 ± 9.78	18:12
Neoadjuvant 5-fluorouracil + cisplatin	30	50.73 ± 9.54	22:8	
	Total n=60			
Schuhmacher, 2010[29]	Surgery alone	72	58 [26-69]	50:22
Neoadjuvant cisplatin + folinic acid + fluorouracil	72	56 [38-70]	50:22	
	Total n=144			
Ychou, 2011[32]	Surgery alone	111	63 [38-75]	91:20
Neoadjuvant 5-fluorouracil + cisplatin	113	63 [36-75]	96:17	
	Total n=224			
Compared to adjuvant				
Fazio 2015,[30] Biffi 2010[31]	Adjuvant docetaxel + cisplatin + 5-fluorouracil	35	59 [39 - 76]	24:11
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	34	57 [25 - 75]	23:11	
	Total n=69			
Iwasaki 2020,[35] Terashima 2019[36]	Adjuvant S-1	149	62 [28 - 75]	89:60
Neoadjuvant S1 + cisplatin	151	64 [30 - 75]	87:64	
	Total n=300			
Kang, 2021[34]	Adjuvant S-1	246	58 [51 - 64]	200:46
Neoadjuvant docetaxel + oxaliplatin + S-1	238	58 [51 - 64]	184:54	
	Total n=484			
Xue, 2018[25]	Adjuvant S1 + oxaliplatin	25	<65-years: 19 >=65-years: 6	17:8
Neoadjuvant S1 + oxaliplatin	25	<65-years: 13 >=65-years: 12	19:6	
Adjuvant oxaliplatin + capecitabine	25	<65-years: 18 >=65-years: 7	23:2	
Neoadjuvant oxaliplatin + capecitabine	25	<65-years: 19 >=65-years: 6	17:8	
	Total n=100			
Zhang, 2021[37]	Adjuvant S1 + oxaliplatin	340	59 [53 - 65]	238:102
Neoadjuvant S1 + oxaliplatin	337	60 [53 - 66]	271:66	
Adjuvant oxaliplatin + capecitabine	345	59 [52 - 64]	259:86	
	Total n=1022			

Table 1 (continued)

	Study arms	No. of participants	Age distribution (years)	Gender distribution (M:F)
Zhao, 2020[26]	Adjuvant S1 + oxaliplatin	290	=<60 years: 147 >60 years: 143	219:71
Neoadjuvant S1 + oxaliplatin	223	=<60 years: 177 >60 years: 46	177:46	
Neoadjuvant oxaliplatin + capecitabine	236	=<60 years: 99 >60 years: 137	174:62	
	Total n=749			
Total		3416		2545:871

Table 2 Tumour Characteristics in included studies

	Study arms	T					N			
T0	T1	T2	T3	T4	N0	N1	N2	N3		
Compared to surgery alone										
Basi, 2013[27]	Surgery alone	-	0	5	13	8	2	14	10	-
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	1	5	11	11	2	18	8	-	
Hashemzadeh 2014[28]	Surgery alone	-	0	7	23	1	3	21	6	1
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	0	3	16	0	5	10	4	0	
Ramachandra, 2019[33]	Surgery alone	0	0	6	13	5	7	2	7	8
Neoadjuvant 5-fluorouracil + cisplatin	5	1	6	8	7	15	5	4	3	
Schuhmacher, 2010[29]	Surgery alone	-	-	-	64	7	6	44	5	1
Neoadjuvant cisplatin + folinic acid + fluorouracil	-	-	-	62	8	4	48	6	1	
Ychou, 2011[32]	Surgery alone	0	27		58		17		68	
Neoadjuvant 5-fluorouracil + cisplatin	3	38		57		32		66		
Compared to adjuvant										
Fazio 2015,[31] Biffi 2010[31]	Adjuvant docetaxel + cisplatin + 5-fluorouracil	-	-	-	-	-	-	-	-	-
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	-	-	-	-	-	-	-	-	
Iwasaki 2020,[35] Terashima 2019[36]	Adjuvant S-1	-	-	28	118	3	50	62	37	
Neoadjuvant S1 + cisplatin	-	-	17	128	6.00	55	67	29		
Kang, 2021[34]	Adjuvant S-1	-	-	13	56	177	8	84	121	33
Neoadjuvant docetaxel + oxaliplatin + S-1	-	-	12	60	166	4	81	115	38	
Xue, 2018[25]	Adjuvant S1 + oxaliplatin	-	-	3	9	13	7	8	9	1
Neoadjuvant S1 + oxaliplatin	-	-	1	8	16	10	5	6	4	
Adjuvant oxaliplatin + capecitabine	-	-	2	9	14	10	7	7	1	
Neoadjuvant oxaliplatin + capecitabine	-	-	4	5	16	7	8	8	2	
Zhang, 2021[37]	Adjuvant S1 + oxaliplatin	-	-	-	-	330	10		330	
Neoadjuvant S1 + oxaliplatin	-	-	-	-	327	12		324		
Adjuvant oxaliplatin + capecitabine	-	-	-	-	334	7		335		
Zhao, 2020[26]	Adjuvant S1 + oxaliplatin	-	-	-	-	-	-	-	-	-
Neoadjuvant S1 + oxaliplatin	-	-	-	-	-	-	-	-	-	
Neoadjuvant oxaliplatin + capecitabine	-	-	-	-	-	-	-	-	-	

Table 3 Surgery characteristics and outcomes in included studies

	Study arms	Lymphadenectomy	Nodes removed	R0	Total Complications	Grade 3 or 4 Complications
Compared to surgery alone						
Basi, 2013[27]	Surgery alone	-	-	61.5%	-	-
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	-	85.7%	-	-	
Hashemzadeh 2014[28]	Surgery alone	D1: 48.1% D2: 11.5%	-	-	4	NS
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	D1: 86.4% D2: 0%	-	-	2	NS	
Ramachandra, 2019[33]	Surgery alone	D2: 100%	21.75 ± 8.25	87%	24	1*
Neoadjuvant 5-fluorouracil + cisplatin	D2: 100%	22.33 ± 10.74	96%	32	0*	
Schuhmacher, 2010[29]	Surgery alone	D1: 7.4% D2: 92.6%	33 [10 - 88]	66.7%	20	NS
Neoadjuvant cisplatin + folinic acid + fluorouracil	D1: 2.9% D2: 95.7%	31 [5 - 80]	81.9%	43	NS	
Ychou, 2011[32]	Surgery alone	-	19 [2 - 82]	74%	21	NS
Neoadjuvant 5-fluorouracil + cisplatin	-	19 [1 - 49]	87%	28	NS	
Compared to adjuvant						
Fazio 2015,[30] Biffi 2010[31]	Adjuvant docetaxel + cisplatin + 5-fluorouracil	D2: 88.6% D3: 5.7%	20 [9 - 39]	91%	9	7*
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	D2: 90.6% D3: 0	26 [13 - 76]	85%	9	6*	
Iwasaki 2020,[35] Terashima 2019[36]	Adjuvant S-1	-	-	-	25	19[#]
Neoadjuvant S1 + cisplatin	-	-	-	48	11[#]	
Kang, 2021[34]	Adjuvant S-1	D2: 98%	50 ± 19	84%	-	-
Neoadjuvant docetaxel + oxaliplatin + S-1	D2: 98%	44 ± 19	95%	-	-	
Xue, 2018[25]	Adjuvant S1 + oxaliplatin	D2: 100%	36.2 ± 11.5	96%	8	NS
Neoadjuvant S1 + oxaliplatin	D2: 100%	34.6 ± 16.1	100%	13	NS	
Adjuvant oxaliplatin + capecitabine	D2: 100%	35.3 ± 13.2	100%	15	NS	
Neoadjuvant oxaliplatin + capecitabine	D2: 100%	30.1 ± 11.7	100%	9	NS	
Zhang, 2021[37]	Adjuvant S1 + oxaliplatin	D2: 92%	-	88%	126	NS
Neoadjuvant S1 + oxaliplatin	D2: 96%	-	93%	141	NS	
Adjuvant oxaliplatin + capecitabine	D2: 91%	-	87%	141	NS	
Zhao, 2020[26]	Adjuvant S1 + oxaliplatin	D2: 100%	-	81.7%	-	-
Neoadjuvant S1 + oxaliplatin	D2: 100%	-	87.8%	-	-	
Neoadjuvant oxaliplatin + capecitabine	D2: 100%	-	83.1%	-	-	

*As described by Dindo[52]

[#]As classified by Common Terminology Criteria for adverse events

NS = not specified

p=0.000, while there is no significant difference in DFS between the neoadjuvant therapy regimens p=0.189.

Chemotherapy characteristics and outcomes

Complete pathological response in neoadjuvant arms was noted in 8 studies; the rate of complete pathological response ranged from 1.7% to 18.5%. Partial pathological response was described to varying degrees in the papers, with papers describing response to the neoadjuvant therapy as shrinkage, regression or partial response; the rates of which ranged depending on the extent of the response as seen in Table 4.

In the neoadjuvant groups by Fazio,[30] Biffi,[31] and Xue,[25] comparing the neoadjuvant to adjuvant trials, stage reduction was noted in 3 trials with reduction rates ranging from

Table 4 Chemotherapy outcomes seen in studies

	Regimen	Pathological Response	Changes in TNM	Total complications	Total grade 3 or 4 complications
Compared to surgery alone					
Basi, 2013[27]	Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	T1: 3.6% to 21.4% T2: 17.9% to 50.0% T3: 39.3% to 28.6% T4: 39.3% to 0.0% N0: 7.1% to 64.3% N1: 64.3% to 28.6% N2: 28.6% to 7.1%	6 events	-
Hashemzadeh 2014[28]	Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	Decline in lymph node involvement: 68.2% 30% shrinkage of gastric involvement: 63.3%	-	-	-
Ramachandra, 2019[33]	Neoadjuvant 5-fluorouracil + cisplatin	Complete pathological response: 18.5% Mild or no tumour regression: 37% Moderate tumour response: 26% Marked response: 18%	-	-	-
Schuhmacher, 2010[29]	Neoadjuvant cisplatin + folinic acid + fluorouracil	Complete pathological response: 7.1% Complete clinical response: 5.8% Partial clinical response: 30.4%	-	8 events	-
Ychou, 2011[32]	Neoadjuvant 5-fluorouracil + cisplatin	-	-	NS	63 events*
Compared to adjuvant					
Fazio 2015,[30] Biffi 2010[31]	Adjuvant docetaxel + cisplatin + 5-fluorouracil	-	-	-	-
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	Complete pathological response: 11.7% Partial pathological response: 55.0%	Stage reduction: 60%	-	2 events (G4)	
Iwasaki 2020,[35] Terashima 2019[36]	Adjuvant S-1	-	-	-	-
Neoadjuvant S1 + cisplatin	100% residual tumour: 10.8% >2/3 residual tumour: 29.5% 1/3 - 2/3 residual tumour: 21.6% <1/3 residual tumour: 31.7% 0% residual tumour: 2.2%	-	908 events	104 events^	
Kang, 2021[34]	Adjuvant S-1	-	-	358 events	27 events[#]
Neoadjuvant docetaxel + oxaliplatin + S-1	Complete pathological response: 10.4%	-	708 events in preoperative chemotherapy, 343 events in postoperative chemotherapy	74 events preoperatively, 31 events postoperatively[#]	
Xue, 2018[25]	Adjuvant S1 + oxaliplatin	-	-	84 events	8 events^

Table 4 (continued)

	Regimen	Pathological Response	Changes in TNM	Total complications	Total grade 3 or 4 complications
Neoadjuvant S1 + oxaliplatin	Complete response: 12% Effective response: 28%	Stage reduction: 71.4%	91 events	6 events^	
Adjuvant oxaliplatin + capecitabine	-	-	91 events	6 events^	
Neoadjuvant oxaliplatin + capecitabine	Complete response: 4% Effective response: 32%	Stage reduction: 56.5%	84 events	5 events^	
Zhang, 2021[37]	Adjuvant S1 + oxaliplatin	-	-	282 events	46 events#
Neoadjuvant S1 + oxaliplatin	Complete response: 1.7% Partial response: 39%	-	423 events	68 events#	
Adjuvant oxaliplatin + capecitabine	-	-	226 events	37 events#	
Zhao, 2020[26]	Adjuvant S1 + oxaliplatin			1208 events	154 events in postoperative chemotherapy#
Neoadjuvant S1 + oxaliplatin	Complete response: 4.5% Partial response: 45.3%	-	1190 events	156 events in postoperative chemotherapy#	
Neoadjuvant oxaliplatin + capecitabine	Complete response: 1.7% Partial response: 46.2%	-	1144 events	194 events in postoperative chemotherapy#	

*Graded using WHO criteria

#Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events

^Grading classification not specified

56.5% to 71.4%. In the adjuvant groups however, stage reduction was not stated.

Across the studies, a total of 7217 events were recorded following chemotherapy, of which 4968 events occurred in the neoadjuvant chemotherapy group. A total of 950 grade III or grade IV events were reported; 609 occurred in the neoadjuvant therapy arms in the analysis of neoadjuvant therapy versus chemotherapy trials.

Survival outcomes

PFS, EFS and DFS in neoadjuvant therapy and surgery versus surgery alone

In the neoadjuvant treatment arm studied by Schuhmacher,[29] 3-year PFS was higher at 43.1% compared to 38.9% in the surgery alone group. The 5-year PFS in the neoadjuvant group was also higher at 18.1% compared to 15.3% in the surgery alone group. However, the HR comparing chemotherapy and surgery versus surgery alone was not statistically significant(p=0.20). In Ychou's study, disease free survival was defined from 6 months after random assignment, and neoadjuvant therapy with surgery saw higher DFS with HR 0.69[95% CI: 0.48, 0.89](p=0.003). At 5 years, DFS rates were 34%[95% CI: 26%, 44%] for neoadjuvant therapy with surgery patients and 19%[95% CI, 13%,28%] in surgery alone patients.

OS in neoadjuvant therapy and surgery versus surgery alone

The 5-year OS rates in the neoadjuvant arms were reported by Basi[27] and Ychou.[32] In Basi's trial,[27] 5-year OS rates in the neoadjuvant arms were 36% as compared to 23% in surgery alone arms. While in Ychou's trial,[32] 5-year OS rates were 38% in the neoadjuvant arms as compared to 24% in the surgery alone arm. For YChou, OS was found to be significantly higher in neoadjuvant therapy groups as compared to surgery alone arms with HR for death being 0.69[95% CI: 0.50, 0.95] (p=0.02). Hashemzadeh,[28] and Ramachandra[33] reported neither PFS, DFS, EFS nor OS while Schuhmacher[29] reported OS at 4.1-years and 4.7 years for the surgery and neoadjuvant arms. Due to the low number of studies and significant heterogeneity, a meta-analysis was not conducted for PFS, EFS, DFS and OS in neoadjuvant therapy versus surgery alone trials.

Table 5 Outcomes seen in included studies

	Study arm	Progression of disease	Recurrence	Progression- or event- or disease-free survival	Overall Survival
Compared to surgery alone					
Basi, 2013[27]	Surgery alone	-	-	-	3-month: 92.3% 6-month: 88.5% 9-month: 84.6% 5-year: 23.0%
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	-	-	3-month: 96.4% 6-month: 89.3% 9-month: 85.7% 5-year: 36.0%	
Hashemzadeh 2014[28]	Surgery alone	-	-	-	-
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	-	-	-	
Ramachandra, 2019[33]	Surgery alone	-	-	-	-
Neoadjuvant 5-fluorouracil + cisplatin	-	-	-	-	
Schuhmacher, 2010[29]	Surgery alone	-	-	3-year progression free: 38.9%	4.1-year: 48.6%
Neoadjuvant cisplatin + folinic acid + fluorouracil	-	-	3-year progression free: 43.1%	4.7-year: 54.3%	
Ychou, 2011[32]	Surgery alone	-	Locoregional: 8.1% Distant: 37.8% Both: 18.0%	5-year disease free: 19%	5-year: 14.4%
Neoadjuvant 5-fluorouracil + cisplatin	11.0% after preoperative chemotherapy	Locoregional: 12.4% Distant: 31.0% Both: 12.4%	5-year disease free: 34%	5-year: 23.8%	
Compared to adjuvant					
Fazio 2015,[30] Biffi 2010f[30,31]	Adjuvant docetaxel + cisplatin + 5-fluorouracil	-	48.6%	5-year event free: 44.1% 10-year event free: 43.5%	3-year: 54.3% 5-year: 46% 10-year: 36%
Neoadjuvant docetaxel + cisplatin + 5-fluorouracil	-	47.1%	5-year event free: 44.1% 10-year event free: 29.4%	3-year: 64.7% 5-year: 47% 10-year: 44%	
Iwasaki 2020,[35] Terashima 2019[36]	Adjuvant S-1		Lymph node: 10.0% Peritoneum: 45.6% Distant 10.0% Others: 2.7%	3-year progression free: 47.7%	3-year: 62.4%
Neoadjuvant S1 + cisplatin	1.3% after preoperative chemotherapy 2.0% during NAC	Lymph node: 7.3% Peritoneum: 48.3%% Distant 7.3% Others: 2.6%	3-year progression free: 47.7%	3-year: 60.9%	
Kang, 2021[34]	Adjuvant S-1	-	-	3-year progression free: 60.2%	-
Neoadjuvant docetaxel + oxaliplatin + S-1	-	-	3-year progression free: 66.3%	-	
Xue, 2018[25]	Adjuvant S1 + oxaliplatin	-	-	-	5-year: 74.0%
Adjuvant oxaliplatin + capecitabine	-	-	-		
Neoadjuvant S1 + oxaliplatin	-	-	-	5-year: 70.0%	
Neoadjuvant oxaliplatin + capecitabine	-	-	-		

Table 5 (continued)

	Study arm	Progression of disease	Recurrence	Progression- or event- or disease-free survival	Overall Survival
Zhang, 2021[37]	Adjuvant S1 + oxaliplatin	-	-	3-year disease free: 59.4%	-
Neoadjuvant S1 + oxaliplatin	0.5% after preoperative chemotherapy	-	3-year disease free: 51.1%	-	
Adjuvant oxaliplatin + capecitabine	-	-	3-year disease free: 56.5%	-	
Zhao, 2020[26]	Adjuvant S1 + oxaliplatin	-	-	1-year disease free: 79.8% 2-year disease free: 66.6%	1-year: 84.4% 2-years: 70.0%
Neoadjuvant S1 + oxaliplatin	9.4% after chemotherapy	-	1-year disease free: 92.3% 2-year disease free: 82.4%	1-year: 95.7% 2-years: 86.7%	
Neoadjuvant oxaliplatin + capecitabine	11.8% after chemotherapy	-	1-year disease free: 90.8% 2-year disease free: 80.0%	1-year: 92.1% 2-years: 80.6%	

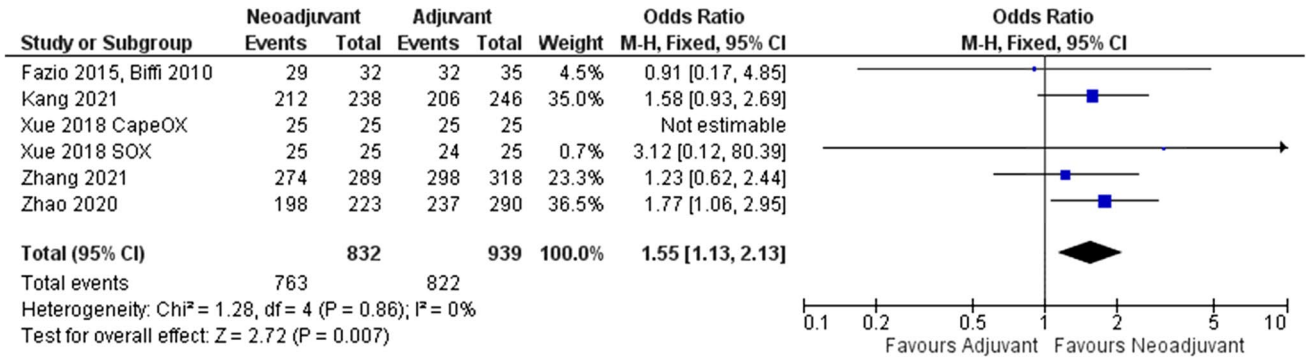

Figure 2 Analysis of R0 resection rates comparing adjuvant therapy vs neoadjuvant therapy arms

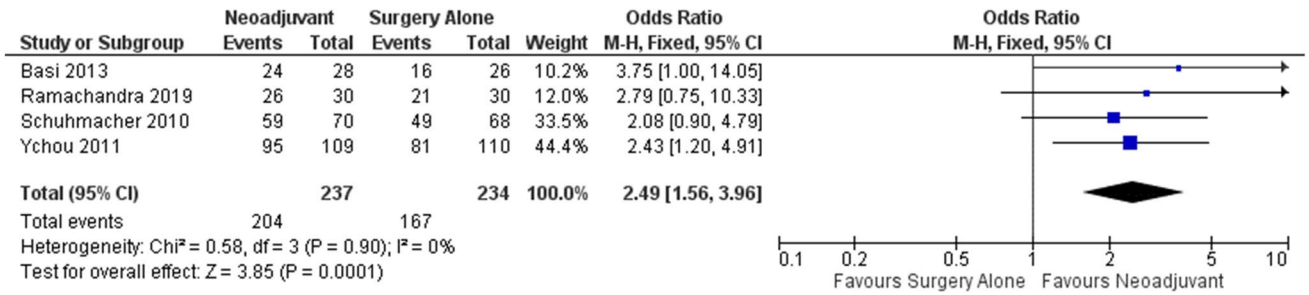

Figure 3 Analysis of R0 resection rates comparing surgery alone vs neoadjuvant therapy arms

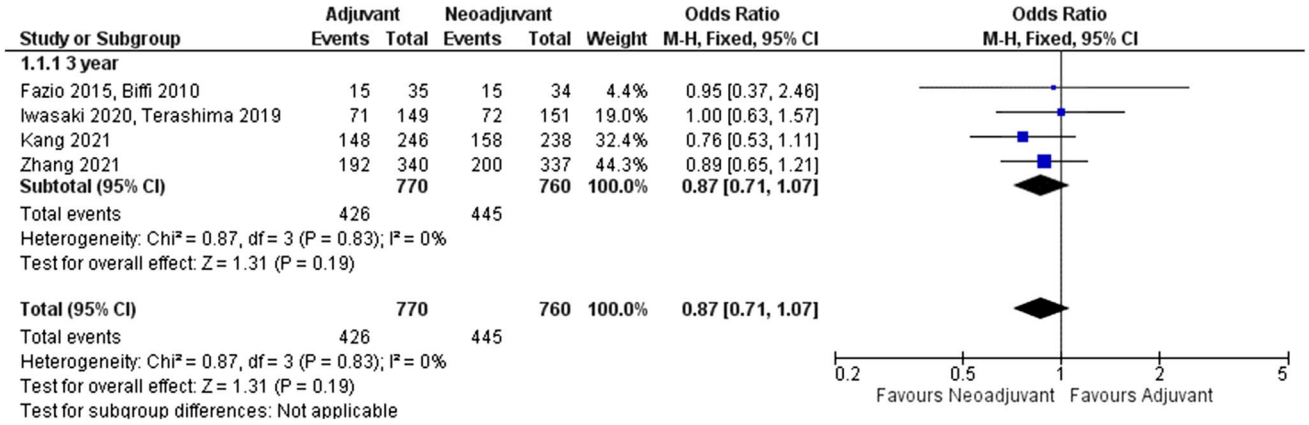

Figure 4 Analysis of 3-year OR for DFS, EFS and PFS between adjuvant therapy and neoadjuvant therapy arms

PFS, EFS and DFS in neoadjuvant therapy and surgery versus adjuvant therapy and surgery

Neoadjuvant therapy was compared to adjuvant therapy. For Fazio and Biffi,[30,31] event-free survival was defined by time to relapse, progression, death from any cause starting from randomization. The EFS at 5 years was 44.1% [95% CI: 27.3%, 59.7%] in adjuvant therapy arms compared to 43.5% [95% CI: 26.5%, 59.4%] in neoadjuvant therapy arms. At 10 years, the EFS was 44.1% [95% CI: 27.3%, 59.7%] in adjuvant therapy arms versus 29.4% [95% CI: 14.7%, 45.8%] in neoadjuvant arms. There was no significant difference in EFS at 2.5 years in both arms(p=0.5). For Iwasaki and Terashima,[35,36] progression-free survival was defined as the time from randomization to the first occurrence of disease progression, diagnosis of being able to undergo R0 or R1 or death from any cause. The 3-year PFS was 47.7% in both arms, HR 0.976[95% CI: 0.738, 1.292](p=0.87). Kang's PRODIGY trial[34] defined PFS as progression of disease or death, definition of progression involved distant metastasis, persistence of cancer at resection margins or recurrence. In the PRODIGY trial, PFS was better in the patients treated with neoadjuvant therapy HR 0.70[95% CI: 0.52, 0.95] (p=0.023). The 3-year PFS was 66.3%[95% CI: 59.6, 72.1] in the neoadjuvant therapy arm compared to 60.2%[95% CI: 53.6, 66.3] in the adjuvant therapy arms. Disease-free survival was defined as time from randomisation to recurrence of primary cancer, new gastric cancer, distant metastases or death from any cause seen in Zhang's RESOLVE trials.[37] Comparing perioperative SOX to adjuvant CapOx, DFS was higher, HR 0.77[95% CI: 0.61, 0.97](p=0.028). As the definitions of EFS, DFS and PFS were similar, a meta-analysis for HR was attempted but only 2 studies[34–36] provided sufficient data and there was significant heterogeneity, hence OR analysis was conducted.

OS in neoadjuvant therapy and surgery versus adjuvant therapy and surgery

For 3- and 5- year OS, 3-year OS was reported in 2 papers while for 5-year OS, 2 papers report these outcomes. The 3-year OS between the two treatment arms analysed had an HR of 0.88[95% CI: 0.70, 1.11], p=0.71 (Fig. 5). For OR calculation, 3-year and 5-year data were analysed. The 3-year OS between the treatment arms were analysed and an OR of 1.18 [95% CI:0.90, 1.55], p=0.22 while 5-year OS had an OR of 1.27 [95% CI:0.67, 2.42], p=0.47 (Fig. 6).

Discussion

Neoadjuvant therapy demonstrates utility in attaining R0 resections in patients treated with this modality. Attaining R0 resection has been shown to increase the chance of cure

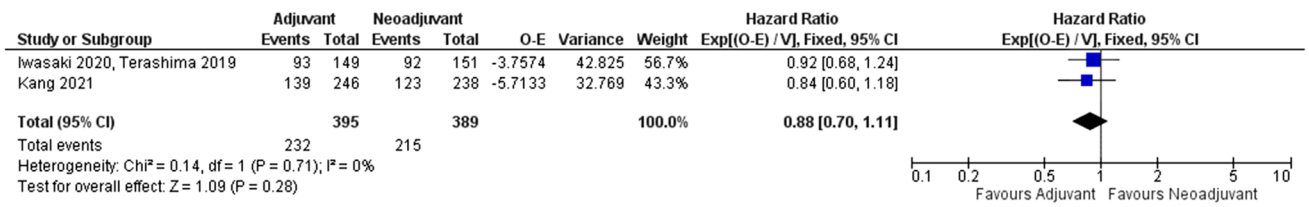

Figure 5 Analysis of 3-year HR for OS comparing adjuvant therapy and neoadjuvant therapy arm

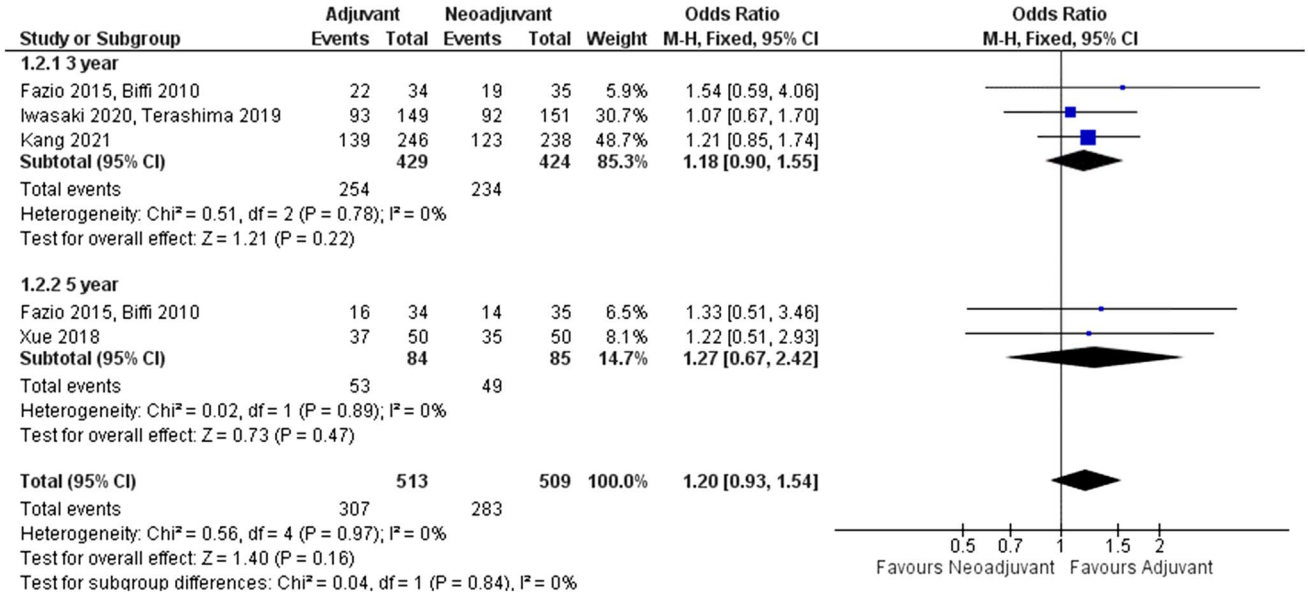

Figure 6 Analysis of 3-year and 5-year OR for OS comparing adjuvant therapy and neoadjuvant therapy arms

for the patients.[38] The higher rates of R0 resection also seem to predict the increased rate of survival achieved in the paper by Basi.[27] This, combined with the pathological response noted in the papers, hint towards the possibility of utilising neoadjuvant chemotherapy to facilitate subsequent surgery of advanced gastric cancers that would normally pose difficulties in resection due to size or spread. The idea of utilising neoadjuvant therapy to downstage tumours is not novel and has been used frequently in monitoring the response of other cancers.[39,40] However, surgical complications occurred more frequently in the neoadjuvant therapy groups which suggests an increased surgical technically difficulty or perhaps more vigilance in post-operative care in neoadjuvant therapy patients who had previously suffered from adverse effects in the chemotherapy.[41] Nonetheless, it is well known that neoadjuvant chemotherapy is considered a personalised in-vivo drug test to assess chemotherapy efficacy and to further guide treatment planning.[42]

Comparing 3-year and 5-year PFS, DFS, EFS and OS to that in adjuvant therapy regimens, our analysis demonstrates a lack of evidence supporting the utility of neoadjuvant therapy in providing patients with long term benefits. Furthermore, given the notable adverse effects following chemotherapy treatments, the benefits may not outweigh the harms experienced by the patient. In Kang's study,[34] we noted that there were already 704 adverse events, of which 74 (10.5%) were grade III or IV toxicities reported in response to chemotherapy before surgery was performed. The harms brought to the patient through the neoadjuvant chemotherapy regimen were compounded by the 343 events, where 31 events were grade III or IV adverse events in the adjuvant therapy stage. The significant rates of dropouts following neoadjuvant chemotherapy, intervals between treatment and adverse events that may have resulted in a small percentage of patients facing progression of their conditions before receiving the necessary surgery. Given the inability to conduct a meta-analysis for neoadjuvant therapy as compared to surgery alone trials, this paper is unable to commit to the efficacy of neoadjuvant therapy as compared to surgery alone. However, there appears to be higher rates of survival in patients receiving neoadjuvant therapy and surgery as compared to having surgery alone.

In the landmark MAGIC trial, it was found that neoadjuvant therapy was associated with improved long-term outcomes. This is also corroborated by the meta-analysis by Xiong,[43] where similar findings supported improved outcomes for neoadjuvant chemotherapy. In the same paper, 1820 patients were included from 12 RCTs which showed that neoadjuvant chemotherapy slightly improved survival rates [OR = 1.32, 95% confidence interval (CI): 1.07-1.64, P=0.01]. There was also significantly improved three-year progression-free survival (PFS) rates [OR: 1.85 (1.39, 2.46), p < .0001], tumour down-staging rates [OR: 1.71 (1.26, 2.33), p=.0006] and R0 resection rates [OR: 1.38 (1.08, 1.78) p=.01] in these patients. This was also seen in other meta-analyses by Xu[44] and Cai.[45] In the paper by Xu,[44] the nine RCTs with a total of 1056 participants illustrated higher R0 rates in neoadjuvant therapy subjects as compared to those in the surgery alone intervention group. [25.68% vs 16.95%, RR: 1.92, 95% CI: 1.20–3.06,

$P=0.006$]. In the network meta-analysis by Cai,[45] the eight trials with 2434 participants who underwent multiple regimens of neoadjuvant chemotherapy showed significantly improved survival. However, discordant findings were noted within the meta-analyses. In the meta-analysis by Yu J,[10] and the paper by Liao,[46] neoadjuvant therapy was reported to not be associated with improved long-term outcomes. For Yu J,[10] the team found that in the 20 studies with 3362 total participants, neoadjuvant chemotherapy led to significantly increased R0 resection rates (p=0.003) but no significant differences in overall survival (p=0.240). The lack of improved survival was similar in Liao's[46] study of six trials with 781 patients, however R0 resection in this paper was not significantly improved in the neoadjuvant therapy study arm.

Possible reasons for the varying findings could be due to the different regimens used in the interventions. For example, in the paper by Xiong,[43] regimens included 5-fluorouracil (5-FU) + cisplatin, paclitaxel (PTX) + 5-fluorouracil/leucovorin/oxalipatin (FOLFOX), docetaxel/cisplatin/5-fluorouracil (TCF), 5-FU/Adriamycin/methotrexate (FAMTX) and epirubicin + cisplatin + fluorouracil (ECF). This difference in regimens was seen throughout the other meta-analyses as well.[10,44,45] Furthermore, whether D2 lymphadenectomy was performed was also a variable that could have possibly contributed to the incongruous findings. In the MAGIC trial, only 43% of cases underwent D2 lymphadenectomies while a larger proportion of the patients in this study completed D2 (Table 3).

In the evaluation of adjuvant therapy as compared to neoadjuvant therapy, the large PRODIGY trial involving 18 centres, demonstrated improved PFS(p=0.0227) but OS was not significantly improved(p=0.3383). The findings of the PRODIGY trial disagree with what our meta-analysis has demonstrated. Possible reasons include the small number of trials available for meta-analysis as well as the PRODIGY trial involving patients who were at earlier stages of their disease. Furthermore, the PRODIGY trial also only utilized adjuvant S1 as compared to the other trials utilizing a combination other than JCOG0501 trial by Iwasaki and Terashima.[35,36] Furthermore, the evaluation of improvement of PFS was conducted using the results following 38.6 months, while we evaluated PFS at the 36 months. Looking at another large trial with a total of 749 patients, Zhao[26] demonstrated improved short-term disease-free survival rates in patients treated with neoadjuvant therapy.

Our findings are that outcomes are not improved by neoadjuvant therapy as compared to adjuvant therapy. However, as compared to surgery alone, there may be benefits in PFS, DFS and OS as compared to neoadjuvant therapy; but, more large-scale trials need to be conducted for viability of meta-analysis. Furthermore, given the smaller number of phase III trials available for analysis, there remains a need for more large scale multicentred randomised control trials studying the effects of neoadjuvant chemotherapy versus adjuvant chemotherapy or surgery alone, allowing for more subgroup analyses that take the above into account.[47] With multiple phase III trials ongoing comparing different regimens of neoadjuvant therapy,[48] neoadjuvant chemoradiotherapy,[49] neoadjuvant versus adjuvant therapy,[50] and immunotherapy,[51] a final consensus on the best management would eventually arise and a large-scale trial can then be conducted to fully evaluate if neoadjuvant therapy is indeed superior to surgery alone.

Limitations of the current study

There exists significant heterogeneity in data reporting for some outcomes such as pathological downstaging, morbidity from chemotherapy or surgery. Comparison of data from the various papers were limited by the lack of standardised parameters used in documentation and analysis. Although other outcomes would be served better with statistical validation, they were unable to be accorded with the analysis due to this heterogeneity. Therefore, this limits the generalizability of this study towards future trials.

Conclusion

Neoadjuvant therapy yields higher rates of R0 resection but improved long-term survival following neoadjuvant therapy was not observed comparing neoadjuvant to adjuvant therapy. Given that survival appears to be improved as compared to surgery alone, it may be put forth that outcomes of ongoing randomised controlled trials comparing different neoadjuvant regimens to adjuvant regimens would further inform on the survival outcomes regarding neoadjuvant therapy for gastric cancers. However, more large multi-centre randomised control trials should be performed to validate this finding. Furthermore, standard D2 lymphadenectomy should also be performed for better utility of findings. As patients face more side effects with more cycles of chemotherapy, it may be put forth that adjuvant therapy is sufficient for improving long term survival in patients with locally advanced gastric cancers.

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Sarah Neo Hui Wen: acquisition of data, manuscript drafting and approval, agreement for accountability for all aspects of the work

Charleen Yeo Shan Wen: project development, interpretation of data, manuscript drafting and approval, agreement for accountability for all aspects of the work

Tay Kon Voi: project development, interpretation of data, manuscript drafting and approval, agreement for accountability for all aspects of the work

Declarations

Registration and protocol Review was not registered.

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