Neoadjuvant Chemotherapy and Adjuvant Chemoradiotherapy in the Treatment of Gastric Adenocarcinomas

By

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Abstract

Purpose: Gastric cancer is the third leading cause of cancer-related death worldwide. From 1974-1975, patients who received gastric resection only had a 5-year survival rate of 15.3%.[16] With the introduction of chemoradiotherapy, the 5-year survival rate increased to 23.2% from 1995-2001.[16] One question which can be imposed is how necessary is neoadjuvant chemotherapy in addition to surgery compared to surgery then adjuvant chemoradiotherapy in improvement of 5-year survivability of a gastric adenocarcinoma.[1]

Methods and Materials: 7 random control trials using neoadjuvant chemotherapy and 2 random control trials using adjuvant chemoradiotherapy were examined using a network meta-analysis to determine which was the more beneficial for 3-year, 5-year, and Overall Survival. Secondary outcome was to determine which caused more life-altering side effects

Results: There was no statistical benefit found in the use of adjuvant chemoradiotherapy over the use of neoadjuvant chemotherapy. The 5-year and Overall mortality were consistently higher in the adjuvant chemoradiotherapy group, but the strength of data in the network meta-analysis was inconclusive.

Conclusion: Further study the use of neoadjuvant chemotherapy plus surgery in the treatment of gastric adenocarcinomas in order to improve quality of life for the patients is recommended as well as further study of adjuvant chemoradiotherapy to improve survivability.

[1] PICO question

Neoadjuvant Chemotherapy and Adjuvant Chemoradiotherapy in the Treatment of Gastric Adenocarcinomas

Introduction

Epidemiology

Gastric cancer is the third leading cause of cancer-related death worldwide.[1] From a global perspective, gastric cancer is the 4th most common cancer to be diagnosed among men and 5th most common among women. Developing countries have a higher incidence of gastric cancer and account for 70% of diagnosed cases. These countries also have a mortality rate 5-10% greater than developed countries like the United States. This is most likely due to inadequate access to the more contemporary treatments, such as neoadjuvant chemotherapy or adjuvant chemoradiotherapy[2]. Overall, the mortality of gastric cancer is declining.

There are a variety of risk factors which may increase the incidence of an adenocarcinoma (Appendix A). Environmental factors are believed to play one of the largest roles in the increase and decrease of gastric cancer. Dietary salt intake is associated with higher incidence and mortality.[3] Light to moderate alcohol consumption poses a slight increase in risk for the development of gastric cancer, whereas heavy alcohol consumption (>4 drinks per day or 60g of alcohol per day) has a proven significant increase in the risk of development.[4] Similar to most other cancers, tobacco use also plays a role; there is strong data which show an association between duration of cigarette use and the likelihood of development of gastric cancer.[5] Fruits and vegetables are observed to be protective against gastric cancer. Two to five servings of fruits and vegetable per day has a proven positive impact; in fact, people who consume recommended amounts of fruits and vegetables over a 40-year period have almost a 30% less risk of gastric cancer.[6,7] Increased vitamin C consumption has also been linked as protective against gastric cancer, although separating the effects, or lack thereof, of ascorbic acid from

H. pylori bacteria is difficult.[6] Although these factors can increase the risk of development of gastric cancer, it can also be caused by an infectious etiology.

There are two known infectious causes of an increase in risk of the development of gastric cancer: *H. pylori* and Epstein-Barr virus (EBV). *H.pylori* is considered a class I carcinogen by the World Health Organization (WHO) for the development of cancer. There is an approximate 3% greater chance of developing a gastric adenocarcinoma after the development of an *H. pylori* infection.[8] Additional risk is attributed to *H. pylori* because the same environmental factors which influence a gastric adenocarcinoma (increase the risk- high salt intake, cigarette use, alcohol consumption; decrease the risk- consumption of fruits and vegetables, increase in dietary Vitamin C) influence the effect of *H. pylori* in the same way, respectively.[8] The specific mechanism of action of how the *Epstein-Barr Virus* affects gastric adenocarcinomas is unknown, but there is a correlation with the presence of the virus and those affected by gastric cancer; approximately 8% of gastric cancer are EBV carcinomas.[9]

There is also a genetic component which increases the risk of gastric cancer. A germline mutation of the *CDH1* gene located on chromosome 16q22 carries an increase risk in the early development of gastric adenocarcinomas.[10] Gastric cancer has also been linked to Lynch Syndrome families carrying the germline mutations MLH1 and MSH2.[11]

Pathophysiology

Gastric cancer should not be recognized as a single disease, but rather a collection of individual diseases within a single organ. Since 1965, Lauren's criteria is the most widely accepted and frequently used classification system of gastric cancer.[12] Historically, the Lauren subtype system breaks down gastric cancer into diffuse and non-diffuse. More recently, a 3 subtypes have been identified: non-cardia intestinal gastric cancer, diffuse gastric cancer, and proximal gastric cancer. Non-cardia intestinal gastric cancer has a multi-step progression affecting the body/antrum aspect of the stomach. It begins with chronic inflammation (usually caused by *H. pylori*) which produces a chronic gastritis. This leads to

intestinal metaplasia, and finally dysplasia. This type of gastric cancer affects males to females in the US at a 3:1 ratio, with Caucasians making up almost 60% of all patients.[2] (what proportion of the gastric cancers fall into each of these subtypes?)

Diffuse gastric cancer is described as widespread thickening and rigidity of the gastric wall.[10,13] This type of cancer has no known precursor lesion and no association with chronic inflammation. Instead there is either a mutation or epigenetic silencing of the E-cadherin gene; *CDH1* gene. E-cadherin is protein which mediates cell interactions and cell polarity by attaching to the cytoskeleton during mitosis. Without this protein, gastric cancer cells are able to dissociate from their matrix and metastasize.

Proximal gastric cancer effects the distal 1/3rd of the esophagus, the gastroesophageal junction, and the gastric cardia. It is commonly caused by gastroesophageal reflux disease (GERD) and has been linked to Barrett's Esophagus. *H. pylori* infections tend to be protective of this type of cancer. The *H. pylori* infection reduces acid production and decreases the GERD's effect. Originally this subtype of gastric cancer was grouped with non-cardia intestinal gastric cancer because of the presentation: chronic inflammation, then intestinal metaplasia, and finally dysplasia. Due to its reversed interaction with *H. pylori*, proximal gastric cancer has become its own subtype.[2]

Approximately 10% of cancer-related deaths worldwide are linked to gastric cancer which has a high fatality to case ratio of 70%.[2] Ove the last 30 years, the 5-year-survivablitily of gastric cancer has increased from approximately 10% to over 20%.[14] This increase is most likely due to improvements in surgical techniques and advancements in chemotherapy. The standard of treatment for gastric cancer is a resection of the tumor. In the 1960s, chemotherapy and radiation were included to assist in the treatment of non resectable tumors. The standard of care with chemotherapies was initially an infusion of 5-fluorouracil, until the 1970s, when a 3 drug regimen of 5-fluorouracil, doxorubicin, and mitomycin (FAM) was found to have better efficacy.[15] Since response rates with FAM were found to be as high as

50%, other chemotherapies began to be tested. Epirubicin, cisplatin, and continuous infusion of 5-fluorouracil were found to have a response rate of approximately 71% as a post-operative adjuvant.[15] These successful treatments led to the belief that gastric adenocarcinomas are chemotherapy sensitive tumors, so research started on different modalities and timings of infusions. In Japan, neoadjuvant chemotherapy research has gained interest in order to increase the number of patients who may be offered a curative resection. In the United States, the addition of postoperative chemoradiotherapy to gastric resections has proven to improve the 5-year survival rate. From 1974-1975, patients who received gastric resection only had a 5-year survival rate of 15.3%.[16] With the introduction of chemoradiotherapy, the 5-year survival rate increased to 23.2% from 1995-2001.[16] One question which can be imposed is how necessary is neoadjuvant chemotherapy in addition to surgery compared to surgery then adjuvant chemoradiotherapy in improvement of 5-year survivability of a gastric adenocarcinoma.[2]

Methods

Literature Search

A systematic literature search was done using the following databeases: Trip, Embase, Pubmed, CINAHL, and Google Scholar. The search terms used were “Gastric/stomach”, “cancer/carcinoma/adenocarcinoma”, “neoadjuvant/preoperative chemotherapy”, “adjuvant Chemoradiotherapy/radiation/chemotherapy”, “surgery/surgery alone”, and “5 year survival”. The special database function “related articles” was used to maximize the search. The references from relevant articles and the randomized controlled trials used within the articles were searched to identify additional relevant articles. Due to the nature of the disease and the therapies provided, relevant data was acceptable from 2000 to current times. The records included 563 articles and after reviewed for duplicates, 552 articles remained. The articles’ title and abstracts were screened for relevance on the

[2] PICO question

topic and 37 remained. Of the 37 remaining articles, 11 studies were primarily used for the data in this report; 9 random controlled trials and a meta-analysis. The meta-analysis was chosen draw from the 7 random controlled trials (RCT) used in its research. Only research translated to/written in the English languae were applied and the last data search done on August 4, 2018.

Inclusion/Exclusion Criteria

The articles were screened using the following criteria: all articles were written or translated to English by the year 2000, all patients were diagnosed with gastric adenocarcinomas of the stomach or gastroesophageal junction which were histologically confirmed, resectable cancers only, no race or gender limitations, clear documentation of each intervention with procedure, only either preoperative chemotherapy or post operative chemotherapy with radiation were used in addition to a resection for the therapy groups, no chemotherapy or radiation were used with the control groups, no distant metasis were noted prior to randomization, the procedure must have complete resection of the carcinoma with margins <1cm, a response to each treatment was documented and the patients were categorized appropriately, and clear documentation of side effects from the medications were noted. Excluded articles with justification are listed in Appendix B.

Data Collection Process

All articles were examined by 1 author and then content and article relevance were reviewed by 2 authors. This meta analysis is written in accordance to PRISMA guidelines, and the following data was extracted from each study: design from 10 RCTs, study population, and inclusion/exclusion criteria. Therapies of the studies were neoadjuvant chemotherapy (NAC) and adjuvant chemoradiotherapy (ACRT) listed in Table 3[17,18]. No specific surgery was studied, as long as it met inclusion criteria. The diagnosis of gastric cancer was done in Xu et al in accordance with the 14th edition of the Union for International Cancer Control (UICC) tumor node metastatic (TNM) classification of malignant tumors and the Japanese Gastric Cancer Classification[17,19]. The diagnoses of gastric cancer were done in MacDonald

et al and Sung Kim et al in accordance with 1988 staging criteria of the American Joint Commission on Cancer[18,20]. Study population includes number of patients studied, race, age and gender.

Determination of Bias

Bias across this study was evaluated with the Cochrane Collaberation tool. High quality data was given a score of 4/5 or higher, medium quality data was given a score of 3/4, and low quality data was given a score of 2/4 or below. All studies will begin at 5 and will be deducted 1/2 of a point per qualified metric of bias. This will standardize the scoring system and assist in evaluation of quantified bias evaluation. These scoring assignments were determined before the study began.

Results

Selected trials

Zero studies were identified which compared neoadjuvant chemotherapy to adjuvant chemoradiotherapy. The most appropriate way to compare the two therapies was determined to compare their effects versus a control (surgery alone) and then contrast the effectiveness of each therapy against each other using a network meta-analysis. The 9 RCTs evaluated began collecting data no later than 1991 and they were all published between 2000 and 2010, and they all followed patients for a minimum of 60 months each. Demographics and Therapies of each study are listed in Appendix C[18,21–25]. The main recorded demographic were T staging of the tumor, age range, and gender. Zhao et al. and Kobayashi et al. did not include an initial T staging due to the studies concentrating on gene expression of PCNA, Fas/FasL and PD-ECGF. The flow diagrams in Appendix F show how each RCT's participation was enacted[18,21–25].

Primary Outcomes

The primary outcomes of the trials were to assess the 3-year survivability (Table 1&2), 5-year survivability (Table 3&4) and Overall Mortality (Table 5&6) of the therapies.[17,21,23–27] There was significant heterogeneity through out all of the studies, so a random effects model was chosen to

determine outcomes. No study out of the NAC group showed any statistically significant improvement in 3-year mortality over surgery alone (RR 1.05, 95%CI 0.91,1.22). Nio, Schuhmaker, and Imano studies generally favored NAC, but the strength of data was low. Both studies out of the ACRT group showed favorable 3-year survivability in the therapy groups, but the favorablitity was minimal. The network meta-analysis (Table 2) shows a benefit of ACRT over NAC, but the benefit is not statistically significant.

Table 1: 3-year Survivability

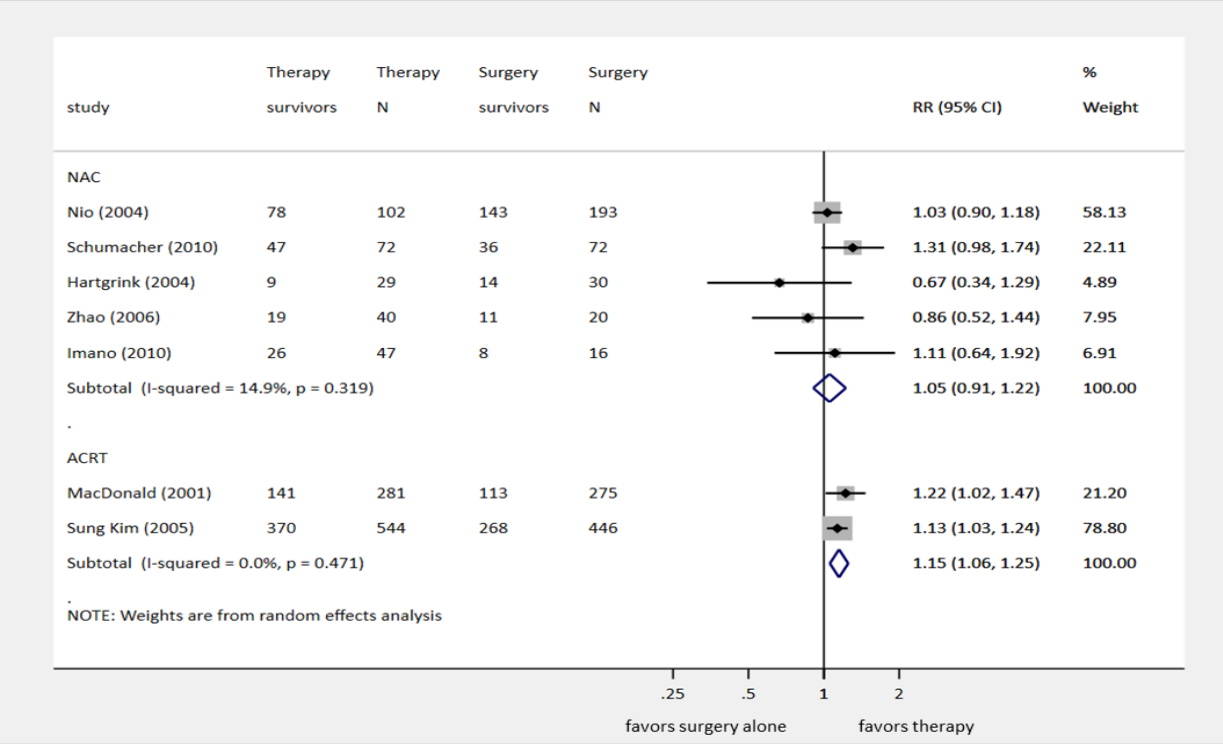
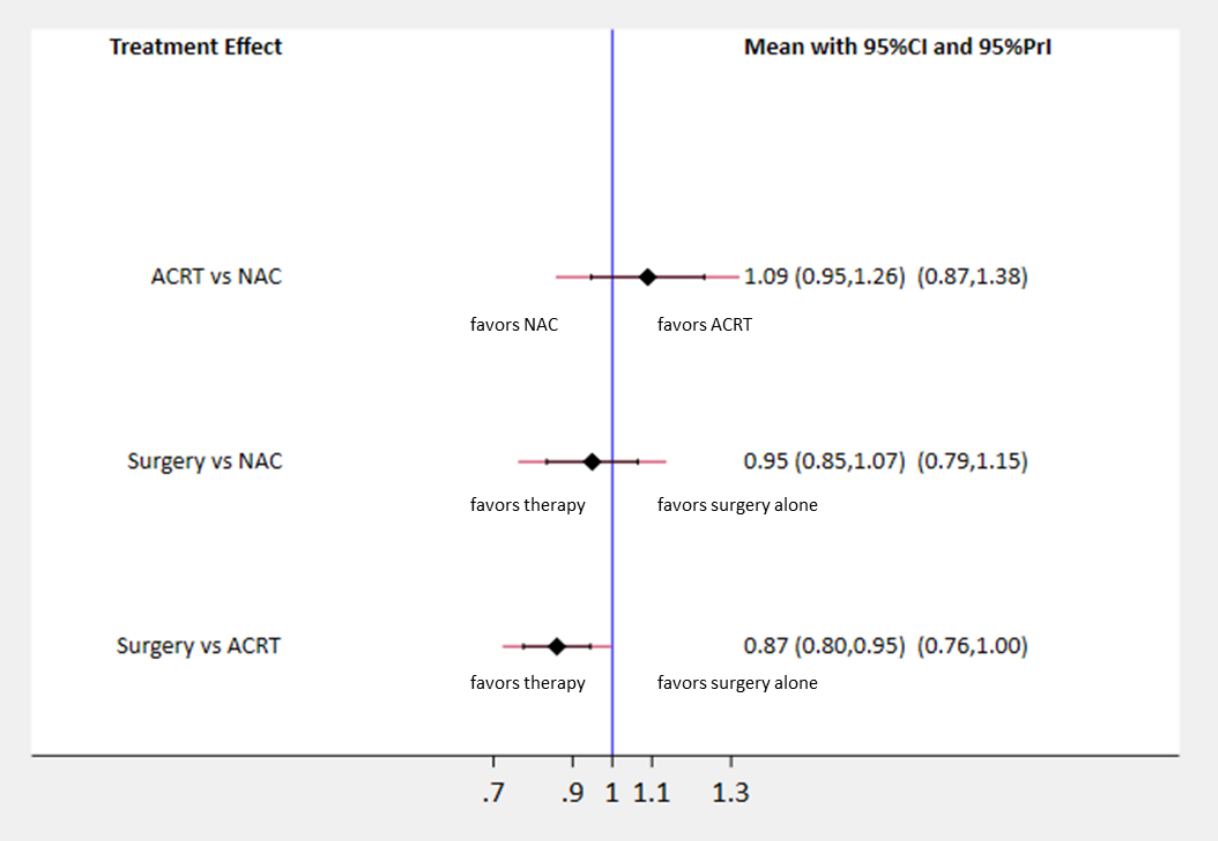


Table 2: 3-year Survivability Network Analysis



No study out of the NAC group showed any statistically significant improvement in 5-year mortality over surgery alone (RR 1.02, 95%CI 0.91, 1.15). Schuhmaker, Imano, and Wang studies generally favored NAC, but the strength of data was low. Nio and Kobayashi showed practically no difference in outcomes for NAC versus SA. Both studies out of the ACRT group showed a favorable 5-year survivability in the therapy groups, although the combined data proved to be not statistically significant (RR 1.42, 95%CI 0.87, 2.31). The MacDonald study' therapy showed to be statistically significant benefitial by itself over surgery alone (RR 1.84, 95%CI 1.42, 2.40). The network meta- analysis (Table 4) once again favored ACRT over NAC, but there was no statistically significant benefit of either therapy.

Table 3: 5-year Survivability

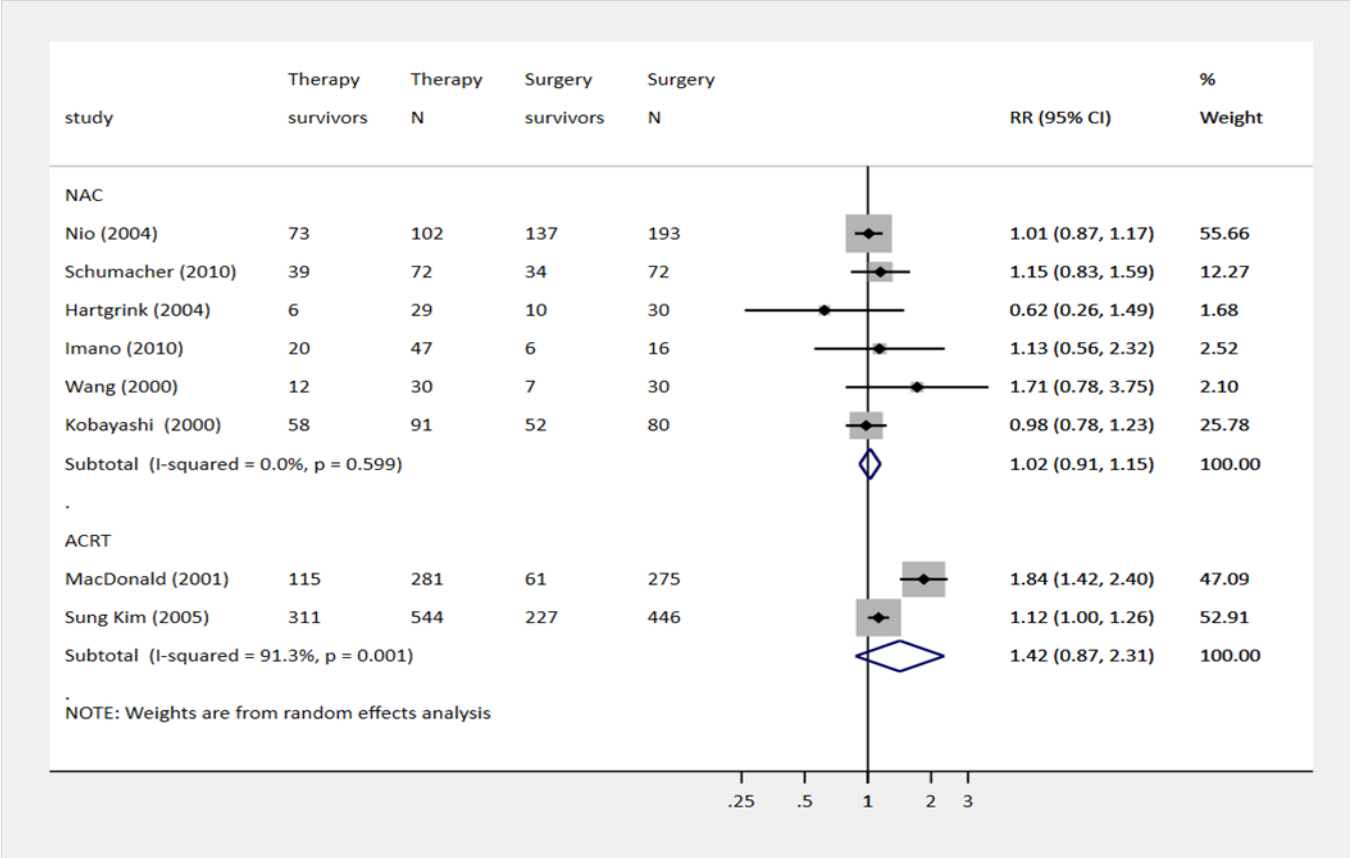
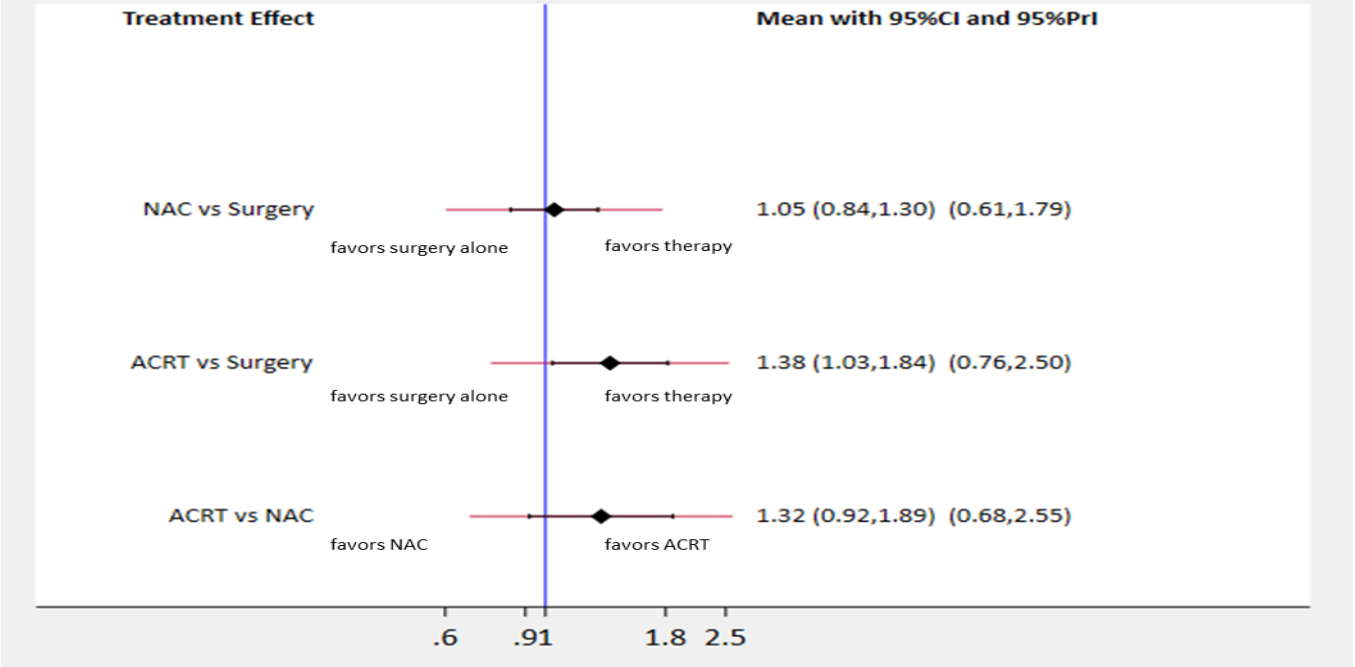


Table 4: 5-year Survivability Network Analysis



No study out of the NAC group showed any statistically significant improvement in Overall Mortality benefit over surgery alone (RR 0.93, 95%CI 0.81, 1.08). Hartgrink and Kobayashi studies tended to favor surgery alone over NAC, while Wang and Zhao showed the most favor toward the therapy group. Both studies out of the ACRT group showed a favorable mortality benefit in the therapy groups (RR 0.81, 95%CI 0.71, 0.92). The MacDonald study showed the most statistically significant benefit in therapy over surgery alone (RR 0.76, 95%CI 0.68, 0.85). The network meta-analysis (Table 6) could not prove a benefit to either therapy.

Table 5: Overall Mortality

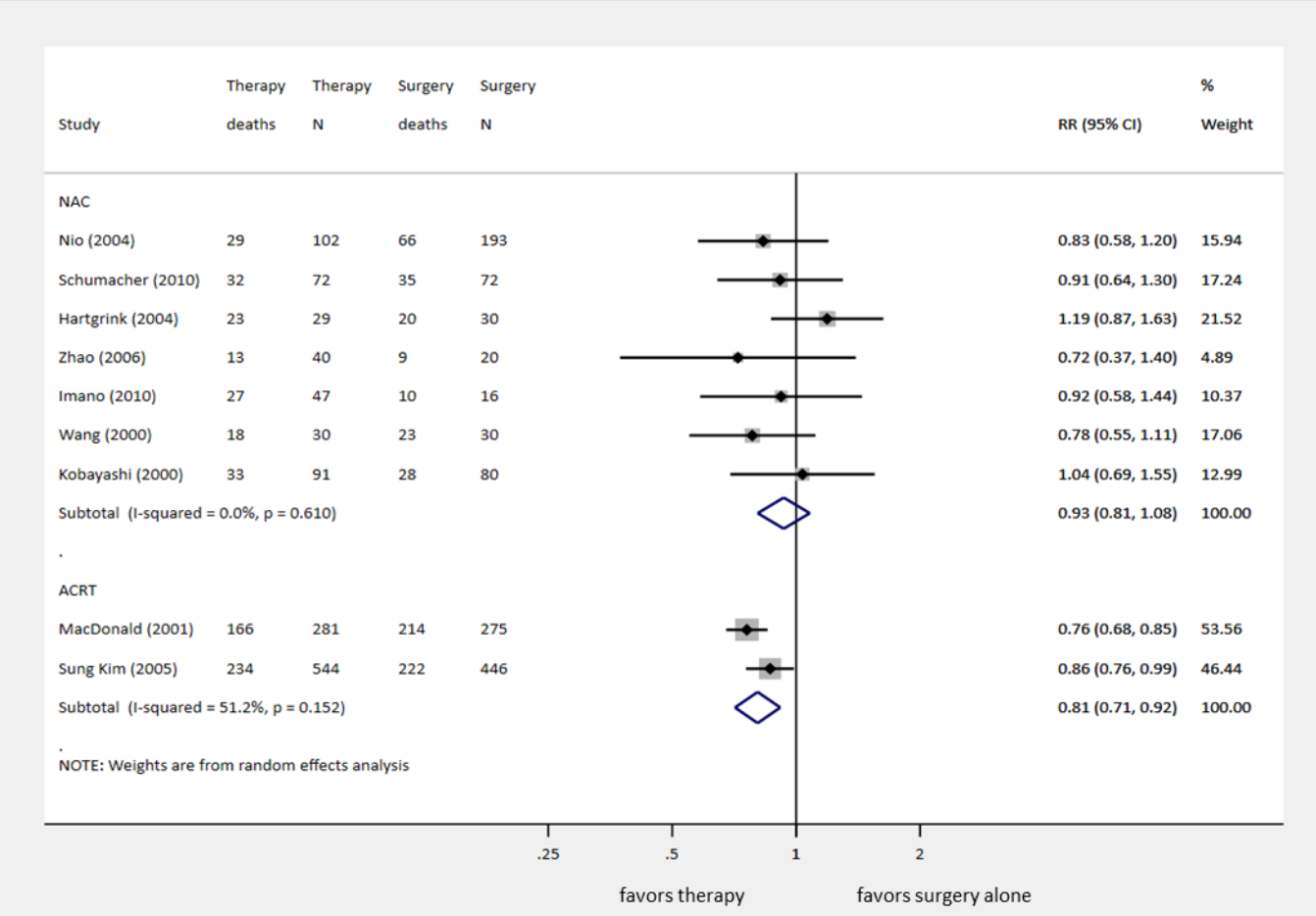
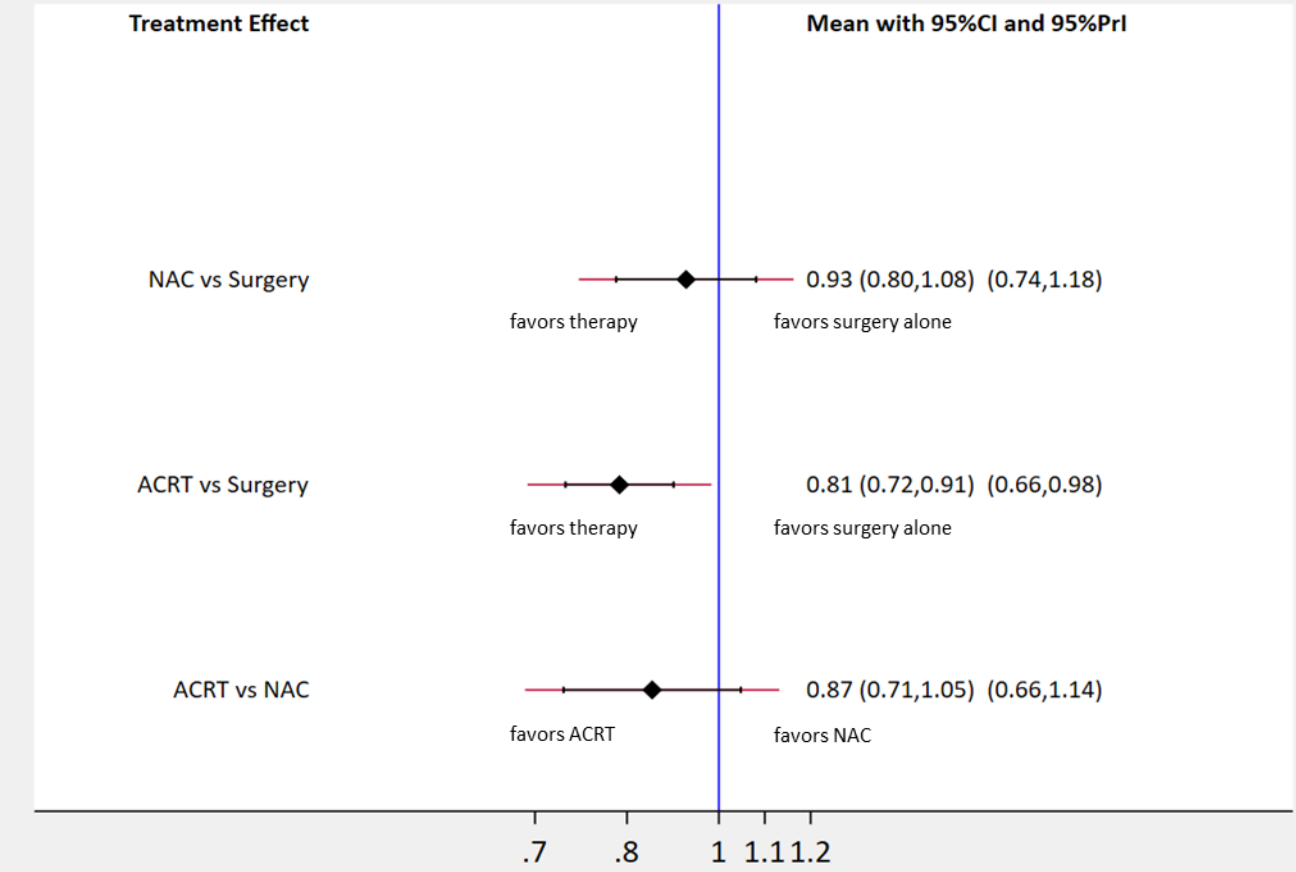


Table 6: Overall Mortality Network Analysis



Secondary Outcome

Side effects and adverse reactions due to therapy was the second outcome being evaluated. Due to the variety of therapies being used, heterogeneity remained a problem in the NAC group. ACRT had the most prevalence for post-operative complications with 49 patients suffering from toxicities which required treatments to stop and an additional 3 who died as a result from the treatment in the MacDonald et al. group [18]. In the Sung Kim et al. study 101 patients could not complete ACRT due to adverse side effects and 217 patients expierenced a Grade 3 or 4 side effect, with 1 person dying as a result of therapy. The most common side effects of the ACRT were severe nausea, vomiting, diarrhea, and leukopenia which happened in over 40% of the patients. All other types of toxicities were in less

than 10% of the population. These side effects included adhesive ileus, myelosuppression, sepsis, pulmonary fibrosis, intestinal fibrosis, hepatic events, pain, neurologic dysfunction, and cardiac events. The side effects varied between treatments for the NAC. Hartgrink reported 5 patients suffering from toxicity[23]. Nio recorded a total of 24 patients suffering from anorexia, leukopenia, thrombocytopenia, liver dysfunction, and massive GI bleeding from carcinoma[21]. Schuhmacher's study reported 8 patients with more mild side effects such as renal toxicity, cardiac toxicity, nausea, vomiting, and diarrhea[22]. In contrast, Imano's study recorded no toxicities[25]. The overall rate of side effects was 18% across all the NAC studies.

Bias Evaluation

The Cochrane Risk of Bias tool (Appendix D) was used to evaluate each study for individual bias and GRADE (Appendix E) was used to evaluate Bias across outcomes.[17,18,21,23–25,27] Allocation and blinding were previously stated problems across all of the NAC studies[17] Nio et al. had a high risk of selection bias due to inadequate generation of a randomised sequence and inadequate concealment of allocations prior to assignment. The article claims NAC cannot be done with randomization due to the possibility of postponing curative resection, therefore the patients determined if they were in the control or therapy group. Nio et al. also had an unclear risk of detection bias due to lack of blinding of the interventions to the providers and patients. The author did not address if this was a possible source of bias. Schumacher et al. has an unclear risk of other bias due to not histologically confirming the gastric cancer prior to treatment. Hartgrink et al has a high risk of selection bias due to inadequate randomization. The trial randomized their patients based on a rule out of the clinic where the therapy was conducted. Zhao et al. has an unclear risk of selection bias. The article states the patients were separated into 3 groups, but it does not say how they were selected into the groups or what randomization process was used. Wang et al. did not address their method to conceal allocation and they had a high risk of performance bias due to not blinding the participants or the providers. It was unclear if the patients were blinded in Kobayashi

et al. Also, the patients were told of the desired outcomes of each trial, so there is a high risk of detection bias.

Another source of bias was small numbers of patients draw inaccuracy of conclusions on Hartgrink, Zhao, Schumacher, and Imano[17]. There were several measurement bias noted throughout the studies. MacDonald had inclusion criteria for pre-operative major organ functions which were not present in any other study[18]. This could have affected the overall health of all the patients in the ACRT study. Every NAC therapy was different. This caused a heterogeneity between that group as a whole. Another source of measurement bias were the varieties of surgeries. Since no specific surgery was tracked, post-operation mortality could be due to an inadequate procedure. Although the NAC did specifically only entail gastric adenocarcinomas, the ACRT studies included gastro-esophageal junction adenocarcinomas as well. This may result in a higher mortality rate along with more severe side effects.

Discussion

The primary outcomes studied in this comparison was the effect on mortality on gastric adenocarcinomas of NAC vs ACRT. No statiscally significant benefit to either therapy could be determined throught the network meta-analysis. Although ACRT was statistically more beneficial in 5-year and overall survival than surgery alone where NAC was not, the evidence was leaning toward a possibility that NAC may have had a benefit. This observation created the possibility that NAC may be as therapeutic in the survivial benefit as ACRT in the treatment of gastric adenocarcinomas.

There were 2 main measurement biases which could have affected the outcomes of the trials. The first measurement bias noted was the inclusion criteria the ACRT study set for organ function prior to surgery. MacDonald AND Sung Kim made sure their patients had a certain level of health defined as[18]:

1. creatinine concentration no more than 25 percent higher than the upper limit of normal
2. hemogram within the normal limits
3. bilirubin concentration no more than 50 percent higher than the upper limit of normal

4. serum aspartate aminotransferase concentration no more than five times the upper limit of normal
5. alkaline phosphatase concentration no more than five times the upper limit of normal and this created a consistency in their participants.

The NAC studies had no overall health of organ function criteria prior to initiation of therapy[21–25]. This may have created a benefit in 3-year survival for ACRT which would not have existed if all participants in all of the studies entered with the same criteria. The second measurement bias was the difference in surgeries. D0, D1, and D2 lymphandectomy/gastrectomy were performed throughout the studies. The ACRT trial did not specify which type of gastrectomy was being performed. As previously stated Hartgrink underperformed in the 3-year period, and all the patients underwent a D1 gastrectomy[23]. This under-performance could then be attributed to the delay in a curative surgery and causing a further progression of the disease or the ACRT could have used a D2 surgery and had an immediate curative effect. Also, the ACRT study included gastroesophageal junction adenocarcinomas, whereas the NAC studies did not[18]. This may have increased probability of overall mortality of the patients in the ACRT group prior to the start of the study. Heterogeniety in the NAC arm was also a contributing factor to the inconclusive data. None of the studies used exactly the same drugs, duration of therapy, or routes of administration; the most common NAC pharmacologic treatment being Fluorouracil used in 3 of the 7 RCT (see Appendix C). There were noted advantages and disadvantages of each NAC therapy. Hartgrink and Zhao's therapies had inferior performance in the 3-year comparisons to the other studies[23,24]. Nio did show improvement over SA, but the improvement was statistically insignificant[21]. Imano's study had the widest variants[25]. Overall the was no consistent data, or even a trend of consistent findings, between the NAC studies.

The secondary outcome which was observed were the adverse reactions noted in each group. The adverse effects and patients withdrawing from studies was considerably lower in the NAC group (53

out of 411) compared to the ACRT (244 out of 825) [18,21–25]. The surgeries and location of the cancers had little to do with the adverse reactions to the therapies administered. The overall health of the patients could be considered a bias with an unfair advantage given to the ACRT group, but NAC still out performed them. The NAC group did use different therapies, and this source of measurement bias may contribute the most to the strength of the evidence. Nio and Schumacher had the highest overall rate of notable toxicities, 23.5% and 32%, respectively, but they are still lower than the rate of toxicity from the MacDonald study (54%) or Sung Kim (34%)[18,21,22].

Overall the strength of the evidence is low to any advantage of survivability of a gastric adenocarcinoma with the use of neoadjuvant chemotherapy plus surgery or surgery then adjuvant chemoradiotherapy. There may be a correlation of evidence which reflects that neoadjuvant chemotherapy has less side effects and this may lead to a higher quality of life for the patients, but the survivability may also be lower. This data leads to a recommendation to further study the use of neoadjuvant chemotherapy plus surgery in the treatment of gastric adenocarcinomas in order to improve quality of life for the patients, and to further study adjuvant chemoradiotherapy to improve survivability.

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Appendix A

Cancer Overview

Table 1 Trends in 5-Year Relative Survival Rates (%) by Race and Year of Diagnosis, United States, 1975 to 2007

	All Races			Caucasian			African American		
	1975 to 1977	1987 to 1989	2001 to 2007	1975 to 1977	1987 to 1989	2001 to 2007	1975 to 1977	1987 to 1989	2001 to 2007
All cancer	49	56	67	50	57	69	39	43	59
Nervous system	22	29	35	22	28	34	25	31	40
Breast (female)	75	84	90	76	85	91	62	71	77
Colon	51	60	65	51	61	67	45	53	55
Esophagus	5	10	19	6	11	20	3	7	13
Hodgkins Lymphoma	72	79	86	72	80	88	70	72	81
Kidney	50	57	71	50	57	71	49	55	68
Larynx	66	66	63	67	67	65	59	56	52
Leukemia	34	43	57	35	44	57	33	36	50
Liver and bile duct	3	5	15	3	6	15	2	3	10
Lung and bronchus	12	13	16	12	13	17	11	11	13
Melanoma of the skin	82	88	93	82	88	93	58	79	73
Myeloma	25	28	41	25	27	42	30	30	41
Non-Hodgkin Lymphom	47	51	70	47	52	71	48	46	62
Oral cavity	53	54	63	54	56	65	36	34	45
Ovary	36	38	44	35	38	43	42	34	36
Pancreas	2	4	6	3	3	6	2	6	4
Prostate	68	83	100	69	85	100	61	72	98
Rectum	48	58	68	48	59	69	45	52	61
Stomach	15	20	27	14	19	26	16	19	27
Testicle	83	95	96	83	95	97	73	88	86
Thyroid	92	95	97	92	94	98	90	92	95
Urinary bladder	73	79	80	74	80	81	50	63	64
Uterine cervix	69	70	69	70	73	70	65	57	61
Uterine corpus	87	83	83	88	84	85	60	57	61

Table 2 Positive and negative diet/lifestyle gastric cancer risk factors

Risk factor	**Hazard Ratio***
Increase risk of gastric cancer	
Salt intake (>16 g/day)	2.67 (1.36-5.24)
Smoking (>40 years)	2.36 (1.42-3.91)
Alcohol	1.65 (1.06-2.58)
Decrease risk of gastric cancer	
Fruits and vegetable consumption	0.56 (0.34-0.93)
Vitamin C (3mg/day)	0.6 (0.5-0.8)
Vitamin C (4mg/day)	0.5 (0.3-0.6)

* The percentage or protection/risks varies with litarature, but the confidence of the data on what increases/decreases risk is reflected above.

Appendix B

Excluded Articles

The following articles were excluded due to use of additional therapies to neoadjuvant chemotherapy:

1. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20
2. Lowy AM, Feig BW, Janjan N, Rich TA, Pisters PW, Ajani JA, et al. A pilot study of preoperative chemoradiotherapy for resectable gastric cancer. Ann Surg Oncol. 2001 Jul;8(6):519–524.
3. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PWT, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol. 2006 Aug 20;24(24):3953–3958.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.

The following articles were excluded due to use of only adjuvant chemotherapy without radiation:

1. Bang Y-J, Kim Y-W, Yang H-K, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315–321
2. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29(33):4387–4393
3. The GASTRIC group. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis.JAMA. 2010;303(17):1729–1737
4. Di Costanzo F, Gasperoni S, Manzione L, et al. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst. 2008;100(6):388–398
5. De Vita F, Giuliani F, Orditura M, et al. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). Ann Oncol. 2007;18(8):1354–1358
6. Cirera L, Balil A, Batiste-Alentorn E, et al. Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. J Clin Oncol. 1999;17(12):3810–3815
7. Bajetta E, Buzzoni R, Mariani L, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. Ann Oncol. 2002;13(2):299–307
8. Coombes RC, Schein PS, Chilvers CE, et al. A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. International Collaborative Cancer Group. J Clin Oncol. 1990;8(8):1362–1369

9. Bouché O, Ychou M, Burtin P, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol. 2005;16(9):1488–1497
10. Krook JE, O'Connell MJ, Wieand HS, et al. A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. Cancer. 1991;67(10):2454–2458 [
11. 24. Lise M, Nitti D, Marchet A, et al. Final results of a phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin, and mitomycin regimen in resectable gastric cancer. J Clin Oncol. 1995;13(11):2757–2763
12. Macdonald JS, Fleming TR, Peterson RF, et al. Adjuvant chemotherapy with 5-FU, adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: a Southwest Oncology Group study. Ann Surg Oncol. 1995;2(6):488–494
13. Nakajima T, Kinoshita T, Nashimoto A, et al. Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg. 2007;94(12):1468–1476
14. Nakajima T, Nashimoto A, Kitamura M, et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. Lancet. 1999;354(9175):273–277
15. Nashimoto A, Nakajima T, Furukawa H, et al. Randomized trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol. 2003;21(12):2282–2287
16. Nitti D, Wils J, Dos Santos JG, et al. Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI Group and the ICCG. Ann Oncol. 2006;17(2):262–269

The following articles were excluded due to unclear documentation of a D1/D2 surgery:

1. Tsavaris NB, Tentas K, Kosmidis P, et al. 5-Fluorouracil, epirubicin, and mitomycin C versus 5-fluorouracil, epirubicin, mitomycin C, and leucovorin in advanced gastric carcinoma. A randomized trial. Am J Clin Oncol. 1996;19(5):517–521
2. Yonemura Y, Sawa T, Kinoshita K, Matsuki N, Fushida S, Tanaka S, et al. Neoadjuvant chemotherapy for high-grade advanced gastric cancer. World J Surg. 1993 Mar;17(2):256–261.

The following articles were excluded due to the abstracts being written in English, but the random controlled trials were only available in Japanese:

1. Lowy AM, Mansfield PF, Leach SD, Pazdur R, Dumas P, Ajani JA. Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. Ann Surg. 1999 Mar;229(3):303–308.
2. Lygidakis NJ, Sgourakis G, Aphinives P. Upper abdominal stop-flow perfusion as a neo and adjuvant hypoxic regional chemotherapy for resectable gastric carcinoma. A prospective randomized clinical trial. Hepatogastroenterology. 1999 Jun;46(27):2035–2038.

3. Masuyama M, Taniguchi H, Takeuchi K, Miyata K, Koyama H, Tanaka H, et al. [Recurrence and survival rate of advanced gastric cancer after preoperative EAP-II intra-arterial infusion therapy]. Gan To Kagaku Ryoho. 1994 Sep;21(13):2253–2255.
4. Nishioka B, Ouchi T, Watanabe S, Umehara M, Yamane E, Yahata K, et al. [Follow-up study of preoperative oral administration of an antineoplastic agent as an adjuvant chemotherapy in stomach cancer]. Gan To Kagaku Ryoho. 1982 Aug;9(8):1427–1432.

Appendix C

Demographics and Therapies

Study Demographics

	NAC							ACRT	
	Hartgrink	Nio	Zhao	Imano	Schumacher	Wang	Kobayashi	MacDonald	Sung Kim
N	29	102	40	47	72	30	91	281	544
Age (yrs)									
Median	na	64	57.5	60	56	54	na	60	54
Range	up to 75	51-75	32-70	46-72	38-70	37-65	up to 75	25-87	23-70
Male sex %	na	70	69	69	69.4	76.7	na	72	65.5
T stage									
T1 or T2	15	62	na	22	0	19	na	31	52.4
T3	4	15	na	25	68	11	na	62	44.3
T4	8	25	na	0	4	0	na	6	3.3
Location of primary tumor									
Antrum	14	na	na	6	na	na	na	53	261
Corpus	15	na	na	8	na	na	na	24	227
Cardia	0	na	na	28	na	na	na	21	48
Multicentric	0	na	na	5	na	na	na	2	9

Thearpies During the Trials

Neoadjuvant Chemotherapy	
Nio	PO Tegafur/uracil 7 mg/kg/d×21 d
Schumacher	DDP (50 mg/m2/d×3 d), d-L-folinic acid (500 mg/m2/d×6 d), 5-FU (2000 mg/m2/d×6 d); 2 courses; intravenous
Hartgrink	IV methotrexate 1500 mg/m2 plus IV Fluorouracil 1500 mg/m2 plus leucovorin 30 mg/6 h×2 d plus doxorubicin 30 mg/m2 for 4 courses
Zhao	PO doxifluridine 800–1200 mg/d or IV 500mg Fluorouracil plus Cisplatin/Fluorouracil 200 mg/d ×3–5 d
Imano	IV Fluorouracil 330 mg/m2/d×3 d or IV Cisplatin 18 mg/m2 x 3d or IV Cisplatin/Fluorouracil 200 mg/d ×3
Wang	PO Flourouracil 2x20ml/day, over 12.5 days, total dosing being 2g, oleic acid, ginseng polysaccharides, bean phosopholipids, and cholesterol
Kobayashi	PO doxifluridine 610 mg/m2/d 6 10 d
Adjuvant Chemoradiotherapy	
MacDonald	400 mg/m2 of fluorouracil plus 20 mg/m2 of leucovorin for 5 days, followed by 4,500 cGy of radiotherapy for 5 weeks, with fluorouracil and leucovorin on the first 4 and the last 3 days of radiotherapy. Two 5-day cycles of fluorouracil and leucovorin were given 4 weeks after the completion of radiotherapy. The dose of fluorouracil was reduced in patients who had grade 3 or 4 toxic effects.
Sung Kim	400 mg/m2 of fluorouracil plus 20 mg/m2 of leucovorin for 5 days, followed by 4,500 cGy of radiotherapy for 5 weeks, with fluorouracil and leucovorin on the first 4 and the last 3 days of radiotherapy. Two 5-day cycles of fluorouracil and leucovorin were given 4 weeks after the completion of radiotherapy.

Appendix D

Cochrane Risk of Bias

	Random Sequence Generation	Allocation of Concealment	Selective Reporting	Other Bias	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data
Nio	-	-	+	+	-	?	+
Schumacher	+	+	+	?	+	+	+
Hartgrink	+	-	+	+	+	+	+
Zhao	?	+	+	+	+	+	+
Imano	+	+	+	+	+	+	+
Wang	+	?	+	+	-	+	+
Kobayashi	+	+	+	+	?	+	+
MacDonald	?	?	+	-	?	?	+
Sung Kim	?	?	+	-	?	?	+

Key	
Low risk of Bias	+
High Risk of Bias	-
Unclear risk of Bias	?

Appendix E

GRADE

Question: How necessary is neoadjuvant chemotherapy in addition to surgery compared to surgery then adjuvant chemoradiotherapy in improvement of 5-year survivability of a gastric adenocarcinoma?

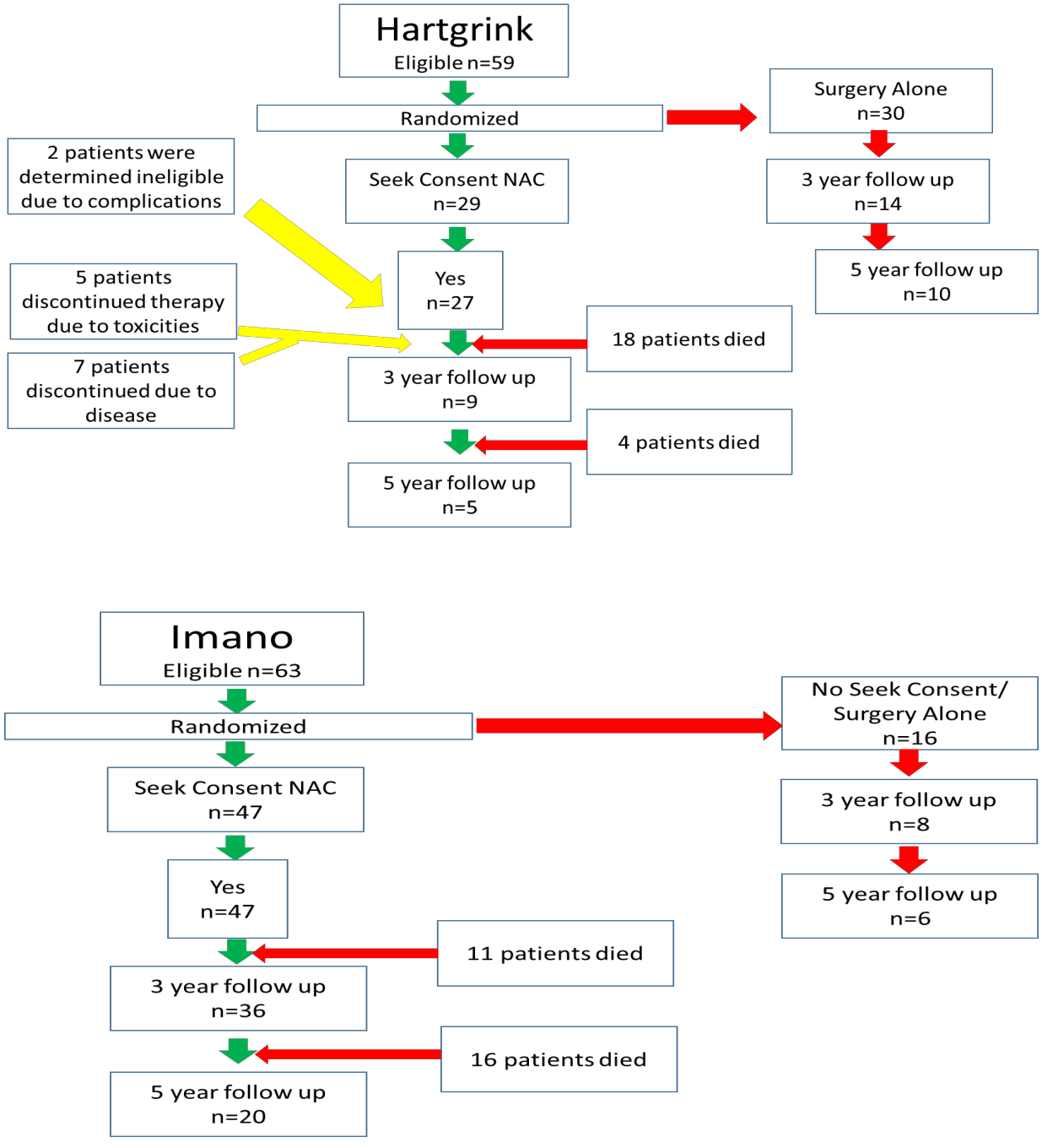
Quality Assessment							Summary of Finding					
							No of Patients		Effect			
No of studies	Design	Limitations	Inconsistencies	Indirectness	Imprecision	Other Considerations	NAC	Surgery Alone	Relative Risk (95% CI)	Absolute	Quality	Importance
3-Year Survivability- NAC												
7	randomized trials	Participants due to side effects of the therapies	NAC's were not the same Surgeries were not the same Inclusion criteria of patients were not the same	direct	Staging of cancers before the study was done from different literature	Post operative illness confounding Surgical complication confounding	179/290	212/331	1.05 (0.91, 1.22)	26 per 1000 people benefit from NAC over Surgery Alone	2/5	Critical
5-Year Survivability- NAC												
7	randomized trials	Participants due to side effects of the therapies	NAC's were not the same Surgeries were not the same Inclusion criteria of patients were not the same	direct	Staging of cancers before the study was done from different literature	Post operative illness confounding Surgical complication confounding	208/371	246/421	1.02 (0.91, 1.15)	17 per 1000 people benefit from NAC over Surgery Alone	2/5	Critical
All Purpose Mortality (# of deaths/participants)- NAC												
7	randomized trials	Participants due to side effects of the therapies	NAC's were not the same Surgeries were not the same Inclusion criteria of patients were not the same	direct	Staging of cancers before the study was done from different literature	Post operative illness confounding Surgical complication confounding	175/411	191/441	0.93 (0.81, 1.08)	40 per 1000 people benefit from NAC over Surgery Alone	2/5	Critical

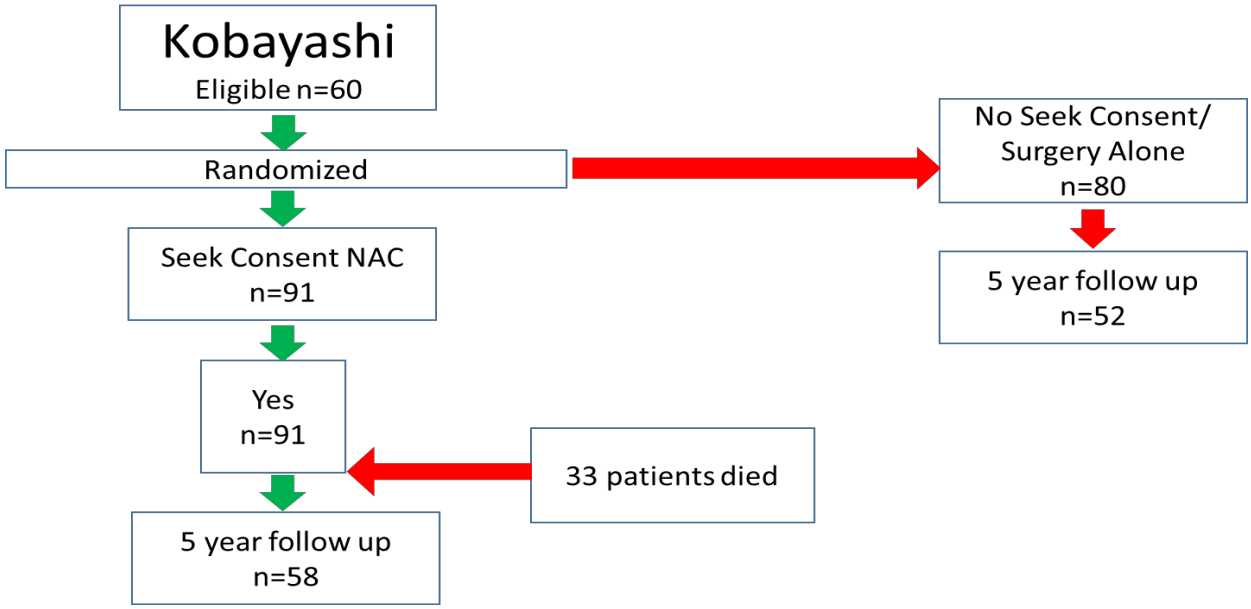
Question: How necessary is neoadjuvant chemotherapy in addition to surgery compared to surgery then adjuvant chemoradiotherapy in improvement of 5-year survivability of a gastric adenocarcinoma?

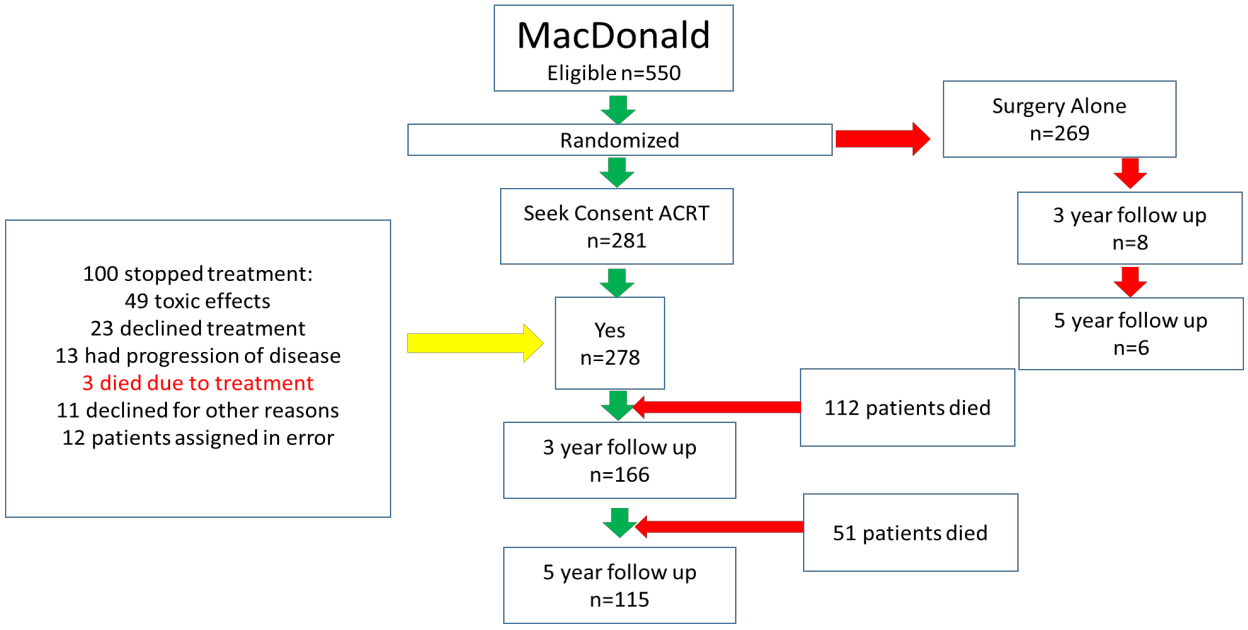
Quality Assessment							Summary of Finding					
							No of Patients		Effect			
No of studies	Design	Limitations	Inconsistencies	Indirectness	Imprecision	Other Considerations	ACRT	Surgery Alone	Relative Risk (95% CI)	Absolute	Quality	Importance
3-Year Survivability- ACRT												
2	randomized trials	Participants due to side effects of the therapies	Surgeries were not the same	direct	None	Post operative illness confounding Surgical complication confounding	511/825	381/721	1.15 (1.06, 1.25)	83 per 1000 people benefit from ACRT over Surgery Alone	4/5	Critical
5-Year Survivability- ACRT												
2	randomized trials	Participants due to side effects of the therapies	Surgeries were not the same	direct	None	Post operative illness confounding Surgical complication confounding	426/825	288/721	1.42 (0.87, 2.31)	123 per 1000 people benefit from ACRT over Surgery Alone	3/5	Critical
All Purpose Mortality (# of deaths/participants)- ACRT												
2	randomized trials	Participants due to side effects of the therapies	Surgeries were not the same	direct	None	Post operative illness confounding Surgical complication confounding	400/825	436/721	0.81 (0.71, 0.92)	130 per 1000 people benefit from ACRT over Surgery Alone	4/5	Critical

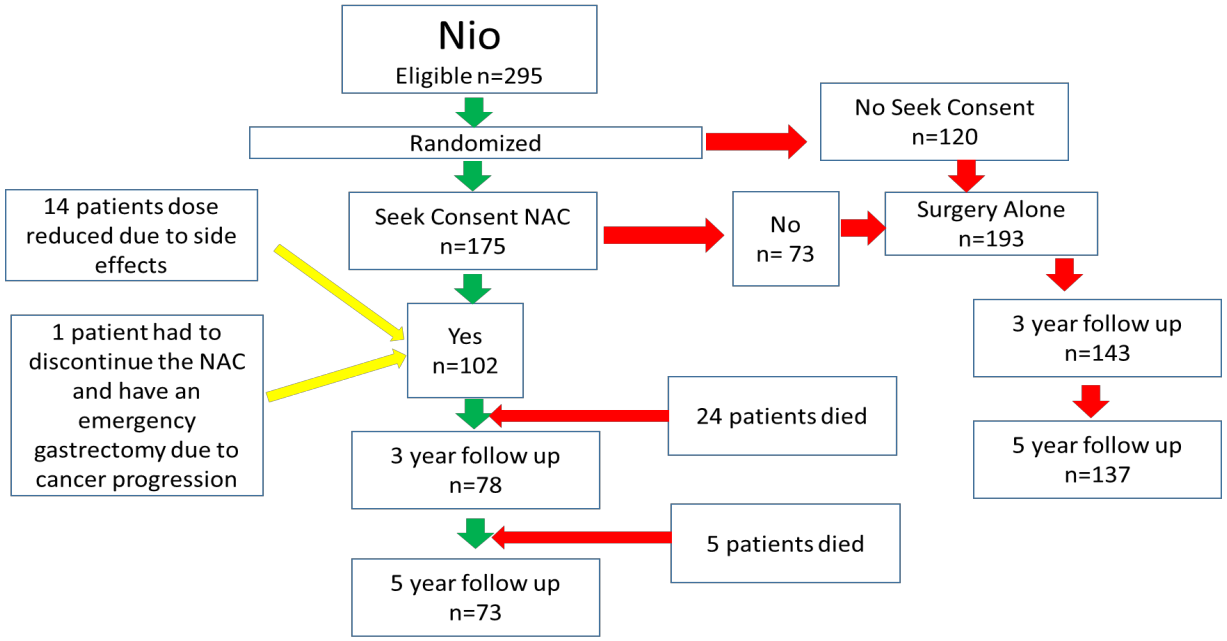
Appendix F

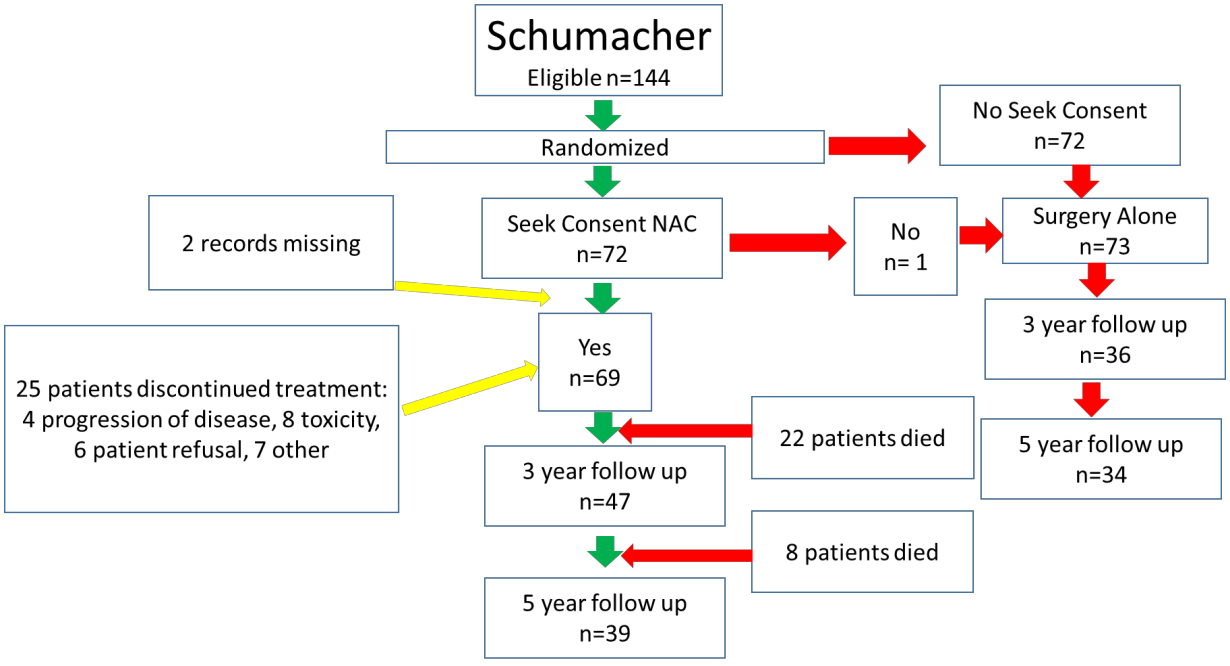
Random Control Trial Flow Diagrams

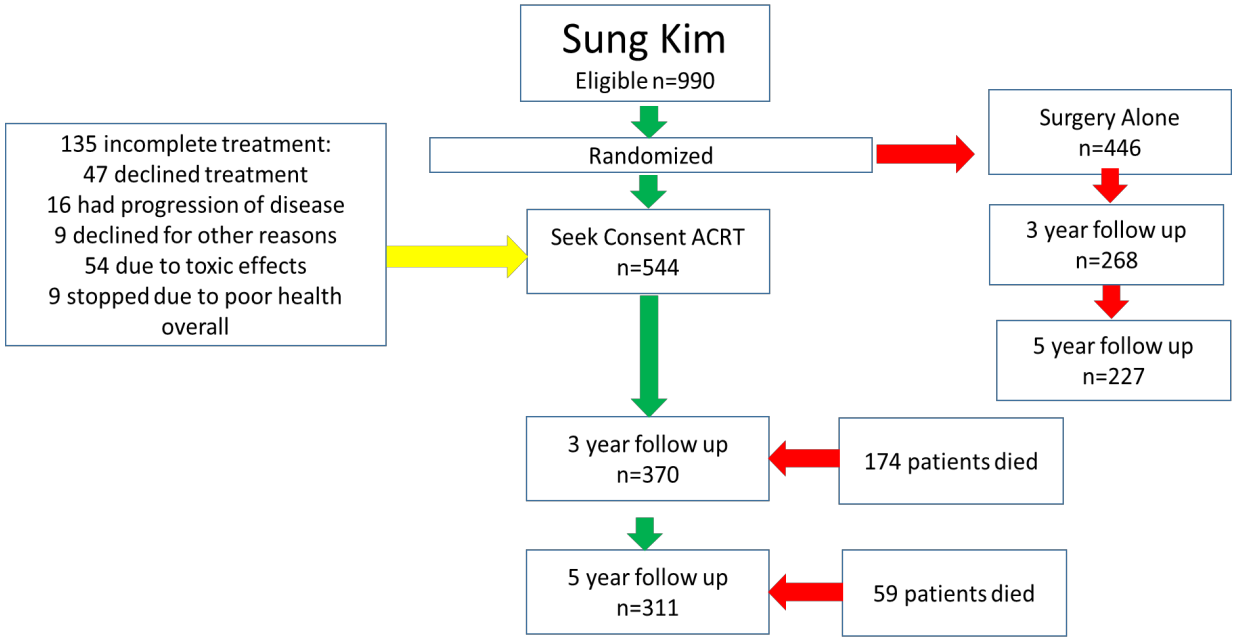


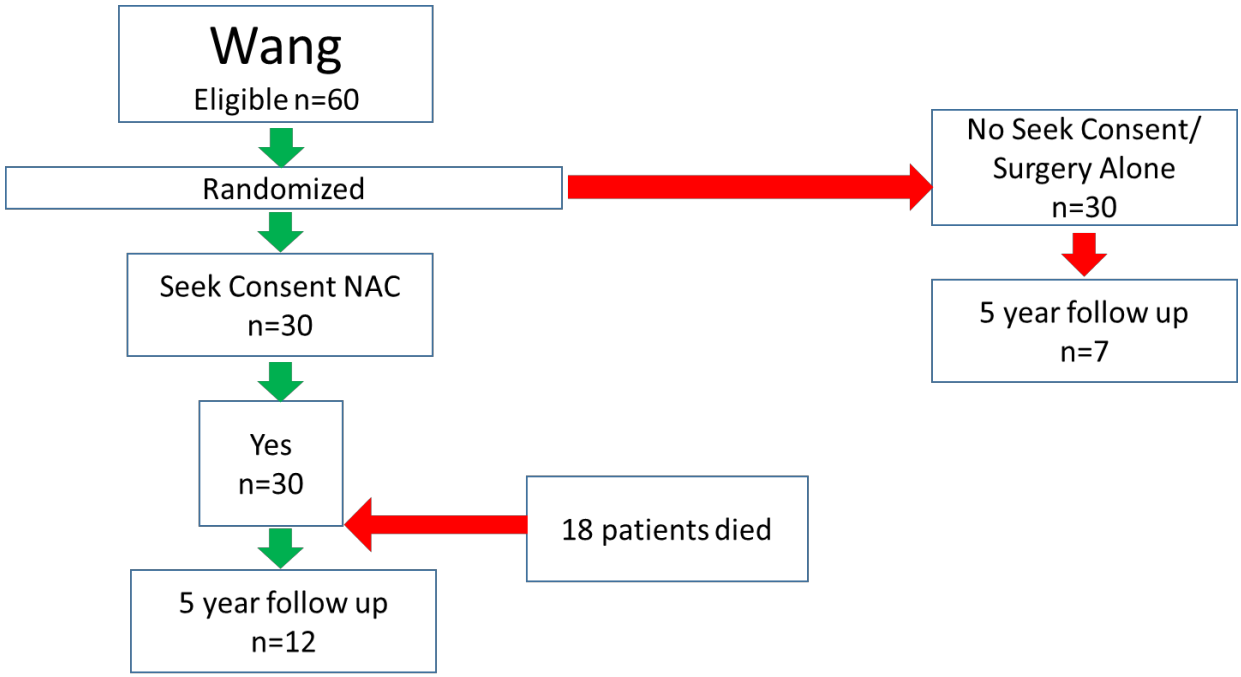

Kobayashi
Eligible n=60
Randomized
No Seek Consent/
Surgery Alone
n=80
5 year follow up
n=52
Seek Consent NAC
n=91
Yes
n=91
33 patients died
5 year follow up
n=58

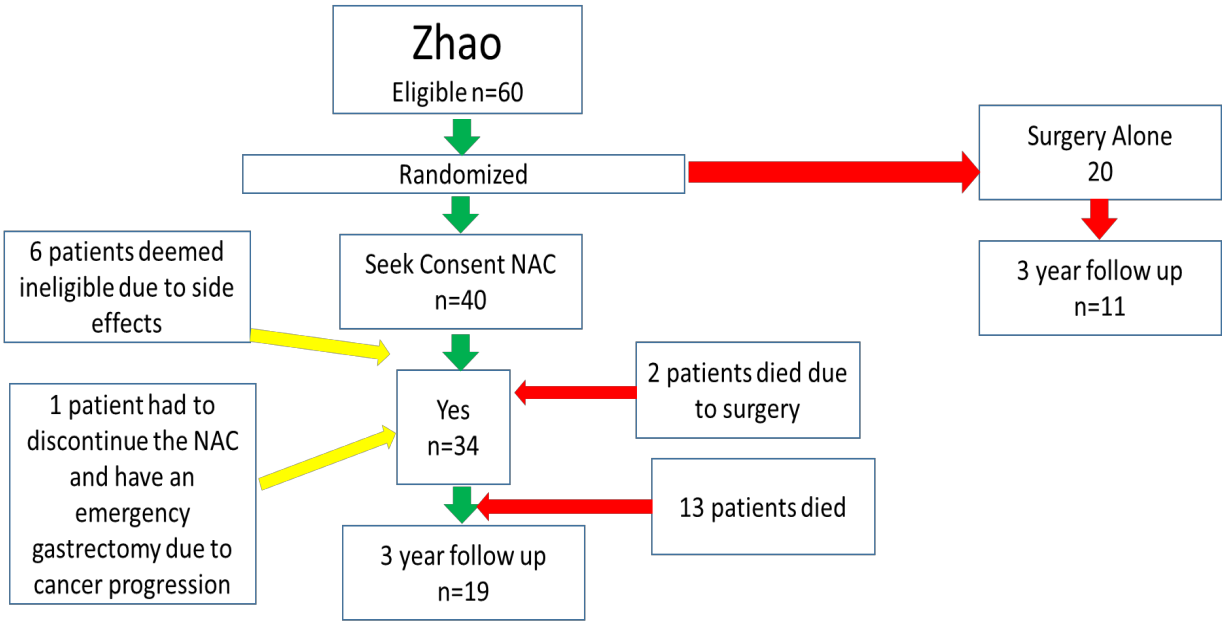

MacDonald
Eligible n=550
Randomized
Surgery Alone
n=269
3 year follow up
n=8
5 year follow up
n=6
Seek Consent ACRT
n=281
100 stopped treatment:
49 toxic effects
23 declined treatment
13 had progression of disease
3 died due to treatment
11 declined for other reasons
12 patients assigned in error
Yes
n=278
112 patients died
3 year follow up
n=166
51 patients died
5 year follow up
n=115


Nio
Eligible n=295
Randomized
No Seek Consent n=120
Surgery Alone n=193
3 year follow up n=143
5 year follow up n=137
14 patients dose reduced due to side effects
Seek Consent NAC n=175
No n= 73
1 patient had to discontinue the NAC and have an emergency gastrectomy due to cancer progression
Yes n=102
24 patients died
3 year follow up n=78
5 patients died
5 year follow up n=73


Schumacher
Eligible n=144
Randomized
No Seek Consent n=72
Surgery Alone n=73
3 year follow up n=36
5 year follow up n=34
2 records missing
Seek Consent NAC n=72
No n= 1
25 patients discontinued treatment: 4 progression of disease, 8 toxicity, 6 patient refusal, 7 other
Yes n=69
22 patients died
3 year follow up n=47
8 patients died
5 year follow up n=39


Sung Kim
Eligible n=990
Randomized
Surgery Alone
n=446
3 year follow up
n=268
5 year follow up
n=227
135 incomplete treatment:
47 declined treatment
16 had progression of disease
9 declined for other reasons
54 due to toxic effects
9 stopped due to poor health overall
Seek Consent ACRT
n=544
3 year follow up
n=370
174 patients died
5 year follow up
n=311
59 patients died


Wang
Eligible n=60
Randomized
No Seek Consent/
Surgery Alone
n=30
5 year follow up
n=7
Seek Consent NAC
n=30
Yes
n=30
18 patients died
5 year follow up
n=12


Zhao
Eligible n=60
Randomized
Surgery Alone
20
3 year follow up
n=11
6 patients deemed ineligible due to side effects
Seek Consent NAC
n=40
2 patients died due to surgery
Yes
n=34
1 patient had to discontinue the NAC and have an emergency gastrectomy due to cancer progression
13 patients died
3 year follow up
n=19