Review

Survival outcomes in patients with stages I–III gastric adenocarcinoma treated with surgery alone versus surgery plus adjuvant chemotherapy: A systematic review

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Abstract

Background: Gastric adenocarcinoma, the malignant proliferation of glandular cells in stomach epithelium, is a type of gastric cancer with a statistical disease burden of the fifth most common cancer globally and the 17th most common malignancy in the United Kingdom. Prognosis varies with stage (I–IV), with stages I–III showing promising 5-year survival rates up to 71.8%, warranting timely diagnosis and treatment. Surgery is the gold-standard treatment; however, due to complex tumor pathophysiology, there is growing interest in the use of multimodal therapies. Specifically, the combination of surgery and adjuvant chemotherapy has become a key focus of the treatment for stages I–III gastric adenocarcinoma. **Objective:** The study reviewed patients with stages I–III (non-advanced) gastric adenocarcinoma to assess whether adjuvant chemotherapy combined with surgery provides better disease-free/disease-specific/cause-specific survival, overall survival, and reduced recurrence rates/improved recurrence-free survival, compared to surgery alone. Analyzed were 17 English-language, full-text, levels I–III peer-reviewed studies from MEDLINE and Embase from the past 10 years were analyzed. No age/sex/ethnicity/country restrictions were applied, and the dimension of interest was limited to stages I–III gastric adenocarcinoma patients who underwent tumor resection through surgery and received chemotherapy as the only adjuvant therapy. Seven (41.2%) studies have more than one statistically significant outcome measure supporting the benefit of adjuvant chemotherapy in combination with surgery over surgery alone. Ten (58.8%) studies showed no statistically significant benefit of adjuvant chemotherapy. **Conclusion:** The findings contrasted with previous large-scale meta-analyses, which were limited by sample size and biases in individual studies reviewed. Continued research, incorporating advances in surgical techniques and new chemotherapeutic combinations, is necessary to ascertain best-tailored treatments for gastric adenocarcinoma.

Keywords: Gastric adenocarcinoma, Adjuvant chemotherapy, Gastrectomy, Disease-free survival, Overall survival, Recurrence-free survival

1. Introduction

1.1. Epidemiology

Gastric adenocarcinoma, localized to the stomach, is the fifth most common cancer globally, accounting for 7.7% of deaths yearly.[1] The highest incidences worldwide are present in Eastern Asia, followed by Central and Eastern Europe, where these populations show strong dietary association with intake of salted, pickled, and smoked foods, which can form carcinogenic N-nitroso-compounds when reacting with nitrite-reducing bacteria in the stomach.[2] Other notable risk factors include low vitamin A or C intake, smoking, alcohol consumption, *Helicobacter pylori* infection, autoimmune gastritis, and genetic susceptibility. In the United Kingdom,

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gastric cancer is the 17th most common cancer, representing 3% of all cancer-caused deaths, with an increasing incidence in a left-skewed distribution annually at a male-to-female ratio of 1.71:1.[3] Peak incidence in terms of age is 75 – 79 years for males and 80 – 84 years for females.

1.2. Etiopathogenesis

Approximately 95% of stomach neoplasms are adenocarcinomas that develop due to the malignant proliferation of glandular epithelium of endodermal or ectodermal origin. Anatomically, the most common sites for gastric adenocarcinoma are the lower third of the stomach (antrum, pylorus, and angle), accounting for 60.6 – 79.4% of cases. The middle third (cardia and fundus) is affected in 14.5 – 32.3% of cases, while the upper third involvement accounts for 4.3 – 7.1%.[4] Consistent with this, Kang *et al*.[5] reported common regions for tumor growth include the lower part of the stomach (89.6%) and areas along the lesser curvature (43.6%), as they are more prone to damage by reflux of duodenal contents in chronic conditions, such as ulcer. Hematogenous spread is common, particularly to the liver, lungs, adrenals, bone, and the central nervous system. Roughly 74 – 88% of cases have lymphatic spread, with 14% of early-stage cases demonstrating lymph node involvement.[6]

1.3. Diagnostic approach

Clinically, early-stage, localized gastric adenocarcinomas are often asymptomatic. Patients present with the most common clinical signs and symptoms of dyspepsia, weight loss, and ulcer-like epigastric pain. The pain is mild to moderate, gnawing in nature, radiates to the back (if the stomach wall is penetrated posteriorly), and can be exacerbated or relieved by food.[7] Patients with tumors in the cardiac region, near the gastroesophageal junction, can present with dysphagia. Anemic symptoms, such as iron deficiency and hematemesis, can occur if the tumor has caused a hemorrhage along the blood supply of the stomach.[7] Notably, upon examination, the later stages show signs of metastasis, including a palpable mass along lymph node landmarks (i.e., left supraclavicular node, left axial node, and ovaries) and skin changes due to paraneoplastic lesions.[7]

The first-line choice of investigation for diagnosis is esophagogastroduodenoscopy. The Japanese Gastric Cancer Association guidelines classify lesions as type 0–III based on endoscopic appearance. Early lesions can present as either protruding/polypoid (Type 0–I), elevated (Type 0–IIa), flat (Type 0–IIb), depressed (Type 0–IIc), or excavated/ulcerated (Type 0–III),[8,9] The standard protocol is to sample tumor regions (usually base and edge if elevated) or complete excision if the lesion is ≤3 cm, localized to the submucosa, and there is no presence of ulceration visually. The sample is then histologically identified as intestinal/diffuse/mixed-type per Lauren classification.[10,11] Intestinal-type gastric adenocarcinoma is strongly linked to longstanding chronic gastritis secondary to *H. pylori* infection. This progression follows the Correa cascade, which describes the transformation from atrophic gastritis to intestinal metaplasia, dysplasia, and finally, gastric adenocarcinoma. Thus, in patients presenting with a longstanding history of gastritis, *H. pylori* testing (stool antigen testing, C-13 urea breath test, rapid urease test for *Campylobacter*-like organisms, and *H. pylori* antigen test) can aid in diagnosis.[12]

Serum biomarkers identified through biopsy, such as human epidermal growth factor receptor 2, programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1), microsatellite instability, *NTRK* mutation, and somatic mutations, defined as tumor mutational burden, have predictive implications and can further dictate therapeutic measures. For example, tumors with *HER2* overexpression can benefit from adjuvant immunotherapy, while PD-1/PD-L1 expression can indicate suitability for targeted monoclonal antibody therapy. Similarly, tumors demonstrating microsatellite instability can benefit from neoadjuvant chemotherapy/immunotherapy alongside surgery and adjuvant chemotherapy.[13]

Further imaging for gastric adenocarcinoma diagnosis includes barium meal X-ray (limited current use) and computed tomography (CT) to identify tumor locations, margins, and lymph node spread, along with positron emission tomography, which may have a more significant role in monitoring post-treatment recurrence through uptake of 2-fluoro-2-deoxy-D-glucose trace.[14]

1.4. Staging and prognosis

The tumor, node, metastasis (TNM) staging by the American Joint Committee on Cancer remains the standard for staging gastric adenocarcinoma through CT.[15] Clinically determined staging can be referred to as cTNM. After specimens have been excised and sent for laboratory investigation, the stage is referred to as pTNM, where p stands for pathological, and is often used for post-surgically removed tumors that require adjuvant chemotherapy. The 5-year general survival prognosis of stages I–III gastric adenocarcinomas is up to 71.8%. Beyond stage IIIc, this statistic drops to 5.9% for stage IV, warranting that early diagnosis and effective treatment of non-metastatic disease can significantly improve prognosis.[15,16]

1.5. Therapeutic approach

Management of gastric adenocarcinoma can be categorized into surgical and pharmacological management (Figure 1). The gold-standard therapy for gastric adenocarcinoma is resection (R0–3) through a surgical technique of gastrectomy

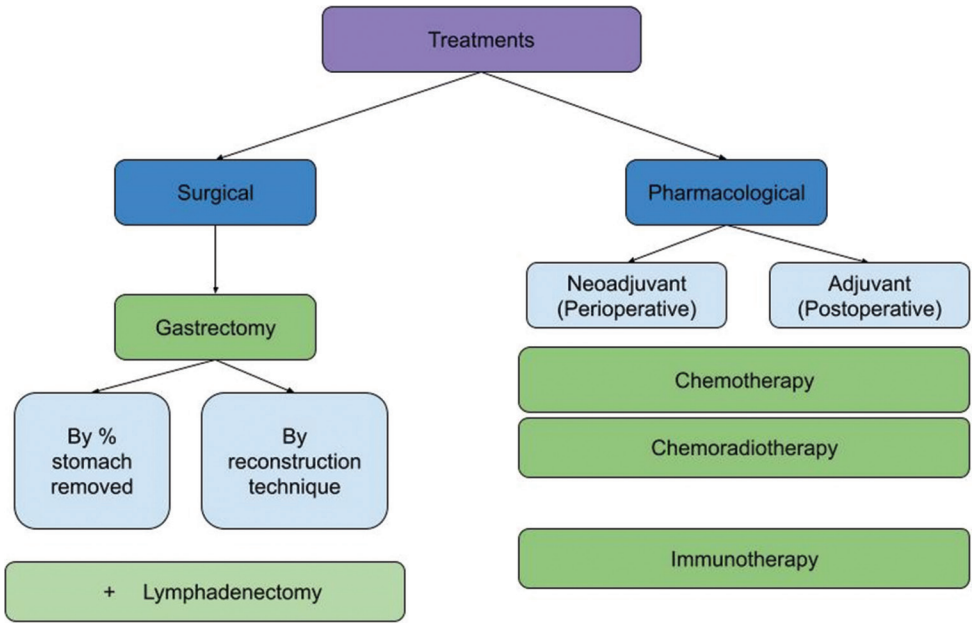

Figure 1. Categorization of treatments for gastric adenocarcinoma

accompanied by reconstruction and/or prophylactic lymphadenopathy (D1–D4).

During gastrectomy (open, laparoscopic, or robotic), surgeons often perform prophylactic lymphadenectomy due to the challenge of accurately predicting lymph nodes that contain malignant cells. The 18 lymph nodes of the stomach are classified into three tiers: Tier 1 (within 3 cm of the primary tumor), Tier 2 (along the main arterial branches), and Tier 3 (non-visible nodes). Lymphadenectomy can be categorized as D1, D2, D3, or D4 in terms of the number of tiers removed: D1 involves the removal of nodes in Tier 1, D2 includes Tier 1 and 2 nodes, D3 removes Tiers 1, 2, and 3, and D4 excises all the above plus paraaortic nodes.[17] Based on the nodal status of stages I–III gastric adenocarcinoma and as reflected in literature, D1/D2 lymphadenectomy is most commonly performed. According to the present JCGA guidelines,[18] D2 (+) lymphadenectomy – removing posterior and paraaortic nodes – should be considered for bulky N2 tumors to improve locoregional control.

The preferred procedure nowadays is R0 resection, typically involving distal total gastrectomy, which can extend from gastroesophageal junction to pyloric or antral tumors.[14] Reconstruction techniques following this procedure include Billroth I (gastroduodenostomy), Billroth II (gastrojejunostomy), and Roux-en-Y anastomosis (gastrojejunostomy to the second jejunal loop with jejunal-jejunal anastomosis of the first and second loops). The reconstruction technique choice depends on the tumor's location and margin extent. He and Zhou[19] reported that Roux-en-Y reconstruction, indicated for more distal tumors, improves gastritis and reflux esophagitis symptoms post-operatively due to the diversion of bilo-pancreatic fluids from the gastric outlet. Wang *et al*.[20] reported 40 – 60% relapse rates across all stages of gastric adenocarcinoma post-initial surgery. Thus, adjuvant chemotherapy after primary surgery has been used in key clinical trials (Table 1) to target cellular mechanisms and optimize therapeutic outcomes.

Central to all management options is the involvement of a multidisciplinary team (MDT), which involves radiologists, oncologists, surgeons (gastrointestinal, hepatobiliary, or thoracic, dependent on the extent of invasion), pathologists, anesthesiologists, nutritionists/dieticians, and specialist nurses. The focus is on generating a personalized treatment plan, managing post-operative symptoms, and follow-up staging/remission monitoring. Studies have shown that MDT discussions lead to an approximately 9.5% improvement in the 3-year overall survival (OS) rate (p=0.005), which can be attributed to a more thorough follow-up and holistic treatment approach.[21] This highlights the critical role of the diagnostic process in facilitating thorough and timely management.

2. Aims

This study aimed to evaluate two commonly used present treatment modalities by comparing surgery alone with surgery combined with adjuvant chemotherapy in the treatment of stages I to III gastric adenocarcinoma. Specifically, it investigated whether surgery alone results in (i) greater disease-free survival (DFS)/disease-specific survival/cause-specific survival, (ii) OS, and (iii) reduced recurrence rates or improved recurrence-free survival (up to 5 years), compared to surgery plus adjuvant chemotherapy. The study's inclusion criteria aimed to provide an updated literature review,

particularly evaluating whether these established treatment modalities have a combinatory effect on accelerated patient outcomes.

3. Methods

3.1. Search strategy

Two databases, MEDLINE and Embase, were used to conduct the initial literature search. The number of results returned by the keywords differed between the two databases (Figure 2). The keywords "stomach adenocarcinoma" or "adenocarcinoma" AND "stomach neoplasms" were used. With these keywords, "gastrectomy" OR "resection" OR "surgery" AND "adjuvant chemotherapy" were used to obtain approximately <400 papers from each database. Further limits, such as English and articles published in the past 10 years (2013 onward), yielded under 200 papers per database for further screening. With this, a more streamlined question was formulated in Table 2 to narrow down papers using the population, intervention, comparison, and outcome criteria.

3.2. Selection criteria and preferred reporting items for systematic reviews and meta-analyses flow diagram

As a secondary process, several inclusion and exclusion criteria were employed (Table 3) to filter articles, resulting in a total of 17 articles (Figure 3), which consisted of three experimental/intervention studies comprising randomized-control trials (level I evidence) and 14 observational studies (10 cohort studies [level II evidence] and four case-control [level III evidence]). Study quality and bias were assessed using the Critical Appraisal Skills Programme appraisal tool, and bias plots were generated visually before inclusion.

3.3. Outcome measures and statistical analysis

All 17 papers included for review had at least one of the pre-defined outcome measures: (i) greater DFS/disease-specific survival/cause-specific survival, (ii) OS, or (iii) decreased recurrence rates or improved recurrence-free survival (up to 5 years), with 14/17 (82.4%) comparing two outcome measures. Five papers (two randomized controlled trials, two cohorts, and one case-control) defined primary and secondary endpoints.

Descriptive statistics (mean, median, ranges, and interquartile ranges) were used for raw data analysis of confounding variables, prognostic factors, risk factors, and patient demographics. All papers analyzed primary outcomes (survival analysis) using Kaplan-Meier survival estimations or Cox proportional hazards regressions, with *p*-values and hazard ratios selected to assess the significance of results across exposure and control groups.

Table 1. Adjuvant chemotherapeutic regimens used in the treatment of stages I–III gastric adenocarcinoma

Regimen	Chemotherapeutic agents
XELOX or CAPOX	Capecitabine+oxaliplatin
ECX or ECF	Epirubicin+cisplatin+capecitabine Epirubicin+cisplatin+5-fluorouracil
UFT	Tegafur+uracil
S-1 or TS-1	Tegafur+gimeracil+oteracil
SOX	S-1+oxaliplatin
DOS	Docetaxel+S-1+oxaliplatin
Fluorouracil derivative+ platinum-coordinate complex	-
5'-DFUR	Doxifluridine
FOLFOX	Oxaliplatin+leucovorin+5-fluorouracil
FLOT	5-fluorouracil+ feucovorin+oxaliplatin+docetaxel
FAM	5-fluorouracil+doxorubicin+mitomycin-c
FOLFIRI	CPT-11 (Irinotecan) + leucovorin+5 -fluorouracil+docetaxel+ cisplatin+dexamethasone

Table 2. Formulation of questions for investigation

Criteria	Description
Population	Patients diagnosed with stages I to III gastric adenocarcinoma
Intervention	Surgery (gastrectomy with or without lymphadenectomy)
Comparison	Surgery combined with adjuvant chemotherapy
Outcomes	• Disease-free survival (1 – 5 years post-treatment) • Recurrence-free survival (1 – 5 years post-treatment) • Disease-specific/cause-specific survival (1 – 5 years post-treatment) • Overall survival (1 – 5 years post-treatment) • Recurrence rates (%)

Ovid MEDLINE(R) and ePub ahead of print, in-process, in-data-review & other non-indexed citations and daily <1946 to February 10, 2023>

1 Adenocarcinoma = 162,476
2 Stomach neoplasms = 108,743
3 Gastrectomy = 40,099
4 Chemotherapy, adjuvant = 45,268
5 1 and 2 and 3 and 4 = 371
6 Limit 5 to (English language and year: "2013–current") = 190

Embase <1974 to February 20, 2023>

1 Neoplasm = 443,581
2 Stomach adenocarcinoma = 18,399
3 Surgery = 747,640
4 Adjuvant chemotherapy = 64,194
5 2 and 3 and 4 = 168
6 Limit 5 to (English language and year: "2013–current") = 131

Figure 2. The search strategy used to obtain initial articles on MEDLINE and Embase databases

Table 3. Inclusion and exclusion criteria according to article specifics and dimension of interest

Criteria	Inclusion criteria	Exclusion criteria
Article specifics	• English-language • Full-text • In peer-reviewed journals • Published in the past 10 years (2013 to present) • Articles with levels I to III on the evidence hierarchy, with primary research (qualitative, quantitative, or mixed data), for example, clinical trials • Any participant group, regardless of age, sex, or ethnicity • All population groups and countries (regional/international)	• Non-English articles • Systemic reviews/meta-analyses • Non-human participants
Dimension of interest	• Patients with a diagnosis of stages I–III gastric adenocarcinoma • Patients who had undergone resection of the tumor through surgery • Patients with only gastric adenocarcinoma • Patients receiving adjuvant chemotherapy (after surgery) • Patients receiving chemotherapy as the only form of adjuvant therapy	• Stage IV gastric adenocarcinoma • Articles where patients present with any adenocarcinoma aside from gastric • Endoscopic/submucosal resection of tumors • Chemotherapy provided to patients non-adjunctly, that is, neoadjuvant/preoperatively • Patients receiving more than one form of adjuvant therapy, that is, radiotherapy, chemoradiotherapy, immunotherapy

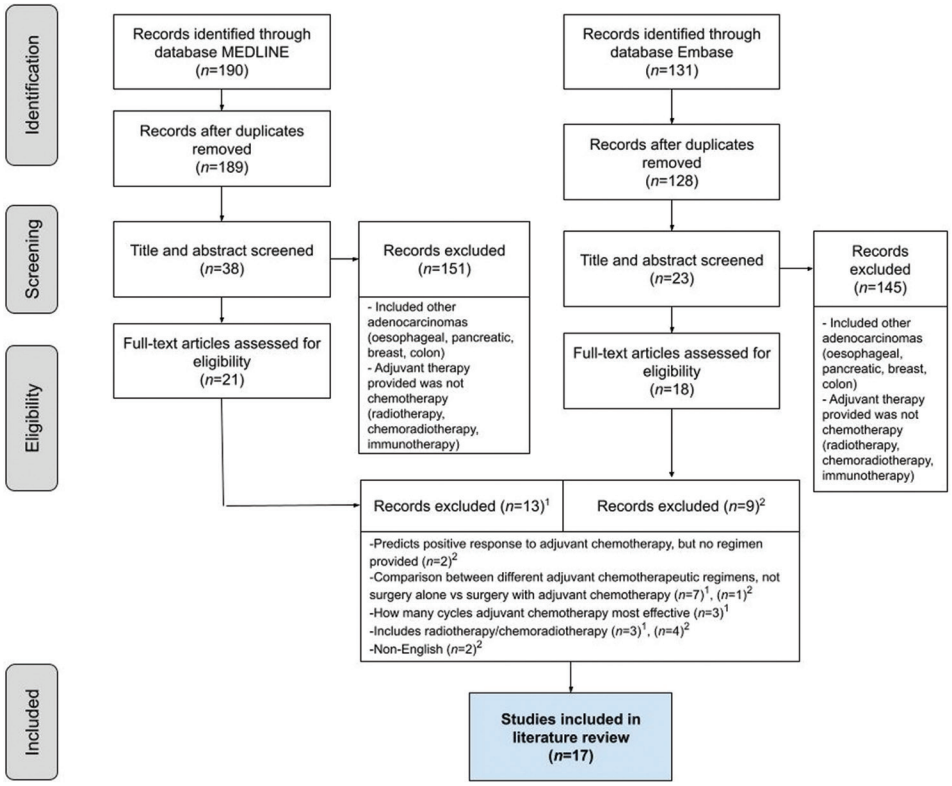

Figure 3. Preferred reporting items for systematic reviews and meta-analyses flow diagram. The flow diagram was used to identify the 17 studies included in the literature review.

4. Results

Seventeen studies[22-24, 29-34, 36-43] identified and filtered through a literature search were compared using two tables: Table S1, summarizing tumor characteristics and interventions received in studies included for review, and Table S2, analyzing outcome measures and factors favoring treatment. Figure 4 summarizes the primary survival endpoints of relapse-free survival (RFS) and OS according to percentage in treatment and control groups. The treatment group is defined as surgery plus at least one course of adjuvant chemotherapy regimen. Figure 5 is a forest plot showing survival (OS, RFS, and DFS) according to hazard ratios (95% confidence interval).

According to the OS as a primary endpoint, over a follow-up period of 48 – 400 months, seven (41.2%) studies reviewed demonstrated, with statistical significance, that surgery in combination with adjuvant chemotherapy was

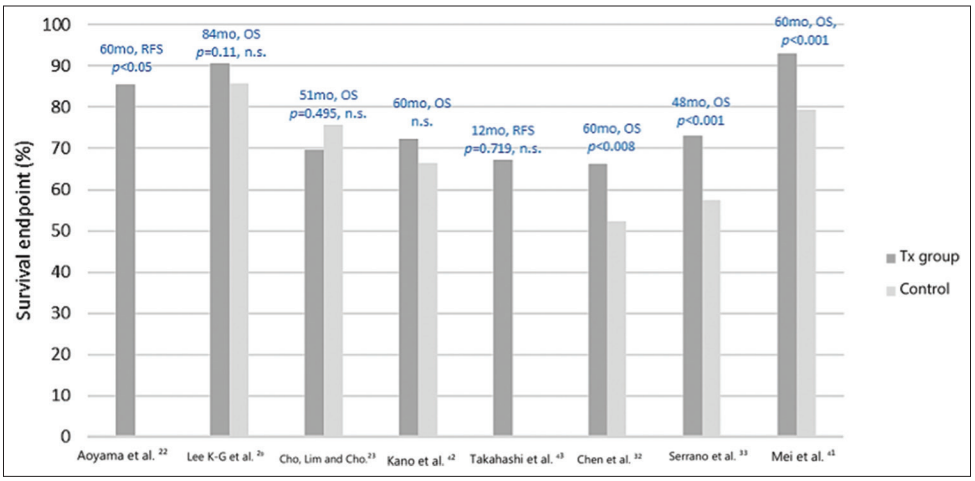

Figure 4. Survival endpoints according to percentage in treatment and control groups. The treatment (tx) group is defined as surgery plus at least one course of adjuvant chemotherapy regimen.
Abbreviations: mo: Months; n.s.: Not significant; OS: Overall survival; RFS: Relapse-free survival.

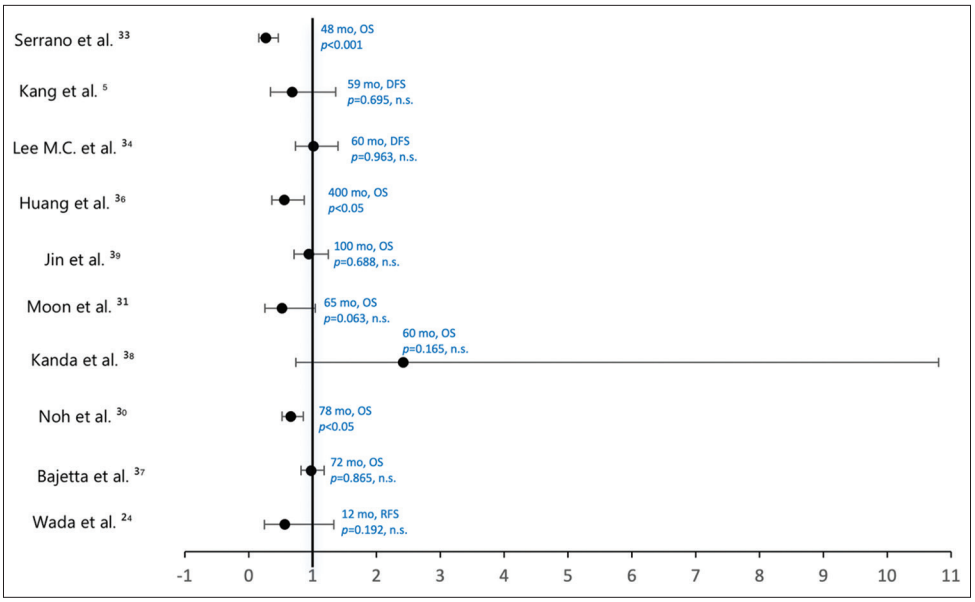

Figure 5. Forest plot showing survival according to hazard ratios (95% confidence interval)
Abbreviations: DFS: Disease-free survival; mo: Months; n.s.: Not significant; OS: Overall survival; RFS: Relapse-free survival.

more effective than surgery alone for the treatment of stages I–III gastric adenocarcinoma. Three (17.7%) of these studies showed significant improvement in OS in treatment groups that received at least one course of adjuvant chemotherapy compared to surgery alone. The study by Aoyama *et al*.[22] was disregarded due to a lack of data compared to a control group. When hazard ratios were evaluated, three studies (17.7%) reported hazard ratio <1, with statistical significance, meaning the treatment group studied had a decreased probability of an adverse event, thus improved survival, compared to the surgery alone control groups. Based on individual outcome measures (Table S2), 16 (94.1%) of the papers reviewed indicated that groups provided with adjuvant chemotherapy showed some improvement compared to groups with surgery alone. However, with no statistical significance, these values are disregarded in terms of generalizability and application to the sample populations in question.

5. Discussion

It can be summarized that the majority of papers do not show that adjuvant chemotherapy combined with surgery offers (i) greater DFS/disease-specific survival/cause-specific survival, (ii) OS, or (iii) decreased recurrence rates or improved RFS (up to 5 years), compared to surgery alone for the treatment of stages I to III gastric adenocarcinoma. Findings from individual analysis in this review revealed that within these sub-stages, small T1N2M0/T1N3M0 tumors had poor overall prognosis after both treatments.[23] Findings from Wada *et al*.[24] also showed that tumor diameter was an independent

predictor for recurrence after adjuvant S-1 chemotherapy in patients who had undergone surgical resection. This study was not contemplated due to insufficient access to raw data, including propensity score and substage analysis of treatment effect across stages I–III gastric adenocarcinoma.

When larger-scale systematic reviews, such as Diaz-Nieto *et al*.[25] comprising 34 randomized controlled trials with 7,824 participants, were compared, there was a statistically significant benefit of adjuvant chemotherapy on OS. Fifteen trials (comprising 4,133 participants) showed statistically significant DFS. While these trials investigated all stages of gastric cancer, Peters[26] noted no significant difference in the stage or chemotherapy regimen provided to patients. Older meta-analyses such as Mari *et al*.[27] reported that adjuvant chemotherapy reduced the risk of death by 18% but showed discrepancies in the significance of specific chemotherapeutic regimens used (5-fluorouracil and anthracyclines, for example, epirubicin did not show an improvement). The GASTRIC group meta-analysis from 2010[28] with 6,390 patients showed a statistically significant benefit of fluorouracil adjuvant chemotherapy on OS and reduced risk of death.

Thus, the difference between the findings of this study and the published literature can be attributed to several limitations of this review. With only 17 papers reviewed from two databases, a significant limitation was a low sample size. Given that most papers were location-based in Eastern Asian countries, several papers that met the selection criteria were excluded as they were not in English. Hence, the lack of translation and language bias could have resulted in a loss of pertinent results related to the research question. In line with strong epidemiological and dietary risk-factor associations, the incidence of gastric cancer in Eastern Asia, followed by Central Asia and Eastern Europe – the most recent literature included in this review represents a strongly Eastern approach to treatment for gastric adenocarcinoma. Thus, landmark papers representing Western approaches may have differing implications.

Further strict inclusion and exclusion criteria, particularly in the publication year, excluded earlier trials that showed substantial benefit of adjuvant chemotherapy after surgery to treat gastric adenocarcinoma. Although all papers analyzed in this review meticulously referenced these papers, it would have been interesting to examine differences in methodology, results, and significance of findings between recent literature and these larger trials. Searching more databases and extending the search years is plausible as interventions (particularly chemotherapeutic drugs used) have not changed significantly. Conversely, advances in surgical techniques (laparoscopy and robotic surgery) may improve patient outcomes, lessening the need for adjuvant chemotherapy. A comparison evaluating the role of serum biomarker identification in more targeted novel therapies, such as neoadjuvant, would determine whether it reduces tumor burden and improves post-surgical outcomes, thereby impacting the need for adjuvant therapies. Within this sphere, comparing outcomes in patient groups receiving neoadjuvant or adjuvant chemotherapy in addition to surgery could highlight differing effects of treatment modalities on survival statistics and longevity and help classify the benefiting patient groups. Overall, the sample size can be increased for review, but it should include new and up-to-date published results.

Restricting the analysis to stages I–III gastric adenocarcinoma limited the assessment of adjuvant chemotherapy effects across all stages. While results tables were designed to highlight key survival measures for comparison, reporting bias was inherent due to the variability of outcomes present in the studies. Therefore, the values selected may not fully represent all factors investigated in each of the individual papers. This is coupled with a lack of in-depth statistical analysis of all outcome measures present in the papers. Prognostic and independent risk factors were measured in multiple papers as factors that can influence recurrence rates or occurrence of an event such as death, thereby affecting the effectiveness of adjuvant chemotherapy. However, these were not considered in this review. While a column for factors favoring treatment was added, only univariate statistical values with significance or significantly low hazard ratio values (<1) were selected for consistency. Thus, to draw more plausible conclusions between adjuvant chemotherapy plus surgery on treatment outcomes and surgery alone, bivariate or multivariate analysis should be conducted, and the data can be stratified into several subcategories to increase the accuracy of reported results.

In terms of specific outcome measures, OS was defined as the time from randomization to date of death from any cause, as the primary endpoint in some of the studies,[29-33] making it difficult to distinguish between the OS being cause-related (as a direct result of cancer) or due to secondary non-malignant processes or poor treatment response (i.e., to chemotherapy). Secondary endpoints in Moon *et al*.[31] were defined by DFS, RFS, site of relapse, and relapse rate. Conversely, Noh *et al*.[30] defined their primary endpoint as DFS and secondary endpoints as OS and safety. Lee *et al*.[34] also defined their primary endpoint as DFS, and while Aoyama *et al*.[22] defined their primary endpoint as DFS, the quantitative values in the paper accounted for RFS instead. According to Oba *et al*.,[35] there was a very close association between DFS and OS (Spearman correlation coefficient = 0.974, 95% confidence interval = 0.971 – 0.76) (R^2 almost = 1) as outcome measures in adjuvant trials for gastric cancer, indicating that DFS can similarly represent variability in treatment effects measured by OS. Thus, DFS can reduce trial duration when patients

experience adverse cancer-related effects (rather than lifetime duration, which can depend on several confounders), reduce overall trial costs, and minimize data loss due to decreased patient compliance or low follow-up rates. The realization of DFS being an effective survival analysis measure over OS was noted by Aoyama *et al*.[22] However, this paper was subject to high classification bias as measurement methods were changed toward the end of the study (initially, OS was intended to be reported, followed by DFS, but statistical data were only provided for RFS). Finally, across both OS and DFS, discrepancies were noted in the duration for which the outcome measures were studied. While many papers reported 5-year DFS/RFS and OS rates, most data in graphs and tables accounted for different values (in months), often not extending to 5 years. Huang *et al*.[36] used a nomogram (computer-generated predictive tool) to predict the 5-year OS based on patient characteristics classified as "high/low-benefit." While objective, this method implied that patients did not actually undergo the study in exposure and control groups for the intended durations, resulting in potentially low generalizability, high selection bias (participants with demand characteristics), and classification bias.

Critical appraisal of present studies is also necessary to recognize future research directions. Multicenter, multicountry studies, such as the one conducted by Noh *et al*.,[30] which adjusted for prognostic factors with multivariate analysis, provided a model for further sample study design. Accounting for balanced, cross-matched, and blinded patient exposure and control groups studied in a prospective study could offer a more representative analysis of treatment effects. As survival statistics are key tools for assessing treatment effectiveness, generating streamlined guidelines for the frequency and duration of follow-up will enable a more reliable evaluation of the most effective, up-to-date treatments for stages I–III gastric adenocarcinoma.

6. Conclusion

The results from the 17 studies reviewed showed no statistically significant benefit of adjuvant chemotherapy after surgery for the treatment of stages I–III gastric adenocarcinoma, compared to surgery alone. These findings contradict large-scale meta-analyses that have established significant benefits of adjuvant chemotherapy beyond the past 10 years. However, the discrepancy may stem from the selective nature of this study and its specific aims, underscoring the need for more in-depth statistical analysis and expanded selection criteria to include all substages, among other limitations. Given the recent advances in surgical techniques, the application of new chemotherapeutic combinations, and the mounting emphasis on MDT involvement, ongoing research is essential to the determination of the efficacy of multimodal treatments alongside surgery as the cornerstone for gastric adenocarcinoma management.

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Conflict of interest

The author declares no conflicts of interest.

Author contributions

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Consent for publication

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Availability of data

Not applicable.

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