



## Strategy for Treating the Gastric Cancer: A Systematic Review and Meta-analysis

Somaye Jamali<sup>a,\*</sup>, Ehsan Kasraei<sup>b</sup>, Armita Rezazadeh Kalashami<sup>c</sup>, Mahdie Barri Dizaj<sup>d</sup>

<sup>a</sup> Department of Internal Medicine, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Department of Cardiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

<sup>c</sup> School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

<sup>d</sup> Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

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### ABSTRACT

**Background and aim:** Contemporary approaches to treat the stage IV patients could be generally divided into five groups of the palliative gastrectomy, radiotherapy, Chemotherapy, bypass, and gastric stent. The present systematic review and meta-analysis evaluated the overall survival to treat stage IV gastric cancer (GC) based on distinct signs and prognosis.

**Materials and methods:** MEDLINE, PubMed, Cochrane Library, Embase, ISI, google scholar have been utilized as the electronic databases for searching systematic literature until 2019. Then, Endnote X9, which is one of the software programs in the market, has been applied to manage the titles electronically. Searches were performed with keywords, "Gastric cancer", "cancer", "Gastric", "Stage IV", "Radiotherapy", "Chemotherapy", "Gastrectomy", "treatment of gastric cancer", "bypass".

**Results:** A total of 150, 93, 21 studies respective abstracts and topics have been discovered in the course of manual and electronic searches in the internet. Finally, a total of 10 studies for Palliative gastrectomy, five studies for Chemotherapy, and three studies for Radiotherapy required for this systematic review.

**Conclusion:** According to the meta-analysis, palliative gastrectomy exhibited a statistically significant survival advantage for the patients with the untreatable developed GC.

### 1. Introduction

Based on the research Gastric Cancer (GC) could be a disease in which malignant (cancer) cells frame within the lining of the stomach. Gastric cancer is an imperative health problem, being the 5th most prevalent malignancy as well as the 3rd primary reason for cancer-related deaths worldwide.<sup>[1]</sup> Despite a decreased occurrence and mortalities and critical propels in recognition of pathology, epidemiology, therapeutic choices and procedures, and molecular mechanism, the burden remained at the increased level.<sup>[2]</sup> The 5-year relative survival has been reported to be 30.6% for regional, 5.2% for distant (metastatic), and 68.1% for localized stage GC.<sup>[3]</sup> Therefore, the GC's rate and pathology vary considerably by geographical region, particularly between the West and East. All-inclusive, half of the diseases that occurred in Eastern Asia, the disease stage at the starting interview, and the site of the tumor and treatment results have been distinctive.<sup>[4]</sup> As for repetitive and metastatic GC, experts in the field created a few modern regimes to enhance the patients' survival rate.<sup>[5]</sup> In any case, the median survival time (MST) remained at 13 to 16 months. Thus, when arranging to advance the survival rate of the patients in stage IV GC, current treatment procedures should be investigated. Even though prognosis the stage IV GC enhanced owing to the novel chemotherapeutic and molecular targeting factors, this remained

unacceptable. However, as responses of the chemotherapy regime developed, experts in the field experienced successful application of some therapeutic conversion procedures in the stage IV GC.<sup>[6]</sup> Therefore, probable randomized controlled trials (RCTs) have been exceptionally troublesome for conducting with the stage IV patients as a result of various conditions of the disease expansion, performance status (PS), as well as they age. Hence, review examination has been vital for considering the GC within the clinics.<sup>[4]</sup> When arranging the IV GC, Borrmann type IV has been distinguished as a free prognostic agent.<sup>[7]</sup> A few creators have centered on the systemic inflammatory reaction in stage IV GC. Therefore, using the information from the peripheral blood tests as the prognostic variables has been valuable and straightforward for general and objective assessment. However, pre-treatment assessment of the peripheral blood factors detailed utilizing neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), the inflammation-based Glasgow Prognostic Score (GPS: the scoring framework utilizing CRP as well as the egg whites), for foreseeing the patient prognoses.<sup>[8, 9]</sup> Moreover, during the ten years ago, numerous publications tended to subjects associated with the stage IV gastric cancer; the 7th Union for the International Cancer Control (UICC) TNM mechanism varied the respective stage IV categorization; modern chemotherapy regimes were devised via the randomized ECF to the

\* Corresponding author. Somaye Jamali

E-mail address: somaye\_jamali@yahoo.com

Department of Internal Medicine, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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progressed and locally progressed esophagogastric cancer (REAL)-II, S-1 also cisplatin against the S-1 in the RCT to treat the stomach cancer (SPIRITS), trastuzumab for GC (Robe), ramucirumab mono-therapy for the formerly-treated progressed gastric or gastro-oesophageal junction adenocarcinoma (Respect), as well as the ramucirumab paclitaxel against the placebo also paclitaxel in the people with the formerly-treated, progressed gastric or gastroesophageal junction adenocarcinoma (RAINBOW) trials. A reductive gastrectomy rejected the survival viability of the palliative gastrectomy for the developed tumor in three Asian countries (REGATTA) trials. However, contemporary approaches to treat the stage-IV patients could be generally divided into five groups of the Chemotherapy, palliative gastrectomy, gastric stent, radiotherapy, and bypass. The present systematic review and meta-analysis aimed to evaluate the overall survival to treat the stage-IV GC based on the distinct signs and prognosis.

## 2. Materials and methods

### Search strategy

MEDLINE, PubMed, Cochrane Library, Embase, ISI, google scholar have been electronically searched in the respective data-bases for obtaining the systematic literature until 2019. Therefore, Endnote X9, a software program in the market, has been utilized to manage the titles electronically. Searches were conducted with keywords, “Gastric cancer”, “cancer”, “Gastric”, “Stage IV”, “Radiotherapy”, “Chemotherapy”, “Gastrectomy”, “treatment of gastric cancer”, “bypass”.

### Selection criteria

#### Inclusion criteria

1. Median survival time
2. Sample size
3. Follow-up comparing
4. Survival rate
5. in English

#### Exclusion criteria

1. Animal studies

### Data Extraction and method of analysis

The following data were extracted from the research included: study, years, follow-up period, and Sample size. Overall survival was analyzed by meta-analysis. Then, the forest plots were evaluated using one of the software programs provided in the market (Comprehensive Meta-Analysis Stata. V14).

## 3. Results

A total of 150, 93, 21 studies respective topics and abstracts have been searched in the course of electronic and manual searches. Therefore, in the course of the first stage of the research selection, 100, 60, 11 studies have been discarded about titles and abstracts. In the second stage, complete full-text papers of the other 50, 33, 10 research have been thoroughly assessed. Then, 40, 28, 7 articles have been disregarded due to the lack of fulfillment with the inclusion criteria of this study. Ultimately, ten papers for Palliative gastrectomy, five studies for Chemotherapy, and three studies for Radiotherapy needed for the present systematic review (Fig. 1). Tables 1, 2, 3 showed individual studies in this meta-analysis.

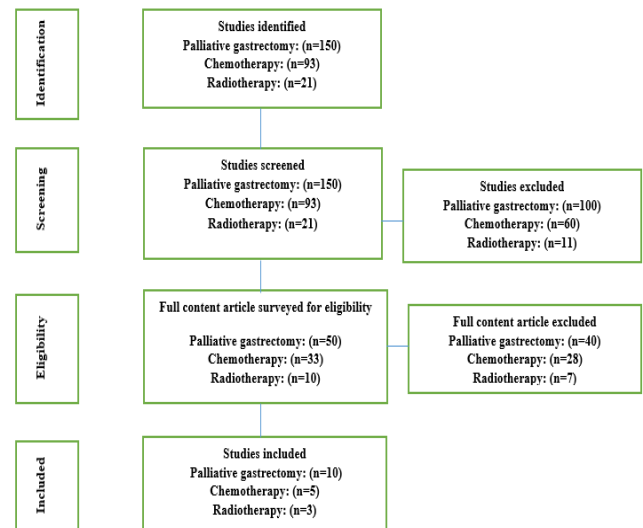


Fig. 1. Study Attrition Diagram.

### Palliative gastrectomy

All studies reported median survival times with range 10.8-17.8 months and weighted average 8.64 months for 1002 Patients With palliative gastrectomy and range 4-6.4 months and weighted average 4.18 months for 1034 Patients Without palliative gastrectomy (table1). The hazard ratios (HR) for overall survival was 0.62 (95% CI 0.36-1.85). The heterogeneity has been considerable ( $I^2 = 91\%$ ;  $P = 0.000$ ) (Fig. 2). Moreover, the meta-analysis revealed the significant survival advantage of the palliative gastrectomy in the cases with untreatable developed GC.

### Chemotherapy

Five studies included in the meta-analysis for Chemotherapy indicated that the number of patients was 1970 with 6.62 overall survival (OS) (table2). OS in patients were (OS 6.62 months, HR 5.76, 95%CI 1.786-9.751,  $p=0.027$ ) (Fig. 3).

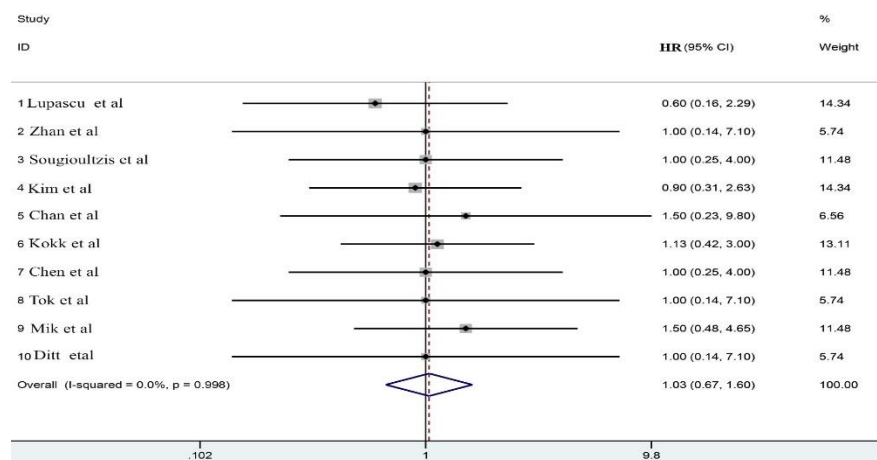
### Radiotherapy

Numerous studies have detailed radiotherapy efficacy for the stage-IV GC patients. In any case, many cases have been described as the stage-IV based on the T4N1- 3M0 or T1-3N3M0 method within the 6<sup>th</sup> version of the UICC TMN categorization. No studies find to perform a meta-analysis; only studies were reviewed systematically (Table3). Asakura et al.<sup>[10]</sup> reported that 73% of patients responded to radiotherapy with 50% rebleeding occurring, results showed radiotherapy with 30 Gy in 10 fractions has been appropriate to treat the bleeding in the cases with poorer prognoses. Kawabata et al.<sup>[11]</sup> reported that use radiotherapy with 30 Gy in 10 fractions, the progression of anemia stopped, and outpatient chemotherapy became possible. Lee et al.<sup>[12]</sup> reported that EBRT had been considered a functional and efficient therapeutic modality to palliate the tumor bleeding in the cases with the progressed GC. Finally, our research reflected that a BED10  $\geq 36$  Gy could cause better responses to the EBRT to treat the bleeding of the gastric tumor.

**Table 1. Studies selected for Systematic Review and Meta-analysis for Palliative gastrectomy.**

Study/year	AC	Metastasis	With palliative gastrectomy		Without palliative gastrectomy		One-year survival		Three-year survival		Five-year survival		Follow-up
			N.Patients	Median survival time (Mo)	N.Patient	Median survival time (Mo)	with PG	Wo PG		Wo PG	With PG	Wo PG	
Lupascu et al/2010 <sup>[13]</sup>	M0 + M1	±	30	17.8	45	6.4	-	-	-	-	-	-	30
Zhan et al. 2011 <sup>[14]</sup>	M0 + M1	-	184	16.4	152	5.5	51.4%	0.00	-	-	-	-	60
Sougioultzis et al. 2011 <sup>[15]</sup>	M0 + M1	-	218	13.25	93	4	-	-	8.1%	3.5%	-	-	75
Kim et al. 2011 <sup>[16]</sup>	M1	+	47	15.5	185	9	-	-	-	-	-	-	60
Chan et al. 2011 <sup>[17]</sup>	M1	±	108	12.7	57	11.2	-	-	-	-	-	-	60
Kokk et al. 2012 <sup>[18]</sup>	M1	±	23	10.8	32	5.7	-	-	-	-	-	-	60
Chen et al. 2012 <sup>[19]</sup>	M0 + M1	±	392	Na	470	Na	-	-	-	-	-	-	48
Tok et al. 2012 <sup>[20]</sup>	M1	±	82	13.1	66	12	-	-	-	-	-	-	60
Mik et al. 2012 <sup>[21]</sup>	M1	±	38	25.6	12	8.7	64.4%	36.7%	36.1%	12.2%	29.4%	0.00	83
Ditt et al. 2012 <sup>[22]</sup>	M0 + M1	±	48	15	45	6	-	-	-	-	-	-	60

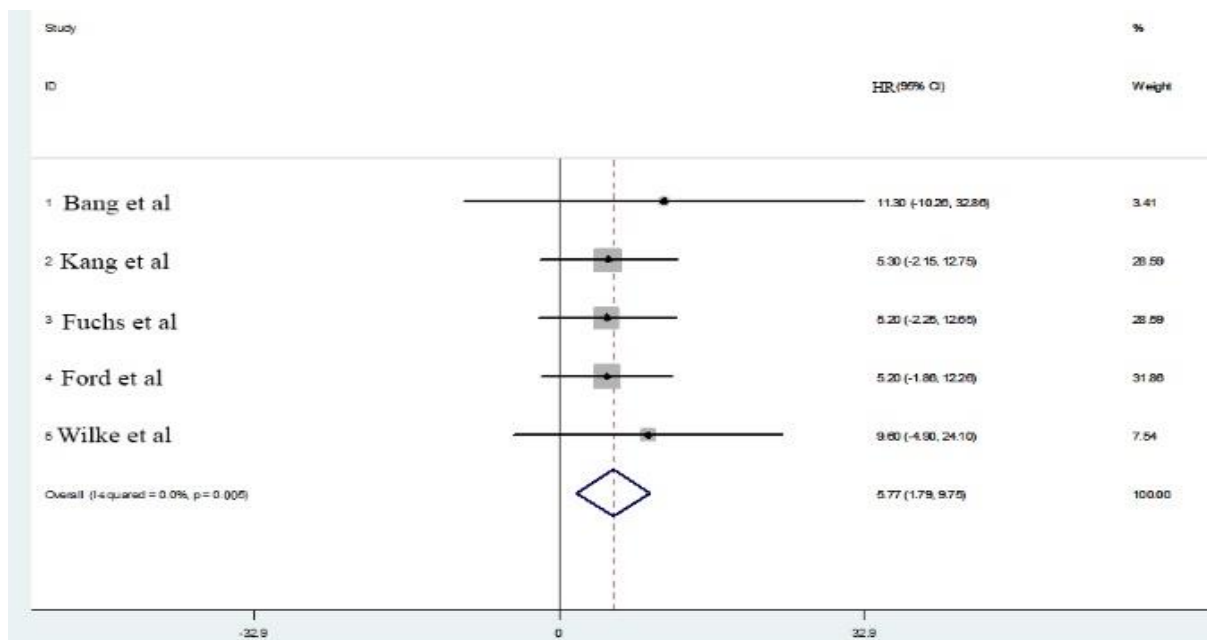
AC: Adjuvant chemotherapy. Mo: month. Wo: without.



**Fig. 2. Forest plots showed Hazard ratio for overall survival.**

**Table 2. Studies selected for Systematic Review and Meta-analysis for Chemotherapy.**

Study/year	Regimens	Sample size	Overall survival (OS)
Bang et al/2010 <sup>[23]</sup>	Cisplatin+5-Fluorouracil/ Capecitabine +Trastuzmab	294	11.3
	Cisplatin+5-Fluorouracil/ Capecitabine	290	11.0
Kang et al./2012 <sup>[24]</sup>	Docetaxel/Irinotecan	133	5.3
	BSC	69	3.8
Fuchs et al./2014 <sup>[25]</sup>	Ramucirumab	236	5.2
	Placebo	115	3.8
Ford et al/2014 <sup>[26]</sup>	Docetaxel	84	5.2
	BSC	84	3.6
Wilke et al/2014 <sup>[27]</sup>	Ramucirumab+Paclitaxel	330	9.6
	Placebo+Paclitaxel	335	7.4

**Fig. 3. Forest plots showed Hazard ratio for overall survival.****Table 3. Studies selected for systematic review and meta-analysis for Radiotherapy.**

Study/year	Number of patients	Patients responded to radiotherapy	Rebleeding occurring	Median actuarial time	Radiotherapy	Conclusion
Asakura et al/2011 <sup>[10]</sup>	30	22 (73%)	11 (50%)	3.3 months	30 Gy for 10 fractions	poor
Kawabata et al/2017 <sup>[11]</sup>	1	1 (100)	NA	2 months	30 Gy for 10 fractions	The progression of anemia stopped and outpatient chemotherapy became possible. Palliative radio-therapy for persistent bleeding from unresectable progressed gastric cancer has been considered an effective treatment option to control bleeding.
Lee et al/2017 <sup>[12]</sup>	42	29 (69.0%)	NA	2.6 weeks and 14.9 weeks.	10 ≥ 36 Gy	External beam radiotherapy (EBRT) has been one of the efficient methods to treat the tumor bleeding in the progressed GC, and did not involve serious poisonousness.

#### 4. Discussion

In this systematic review and meta-analysis, we examine the existing procedures to treat the Stage-IV GC based on the person signs and prognosis. In palliative gastrectomy, two aimed had seen, one aim has been to relieve the symptoms, and the other one has been the survival advantage.<sup>[4]</sup> Also, surgical resections have been regarded to be an affect specific procedure to alleviate the cancer-associated signs. Sometimes, a crisis activity ought to be prevented from sparing the patients' lives.<sup>[28-30]</sup> Such a condition could not be an inescapable procedure in any case of death or survival rate. About the survival advantages of the palliative gastrectomy, the National Comprehensive Cancer Network rules propose that the gastrectomy isn't demonstrated in the cases with the metastatic diseases with no main symptom.<sup>[31, 32]</sup> It is notable that palliative gastrectomy already appeared to possess a higher rate of deaths and morbidity rates. Information obtained from fourteen years ago revealed the increased rate of fatalities that regularly come to 20%.<sup>[6, 33, 34]</sup> Kim et al.<sup>[35]</sup> retrospectively inspected, just a significant prognostic factor has been the presence of the peritoneal dissemination (HR 0.739, 95% CI 0.564 to 0.967,  $p < 0.05$ ). In this systematic review and meta-analysis, HR for the overall survival rate has been 0.62 (95% CI 0.36-1.85); other meta-analysis Reported similar results; the result of Sun et al.<sup>[30]</sup> study report, palliative gastrectomy in the cases with the stage-IV gastric cancer considerably enhanced the OS (HR 0.62, 95% CI, 0.49 to 0.78,  $p < 0.0001$ ) and Lasithiotakis et al.<sup>[36]</sup> showed, (OR 2.6, 95% CI 1.7-4.3,  $p < 0.0001$ ). The over considers demonstrated that the stage-IV cases with the great PS and one metastasis calculate, particularly peritoneal dissemination, to be a great candidate for the two diminishments of surgical operation and systemic Chemotherapy. Retrospectively inspected the survival advantage of the adjuvant surgical operation after the chemo-therapy for cases with at first unrespectable stage-IV GC. However, the three-year OS rate within the adjuvant surgery gather has been 65.6% vs. 7.7% within the nonadjuvant surgery gather ( $p < 0.0001$ ).<sup>[37]</sup> Izuishi et al.<sup>[4]</sup> showed that peritoneal dissemination could be one of the encouraging candidates as one of the non-curative clinical factors for adjuvant surgeries. The opposite approach wherein the surgical resection has been conducted after the chemotherapy, auxiliary gastrectomy could be of intrigued in the coming years considers to drag out the survival rate of the patients with the stage-IV GC. Quick propels within the improvement of the chemo-therapeutic factors to treat the GC altogether promoted the disease guesses. In this systematic review and meta-analysis, OS in patients were (OS 6.62 months, HR 5.76, 95% CI 1.786-9.751,  $p = 0.027$ ), other studies Reported similar results, such as McCloud et al.<sup>[38]</sup> reflected more reasonable OS in the cases given treatment with the capecitabine combination compared to the 5-FU combination in the progressed oesophagogastric cancer (OS 322 versus 285 days, HR equal to 0.87, 95% CI 0.77 to 0.98,  $p = 0.027$ ). Improvement of advanced molecular innovation would empower quicker and comprehensive investigations of the GC's quality enhancements and genetic modifications. Amid the current ten years, researchers created numerous targeted treatment regimes to treat different types of cancer. Thus, the advancement of more powerful cancer development suppressors has been anticipated in close years. Based on the findings of this study from the results of other studies,<sup>[10, 11, 12]</sup> people with an indication for radiotherapy have been those with exceptionally weak forecasts. In any case, since the probable chemo-therapeutic operators, which considerably increment the patient prognosis have been created, a part of the hemostasis utilizing radiations would be more imperative. Radio-chemotherapy that combines the chemotherapy and radiotherapy could be one of the promising approaches for T4 patients with M1 within the coming years.

#### 5. Conclusion

The most objective of treating the stage-IV GC patients has been successful healing of cancer or the most exceptional conceivable life quality that significantly prolongs the patients' lives. However, a fundamental issue has been the improvement of common chemotherapeutic factors. Mainly, the molecular focused on treatment appeared the useful outputs to treat cancers.

#### Conflict of Interest

The authors declared that there is no conflict of interest.

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