J Cancer Res Clin Oncol (2015) 141:361–367
DOI 10.1007/s00432-014-1816-y

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Adjuvant chemoradiotherapy after D2 resection in gastric cancer: a single-center observational study

Esra Kaytan Saglam · Serap Yucel · Emre Balik · Sezer Saglam · Oktar Asoglu · Sumer Yamaner · Dursun Bugra · Ethem N. Oral · Ahmet Kizir · Yersu Kapran · Burak Sakar · Ali Akyuz · Mine Gulluoglu

Received: 14 August 2014 / Accepted: 26 August 2014 / Published online: 5 September 2014

Abstract
Purpose Previous studies demonstrated survival benefits in association with the addition of chemoradiotherapy after surgery in gastric cancer. This study aimed to examine the efficacy in terms of loco-regional control and survival and safety of 5-FU-based adjuvant chemoradiotherapy after D2 curative surgery.
Methods This study included 228 patients (81 female, 147 male) treated for gastric cancer with curative surgery plus adjuvant chemoradiotherapy. Majority of the patients underwent at least D2 lymph node resection. Median three cycles of fluorouracil chemotherapy were administered, and 45-Gy radiotherapy was delivered at 1.8 Gy/fraction concomitantly during the second cycle of chemotherapy. Local control, regional control, distant metastasis and overall survival rates were estimated.
Results The median age of the patients was 54 years (range 25–74 years). The most common grade III toxicities were nausea (10 %) and neutropenia (9 %). During radiotherapy, grade IV local skin reaction occurred in one patient. Median duration of follow-up was 47 months. Local, regional and distant recurrence developed in 9 (4 %), 41 (18 %) and 45 (20 %) patients, respectively. Overall 5-year survival rate was 57.2 %, and disease-free 5-year survival rate was 53.8 %. Multivariate analysis identified less than 15 lymph node involvement as an independent predictor of better survival ($p < 0.001$).
Conclusions Concomitant 5-FU-based chemoradiotherapy seems to be an effective and tolerable adjuvant regimen on local control and survival in curatively resected node-positive stomach cancer, particularly when combined with D2 resection.

E. Kaytan Saglam · E. N. Oral · A. Kizir
Department of Radiation Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey

S. Yucel
Department of Radiation Oncology, Medical Faculty, Acibadem University, Istanbul, Turkey

E. Balik · D. Bugra
Department of General Surgery, Koc University, School of Medicine, Istanbul, Turkey

S. Saglam (✉)
Department of Medical Oncology, Medical Faculty, Avrupa Florence Nightingale Oncology Hospital, Istanbul Bilim University, Sishane, 34440 Istanbul, Turkey
e-mail: saglam@istanbul.edu.tr

O. Asoglu
Department of General Surgery, Liv Hospital, Istanbul, Turkey

S. Yamaner
Department of General Surgery, Florence Nightingale Hospital, Istanbul, Turkey

Y. Kapran
Department of Pathology, VKV American Hospital, Istanbul, Turkey

B. Sakar
Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey

A. Akyuz
Department of General Surgery, Medical Faculty, Istanbul University Istanbul, Istanbul, Turkey

M. Gulluoglu
Department of Pathology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

Keywords Adjuvant therapy · Chemoradiotherapy · Gastric cancer · D2 resection

Introduction

Despite dramatic decline in the frequency of gastric cancer over the past 70 years, only 25–40 % of all gastric cancer patients are diagnosed at a potentially curable stage (Howson et al. 1986). Gastric cancer represents an important public health burden since it is still the leading cause of cancer-related mortality worldwide (Jemal et al. 2006). In the USA, there will be an estimated 22,000 new cases of gastric cancer per year and 13,000 deaths, during the early twenty-first century (Jemal et al. 2006). In Turkey, gastric cancer is the second leading cause of death in men and the third leading cause of cancer mortality in women. The anatomical site of origin of gastric cancer among Turkish patients differs from that reported for Western countries, with 48.1 and 41.2 % of cancers in Turkish patients occurring at the antrum and corpus, respectively, and 51.6 % of patients having a pathological grade III cancer (Saglam et al. 2011).

Until Southwest Oncology Group/Intergroup 0116 (INT-0116) trial results were published, the curative treatment of gastric cancer consisted of only gastric resection (Macdonald et al. 2001). INT-0116 trial demonstrated survival benefits in association with the addition of chemoradiotherapy to surgery; thus, changed the standard of care in USA, although not uniformly accepted in Europe.

Based on the findings of INT-0116 trial, in our institution, gastric cancer patients from stage T1N1 (IB) disease are treated with D2 surgery followed by adjuvant 5-fluorouracil-based chemotherapy and concomitant radiotherapy administered during the second chemotherapy cycle.

The aim of this study was to examine the efficacy (in terms of loco-regional control and survival) and safety of adjuvant chemoradiotherapy after D2 gastric surgery in patients with stage IB–IIIC adenocarcinoma of the stomach.

Materials and methods

Patients

This study included 228 patients (81 female, 147 male) treated for gastric cancer at the Institute of Oncology, Istanbul University between January 2002 and December 2009 with curative surgery (total or subtotal gastrectomy and D2 or D3 lymphadenectomy) plus adjuvant chemoradiotherapy. Inclusion criteria were as follows: histologically confirmed adenocarcinoma, stage IB through IV according to sixth edition TNM staging criteria of the American Joint Commission on Cancer (Greene 2002) and ECOG performance status ≤ 1. Patients who had coexisting malignant conditions were excluded. In addition, patients with any evidence of distant metastases, macroscopic, or microscopic residual tumor after surgery were excluded. All patients provided informed consent prior to study entry. Medical records of the patients fulfilling eligibility criteria were reviewed using a standardized data sheet. Local control, regional control, distant metastasis and overall survival (OS) rates were estimated. Following curative resection, patients received adjuvant chemoradiotherapy. The median time from surgery to the start of adjuvant regimen was 4 weeks (range 2–6 weeks).

Surgical technique

All patients underwent endoscopic evaluation at surgery department, and thoracic and abdominal CT examinations were done. After thorough preoperative evaluation, patients were scheduled for gastrectomy plus lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total or a distal subtotal gastrectomy. D2 lymphadenectomy was the standard procedure for dissection of tumors located in the upper two-thirds of the stomach as defined in the twelfth edition of the Japanese Classification (1993) when the study was initially designed (Japanese Research Society for Gastric Cancer: Japanese Classification of Gastric Carcinoma 1995). This technique was frequently performed as a standard procedure in this study. In total or distal subtotal gastrectomy tumors, the spleen was not removed in principle instead a splenic hilar lymphadenectomy was done.

Adjuvant chemoradiotherapy

Chemotherapy including fluorouracil (Mayo Regimen 425 mg/m^2, Leucovorin 20 mg/m^2 a day D1–5/q28) was administered in the first cycle. After a 28-day interval, the second cycle of chemotherapy started with concomitant radiotherapy. Fluorouracil dosage changed to 400 mg per square meter and administered at the first 4 days and the last 3 days of radiotherapy during the second cycle. One month after the completion radiotherapy, following cycles of chemotherapy were given (median three cycles; range 2–5 cycles).

Until 2005, 61 patients (27 %) were treated with two-dimensional radiotherapy using 4–6 megavoltage photon beams. The radiation fields encompassed the remnant stomach, tumor bed and regional lymph nodes (celiac, porta hepatis, superior mesenteric artery, and splenic nodes identified on CT, and pancreaticoduodenal nodes) with customized blocks. The median radiation dose was 45 Gy delivered at 1.8 Gy/fraction. Two opposite anteroposterior–posterioanterior fields were used.

Between 2005 and 2009, 167 patients (73 %) were treated with 3D conformal RT. A computed tomography (CT) scan (5-mm-thick slices) was performed from the top of diaphragm to the bottom of L4 with intravenous contrast. Radiation fields of the patient (CTV) were defined as gastric remnant, tumor bed, and nodal coverage depends on the location of the primary disease (perigastric, celiac, splenic, suprapancreatic, porta hepatic, pancreaticoduodenal and periesophageal lymph nodes). PTV was defined as CTV plus 1 cm. Treatment dose (45 Gy/25 fr) was defined as 95 % isodose of PTV. Organs at risk (kidneys, liver, small bowel and spinal cord) were delineated.

Follow-up

Follow-up visits were scheduled at 3-month interval for the first 2 years, then at 6-month interval for the next 3 years. At each visit, physical examination, complete blood count, liver function tests and chest radiography were done. In addition, abdominal computed tomography and gastroscopy were done, when clinically indicated. Any suspected recurrence was confirmed by biopsy, if possible. Recurrences occurring within the radiotherapy area at remnant stomach, surgical anastomosis and gastric bed regions were defined as local recurrence. Recurrences at regional lymph nodes were defined as regional recurrence, whereas other recurrences were classified as 'distant recurrence.'

Statistical analyses

Statistical analyses were performed using Statistical Package for Social Sciences software (SPSS, ver.15.1, SPSS Inc., Chicago, IL). Relapse-free survival (RFS) and OS rates at 5 years were calculated using Kaplan–Meier estimates. The OS rates were calculated from the date of surgery to death or the date of the last follow-up visit for patients who were still alive. The RFS rates were estimated from the date of surgery to the time of any documented disease after radiotherapy or to the date of the last follow-up visit for those remaining disease free. Univariate and multivariate analyses were done. For multivariate analysis, log-rank test and Cox's proportional hazards regression model were used. Statistical tests were based on a two-sided significance level, and a p value of 0.05 or less was considered as an indication for statistical significance.

Results

Patient characteristics

Table 1 shows patient characteristics. The median age of the patients was 54 years (range 25–74 years). The most frequent tumor location was antrum (69.7 %). Majority of the patients had T3 disease ($n = 188$, 82.4 %). Most tumors were located in distal stomach (69.7 %), and D2 dissection was done in more than 80 % of the patients. Median number of resected lymph nodes was 28 (20–74), and postoperative pathological examination revealed lymph node involvement in 87.3 % of the patients ($n = 199$). All patients were ambulatory or asymptomatic after surgery. Full-course radiotherapy was completed by all of patients. Chemotherapy was given median three cycles: two cycles in 27 patients (12 %), three cycles in 120 patients (53 %), four cycles in 34 patients (15 %) and five cycles in 47 patients (21 %).

Toxicity of adjuvant treatment

Table 2 shows major treatment-related toxicities. The most common grade III toxicities were nausea (10 %) and neutropenia (9 %). During RT, grade IV local skin reaction occurred in one patient. Weight loss more than 10 % was observed in 21 patients (9 %).

Survival

Median duration of follow-up was 47 months. At the time of the analysis, 120 patients (53 %) were alive without disease and three patients were alive with recurrences. Overall, 95 patients (42 %) developed recurrence during follow-up period. Local, regional and distant recurrence developed in 9 (4 %), 41 (18 %) and 45 (20 %) patients, respectively. Among all recurrences, most frequent was distant metastasis (48 %), followed by regional recurrence (43 %) and local recurrence (9 %). Liver was the most frequent site of distant metastasis ($n = 36$, 80 %). Overall 5-year survival rate was 57.2 %, and disease-free 5-year survival rate was 53.8 %. Figure 1 shows Kaplan–Meier curve for overall survival.

Prognostic factors

Table 3 shows the univariate analysis of potential factors for overall survival. In univariate analysis, female gender, lower T stage (T1–T2) and involvement of <15 lymph nodes were associated with better survival. Multivariate analysis identified only less than 15 node involvement as an independent predictor of better survival ($p < 0.001$).

Discussion

According to western studies, loco-regional recurrences comprise 57 % of failures after resection of gastric cancer, which commonly occur in gastric bed and in lymph nodes,

Table 1 Demographical and clinical characteristics

Characteristic	$n = 228$
Age (years), median (range)	54 (25–74)
Male gender	147 (64.5 %)
Tumor location	
Cardia	45 (19.7 %)
Antrum	159 (69.7 %)
Diffuse	20 (8.7 %)
Gastric remnant	4 (1.7 %)
Histological subtypes	
Adenocarcinoma	148 (64.9 %)
Signet ring cell adenocarcinoma	78 (34.2 %)
Mucinous adenocarcinoma	4 (1.7 %)
Histological grade	
G1	9 (6.4 %)
G2	44 (31.2 %)
G3	70 (49.6 %)
T stage	
T1	4 (1.8 %)
T2	25 (11.6 %)
T3	188 (82.4 %)
T4a	11 (4.8 %)
N stage	
N0	29 (12.7 %)
N1	119 (52.1 %)
N2	66 (28.9 %)
N3	14 (6.1 %)
Surgery type	
Total gastrectomy	143 (62.7 %)
Subtotal gastrectomy	85 (37.3 %)
No. of positive nodes	
<15	214 (93.9 %)
≥15	14 (6.1 %)
Type of lymph node dissection	
D2	192 (84.2 %)
D3	36 (15.8 %)

Unless otherwise stated, data are expressed as *n* (%)

Table 2 Major toxicities ($n = 228$)

	Grade I–II *n* (%)	Grade III *n* (%)
Nausea	57 (25 %)	22 (10 %)
Neutropenia	53 (23 %)	21 (9 %)
Esophagitis	51 (22 %)	7 (3 %)
Diarrhea	21 (9 %)	9 (4 %)
Weight loss		
<5 %	127 (56 %)	
5–10 %	71 (31 %)	
>10 %	21 (9 %)	

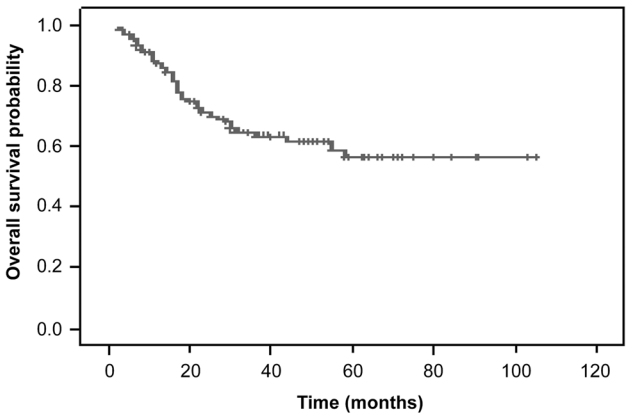

Fig. 1 Kaplan–Meier curve for overall survival

Table 3 Univariate analysis of the potential prognostic factors for survival

Factors	5-Year survival (%)	Log-rank SD	*p*
Age (years)			
≤50	57.8	3.53-1	0.06
>50	47.3		
Gender			
Male	46.8	4.07-1	**0.04**
Female	63.7		
Histological subtypes			
Adenocarcinoma	54.6	1.05-1	0.30
Signet ring cell	49.8		
Histological grade			
G1	53.6	1.399-2	0.49
G2	54.2		
G3	42.9		
T stage			
T1–T2	82.4	5.88-1	**0.01**
T3–T4	47.1		
Surgery type			
Total gastrectomy	48.5	3.61-1	**0.05**
Subtotal gastrectomy	60.1		
No. of positive nodes			
<15	51.4	27.6-2	**<0.001**
≥15	11.2[a]		
0	84.4		

Bold values indicate significance ($p < 0.05$)

[a] Median survival: 21 months

despite radical lymph node dissections (Gilbertsen 1969; Gunderson 2002; Landry et al. 1990; Meyers et al. 1987). This high rate of local recurrences has formed the rationale of adjuvant treatment trials studying the roles radiotherapy and chemotherapy with varying treatment schedules and conflicting results.

In a British Study, postoperative treatment modalities were investigated (Hallissey et al. 1994). In that prospective, randomized, controlled trial, patients were assigned into one of three groups. The first group received surgical treatment only, the second group received adjuvant radiotherapy in addition to surgery (45–50 Gy of total dose), and the third group received fluorouracil-based chemotherapy adjuvant to surgery. No survival advantage has been shown for patients receiving either of the adjuvant therapy compared to the group of patients that received surgery alone. However, loco-regional recurrence rate was 10 % in adjuvant radiotherapy group compared to 27 % in the surgery alone group and 19 % in the adjuvant chemotherapy group. However, it is of note to emphasize that only 68 % of the patients in the adjuvant radiotherapy group could receive a dose ≥40.5 Gy, which may partly explain the failure to find a survival advantage in favor of adjuvant radiotherapy in that study.

INT-0116 a large prospective randomized study compared surgery alone with surgery plus adjuvant chemoradiotherapy in patients with adenocarcinoma of the stomach or gastroesophageal junction and found a significant survival advantage in favor of adjuvant chemoradiotherapy (median survival 27 vs. 36 months) (Macdonald et al. 2001). Three-year disease-free and overall survival rates were better with the latter modality, despite only 10 % of the patients underwent D2 resection. The benefit of adjuvant therapy also included patients with stage IB–IV (M0). These findings suggest that all patients with gastric wall extension and/or nodal involvement would benefit from adjuvant treatment when compared to surgery alone.

In Western countries, D2 resection is known as 'extended lymphadenectomy,' whereas Japanese surgeons employ D2 resection as a standard technique and reserve the term 'extended lymphadenectomy' for para-aortic dissection. Since para-aortic nodes may represent the final station of nodes that can be dissected to remove the threat of systemic metastases originating from the lymphatic system, para-aortic lymph node dissection may be worthwhile. On the other hand, risks associated with para-aortic dissection require advanced operative skills and intensive postoperative care.

An analysis of 1991 data from Japan nationwide registry showed that D2–D4 lymph node resection was associated with better 5-year survival when compared to D0–D1 resection 62 vs. 33 % (Maruyama et al. 2006). In that population, loco-regional recurrence was not a common disease failure pattern, which may reflect the effect of more extensive lymph node dissection in terms of local control. On the other hand, Sasako et al. (2008) compared D2 lymphadenectomy alone or with para-aortic lymph node dissection in an attempt to test the potential contribution of more extensive dissection; however, failed to find a survival difference between the two modalities (5-year survival, 69.3 vs. 70.3 %). It is of note to emphasize that none of the patients received adjuvant treatment in that study. A large phase III trial included stage II–III gastric cancer patients that received surgery with D2 lymphadenectomy and compared surgery alone versus additional adjuvant treatment (Sakuramoto et al. 2007; Sasako et al. 2011). In the surgery alone arm, 3- and 5-year survival rate was 70.1 and 61.1 %, respectively, reflecting potential contribution of D2 lymphadenectomy in this group of patients. In that study, S-1 adjuvant chemotherapy resulted in survival benefit when compared to surgery alone, despite no radiotherapy was given.

Zhu et al. (2012) tested the additional role of radiotherapy by comparing chemoradiotherapy with chemotherapy alone in gastric cancer patients with D2 resection, in adjuvant setting. Intensity-modulated radiotherapy with chemotherapy (IMRT-C) improved disease-free survival, but not significantly improved overall survival: 5-year overall survival, 48.4 versus 41.8 %, 5-year disease-free survival, 45.2 versus 35.8 %, for IMRT-C versus surgery alone, respectively. Survival rates are similar to that of INT116 study where most patients underwent D0–D1 resection. However, we do not have any information on the number of removed lymph nodes, which may explain such low survival rates following D2 resection. In ARTIST study on the other hand, two adjuvant treatment modalities were compared in patients that underwent D2 resection and a disease-free survival advantage for chemoradiotherapy over chemotherapy alone was demonstrated, but only for patients with pathologic lymph node metastasis at the time of surgery (Lee et al. 2012). A recent meta-analysis confirmed these findings by demonstrating superiority of chemoradiotherapy over chemotherapy alone in patients that underwent D2 lymphadenectomy, for loco-regional recurrence-free survival and disease-free survival, but not for distant metastasis-free survival or overall survival (Huang et al. 2013).

To date, several studies have tested adjuvant radiochemotherapy in association with D2 resection, in different populations. Table 4 summarizes the findings of these studies in reference to the INT-0116 study.

In two recent Korean studies, CLASSIC (Bang et al. 2012) and ARTIST (Lee et al. 2012) trials, which tested adjuvant treatments particularly in patients that underwent D2 resection, 3-year survival rates around 75 % could be achieved in association with D2 resection and adjuvant therapies in addition to surgery.

Following the demonstration of the survival advantage of adjuvant chemotherapy after curative gastrectomy in INT-0116 study, our clinic adopted a similar protocol for all gastric cancer patients that underwent radical surgical resection (5-FU/LV with 45 Gy RT). However, our surgical approach involves more extensive lymph node resection.

Table 4 Previous studies on the treatment of gastric cancer with D2 surgery and adjuvant chemoradiotherapy, in reference to the INT-0116 trial

Study	Design	No. of patients	Surgery type	% of T3/T4 patients	% with (+) nodes	No. of removed nodes	Median follow-up (m)	Overall 5-year survival
Macdonald et al. (2001)[a]	Prospective randomized	281	D0–D1	68	85	≤15	60	50 % (3-year)
Kim et al. (2005)	Retrospective	544	D2	48	94.1	≥25 (87 %)	66	57.1 %
Leong et al. (2008)	Retrospective	70	D2	60	91	>15 (86 %)	27	60.6 % (3-year)
Zhu et al. (2012)	Prospective randomized	186	D2	70	85	?	54	48.8 %
Lee et al. 2012[b]	Prospective randomized	230	D2	?	88.3	40	53.2	78.3 % (DFS)
Jacome et al. (2013)	Retrospective	104	D2	88	63	?	30.8	64.4 % (3-year)
This study	Prospective observational	288	D2	87	87	20–28	47	57.2 % (5-year)

[a] INT-0116 trial, [b] ARTIST trial. For comparative studies, only data of radiochemotherapy arm is given

Most patients underwent D2 resection and a small fraction had D3 dissection, whereas most patients in the INT-0116 study had D0 (54 %) and D1 (36 %) resection. Lower local recurrence rate observed in this study when compared to INT-0116 study (4 versus 19 %) may be attributed to more aggressive lymph node resection.

In this study, 5-year survival rate (57 %) was similar to that obtained in a large Korean study (Kim et al. 2005), although our study included patients with more advanced disease: T3–4 disease, 87 versus 43 %; pathological lymph node rate, 87 versus 51 %. Majority of the patients in this study completed all planned treatment with tolerable side effects. No hospitalization has been observed during adjuvant treatment schedules and grade IV local skin reaction occurred in only one patient. These findings suggest that postoperative chemoradiotherapy can be successfully administered without altering treatment modalities.

In this study, number of positive lymph nodes (>15) emerged as an independent predictor of prognosis. Although limited in number, early abdominal dissemination and distant metastasis were seen among patients with more than 15 positive nodes. Patients with advanced nodal involvement can be candidates for metastatic disease protocol; thus, number of removed lymph nodes seems to be critical for treatment planning.

The chemotherapy regimen used in this study may be modified to achieve better outcomes. For example, a single-agent adjuvant therapy may not be sufficient following D2 resection. A meta-analysis showed better survival rates with three-drug regimen in patient with metastatic gastric cancer (Wagner et al. 2006). However, so far, there is no application of three-drug regimen in the adjuvant setting.

In conclusion, concomitant chemoradiotherapy seems to be an effective and tolerable adjuvant regimen on local control and survival in curatively resected node-positive stomach cancer, particularly when combined with D2 resection. Further modification of chemotherapy regimen may give better results.

Conflict of interest None.

References

Bang YJ et al (2012) Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 379:315–321. doi:10.1016/S0140-6736(11)61873-4

Gilbertsen VA (1969) Results of treatment of stomach cancer. An appraisal of efforts for more extensive surgery and a report of 1,983 cases. Cancer 23:1305–1308

Greene FL (2002) American Joint Committee on Cancer staging manual. 6th edn, New York

Gunderson LL (2002) Gastric cancer—patterns of relapse after surgical resection. Semin Radiat Oncol 12:150–161. doi:10.1053/srao.2002.30817

Hallissey MT, Dunn JA, Ward LC, Allum WH (1994) The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 343:1309–1312

Howson CP, Hiyama T, Wynder EL (1986) The decline in gastric cancer: epidemiology of an unplanned triumph. Epidemiol Rev 8:1–27

Huang YY, Yang Q, Zhou SW, Wei Y, Chen YX, Xie DR, Zhang B (2013) Postoperative chemoradiotherapy versus postoperative chemotherapy for completely resected gastric cancer with D2 lymphadenectomy: a meta-analysis. PLoS ONE 8:e68939. doi:10.1371/journal.pone.0068939

Jácome et al (2013) Effect of adjuvant chemoradiotherapy on overall survival of gastric cancer patients submitted to D2 lymphadenectomy. Gastric Cancer 16:233–238

Japanese Research Society for Gastric Cancer: Japanese Classification of Gastric Carcinoma (1995). 1st English edn. Kanehara, Tokyo, Japan

Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ (2006) Cancer statistics. CA Cancer J Clin 56:106–130

Kim S et al (2005) An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 63:1279–1285. doi:10.1016/j.ijrobp.2005.05.005

Landry J, Tepper JE, Wood WC, Moulton EO, Koerner F, Sullinger J (1990) Patterns of failure following curative resection of gastric carcinoma. Int J Radiat Oncol Biol Phys 19:1357–1362

Lee J et al (2012) Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 30:268–273. doi:10.1200/JCO.2011.39.1953

Leong CN et al (2008) Outcomes of adjuvant chemoradiotherapy after a radical gastrectomy and a D2 node dissection for gastric adenocarcinoma. Cancer J 14:269–275

Macdonald JS et al (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725–730. doi:10.1056/NEJMoa010187

Maruyama K et al (2006) Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer 9:51–66. doi:10.1007/s10120-006-0370-y

Meyers WC, Damiano RJ Jr, Rotolo FS, Postlethwait RW (1987) Adenocarcinoma of the stomach. Changing patterns over the last 4 decades. Ann Surg 205:1–8

Saglam S, Aykan NF, Sakar B, Gulluoglu M, Balik E, Karanlik H (2011) A pilot study evaluating the safety and toxicity of epirubicin, cisplatin, and UFT (ECU regimen) in advanced gastric carcinoma. J Gastrointest Oncol 2:19–26. doi:10.3978/j.issn.2078-6891.2010.030

Sakuramoto S et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820. doi:10.1056/NEJMoa072252

Sasako M et al (2008) D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 359:453–462. doi:10.1056/NEJMoa0707035

Sasako M et al (2011) 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 29:4387–4393. doi:10.1200/JCO.2011.36.5908

Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE (2006) Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 24:2903–2909. doi:10.1200/JCO.2005.05.0245

Zhu WG et al (2012) A randomized, controlled, multicenter study comparing intensity-modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. Radiother Oncol 104:361–366. doi:10.1016/j.radonc.2012.08.024