

Saudi Oncology Society clinical management guideline series

Gastric cancer 2014

Magdy S. Kandil, MD, PhD, Shouki N. Bazarbashi, MBBS, Mohammed M. Rabal, MD, PhD, Ahmed S. Al-Shebri, MBChB, FRCPC, Ali M. Alzabrani, MBChB, FRCR, Ali H. Aljubran, MD, Jamal E. Zekri, MBChB, FRCP (UK), Ashwaq A. Al Olayan, MBBS, Abdullah A. Alsharm, MD, Nizar M. Yamani, MBBS, ABS, Ibrahim S. Alomary, MD, Mosa A. Fagih, MBBS, FRCPC.

A total 291 cases of stomach cancer were diagnosed in 2010 in the Kingdom of Saudi Arabia according to the Saudi Cancer Registry data.¹ Stomach cancer ranked eleventh among the male and female population. It account for 2.9% of all diagnosed cancers. The overall age standardized rate was 2.7/100,000, with a rate of 3.1/100,000 for males and 2.3/100,000 for females. The median age at diagnosis was 65 years for males (range 4-94 years), and 60 years for females (range 23-100 years).

A committee of experts in the medical and surgical treatment of colorectal cancer was established under the supervision of the Saudi Oncology Society (SOS). The evidence adopted in these guidelines is rated at 3 levels: 1) Evidence level (EL)-1 (highest level) evidence from phase III randomized trials or meta-analyses, 2) EL-2 (intermediate-level) evidence from good phase II trials or phase III trials with limitations, and 3) EL-3 (low-level) from retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient for the reader and allows accurate assessment of the applicability of the guidelines in individual patients.²

All gastric cancer cases are preferably seen or discussed in a multidisciplinary form.

Definitions

The term “esophagogastric junction tumor” covers lower esophageal adenocarcinoma, junctional tumors, and cancer of the cardia. The Siewert classification is used to subdivide esophagogastric junction tumors into type I, II, and III.³ The classification covers the area 5 cm either side of the gastro-esophageal junction.

- 1.1 Type I - the center of the cancer or more than two-thirds of identifiable tumor mass is located >1 cm proximal to the anatomical gastro-esophageal junction
- 1.2 Type II - the center of the cancer or the tumor mass is located in an area extending one cm proximal to the gastro-esophageal junction to 2 cm distal to it
- 1.3 Type III - the center of the tumor or more than two-thirds of identifiable tumor mass is located >2 cm below the gastro-esophageal junction
- 1.4 Barrett's esophagus is identified as an esophagus in which the normal squamous lower esophageal epithelium has been replaced by intestinal type mucosa, which is visible macroscopically.

Type I will be treated as esophageal cancer and types II and III will be treated as gastric cancer.

From the Oncology Department (Alzabrani, Kandil) Prince Sultan Military Medical City, Section of Medical Oncology (Bazarbashi, Aljubran), Department of Oncology (Zekri), Oncology Center, King Faisal Specialist Hospital and Research Center, Department of Oncology (Al Olayan), Department of Surgery (Yamani), King Abdulaziz Medical City, Medical Oncology Department (Alsharm), Anatomic Pathology Department (Fagih), King Fahad Medical City, Riyadh, Department of Oncology (Rabal), Oncology Center, King Fahad Specialist Hospital, Dammam, and the Department of Oncology (Al-Shebri, Alomary), Princess Nora Oncology Center, King Abdulaziz Medical City, Jeddah, Kingdom of Saudi Arabia.

Received 15th July 2014. Accepted 19th October 2014.

Address correspondence and reprint request to: Dr. Shouki N. Bazarbashi, Oncology Center, King Faisal Specialist Hospital and Research Center, PO Box 3354 (MBC 64), Riyadh 11211, Kingdom of Saudi Arabia. Tel. +966 (11) 4423935. E-mail: Bazarbashi@gmail.com



OPEN ACCESS

1. Pre-treatment evaluation

- 1.1 Clinical and physical examination
- 1.2 Blood count, renal, and hepatic function tests
- 1.3 Tumor markers (optional: carcinoembryonic antigen, CA-19-9)
- 1.4 Flexible upper gastrointestinal endoscopy is recommended as the diagnostic procedure of choice in patients with suspected esophageal or gastric cancer⁴
- 1.5 Biopsy: all biopsy pathologic reports should include the following checklist:⁵
 - 1.5.1 Histologic type
 - 1.5.2 Histologic grade
 - 1.5.3 Ancillary studies: HER-2 immunoperoxidase studies (in accredited labs or with external quality control) and HER-2 florescent *in-situ* hybridization (FISH) - for patients with immuno score 2+ (in accredited labs or with external quality control)
- 1.6 Computed tomography (CT) scan of the chest, abdomen, and pelvis to assess the local, nodal, and distant spread. Limitations include low sensitivity to detect peritoneal metastasis <5 mm and underestimation of depth of wall invasion⁶⁻⁹ (EL-2)
- 1.7 Barium studies (optional to define extent of surgery)¹⁰
- 1.8 Endoscopic ultrasonography (optional)¹¹⁻¹⁵ (EL-2)
- 1.9 Staging laparoscopy: recommended for gastric tumors being considered for surgery where full thickness gastric wall involvement is suspected, T3-4 or N positive (EL-2)¹⁶⁻²⁰

2. Surgical pathology report requirements:^{5,21}

- 2.1 Specimen
- 2.2 Procedure
- 2.3 Tumor site (select all that apply)
- 2.4 Tumor size
- 2.5 Histologic type
- 2.6 Histologic grade
- 2.7 Microscopic extent of tumor
- 2.8 Margins (select all that apply)
- 2.9 Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)
- 2.10 Lymph-vascular invasion
- 2.11 Perineural invasion
- 2.12 Pathologic staging (pTNM)
- 2.13 TNM descriptors (required only if applicable)
 - 2.13.1 M (multiple primary tumors)
 - 2.13.2 R (recurrent)
 - 2.13.3 Y (post-treatment)
- 2.14 Additional pathologic findings-ancillary studies:
 - 2.14.1 HER2 immunoperoxidase studies (accredited laboratory or external quality control)
 - 2.14.2 HER2 in situ hybridization studies / florescent in-situ hybridization (immuno score 2+) (accredited laboratory or external quality control)

3. Staging

The American Joint Commission on Cancer (AJCC)- 2007 pathological staging system will be used²¹

4. Treatment

- 4.1 Indicators of unresectability: presence of distant metastases, invasion of a major vascular structure, such as the aorta, or disease encasement or occlusion of the hepatic artery or celiac axis/proximal splenic artery

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

- 4.2 Treatment of stage T_{IS} (in-situ), T1a N0M0: Endoscopic mucosal resection of early gastric cancer meeting all of the following (EL2):²²
 - 4.2.1 Well or moderately differentiated type adenocarcinoma
 - 4.2.2 Superficial, elevated, or depressed (<1cm) macroscopic appearance (types I, IIa, IIc)
 - 4.2.3 No ulceration
 - 4.2.4 Diameter of the lesion <30 mm
 - 4.2.5 No apparent invasive findings
- 4.3 Treatment of stage T1b-T4, N0-1, M0: Medically fit and potentially resectable patient should be given either of the following options
 - 4.3.1 Gastrectomy followed by adjuvant concurrent chemoradiotherapy using 5-fluorouracil and leucovorin as per inter group 0116 protocol²³ (EL-1 or modifications²³⁻²⁶ [EL-2]). Radiotherapy dose is 45 Gy in 25 daily fractions of 1.8 Gy on 5 days a week to stomach bed and draining high-risk nodal regions²³⁻²⁶
 - 4.3.2 Perioperative neoadjuvant/adjuvant chemotherapy using epirubicin/cisplatin/5-FU (ECF) chemotherapy regimen, (EL-1) or its modifications (EL-2), based on the Cunningham/Medical Research Council Adjuvant Gastric (MAGIC) trial²⁷ (EL-1), or Cisplatin /5-Fluorouracil as per the Federation Nationale des Centres de Lutte contre le Cancer/Federation Francophone de Cancerologie Digestive (FNLCC/FFCD) trial²⁸ (EL-1)
 - 4.3.3 Gastrectomy to be followed by post-operative adjuvant XELOX for 8 cycles²⁹ (EL-1)
- 4.4 Surgical management:
 - 4.4.1 Gastrectomy.³⁰⁻³⁵ Total gastrectomy was carried out for proximal and mid body gastric tumors with a Roux-en-Y reconstruction to avoid alkaline reflux esophagitis. Distal subtotal gastrectomy for distal gastric tumors (EL-2) with a wide macroscopically negative margin of 5 cm, along with the en bloc resection of lymph nodes (D2 lymphadenectomy, EL-1),³⁶⁻³⁸ and adherent surrounding organs. Spleen and pancreas are spared (EL-2). If a splenectomy is anticipated preoperatively because of tumor adherence shown by CT, we administer pneumococcal polysaccharide, meningococcal, and Haemophilus influenzae vaccines before surgery.
 - 4.4.2 Lymphadenectomy.³⁶⁻³⁸ Resection of lymph nodes in gastric cancer surgery can be carried out at 3 levels: 1) D1, involves removal of all nodal tissue within 3 cm of the primary tumor (perigastric nodes); 2) D2, involves D1 plus clearance of hepatic, splenic, celiac, and left gastric lymph nodes; and 3) D3, involves D2 plus omentectomy, splenectomy, distal pancreatectomy, and clearance of porta hepatis lymph nodes and para-aortic lymph nodes.
- 4.5 Follow up. There is no consensus regarding follow-up after gastrectomy. There is no evidence that regular intensive follow-up improves patient outcomes. Symptom-driven visits are recommended for most cases (EL-3)
- 4.6 Post-operative management of residual disease. This will depend on the degree of residual disease as follows:
 - 4.6.1. R1 (microscopic residual disease): treat with post-operative chemo radiation or chemotherapy
 - 4.6.2. R2 (macroscopic residual disease): treat as metastatic disease
- 4.7 Treatment of stage T4M0 medically fit and unresectable. Treat as metastatic disease (M1) and reassess for resectability
- 4.8 Treatment of stage M1 disease. This will depend on patient performance status:
 - 4.8.1 Patients with performance status (PS) 0-2: palliative chemotherapy with any of the following options: ECF modifications³⁹ (EL-1), docetaxel, cisplatin, and 5-FU (DCF) (EL1) / DCF modifications^{40,41} (EL-2), 5-FU, leucovorin, and oxaliplatin 6 (FOLFOX 6),⁴² (EL-2) or capecitabine and oxaliplatin (XELOX)X⁴³ (EL-2). Add trastuzumab to Cisplatin/Fluoropyrimidine if Her-2/neu +3 on immunohistochemistry or FISH positive⁴⁴ (EL-1)

- 4.8.2 Patients with PS of 3: give single agent chemotherapy or best supportive care
- 4.8.3 If disease progression after first line chemotherapy, consider, when appropriate in good performance status patients, a second line combination paclitaxel-ramucirumab⁴⁵ or single agent irinotecan, taxane or ramucirumab^{46,47} (EL-1)

References

1. Saudi Cancer Registry. Cancer Incidence Report in Saudi Arabia 2010. Riyadh (KSA): Saudi Cancer Registry; 2014.
2. Jazieh AR; Saudi Lung Cancer Guidelines Committee. The lung cancer management guidelines 2012. *J Infect Public Health* 2012; 5 Suppl 1: S4-S10.
3. Natsugoe S, Yoshinaka H, Moriga T, Shimada M, Hokita S, Baba M, et al. Assessment of tumor invasion of the distal esophagus in carcinoma of the cardia using endoscopic ultrasonography. *Endoscopy* 1996; 28: 750-755.
4. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. *Gastroenterology* 1982; 82: 228-231.
5. College of American Pathologists. The College of American Pathologists cancer protocols; 2011. [Updated 2014]. Available from URL <http://www.cap.org/apps/cap.portal>
6. Kim SJ, Kim HH, Kim YH, Hwang SH, Lee HS, Park do J, et al. Peritoneal metastasis: detection with 16- or 64-detector row CT in patients undergoing surgery for gastric cancer. *Radiology* 2009; 253: 407-415.
7. Sussman SK, Halvorsen RA Jr, Illescas FF, Cohan RH, Saeed M, Silverman PM, et al. Gastric adenocarcinoma: CT versus surgical staging. *Radiology* 1988; 167: 335-340.
8. Davies J, Chalmers AG, Sue-Ling HM, May J, Miller GV, Martin IG, et al. Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. *Gut* 1997; 41: 314-319.
9. Lee IJ, Lee JM, Kim SH, Shin CI, Lee JY, Kim SH, et al. Diagnostic performance of 64-channel multidetector CT in the evaluation of gastric cancer: differentiation of mucosal cancer (T1a) from submucosal involvement (T1b and T2). *Radiology* 2010; 255: 805-814.
10. Dooley CP, Larson AW, Stace NH, Renner IG, Valenzuela JE, Eliasoph J, et al. Double-contrast barium meal and upper gastrointestinal endoscopy. A comparative study. *Ann Intern Med* 1984; 101: 538-545.
11. Yoshida S, Tanaka S, Kunihiro K, Mitsuoka Y, Hara M, Kitada Y, et al. Diagnostic ability of high-frequency ultrasound probe sonography in staging early gastric cancer, especially for submucosal invasion. *Abdom Imaging* 2005; 30: 518-523.
12. Pollack BJ, Chak A, Sivak MV Jr. Endoscopic ultrasonography. *Semin Oncol* 1996; 23: 336-346.
13. Kelly S, Harris KM, Berry E, Hutton J, Roderick P, Cullingworth J, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut* 2001; 49: 534-539.
14. Botet JF, Lightdale CJ, Zauber AG, Gerdes H, Winawer SJ, Urmacher C, et al. Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. *Radiology* 1991; 181: 426-432.
15. Ganpathi IS, So JB, Ho KY. Endoscopic ultrasonography for gastric cancer: does it influence treatment? *Surg Endosc* 2006; 20: 559-562.
16. Lowy AM, Mansfield PF, Leach SD, Ajani J. Laparoscopic staging for gastric cancer. *Surgery* 1996; 119: 611-614.
17. Feussner H, Omote K, Fink U, Walker SJ, Siewert JR. Pre-therapeutic laparoscopic staging in advanced gastric carcinoma. *Endoscopy* 1999; 31: 342-347.
18. Power DG, Schattner MA, Gerdes H, Brenner B, Markowitz AJ, Capanu M, et al. Endoscopic ultrasound can improve the selection for laparoscopy in patients with localized gastric cancer. *J Am Coll Surg* 2009; 208: 173-178.
19. Sarela AI, Lefkowitz R, Brennan ME, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. *Am J Surg* 2006; 191: 134-138.
20. Burke EC, Karpeh MS Jr, Conlon KC, Brennan ME. Peritoneal lavage cytology in gastric cancer: an independent predictor of outcome. *Ann Surg Oncol* 1998; 5: 411-415.
21. Edge SBD, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC Cancer Staging Manual. 7th ed. New York (NY): Springer-Verlag; 2010.
22. Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; 41: 751-757.
23. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345: 725-730.
24. André T, Quinaux E, Louvet C, Colin P, Gamelin E, Bouche O, et al. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. *J Clin Oncol* 2007; 25: 3732-3738.
25. Leong T, Joon DL, Willis D, Jayamoham J, Spry N, Harvey J, et al. Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2011; 79: 690-695.
26. Lee HS, Choi Y, Hur WJ, Kim HJ, Kwon HC, Kim SH, et al. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. *World J Gastroenterol* 2006; 12: 603-607.
27. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11-20.

28. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; 29: 1715-1721.
29. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; 379: 315-321.
30. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. *Ann Surg* 1999; 230: 170-178.
31. Gouzi JL, Huguier M, Fagniez PL, Launois B, Flamant Y, Lacaine F, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 1989; 209: 162-166.
32. Yang SH, Zhang YC, Yang KH, Li YP, He XD, Tian JH, et al. An evidence-based medicine review of lymphadenectomy extent for gastric cancer. *Am J Surg* 2009; 197: 246-251.
33. Wu CW, Chiou JM, Ko FS, Lo SS, Chen JH, Lui WY, et al. Quality of life after curative gastrectomy for gastric cancer in a randomised controlled trial. *Br J Cancer* 2008; 98: 54-59.
34. Iivonen MK, Mattila JJ, Nordback IH, Matikainen MJ. Long-term follow-up of patients with jejunal pouch reconstruction after total gastrectomy. A randomized prospective study. *Scand J Gastroenterol* 2000; 35: 679-685.
35. Tyrväinen T, Sand J, Sintonen H, Nordback I. Quality of life in the long-term survivors after total gastrectomy for gastric carcinoma. *J Surg Oncol* 2008; 97: 121-124.
36. Kodama Y, Sugimachi K, Soejima K, Matsusaka T, Inokuchi K. Evaluation of extensive lymph node dissection for carcinoma of the stomach. *World J Surg* 1981; 5: 241-248.
37. Seevaratnam R, Bocicariu A, Cardoso R, Mahar A, Kiss A, Helyer L, et al. A meta-analysis of D1 versus D2 lymph node dissection. *Gastric Cancer* 2012; 15 Suppl 1: S60-S69.
38. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; 359: 453-462.
39. Sumpster K, Harper-Wynne C, Cunningham D, Rao S, Tebbutt N, Norman AR, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. *Br J Cancer* 2005; 92: 1976-1983.
40. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; 24: 4991-4997.
41. Bojic M, Pluschnig U, Zacherl J, Thallinger CM, Ba-Ssalamah A, Maresch J, et al. Docetaxel, cisplatin and 5-fluorouracil plus granulocyte colony-stimulating factor prophylaxis in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: experience at the Medical University of Vienna. *Anticancer Res* 2011; 31: 2379-2382.
42. Fontana A, Losi L, Bertolini F, Zironi S, Depenni R, Malavasi N, et al. FOLFOX6 as first-line treatment in metastatic gastric cancer: Preliminary results of a phase II trial. *J Clin Oncol* 2010; 28: 4091.
43. Yang T1, Shen X, Tang X, Wei G, Zhang H, Du C, et al. Phase II trial of oxaliplatin plus oral capecitabine as first-line chemotherapy for patients with advanced gastric cancer. *Tumori* 2011; 97: 466-472.
44. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687-697.
45. Hironaka S, Shimada Y, Sugimoto N, Komatsu Y, Nishina T, Yamaguchi K, et al. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy-Efficacy analysis in Japanese and Western patients. *J Clin Oncol* 2014; 32: 5s.
46. Kim HS, Kim HJ, Kim SY, Kim TY, Lee KW, Baek SK, et al. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. *Ann Oncol* 2013; 24: 2850-2854.
47. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; 383: 31-39.