Austin Journal of Surgery

Austin Publishing Group

Open Access Full Text Article

Editorial

Recent Treatment Strategies for Advanced Gastric Cancer: Future Perspectives on Multimodality Therapy

Takahashi T* and Kitagawa Y

Department of Surgery, School of Medicine, Keio University, Japan

***Corresponding author:** Takahashi T, Department of Surgery, Keio University; 35 Shinanomachi, Shinjuku-ku, Tokyo 1608582, Japan, Tel: 81-353633802; Fax: 81-333554707; Email: tsunehiro-t@a8.keio.jp

Received: February 25, 2014; **Accepted:** April 02, 2014; **Published:** April 04, 2014

Gastric cancer is the second leading cause of death from malignant disease worldwide, with especially high mortality rates in most parts of Asia, Central and Eastern Europe, and South America [1]. Although early detection of gastric cancer has increased due to the recent advances in imaging modalities, most cases are diagnosed in an advanced stage. The treatment strategy for gastric cancer is recommended according to the stage of each case. Recently, endoscopic resection, which adapted eligibility criteria of curability, has been performed as a minimally invasive treatment for early gastric cancer [2]. Even then, surgical treatment was the mainstream of treatment for gastric cancer. Until recently, the great challenge of surgeons who treat gastric cancer had continued to be improving survival using surgical procedures. Especially with lymphadenectomy, they had been looking for a significant role in controlling the gastric cancer.

In Western countries, D1 lymphadenectomy has been considered a standard surgical procedure according to the results of large phase III trials [3-6] One of the two major trials was the Medical Research Council (MRC) Gastric Cancer Surgical Trial (ST01) reported from the UK in 1999 [4].This study addressed very interesting clinical questions for many surgical oncologists: whether D2 lymphadenectomy could contribute to improving the prognosis of advanced gastric cancer, and whether there was a risk of increasing the postoperative complications with D2 compared with D1 lymphadenectomy. A preliminary report stated that the postoperative mortality and morbidity of patients who received gastrectomy with D2 lymphadenectomy were higher than with D1 lymphadenectomy [3]. Nevertheless, D2 lymphadenectomy could not achieve survival benefits compared with D1 lymphadenectomy [4]. Another randomized trial was reported from the Netherlands at approximately the same time [5,6]. Also in this study, the mortality and morbidity of patients treated with D2 lymphadenectomy were higher than in patients with D1 lymphadenectomy. Thus, a survival benefit was not achieved, as in the MRC trial.

On the other hand, in East Asia, D2 lymphadenectomy has been considered a standard surgical procedure for advanced gastric cancer. There was no large randomized clinical trial that validated the survival benefit of D2 lymphadenectomy; a randomized trial by a single institute was the only one reported [7]. Nevertheless, extended lymphadenectomy, which included the para-aortic lymph nodes, had been performed to improve the cure rate for advanced gastric cancer in Japan. The Japan Clinical Oncology Group (JCOG) conducted a randomized controlled trial that validated the benefit of this extended lymph node dissection compared with standard D2 lymphadenectomy (JCOG9501) [8,9]. As a result, although the safety of extended lymphadenectomy was proven, the survival benefit could not be demonstrated. Many surgeons might be disappointed in these unfavorable results, which implied that the surgical potential in the treatment strategy for advanced gastric cancer is limited.

Therefore, several clinical studies of multimodality treatment, including chemotherapy and radiotherapy, were developed to improve the prognosis of advanced gastric cancer [10,11]. In the US, the INT-0116 trial demonstrated the survival benefit of adjuvant chemotherapy using 5-FU/LV after curative resection (R0) compared with surgery alone [10]. Although there were several drawbacks in this trial, such as insufficient lymph node dissection, the radiotherapy might have had a therapeutic effect that could compensate for the lack of local control obtained with lymphadenectomy. Adjuvant chemo radiotherapy is considered one of the standard treatments for advanced gastric cancer.

In the UK, the MAGIC trial was conducted in patients with curatively resectable gastric cancer, esophagogastric junction cancer, and lower esophageal cancer [12]. This trial compared surgery alone and surgery plus perioperative chemotherapy, consisting of 3 preoperative and 3 postoperative cycles of epirubicin, CDDP, and 5-FU. Since this perioperative chemotherapy achieved a survival benefit compared with surgery alone, this treatment strategy has been recognized as one of the standard treatments for resectable advanced gastric cancer. These two standard treatment strategies in the US and the UK, adjuvant chemoradiotherapy and perioperative chemotherapy, were compared directly by a large prospective randomized trial, the CRITICS trial [13]. Based on the result of this trial, the future course of the treatment strategy for advanced gastric cancer could be determined in Western countries.

In East Asia, several clinical trials on adjuvant chemotherapy after D2 lymphadenectomy have been conducted [14,15]. In Japan, the ACTC-GC trial compared surgery alone and surgery plus adjuvant S-1 chemotherapy for stage II/III gastric cancer [14]. This trial demonstrated the efficacy of the addition of S-1 due to the result of the prolongation of both overall survival and relapse-free survival. Thus, adjuvant chemotherapy with S-1 has been established as a standard treatment after curative resection for advanced gastric cancer. However, there was an issue to be resolved based on the unsatisfactory results in the subgroup analysis of patients with stage III, especially IIIB, disease. The CLASSIC trial was conducted in other East Asia countries, including South Korea, China, and Taiwan and examined the effectiveness of capecitabine plus oxaliplatin

Citation: Takahashi T, Kitagawa Y. Recent Treatment Strategies for Advanced Gastric Cancer: Future Perspectives on Multimodality Therapy. Austin J Surg. 2014;1(2): 1008.

(XELOX) as adjuvant chemotherapy [15]. Compared with the surgery-alone group, the XELOX group had improved 3-year disease-free survival, which was the primary endpoint. Stratified analysis revealed a significant difference between the two groups of stage III patients, the stage of patients with weak therapeutic effects in the ACTS-GC trial. Based on the results of these trials, a consensus about the treatment strategy for respectable advanced gastric cancer has been achieved: systemic adjuvant chemotherapy, which may decrease the risk of recurrence after local control by surgery with D2 lymphadenectomy. Regarding the efficacy of adjuvant chemo radiotherapy after D2 lymphadenectomy, the ARTIST trial examined the addition of radiation therapy to the chemotherapy of capecitabine plus CDDP in adjunctive therapy after D2 lymphadenectomy [11]. Since the hematological and non-hematological toxicities of adjuvant chemoradiotherapy were tolerable, it would be considered that its safety was high. However, there was no significant difference in the 3-year disease-free survival rate, the primary endpoint, between the adjuvant chemoradiotherapy group and the chemotherapy group, even though a stratified analysis showed that the 3-year disease-free survival rate of the adjuvant chemo radiotherapy group was higher than that of the chemotherapy group in patients with histological lymph node metastasis. The addition of radiation as adjuvant therapy might be suitable for patients with locally advanced gastric cancer with positive lymph node metastasis.

The prognosis of advanced gastric cancer has been improved gradually due to several recently established strategies. However, there is still a great need for further treatment improvements for patients with advanced gastric cancer. Therefore it is necessary for these patients to receive more potent adjuvant chemotherapy, such as a combination regimen, to prolong survival. However, it is difficult for postoperative patients to tolerate such potent adjuvant chemotherapy regimens, and compliance would be low. Therefore, neoadjuvant chemotherapy has been highlighted in the last decade [12,16]. Neoadjuvant chemotherapy has several potential advantages, including reducing the viability of micrometastasis, increasing the rate of curability, enhancing treatment compliance, and allowing evaluation of chemosensitivity. In the MAGIC trial, although the completion rate of the 3-course preoperative chemotherapy was high at 86%, only 42% of the patients completed the postoperative treatment [12]. Since the compliance with postoperative chemotherapy was low, preoperative treatment might have a greater impact on survival. These advantages of neoadjuvant chemotherapy might be demonstrated by the results of the MAGIC trial.

Resection is never the goal in the treatment of advanced gastric cancer. It should be considered that the treatment for advanced gastric cancer is long-term, including either adjuvant or neoadjuvant chemotherapy, to prolong survival. The timing of surgical intervention is the most important issue to be addressed now, namely, which is better: either resection that is done first or preoperative chemotherapy that eliminates the micro metastasis? It is necessary to treat advanced gastric cancer with the understanding that respectability and curability are not equal.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127: 2893-2917.
2. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011; 14: 113-123.
3. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet. 1996; 347: 995-999.
4. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer. 1999; 79: 1522-1530.
5. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet. 1995; 345: 745-748.
6. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K. Extended lymph-node dissection for gastric cancer. N Engl J Med. 1999; 340: 908-914.
7. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. Br J Surg. 2004; 91: 283-287.
8. Takeshi Sano, Mitsuru Sasako, Seiichiro Yamamoto, Atsushi Nashimoto, Akira Kurita, Masahiro Hiratsuka, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy—Japan Clinical Oncology Study Group Study 9501. J Clin Oncol. 2004; 22: 2767-2773.
9. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008; 359: 453-462.
10. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001; 345: 725-730.
11. Lee J, Lim do H, Kim S, Park SH, Park JO. 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. 2012; 30: 268-273.
12. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006; 355: 11-20.
13. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, Lind PA, Putter H. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer. 2011; 11: 329.
14. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011; 29: 4387-4393.
15. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012; 379: 315-321.
16. Iwasaki Y, Sasako M, Yamamoto S, Nakamura K, Sano T, Katai H, et al. Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). J Surg Oncol. 2013 107: 741-745.

Austin J Surg - Volume 1 Issue 2 - 2014
ISSN : 2381-9030 | www.austinpublishinggroup.com

Citation: Takahashi T, Kitagawa Y. Recent Treatment Strategies for Advanced Gastric Cancer: Future Perspectives on Multimodality Therapy. Austin J Surg. 2014;1(2): 1008.