Special article

Strategies for gastric cancer treatment in the twenty-first century: minimally invasive and tailored approaches integrating basic science and clinical medicine

MASAKI KITAJIMA

Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Masaki Kitajima
Department of Surgery
Keio University School of Medicine

Introduction

Since the first International Gastric Cancer Congress (IGCC) was held in Kyoto in 1995, we have seen truly remarkable progress in the diagnosis and treatment of gastric cancer as a result of the worldwide interactive

Offprint requests to: M. Kitajima
Marking the 10th anniversary of the International Gastric Cancer Congress.

cooperation and development made possible by the activities of the International Gastric Cancer Association (IGCA). It is our great honor to host the 6th IGCC in May 2005 in Yokohama, Japan on the 10th anniversary of the establishment of the Congress. This gathering of the world's experts at the congress to present their achievements will aid humankind by further advancing the knowledge of gastric cancer treatment, and is the greatest feat we can ever hope to achieve. We anticipate engaged and fruitful discussions focused on the theme of "Strategies for Gastric Cancer Treatment in the 21st Century: Minimally Invasive and Tailored Approaches Integrating Basic Science and Clinical Medicine".

Since Theodor Billroth performed the first gastrectomy in 1881, a vast number of improvements and developments have been made in the surgical management of gastric cancer. Now we are utilizing not only surgical but also multidisciplinary approaches. The twentieth century saw the establishment of standard procedures for resection, lymph node dissection, and reconstruction in gastric cancer surgery. Now, in the twenty-first century, I believe the key word for the further improvement of management of gastrointestinal (GI) cancer is "individualization" [1].

Minimally invasive and individually tailored approaches for early gastric cancer

Because of the well-established health check-up system and the widespread application of videoendoscopy in Japan, many asymptomatic cases of early gastric cancer (EGC) are detected. Endoscopic mucosal resection (EMR) is already accepted as the most minimally invasive procedure for the resection of EGC. Although several controversial issues remain, it is technically feasible to extend the indications of EMR for larger mucosal gastric cancers by novel instrumental advances enabling endoscopic submucosal dissection [2]. We

currently perform a new method using an oblique view double-channel therapeutic videoendoscope. The operator can retract the lesion with the forceps elevator to dissect the submucosal layer. This miniature endoluminal surgery procedure is generally tactilely acceptable for surgeons.

Laparoscopic surgery is an important intermediate option between EMR and open surgery for patients with EGC. The history of laparoscopic surgery for gastric cancer began with the report of laparoscopic distal gastrectomy performed successfully by Kitano in 1991, only a few years after the introduction of laparoscopic cholecystectomy [3], and enthusiasm to develop laparoscopic procedures has grown steadily. Now, skilled laparoscopic surgeons have demonstrated that complete laparoscopic gastrectomy and D2 lymphadenectomy is technically feasible even in advanced gastric cancer (AGC). Although there are a number of advantages of laparoscopic gastrectomy with regard to early-phase recovery after surgery, the significant learning curve, relatively longer operation time, complicated procedures for patients with a high body-mass index, and questions concerning cost benefit are still the subject of debate. We developed a laparoscopic wedge resection (LWR) technique using a lesion-lifting method that enables complete local resection with full thickness of the stomach wall and organ preservation by a laparoscopic approach [4]. Recent advances in EMR technology, including development of endoscopic submucosal dissection (ESD), have improved local control of mucosal gastric cancer for which laparoscopic local resection was previously indicated. Although LWR for submucosal gastric cancer is technically feasible, the limited diagnostic sensitivity of preoperative imaging with regard to the detection of micrometastasis in regional lymph nodes is a major obstacle to its wider clinical application. As a means to overcome this problem, the sentinel node (SN) concept has attracted much attention in recent years, and it is anticipated that it will become an effective diagnostic tool for identification of clinically undetectable lymph node metastasis in patients with EGC [5]. Now we must pay attention to both minimal invasiveness for early-phase recovery and achieving satisfactory late-phase function after gastric cancer surgery. For early-stage gastric cancer in which a better outcome has generally been achieved by conventional surgical approaches, individualized minimally invasive surgery should be established as the next surgical challenge of the twenty-first century. A combination of laparoscopic surgery with SN navigation surgery has the potential to achieve this goal.

Laparoscopic surgery is a relatively difficult procedure for surgeons because of the limitations of maneuverability and tactile sensation, thus the introduction of novel sophisticated technologies is necessary. To over-

come this problem, advanced engineering technology, especially robotics, has been introduced in laparoscopic surgery. Recently we have developed a combined master-slave manipulator, which is relatively simple and yet suitable for general surgery [6]. We have started using this system clinically to perform high-quality GI cancer surgery. This new device will enable more advanced laparoscopic surgery for GI cancer. While clinical trials are necessary to clarify both the safety and quality as a therapeutic modality, robotic surgery will become one of the optimal procedures in the treatment of EGC.

Integration of basic science and clinical medicine to improve the outcome of advanced gastric cancer

Curative surgery is the most common and desirable treatment for gastric cancer at present, but macroscopically curative resection of AGC does not always mean curative outcome, suggesting that surgical treatment alone does not allow control of microscopic metastasis or disseminated carcinoma cells. To achieve a satisfactory clinical outcome, detailed understanding of carcinogenesis, cancer biology, and cancer genetics/epigenetics is essential. Our own stem cell research projects seek to identify and localize gastric stem cells, establish a chronic inflammation model through carcinogenesis, and clarify critical biological behavioral aspects of cancer stem cells in the stomach.

Although adjuvant therapy for AGC after surgical resection has been investigated clinically for decades, there has been insufficient scientific evidence until recently concerning the effectiveness of adjuvant therapy in terms of survival; however, several meta-analyses have shown a beneficial outcome of adjuvant chemotherapy after surgery. A recent Western trial showed significant benefit from postoperative chemoradiotherapy, and several Japanese groups have also shown beneficial survival effects of adjuvant chemotherapy (JCOG 8801, JCOG 9206, and NSAS-GC trials), suggesting that it could become the standard treatment for gastric cancer after curative resection [7–9]. Since 1988, we have employed chemosensitivity testing (MTT assay) to select the most appropriate adjuvant chemotherapy, and we have proposed its importance in evaluating the indications of particular adjuvant cancer chemotherapies in individual AGC patients [10]. The assay categorizes stage III and IV gastric cancer patients as chemosensitive or nonsensitive, resulting in a better survival outcome in the sensitive group than in the nonsensitive group in cases without peritoneal dissemination. In AGC, chemosensitivity testing is anticipated to be a powerful tool to select effective chemotherapy regimens and avoid ineffective regimens.

Recently, novel anticancer drugs such as S-1, CPT-11, and taxanes have obtained good clinical efficacy while preserving good quality-of-life (QOL) levels. We have demonstrated the usefulness and high effectiveness of first-line chemotherapy, consisting of a S-1/low-dose CDDP combination (TSLD) and TSLD with radiation (TSLDR) for stage IV gastric cancer, obtaining both good outcome and QOL levels [11]. Preoperative TSLD yields good efficacy (52.4%) with tolerable toxicity, long median survival time (526 days), and 1- and 2-year survival rates of 64.9% and 41.7%, respectively. In addition, a clinical phase I/II study of TSLDR demonstrated a higher efficacy rate than TSLD, with toxicity similar to that of TSLD. Although it is well recognized that even highly effective chemotherapy rarely achieves histological complete response in the stomach or metastatic lymph nodes, we have reported two patients treated with chemoradiation who obtained histological complete response (Grade 3) [12].

By contrast, nonresponders to chemotherapy also show progressive disease even after intensive chemotherapy, sometimes with critical toxicity, suffering harmful effects of the chemotherapy in terms of both toxicity and medical cost. Thus, the early determination of chemosensitivity after initiation of therapy is ideal for clinical applications, and chemosensitivity tests can help determine the value of continuation or cessation of further chemotherapy. We are trying, therefore, to develop a novel chemosensitivity testing method that monitors altered gene expression of several tumor molecules in order to predict future chemotherapeutic outcome soon after initiation of chemotherapy. We are testing three molecules, GADD153, p21, and c-Jun, as candidate genes and have confirmed their usefulness in vitro and in vivo for prediction of chemotherapeutic outcome [13]. This might become a standard diagnostic or therapeutic tool in the future.

While many trials to diagnose accurately and treat appropriately based on scientific evidence are needed to obtain a consistent standard therapy against gastric cancer, curative surgical resection is the gold standard for treatment of gastric cancer now. However, we still encounter advanced or sometimes even EGC with poor outcome. Thus we urgently need to find strategies other than surgery to overcome gastric cancer. Establishment of standardization and investigation of approaches to individualization might point in different directions at this juncture, but it is essential to establish a standard therapy, including individualization aspects, which can respond to each characteristic, including tumor status and host status, to obtain the ideal therapy with good QOL and long survival, even in AGC.

Art, science, and humanity

In conclusion, I believe we have to make even greater efforts for the development and establishment of minimally invasive approaches for EGC and novel strategies for AGC. While these may be two separate goals, both are related to the concept of “individualization” as the most important key theme in the future of this field. Building upon the great achievements of our predecessors since the age of Billroth, we have to make further and greater efforts in the future. Although the technologies have been developing and changing, the basic guiding elements of the spirit of the ethos of surgery have been consistent: art, science, and humanity. Humanity is the most important motivation for our duty to contribute to the future of managing gastric cancer.

Acknowledgment The author is indebted to Prof. J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this manuscript.

References

1. Kitajima M. Grey Turner Memorial Lecture. Progress in gastrointestinal cancer management: challenges of the twenty-first century. *World J Surg* 2002;26(10):1189–94.
2. Ono H, Kondo H, Gotoda T, Shirao K, Saito D, Hosokawa K, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001;48:225–9.
3. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994;4: 146–8.
4. Ohgami M, Kumai K, Otani Y, Kubota T, Kitajima M. Laparoscopic wedge resection of the stomach for early gastric cancer using a lesion-lifting method. *Dig Surg* 1994;11:64–7.
5. Kitagawa Y, Fujii H, Mukai M, Kubota T, Ando N, Watanabe M, et al. The role of sentinel lymph nodes in gastrointestinal cancer. *Surg Clin North Am* 2000;80(6):1799–809.
6. Matsuhira N, Jinno M, Miyagawa T, Sunaoshi T, Hato T, Morikawa Y, et al. Development of a functional model for a master–slave combined manipulator for laparoscopic surgery. *Adv Robotics* 2003;17(6):523–39.
7. Yamamura Y, Nakajima T, Ohta K, Nashimoto A, Arai K, Hiratsuka M, et al. Determining prognostic factors for gastric cancer using the regression tree method. *Gastric Cancer*. 2002; 5(4):201–7.
8. Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, et al. Gastric Cancer Surgical Study Group, Japan Clinical Oncology Group. Randomized trial of adjuvant chemotherapy with mitomycin, Fluorouracil, and Cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Jpn Clin Oncol Group 9206–1. *J Clin Oncol* 2003;21(12): 2282–7.
9. Sakamoto J, Morita S, Kodera Y, Rahman M, Nakao A. Adjuvant chemotherapy for gastric cancer in Japan: global and Japanese perspectives. *Cancer Chemother Pharmacol* 2004;54(Suppl 1): S25–31.
10. Kubota T, Egawa T, Otani Y, Furukawa T, Saikawa Y, Kitajima M, et al. Cancer chemotherapy chemosensitivity testing is useful in evaluating the appropriate adjuvant cancer chemotherapy for

- stage III/IV gastric cancers without peritoneal dissemination. *Anticancer Res* 2003;23:583–8.
11. Saikawa Y, Akasaka Y, Kanai T, Otani Y, Kumai K, Kubota K, et al. Preoperative combination chemotherapy with S-1 and low dose cisplatin against highly advanced gastric cancer. *Oncol Rep* 2003;10:381–6.
 12. Saikawa Y, Kubota T, Takahashi T, Akatsu Y, Nakamura R, Yoshida M, et al. Is chemoradiation effective or harmful for stage VI gastric cancer patients? *Oncol Rep* 2005 (in press).
 13. Akatsu Y, Saikawa Y, Kuobata T, Yoshida M, Frukawa T, Otani Y, et al. Novel method of molecular-based chemosensitivity test by measuring DNA damage inducible genes for the prediction of chemotherapeutic effect. Proceedings of the 95th annual meeting of the American Association for Cancer Research, Orlando, FL, 2004.