Historical Review of Research and Treatment of Gastric Cancer in Japan: Clinical Aspect

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Introduction

Gastric cancer has been decreasing in incidence in Western countries, but it still remains a leading cause of death in the world. Recent Japanese statistics (http://homepage3.nifty.com/mickeym/simin/140toukei-sibou.html) show that mortality due to gastric cancer is the second highest among males and the highest among females. However, in the past two decades, the death rate itself has been gradually decreasing in Japan as well as in Western countries, and this change is regarded as the result of the development of diagnosis, surgical techniques, effective chemotherapeutic agents, and patient care. Figure 1 shows the chronological changes in 5-year survival rate of gastric cancer patients treated in the Cancer Institute Hospital (1946–1999) by clinical stage, which clearly demonstrates the gradual increase decade by decade in all stages, especially remarkable in moderately advanced stage II and III diseases, and also shows concurrent decrease in morbidity and mortality. These improvements in treatment results are not prominent in other countries. The historical review of gastric cancer research in Japan may give some encouragement to clinicians who still struggle with the high morbidity and mortality rate of gastric cancer.

Diagnosis of Gastric Cancer

Development in the morphological diagnosis of gastric cancer in early days originated from the invention of the X-ray fluoroscopy apparatus, which Holzknecht [1,2] applied for the diagnosis of gastric disease in 1906 (Table 1). It has become one of the routine procedures in the diagnosis of gastric cancer. Conventional fluoroscopy and direct radiography were useful to detect advanced gastric cancer by a deformity, or filling defect using barium meal but were not sufficient for detection of early-stage cancer that could be cured by surgery.

Poor treatment results drove physicians to develop an effective mass-survey system with the aim of detecting early-stage cancer. Hauser employed X-ray fluoroscopy as a

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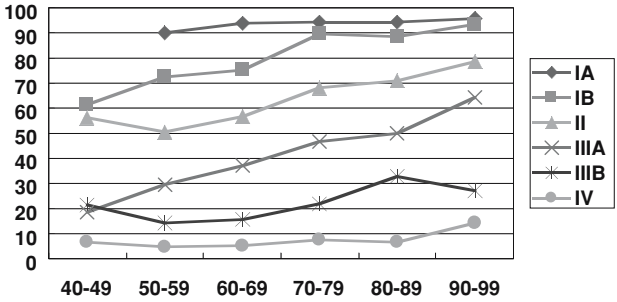

Fig. 1. Chronological changes in 5-year survival rates by clinical stage for 10 688 patients who underwent surgery at Cancer Institute Hospital from 1946 to 1998

Table 1. Historical events in diagnosis

Year	Reporter	Events
1906	Holzknecht	Gastrofluoroscopy for gastric cancer
1911	Elsner	Hard gastroscope
1929	Porges	Gastrocamera
1932	Schindler	Soft gastroscope
1934	Kirihara	Soft gastroscope in Japan
1934	Hauser	Mass surgery with gastrofluoroscopy
1944	Castro	Indirect gastrofluoroscopy
1950	Uji, Sugiura	Gastrocamera
1953	Irie	Mass surgery with indirect gastrofluoroscopy
1957	Hiroschowitz	Fiberscope
1958	Shirakabe	Double-contrast method for early cancer
1958	Ariga, Kurokawa	Systematic mass survey in regional district

tool of mass survey of this disease in 1934, and Castro invented indirect radiography of the stomach in 1944, which facilitated later development in the mass-survey system [3]. In Japan, where gastric cancer had been prevalent, Irie initiated the mass-survey system with indirect radiography in 1953 [3], and this system was later incorporated into one of the important national health policies, which owed greatly to the endeavor of Ariga [4] and Kurokawa. Fluoroscopy was further developed as a tool of early detection of gastric cancer by incorporation of the double-contrast method by Shirakabe [5] in 1958. He found a mixture of barium meal and air in the stomach gives a clear contrast shadow of early cancer in the gastric mucosa. The curative resection rate was relatively low until this novel technique had been incorporated into clinical routines and the mass-survey system in Japan.

Endoscopy is another important tool for finding gastric cancer. Elsner [6] invented a metal gastroscopy in 1911, followed by a soft gastroscopy by Schinder in 1932, and in Japan, improved by Kirihara in 1934. The gastrocamera was invented by Uji [7] and Sugiura in 1950, which allowed color photography of the gastric lumen. The gastrocamera attracted the enthusiastic attention of physicians and drove them to detect mucosal, or early-stage, cancer. Hiroschowitz [8] demonstrated the principle of light transmission through glass fibers in 1957, and Japanese researchers and industries

succeeded in the practical use of fiberscopy. Thus, the 1950s was a memorable era of the beginning of the early detection of gastric cancer in Japan. Tasaka [9] reported the nation-wide registry of early gastric cancer in 1962, and the incidence of early gastric cancer was 6.2% of resected cases. Recent statistics show that early-stage cancer is seen in more than half of the resected specimens among major cancer centers in Japan, which owes greatly to the recent development of diagnostic modalities.

Pathology and Biology

Pathology and biology are important for clinicians, not only to confirm the diagnosis but also to make an individual treatment plan for a given patient. Borrmann [10] reported macroscopic classification of tumor types in 1926, and his study has given most important information to clinicians as to how to proceed with treatment plans. He classified gastric cancer into four types according to the gross appearance of tumors, namely (1) localized, protruded, (2) localized, ulcerated, (3) infiltrating, ulcerated, and (4) diffuse, infiltrating types. This classification is the prototype of the later Japanese classification of macroscopic tumor types, and later studies reported a close correlation between the types of tumors and pattern of metastasis. In contrast to the macroscopic classification of advanced gastric cancer by Borrmann, that of early gastric cancer was defined in 1962 in Japan based on the proposal by Murakami et al. [11]. They defined three basic types (I, II, III) and four subbasic types (IIa, IIb, IIc, IIc + III) according to the macroscopic appearance of early gastric cancer.

Lymph node metastasis is the most frequent pattern of metastasis of gastric cancer. Inoue [12] reported close observation of the regional lymph node system in the upper abdomen of cadavers, and completed the map of lymphatic nodes and channels around the stomach in 1936. This map is also the prototype of lymph node station in the Japanese Classification of Gastric Carcinoma in 1961, and provided the basis for the theoretical concept of radical lymphadenectomy in Japan.

Associated with the diagnostic development of gastric cancer, relatively early-stage cancer increased in number among the resected cases. Although Borrmann already described incidental mucosa cancer in his text, Ayabe [13] reported the first two cases of mucosal cancer that were diagnosed preoperatively in 1949, and triggered enthusiasm for early diagnosis of gastric cancer in the 1950s. He introduced in his text that Bertrand and Konjetzny had separately reported a case of early gastric cancer with regional node metastasis, despite no infiltrative changes of atypical cells in the submucosal layer. He insisted that atypical cells in the mucosal epithelium that had hyperstained, various-sized nuclei, and the disappearance of normal glandular structures even with no metastasis, were enough to suggest malignancy. His idea is consistent with those of Bertrand, Konjetzny, and current Japanese pathologists. Western pathologists were reluctant to admit it as malignant when there were abnormal changes in epithelial cells without invasion into submucosal layer or lymph nodes, and instead defined such changes as dysplasia [14,15]. Thus, such discrepancy in the diagnosis of cancer or dysplasia in the mucosa between Japan and Western countries has continued for more than 50 years. Referring to the reports by Bertrand and Konjetzney might give some hints to solve this discrepancy between Japan and Western countries.

Although Hauser discussed the pathogenesis of gastric cancer arising from the scar of chronic gastric ulcer in 1883, in Japan, Takizawa, Ohta, Murakami, and many other

researchers devoted their efforts to such issues as histological classification, macroscopic classification of early cancer, pathogenesis, morphological aspects of early cancer, malignant cycles of early cancer, and the process of developing from early to advanced cancer [16].

The current of early cancer detection resulted in founding the Japan Anti-Cancer Association (chaired by Shioda, Sugimura) in 1958, the Japanese Research Society for Gastric Cancer Study (chaired by Kajitanl, Niski) in 1962, and several research societies for early gastric cancer or mass-screening in 1962. Recently *Helicobacter pylori* has attracted the attention of etiologists and physicians because of its potential to cause gastric cancer, but it is still controversial as to its definite evidence for carcinogenesis [17].

Surgery

Dawn of Gastric Cancer Treatment [1,18,19]

No one is likely to disagree with the idea that surgery still remains the first choice of treatment modalities for gastric cancer, even at the beginning of the 21st century. The first gastrectomy was attempted by Pean in 1879, and successfully followed by Billroth in 1881 (Table 2). Mikulicz also succeeded in making the precise diagnosis of gastric cancer with gastroscopy and performed successful distal gastrectomy in 1883. Schlatter succeeded in total gastrectomy in 1897. In the same year, in Japan, Kondo [20] reported his first success in distal gastrectomy, followed by Itoh who succeeded in the first case of total gastrectomy in 1906. He placed a proximal cut line in the cardia, and true total gastrectomy was owing to Miyake in 1918, who placed the proximal cut line in the esophagus. Successful cardiectomy was reported by Mikulicz in 1896. Miyake [21] reported in 1914 his 10 years experience, in which resectability was 42.9% (167/389), postoperative mortality was 14.6%, and 3-year survival rate was 19.2% (19/39). Mutou [22] compared the mortality rate between Japan and Western countries in 1965: (1) decreased tendency of mortality rate in Japan and Western countries was observed associated with decades; (2) Japanese mortality rate ranged from 13.8% to 21.1% before World War II and fell below 10% after the war, whereas, in Western countries it ranged from 11.0% to 38.8% in the former period and from 6.0% to 18.6% in the latter period; and (3) these results suggested that Japanese surgery was superior to that in Western countries in terms of number of operated cases and treatment results.

Standard Gastrectomy

From the point of view of radicality, eradication of malignant lesions as complete as possible might allow us to expect longer survival of patients with gastric cancer. Radical gastrectomy aims to eradicate both the primary lesion and lymphatic spread regional to the stomach. Based on meticulous examination of the surgical stump of resected specimens, Tomoda [23] advocated wide indication of total gastrectomy in 1950. This idea coincides with total gastrectomy *de principe* in the later period [24]. As is discussed in the next paragraph, systematic radical lymph node dissection was advocated by Kuru [25], Kajitani [26], and Jinnai [27]. To avoid the suture insufficiency of gastroduodenostomy, Nakayama fixed the posterior wall of the remnant stomach

Table 2. Historical events in surgery

Year	Reporter	Events
1879	Pean	First attempt of distal gastrectomy
1881	Billroth	First success in distal gastrectomy
1883	Mikulicz	Diagnosis with gastroscopy and successful gastrectomy
1896	Mikulicz	First success in cardiectomy
1897	Schlatter	First success in total gastrectomy
1897	Kondo	First success in distal gastrectomy in Japan
1908	Voelcker	Success in cardiectomy
1918	Miyake	First success in total gastrectomy in Japan
1940	Seo	Jejunal interposition after total gastrectomy
1940	Morton	Total gastrectomy *de principe*
1942	Kajitani	Wide dissection of lymph nodes
1947	Brunshwig	Pancreaticoduodenectomy (PD) for distal gastric cancer involving pancreas head
1949	Yoshioka, Kajitani	PD for distal gastric cancer in Japan
1950	Tomoda	Total gastrectomy de principe
1950	Weinberg	Vital staining of lymph nodes during surgery
1952	Kajitani	Extended radical dissection
1953	Appleby	Appleby surgery
1955	Kajitani, Yamada	Vital lymph node staining with sky blue
1961	Jinnai	Extended radical gastrectomy
1969	Wada	Introduction of Appleby surgery into Japan
1969	Hauser	Lymph node scanning with isotope
1980	Takekoshi	Endoscopic mucosal resection (EMR) with endoscopic double snare polypectomy (EDSP)
	Hirao	EMR with endoscopic resection with hypertonic saline-epinephrine (ERHSE)
1984	Tada	EMR with strip biopsy
1984	Kajitani, Ohashi	Left upper abdominal evisceration
1984	Aiko	Lymph node scanning with isotope in Japan
1987	Takahashi	Lymph node staining with active carbon particles
1992	Goh	Laparoscopic Billroth II gastrectomy (ulcer)
1994	Kitano Uyama	Laparotomy-assisted gastrectomy (LAG) with abdominal wall elevating method
1999	Bonenkamp	Randomized controlled trial (RCT) of D1 vs. D2 dissection in radical gastrectomy

to the pancreas head [28]. Before this report, most surgeons preferred Billroth II type anastomosis after Miyagi [29], or the Shioda method because of its safety. General consensuses on safe and radical gastrectomy were reflected in the statement of radical gastrectomy in the General Rules for the Gastric Cancer Study issued by the Japanese Research Society for Gastric Cancer Study in 1961 in Japan. Instead of total gastrectomy *de principe*, the resection line has been recommended to be placed properly according to the tumor type, namely, 3 cm in localized cancer, and 5 cm in diffused cancer apart from the tumor margin. There is no comparative study related to total versus subtotal gastrectomy in our country, but two randomized controlled trials (RCTs) [30,31] are available in Europe. There were no differences in stump recurrence at resection margin and survival benefit between the two methods.

Since 1961, D2 dissection (eradication of all nodes in N1–N2 stations) has been the Japanese standard procedure of radical gastrectomy for locally advanced gastric cancer. The General Rules define the degree of lymph node dissection as R0–R3 (later D0–D3) according to the anatomic stations of lymph nodes. Radicality of surgery is defined as curative (D-number ≧ N-number with M0) or noncurative (D-number < N-number, or M1) in relation to the extent of surgery and spread of disease based on the meticulous postoperative dissection of the resected specimen. All documents of operative findings are described and recorded in relation to the extent of disease (T, N, and M categories) and extent of surgery (type of surgery and radicality) based on the General Rules. It has provided the common basis of documentation to facilitate the Nationwide Registry of Gastric Cancer since 1969 [32].

Lymph Node Dissection

As stated previously, metastasis to the lymph nodes is the most frequent type of cancer spread, which could only be controlled by surgeons with meticulous lymphadenectomy. Kajitani [26] stressed the importance of wide dissection of regional lymph nodes to eradicate lymphatic spread in 1944, and Jinnai [27] also advocated a systematic radical gastrectomy in 1961. Use of intraoperative vital dye staining of lymph nodes with pontamine sky blue was reported by Weinberg and Greaney [33] in 1950 to facilitate the identification of regional lymph nodes to perform radical dissection. Intraoperative or preoperative lymph node staining was studied by many investigators with sky blue [34] or iodine contrast medium [35], radioisotopes [35–37], or activated carbon particles [38]. Approach to the regional lymphatic channels with radioisotopes paved the way to later development of sentinel node navigation surgery, although its significance is still controversial in gastric cancer surgery.

D2 dissection is supported in Japan and in some Asian and Western countries [39–42] as a standard surgery for locally advanced gastric cancer. D2 dissection has been advocated from the theoretical and anatomic point of view to minimize the residual tumor after surgery. There is no critical evaluation on the comparison between D1 and D2 in Japan. However, in Europe, a large-scale phase III trial was performed in Holland, reporting that higher incidences of postoperative morbidity and mortality were observed in D2 than in D1 [43], and in 1999, later results of two prospective randomized controlled trials (RCT) in Europe [44,45] reported that no survival advantage of D2 was observed over D1. These reports seemed to be a challenge to D2 supporters and led to heated arguments among surgeons [46–48]. Up to date, the results seem to be accepted as true in most Western countries, but are subject to criticism by D2 supporters because very high postoperative morbidity and mortality are thought to have spoiled the survival benefit of radical dissection, mainly due to low hospital and surgeon volumes. The benefit of D2 surgery should be established by further RCT to determine whether to adopt it as a standard surgery.

Extended Surgery

As part of the combined multiorgan resection of involved organs that are adjacent to the stomach, pancreatoduodenectomy (PD) for distal gastric cancer involving the head of the pancreas was reported by Brunshwig in 1947 [19]. In Japan, Yoshioka [49] and Kajitani [50] also paved the way to extended radical surgery with PD in 1949.

Appleby [51], in 1953, advocated an approach to the celiac axis for the radical eradication of the whole stomach, distal pancreas, spleen, and regional lymph nodes. This procedure was introduced to Japan by Wada [52] in 1969. Extended lymph node dissection was advocated by Jinnai [27] in 1961. Prophylactic combined resection, including pancreatosplenectomy or splenectomy, has been justified as the standard procedure to perform complete D2 dissection of lymph nodes along the lienal artery and those at the splenic hilum in upper or middle gastric cancer in Japan. However, these prophylactic combined resections involving the pancreas are subject to argument in Western countries because of the high incidence of postoperative complications. Dissection of lymph nodes along the abdominal aorta, which was initiated in the Cancer Institute Hospital in the 1950s, attracted the attention of surgeons to these terminal nodes in 1976 by yielding long-term survivors who had nodal involvement in the terminal stations [53]. Indications for paraaortic nodes were discussed positively [54–56] and negatively [57]. Left upper abdominal evisceration (LUAE) was proposed by Kajitani for the eradication of proximal advanced gastric cancer in 1984 [58]. LUAE includes total gastrectomy, pancreatosplenectomy, transverse colectomy, and sometimes left hepatectomy if necessary. These methods of extended radical gastrectomy have been proposed from the theoretical and anatomic points of view, and somewhat improved treatment results of moderately advanced gastric cancer, namely, stage II and III disease [59]. However, the survival benefit is not yet confirmed by prospective RCTs.

Less-Invasive Surgery

In contrast to extended gastrectomy, modified minimized gastrectomy has attracted the attention of surgeons in accordance with the increased number of occurrences of relatively early-stage cancer. Modified gastrectomy includes reduction of the resected area, reduced extent of lymphadenectomy (D1 or less), and some function-preserving procedures such as pylorus ring or vagal nerve preservation [60]. Mucosal cancer supposedly without lymphatic spread is safely subjected to endoscopic mucosal resection (EMR) in Japan since 1980 [61–64].

Endoscopic intervention later developed into the laparoscopic approach to gastrectomy. In 1992, Goh et al. [65] reported success in laparoscopic Billroth II gastrectomy for gastric ulcer, and Kitano et al. [66] and Uyama et al. [67] succeeded in laparoscopic gastrectomy for early cancer in 1994. These minimal invasive approaches clearly have contributed to improvements in the postoperative quality of life of treated patients, but still remained to be evaluated in terms of radicality and technical skill.

Common Podium for Research and Practice

Associated with developments in treatment modality, clinicians have had a variety of treatment options according to disease extent, and some confusion was raised concerning the proper indication. The Japanese Gastric Cancer Association (JGCA) issued gastric cancer treatment guidelines for doctors [60] and patients [68] in 2001 to provide a standard indication to the complexity of various disease extents. The Japanese Classification of Gastric Carcinoma [69] and Treatment Guidelines now consist of two columns that provide a common podium for research and practice of gastric cancer.

Chemotherapy

Short History of Chemotherapy for Advanced Gastric Cancer in Japan [70,71]

Modern anticancer chemotherapy is well known to have its origin from a chemical weapon in World War II, nitrogen mustard. One of the various derivatives, nitromin, developed by Ishidate et al. [72], was incorporated into clinical practice in the early 1950s in our country. A rush of clinical reports appeared in medical journals on its marginal anticancer effect associated with serious side effects. Nitromin was succeeded in the late 1950s by mitomycin C (MMC) and 5-fluorouracil (5-FU), a stem combination regimen in later studies for advanced gastric cancer. Tegafur and adriamycin (ADM) were introduced to clinical practice in the late 1960s, and used as a single agent or a part of combination regimens for advanced gastric cancer. Their response rates (RR) were around or less than 20% with minimum survival benefit. FAM therapy [73], a combination of 5-FU, ADM, and MMC, was widely used as a standard regimen in Western countries, and primarily produced a 50% RR, although such high response was not proved in the following trials (Table 3).

Incorporation of cisplatin (CDDP) to clinical trials in the late 1970s was an epochmaking event in terms of its contribution to improving RR of CDDP-containing regimens. Recent effective regimens include a combination of 5-FU and CDDP, which is followed by S-1, taxanes, and CPT-11 in current chemotherapy. Phase I and II studies of S-1-based regimens [74–76], or a combination of taxanes and CDDP [77], or CPT-11 and CDDP [78,79] showed RR higher than 50% with potential survival benefit, although phase III trials do not yet include the standard chemotherapy to date.

Oral Chemotherapy

Principles of traditional Western chemotherapy had been based on the total cell kill theory in the treatment of leukemia [80], and systemic dose-intensive regimens have been employed until recently. Therefore, Western oncologists did not favor the oral administration of anticancer drugs.

However, the efficacy of oral chemotherapy has been established in breast [81] and lung cancer [82], but not in gastrointestinal (GI) cancer [83–85], in Western countries. Negative results of previous trials of GI tract cancers in Western countries could be attributed to the use of active-type drugs. In contrast, oral administration of masked compounds has been a popular and characteristic drug delivery route in Japan. This delivery route is reported to have an advantage of keeping a constant drug concentration in the peripheral blood for a relatively long time because of gradual conversion from masked to active type in the liver. It is also convenient for treating patients at home. Oral tegafur, 5-FU, 5′-DFUR (doxifluridine), and HCFU (carmofur) were used in Japan in the 1980s, and UFT (tegafur, uracil) and S-1 (TS-1) were applied in the 1990s to this delivery route. Reviewing recent literature shows that beneficial evidence of oral chemotherapy has been accumulated not only in our country but also in Western countries. One RCT showed that a combination of UFT and leucovorin (both oral) showed a comparable effect with less toxicity than intravenous 5-FU and leucovorin (LV) in colorectal cancer [86,87]. A comparative UFT/LV study between Japan and the United

Table 3. Historical events in cancer chemotherapy

Year	Reporter	Event
1952	Tasaka, Ohtsuki, Katsunuma	Chemotherapy with nitromin
1956	Yamamoto	Chemosensitivity test with CAP (cylinder agar plate method)
1957	Ishibashi Nishioka	Sensitivity test with I.N.K. (Institute for Infectious Diseases, National Institute for Health, Kimoto Clinic) method
1957	Heidelberger	5-Fluorouracil
1959	Tasaki, Taguchi, Tasaka, Kimura	Chemotherapy for gastric cancer with mitomycin C (MMC)
1962	Moore, Longmire	Adjuvant chemotherapy with Thio-TEPA Multicenter randomized controlled study
1962	Shiba	Adjuvant chemotherapy with MMC
1962	Inokuchi	Intraceliac artery chemotherapy
1964	Skipper	Total cell kill theory
1964	Watkins	Continuous intraarterial (ia) chemotherapy pump
1964	Kondo	Succinic dehydrogenase inhibition (SDI) test
1967	Karnofsky	Performance status and outcome
1967	Yamagata	Chemotherapy response criteria by Japanese Society for Clinical Oncology
1972	Folkman	Tumor dormancy concept
1976	Ohsawa	Introduction of in vivo chemosensitivity test with nude mouse
1979	WHO	Chemotherapy Response Criteria
1982	Miura	Introduction of infusaid (implantable continuous infusion pump)
1993, 1994	Hermans	Meta-analysis of adjuvant chemotherapy
1995	Holmgren	Angiogenesis suppression
	Takahashi	Long NC for new endpoint of chemotherapy, and tumor dormancy therapy
1998	Sakata	49% response rate (RR) with S-1 alone
2000	Therasse	RECIST
2001	Macdonald	Survival benefit with adjuvant chemoradiotherapy

States showed similar effects and mild toxicities in advanced colorectal cancer [88]. A combination of VP-16, UFT, and leucovorin was also proved to be effective in advanced gastric cancer [89]. 5′-DFUR–based chemotherapy was also active in advanced gastric cancer [90,91]. S-1, as a single agent, was proved to have an outstanding RR, up to 50%, with marginal survival benefit [74,92], and S-1-based combination chemotherapy seems to be useful regarding both safety and higher local response [75,76,93]. These results seems to crush persistent adherence to i.v. chemotherapy in Western countries [94], and oral chemotherapy should properly be evaluated to be one of the useful delivery routes in GI tract cancers.

Regional Chemotherapy

Chemotherapy outcome may partly depend on the local concentration of drugs at the tumor site. To increase drug concentration, regional chemotherapy has been

attempted in various delivery routes such as intraarterial or intraabdominal. One-shot intraarterial (ia) chemotherapy was used in the early days with the introduction of a catheter into the artery. Inokuchi et al. reported a method of ia chemotherapy into the celiac artery with an artificial artery and plastic catheter [95]. Invention of portable, and later implantable, infusion pumps [96–98] and implantable portal devices facilitated continuous ia chemotherapy. Good local response and some survival benefit were reported by many clinicians [99–101], but the survival benefit of ia chemotherapy is not established compared with systemic chemotherapy. Survival benefit would be obtained by curative resection after achieving tumor reduction with regional chemotherapy. Nakajima et al. [102] reported long-term survivors, more than 5 years, who had extensive paraaortic lymph node metastasis treated with systemic and ia chemotherapy followed by radical surgery.

Reevaluation of Endpoints and Evaluation Criteria in Chemotherapy

Response rate (RR) has been adopted as the primary endpoint in almost all cancer clinical trials. However, it should essentially be a surrogate endpoint for survival benefit. Survival benefit is usually evaluated by median survival time (MST), survival rate at a certain time, or median time to progression (TTP). Recent trials often employ both RR and MST for their endpoints. RR sometimes correlates with survival time, but does not correlate with other time measures. It is an important issue to solve the conflict in evaluation when there is a discrepancy between local response and survival endpoints. 5′-DFUR is reported to yield a low, not encouraging, RR with a very long stable state so long as the drug is administered [103]. If RR is employed as the only endpoint, this kind of drug might not be evaluated as being effective. Takahashi and Nishioka [104] employed the concept of tumor dormancy to make a reasonable explanation of these observations, and recommended median TTP as an endpoint superior to RR in this case. TTP may be better than MST because the former endpoint could eliminate the effect of secondary survival benefit, which might be actually attributed to second- or third-line chemotherapy with recent new drugs. Quality of life (QOL) and cost–benefit efficiency may serve as a complimentary endpoint when survival benefit is equal in a comparative study. As mentioned previously, comparative study of oral UFT/leucovorin and i.v. 5-FU/leucovorin is a good example of this endpoint. There are several QOL evaluation criteria available in Japan and in Europe.

Common evaluation criteria for treatment response are mandatory to make a fair evaluation of effect and to compare the results from different groups. For this purpose, WHO issued common response criteria of chemotherapy in 1979, followed by the Japanese Society of Clinical Oncology [105] in 1986. Recent RECIST criteria [106] are widely accepted for available response evaluation. NCI-CTC [107] is also commonly used in many recent trials for evaluation of toxicity. Japanese clinical trials employ JSCO or JGCA response criteria combined with these for gastric cancer chemotherapy.

Adjuvant and Neoadjuvant Chemotherapy

Prophylactic use of anticancer drugs after curative gastrectomy aims at suppressing cancer relapse from minimum residual foci after curative surgery. Clinical trial of

adjuvant chemotherapy for gastric cancer in Japan was initiated in the late 1950s. According to reviews [108–110] on adjuvant chemotherapy trials in Japan, two groups, namely the National Hospital Group (chaired by Dr. Y. Koyama) and University Hospital Group (Dr. H. Imanaga), took leadership in conducting multicenter trials in phase III type with MMC alone, or MMC and 5-FU-based combination chemotherapy such as MFC (combination of MMC, 5-FU, and cytosine arabinoside) [111–113]. The Japanese Research Foundation for Multi-disciplinary Therapy (formerly chaired by Inokuchi, succeeded by Saji) carried out a series of clinical trials of nonspecific immunotherapy with PSK (Krestine: a polysaccaride), or OK-432 in the late 1970s [114,115], and also oral chemotherapy with tegafur was incorporated into clinical trials in the late 1970s [116–120]. The Japan Clinical Oncology Group (JCOG), supported by the Ministry of Welfare and Labor, is also active in clinical trials in this field [119,121]. These studies suggested no overall survival benefit, but some marginal benefit in certain subsets, namely moderately advanced stage II or III disease. Meta-analysis in Western countries and ours [122–127] revealed significant survival benefit from adjuvant chemotherapy in gastric cancer, and further studies are warranted for yielding solid evidence for survival benefit by single (namely not combined) trial. In response to this need, a large-scale adjuvant chemotherapy trial is now comparing curative gastrectomy followed by adjuvant S-1 with surgery alone (ACTS-GC trial).

Encouraged by good response to recent chemotherapy for advanced cancer, neoadjuvant chemotherapy has become an alternate approach for locally advanced gastric cancer. The concept of neoadjuvant chemotherapy was introduced by Frei et al. [128], who claimed that preoperative chemotherapy could minimize the viability of residual microfoci left behind after surgery. However, in Japan, neoadjuvant chemotherapy has been used in inoperable advanced gastric cancer, with the aim of downstaging the disease enough to be operable. Table 4 shows a series of novel neoadjuvant chemotherapy trials in our country and abroad, which sometimes yielded more than 50% RR and long-term survivors. Most Japanese neoadjuvant chemotherapies include a combination of 5-FU or its derivatives and CDDP as an essential part of the regimens [102,129,130]. Protracted continuous infusion of 5-FU associated with low-dose CDDP is a favorite regimen for neoadjuvant therapy among surgical oncologists [131–134] because of its relatively high response rate with mild toxicities, although

Table 4. Neoadjuvant chemo (radio) therapy with excellent results

Year	Reporter	Event
1993	Yonemura	Good local response (66%) and survival benefit (MST 17 months) in stage IV patients with PMUE
1996	Kondo	Low-dose cisplaton (CDDP) + protracted 5-fluorouracil (5-FU) produced good local response (55%) and increased resectability (71%)
1996	Suga	UFT + CDDP yielded good local response in scirrhous cancer
1997	Nakajima	FLEP yielded good local response (50%) and long survivors in unresectable cancer (5-year survival rate, 17.7%)
2001	Lowy	Continuous 5-FU and pre- and intraoperative radiotherapy produced good local response (RR, 74%)

MST, median survival time; PMUE, CDDP + MMC + etoposide + UFT; FLEP, 5-FU + leucovorin + etposide + CDDP; RR, response rate

the late survival outcome is not yet available in most trials. Comparative study is necessary between the standard and low-dose regimen of FP therapy.

It is difficult to carry out phase III trials of neoadjuvant chemotherapy in inoperable disease to determine survival benefit, and no trials are available in our country. However, some trials were done abroad in operable disease. These trials showed that neoadjuvant chemotherapy failed to suggest either survival benefit [135] or improvement in curability [136]. However, this approach is mandatory in Japan to clarify the survival benefit of neoadjuvant chemotherapy.

Chemosensitivity Test

As an in vitro chemosensitivity test for gastric cancer in Japan, CAP (cylinder agar plate) method [137] and INK method (Institute for Infectious Diseases, National Institute for Health, and Kimoto Clinic [138]) were used in early days. Ishibashi et al. [139] reported with the INK method that 33% (6/18) of gastric cancers responded to nitromin, 40% (8/26) to sarkomycin, and 29% (5/17) to TESPA. In 1964, Kondo et al. [140] reported with the succinic dehydrogenase inhibition (SDI) test that the response rate was 62% to nitromin, 24% to mitomycin C, and 34% to toyomycin. Ohsawa [141] introduced to Japan the in vivo sensitivity test with xenograft transplanted in the nude mouse in 1975. Since then, various in vitro and in vivo sensitivity tests have been developed in Japan. According to Tanigawa [142], the most popular test currently is CD-DST (collagen gel droplet embedded drug sensitivity test), followed by the MTT assay, HDRA (histoculture drug response assay), and SDI test. These sensitivity tests seem to produce a favorable outcome in clinical trials [143], but the clinical significance still remains to be elucidated.

Summary

The history of basic and clinical research in gastric cancer originated from the 19th century in Europe, but surprisingly rapid response to this flow abroad occurred in Japan in every aspect of research and treatment of this disease. Researchers in early days devoted their best efforts to conquer the most frequent cancer in Japan. Diagnosis of gastric cancer has been highly elaborated with the aid of the double-contrast method of X-ray fluoroscopy and meticulous endoscopic apparatus, which facilitated both minimum and extended surgery according to the extent of disease. Effective anticancer drugs are available now, some of which were developed originally in our country. Daily use of gene diagnosis and treatment could be expected in the near future. Now we can enjoy a high level of treatment results in the fields of surgery and chemotherapy and should try to establish a global standard of diagnosis and treatment of gastric cancer. International corroboration is mandatory to achieve these goals, and we could expect the International and Japanese Gastric Cancer Associations and the WHO Collaborating Center for Primary Prevention, Diagnosis and Treatment of Gastric Cancer (chaired by Suemasu, Maruyama, Sasako) will take a leading role in this field. Gastric cancer still remains one of the prevailing cancers in our country, and our next goal should be based in prophylaxis to reduce the incidence of gastric cancer.

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