

Surgical Treatment of Gastric Cancer in Japan, Trend from Standardization to Individualization

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Rezumat

Tratamentul chirurgical al cancerului gastric în Japonia, tendința de la standardizare către individualizare

Japonia prezintă un număr enorm de cazuri de cancer gastric și a dezvoltat diverse tratamente chirurgicale pentru această patologie. Scopul acestei lucrări este de a prezenta strategiile noastre în tratamentul cancerului gastric. Asociația Japoneză pentru Cancer Gastric a fost fondată în 1962. Țintele sale majore sunt reprezentate de promovarea cercetării clinice și fundamentale și punerea la curent a populației cu informațiile și tehnologiile de ultimă oră. În aceste scopuri, Asociația a organizat întruniri științifice anuale, a creat împreună cu spitalele membre un registru național, și a publicat Clasificarea Japoneză a Cancerului Gastric (1) și Ghidul de Tratament în Cancerul Gastric (2). Registrul național a raportat că proporția de cancere gastrice în Stadiul I a fost de 22.5% între 1963-66, crescând la 59.3% în 2008 (3,4,5). 11 261 de pacienți cu rezecție gastrică au fost luați în evidență de către 187 de spitale în 2008. 63 de pacienți au decedat în primele 30 de zile post-operatorii, iar rata mortalității directe a fost de 0.55%. Rata de supraviețuire la 5 ani (5YSR) a fost de 37.5% pentru cazurile de rezecții gastrice în perioada 1963-66, care a crescut la 70.1% în 2008. 5YSR a crescut de la 55.1% la 74.1% pentru Stadiul II și de la 39.1% la 48.8% pentru Stadiul III în aceeași perioadă. În conformitate cu creșterea remarcabilă a numărului

de cancere în stadii incipiente, principiile terapeutice chirurgicale s-au modificat de la „intenție de radicalitate prin chirurgie extensivă și standardizată” la „abordare chirurgicală individualizată și rezonabilă, axată pe siguranță și calitate a vieții”. Această tendință a dat naștere unei palete variate de tratamente chirurgicale, și anume: 1) operații minim invazive, 2) operații de preservare a funcționalității, 3) extensie optimă a limfadenectomiei și 4) operații agresive, dar sigure. Scopul acestei lucrări este de a explica aceste proceduri, intențiile, indicațiile și rezultatele tratamentelor.

Cuvinte cheie: cancer gastric, tratament chirurgical, experiența japoneză

Abstract

Japan has a huge number of patients with gastric cancer and has developed various surgical treatments for this disease. This paper intends to introduce our strategies against gastric cancer. The Japanese Gastric Cancer Association was established in 1962. Its major purposes are promotion of basic and clinical researches and popularization of the latest knowledge and technologies. For the purposes, the association organized the annual scientific meeting and the nationwide registry by member hospitals, and published the Japanese Classification of Gastric Cancer (1) and the Treatment Guide Line (2). The nationwide registry reported that proportion of Stage-I cancer was 22.5% in 1963-66, which increased to 59.3% in 2008 (3,4,5). 11,261 patients with gastric resection were registered by 187 hospitals in 2008. 63 patients were died within 30 postoperative days and the direct death rate was 0.55%. 5 year survival rate

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(5YSR) was 37.5% for resected cases in 1963-66, which was improved to 70.1% in 2008. 5YSR was improved from 55.1% to 74.1% for Stage-II, and from 39.1% to 48.8% for Stage-III in the period. According to remarkable increase of early stage cancer, principle of surgical treatments was shifted from “extended and standardized surgery for radicality” to “reasonable and individual surgery considering safety and quality of life”. This trend produced a large variation in surgical treatments; namely 1) minimally invasive surgeries, 2) function preserving surgeries, 3) optimal extent of lymph node dissection, and 4) aggressive but safe surgeries. Intention of this paper is to explain these procedures, the intentions, the indications, and the treatment results.

Key words: gastric cancer, Surgical treatment, Japanese experiences

History of Japanese medicine and gastric cancer surgery

Teacher of Japanese medicine was China. Culture innovation from China to Japan started in AD 600 crossing the East China Sea. Chinese medicine based on its original and unique philosophy, and used medical herbs, cauterization, acupuncture, acupressure, and dietary therapy. Majority of Japanese doctors were belonging to the group of Chinese medicine until the Meiji revolution in 1868. European culture and Christian religion were firstly introduced to Japan by Portuguese trading ship in 1549, and they gave us a great shock. Japanese governor was very much afraid of the invasion by European countries and refused completely the connection with foreign countries except the Netherlands and China in 1633. The Dutch trading agency built their own hospital in Nagasaki city and a small group of Japanese doctors studied European medicine there in the Isolation Period. In 1868, Japan opened the nation and introduced actively Western culture, namely the Meiji revolution. We studied modern medicine mainly from Germany, and we gradually expanded the field all over the world (Fig. 1).

Progress of gastric cancer surgery in the world and in Japan is shown in the Fig. 2. The first successful gastric resection was done by Th. Billroth in 1881. In this period, many Japanese surgeons were studying in Germany, and they introduced the latest surgical technologies. In 1897, 16 years after the Billroth's success, the first gastric cancer resection was done by J. Kondo in Japan. C. Schlatter firstly succeeded total gastrectomy in 1887, and O. Kitazawa followed it in 1907, 20 years later. We are proud of the good treatment results in Japan in this period. 3 years survival rate (3YSR) was 19% and mortality rate was 28% in 1910. Furthermore, 3YSR was improved to 39% in 1916. Lymph node dissection is one of the most effective treatments for gastric cancer. T. Kajitani

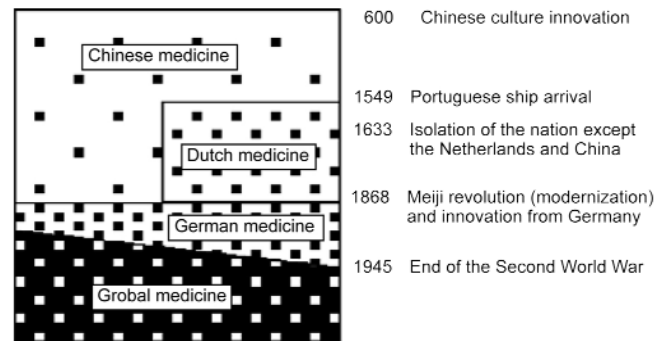


Figure 1. History of Japanese medicine

in the West	in Japan
1881 Distal gastrectomy (Th. Billroth)	1897 Distal gastrectomy (J. Kondo)
1887 Total gastrectomy (C. Schlatter)	1907 Total gastrectomy (O. Kitazawa)
1908 Roux-en-Y (P.P.E. Roux)	1910 3ysr 19%, mortality 28% (H. Miyake)
	1916 3ysr 39% (J. Kondo)
1949 Extended resection 5ysr 27% (McNeer)	1942 Systematic LN dissection (T. Kajitani)

ysr : year survival rate

Figure 2. History of gastric cancer surgery

and gastric cancer study group developed the original systematic lymph node dissection technique, so called “D2 lymphadenectomy” until 1942. After the popularization of the D2 gastrectomy, the survival rate was remarkably elevated in Japan (6).

A large number of gastric cancer patients in Japan and our control strategy

It is well known that Japanese mortality rate of gastric cancer was the highest in the world. Control of this disease was one of the most important social demand in our country. In such situation, the Japanese Research Society for Gastric Cancer was established by leaders of the basic and clinical researchers in 1962. The Society promoted progress of diagnostic and treatment methods, standardized and distributed the effective technologies. The Society was reorganized into the Japanese Gastric Cancer Association in 1997, but the activities has been continued by the new Association. Japanese Government also started the control plans; namely foundation of the National Cancer Center in Tokyo (1962), establishment of the mass screening system, budget for the research, and the social education.

Progress of diagnostic methods

Figure 3 shows progress of diagnostic methods for gastric cancer. Japan developed most of the following diagnostic methods. For the barium meal XP study, double contrast method and remote control television fluoroscopy were developed and popularized in Japan. This progress contributed to realize our screening system of this disease. For the endoscopic diagnosis, dye spray method, flexible video endoscopy, nasal endoscope, and narrow band imaging were the new technologies and could demonstrate small mucosal cancer. Endoscopic biopsy can give the most reliable and final diagnosis. Followings are the supportive diagnostic methods. Abdominal ultrasonography can easily detect ascites, liver metastasis, and sometimes para-aortic node metastasis. Endoscopic ultrasonography is useful to check the depth of cancer invasion, particularly for differentiate mucosal and submucosal cancer for the endoscopic mucosal resection. The other use is to demonstrate the infiltration margin to the esophagus. CT and MRI is helpful to demonstrate liver metastasis, pancreatic invasion, ovarian metastasis, and para-aortic node metastasis. However, usefulness of PET-CT is limited. Major role of the tumor marker, such as CEA, AFP, CA19-9, are used to evaluate chemotherapy effectiveness. They are not useful for the early detection. Our dream is to pick out the high risk group using gene screening, pepsinogen screening, micro RNA, etc. Then the mass screening system will dramatically become efficient.

1	Barium XP study	double contrast method remote control TV fluoroscopy
2	Endoscopy	dye spray method, flexible video endoscope nasal endoscope, narrow band imaging
3	Endoscopic biopsy	biopsy forceps
4	Ultrasonography	abdominal ultrasonography endoscopic ultrasonography
5	Medical imaging	CT, MRI, PET-CT
6	Tumor marker	CEA, AFT, CA-19-9, gene screening pepsinogen screening, micro RNA, etc

Figure 3. Progress in diagnostic methods of gastric cancer

Screening by the government

Over 50 years old, for unemployed people
They receive a post card for the cost-free screening in every September. The cost is covered by the Government.

Screening by the employer

Over 50 years old, for employed people and their family
The screening is organized and payed by the employer.

Personal health check

Private screening is also popular in Japan. People can select the good hospital and they have to pay by themselves.

Figure 4. Mass screening systems in Japan

Mass screening of gastric cancer and its outcome

For the mass screening of gastric cancer, Japan has used barium XP study and endoscopy. We have three mass screening systems (Fig. 4). The first is the screening for non-organized people over 50 years old such as farmers, storekeepers, old unemployed people, etc. This system is supported by the government. The second is the screening for company workers and their families supported by their employers. The third is the personal health check payed by themselves. Approximately 45% of the population over 50 years old are now receiving annual check of the upper GI tract.

According to the Nationwide Registry of Gastric Cancer (Fig. 5) (3,4,5), proportion of Stage-I was 22.5% in 1963-66 which was elevated to 59.3% in 2008. Proportion of early cancer, namely pT1 tumor, had increased from 15.9% to 52.7% in the same period. Stage-IV cancer had decreased from 33.7% to 15.2%. These trends were brought by development of diagnostic methods and establishment of mass screening systems. The Japanese screening system is expensive, but Japanese people understand the meaning and accept the cost for reducing the gastric cancer death.

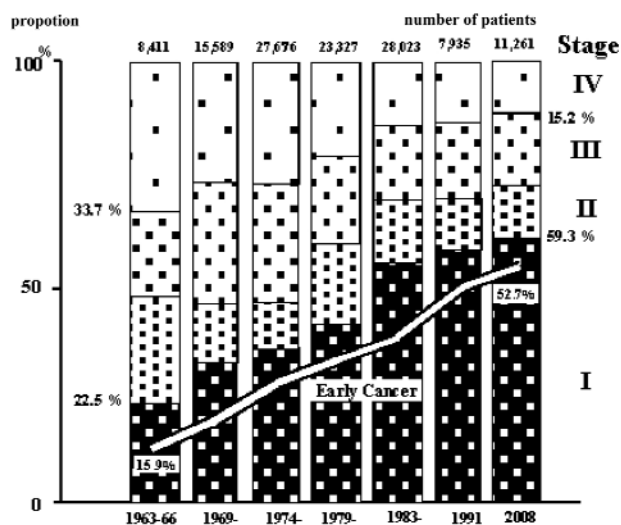


Figure 5. Increase of early stage gastric cancer

primary gastric cancer treated by gastric resection Japanese nationwide registry of gastric cancer patients, 1963 - 2008

Establishment of standard gastrectomy (D2) and the treatment results

Figure 6 shows the most important prognostic factors for gastric cancer patients evaluated by multivariate analysis of 2,913 patients using SAS software (6). The most significant

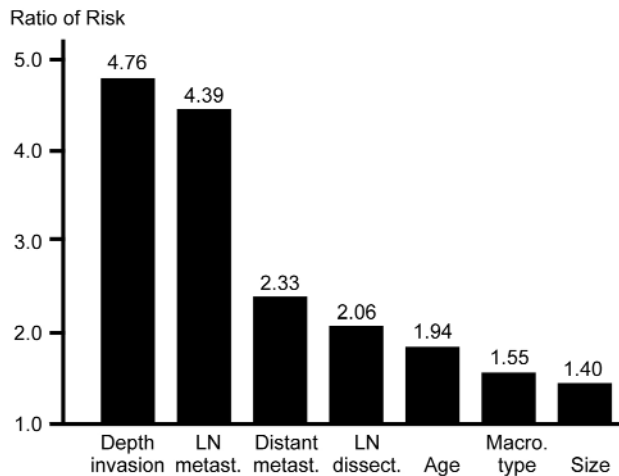


Figure 6. Prognostic factors for gastric cancer patients
Multi-variate analysis of 2,913 gastric cancer patients treated by gastric resection at the National Cancer Center in 1969-1991 Cox's proportional hazard model, SAS software

factor was depth of invasion (T category) followed by lymph node metastasis (N category), distant metastasis (M category), and lymph node (LN) dissection (D category). T category, N category, and M category are fixed at the starting of treatment and we can not change them. But we can change the D category. Its Ratio of risk was 2.06 and it means the survival could be improved twice by accurate and effective LN dissection. The Japanese Gastric Cancer Association published the Classification of Gastric Cancer in 1962 including detailed definition of the regional LN stations and the N-classification. The latest Classification was translated into English and published in 1998 (Fig. 7) (1). Complete removal of N1 and N2 nodes is called as "D2 or systematic LN dissection" and this procedure became golden standard in Japan (Fig. 8) (7). 5 year survival rate (5YSR, Kaplan-Meier method) of patients with gastric resection was 37.5% in 1963-66, which was elevated to 70.1% in 2008 according to the Nationwide Registry (Fig. 9) (3,4,5). Improvement of the 5YSR was remarkable for Stage-II; from 47.7% to 73.1%. The improvement was also remarkable for Stage-III; from 26.4% to 44.5.0%. This improvement was brought by popularization of the systematic LN dissection.

New trend; from standardized surgery to individual surgery

Japan had a new trend for the surgical treatment since 1995; from "Extended and standardized surgery for radical treatment" to "Reasonable and individual surgery considering safety and quality of life (QOL)". Background of this shift were 1) remarkable increase of early stage cancer, 2) demand for safe surgery and QOL, 3) progress of technology and instruments, and 4) storage of knowledge and experiences. This new trend produced a large variation in surgical

regional LN station	tumor location			
	L LM	M ML, MU	U UM	LMU, MUL MLU, UML
No. 1 Right paracardial LN				
No. 2 Left paracardial LN				
No. 3 LN along the lesser curvature			N1	
No. 4 LN along the greater curvature				
No. 5 Suprapyloric LN				
No. 6 Infrapyloric LN				
No. 7 LN along the left gastric a.				
No. 8 LN along the common hepatic a.				
No. 9 LN around the celiac a.			N2	
No.10 LN at the splenic hilum.				
No.11 LN along the splenic a.				
No.12 LN in the hepatoduodenal ligament				
No.13 LN behind the pancreatic head				
No.14 LN along the sup. mesenteric vessels			N3	
No.15 LN along the middle colic vessels				
No.16 LN around the abdominal aorta				
No.19 Infradiaphragmatic LN			N4	
No.20 LN in the esophageal hiatus	M			

L: lower third, M: middle third, U: upper third of the stomach

Figure 7. Regional lymph nodes and N Classification by tumor location

Japanese classification of gastric cancer, 2nd English edition, 1998

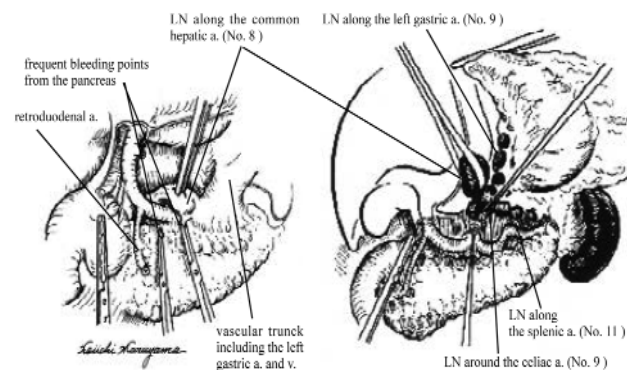


Figure 8. Lymph node dissection along the upper border of the pancreas

Majority are belonging to the N2 Category

treatment. Now, surgeons have to select the most rational treatment for an individual patient.

In such situation, Japanese Gastric Cancer Association published "Guide line for gastric cancer treatment" in 2001. The 2nd edition was now in use from 2004 (2). The guide line was constituted of two parts; "Treatments for general practice" and "Treatments for research trial". Evaluation of the treatments was based on the scientific evidences. Followings are the explanations of the important treatments and the intention, the indication, and the outcome.

Minimally invasive surgery

The most minimally invasive surgery is the "Endoscopic mucosal resection (EMR)". Intention of the EMR is to avoid disadvantages and risk of gastric resection and to get quick

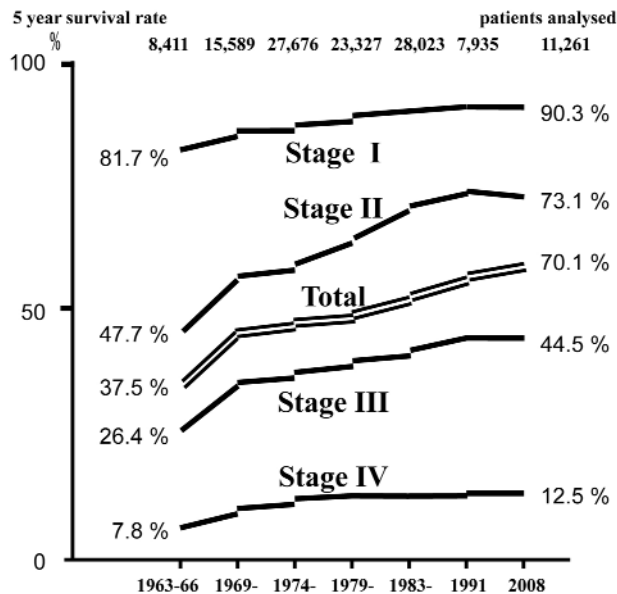


Figure 9. 5 year survival rates were improved in every Stages

Japanese TNM Classification, Nationwide Registry of gastric cancer patients in 1963-2008, resected cases, Kaplan-Meier survival rate, (direct death, other disease death, and lost to follow-up were treated as death)

recovery. This treatment is indicated for the early stage cancer with definitely no LN metastasis and endoscopically resectable; namely 1) mucosal cancer, 2) elevated or flat lesion, 3) differentiated adenocarcinoma, 4) less than 2.0 cm in diameter. And standard gastric resection should be carried out when these conditions are not met or resection margin is positive in the resected specimen. The most easy technique is "Polypectomy technique" (8). For the purpose to get accurate cut line and enough depth resection, "Endoscopic submucosal dissection (ESD) by insulated-ball tipped knife" was proposed by the National Cancer Center Tokyo (Fig. 10) (9,10). They reported no cancer death from their 1,783 patients, treated in 1989-2003 (11).

The laparoscopic surgery became also popular remarkably for gastric cancer. The intention is to get quick recovery, less pain, and cosmetic advantage. The indication is now mostly for early stage cancer but is expanding to advanced cancer. Surgical technique, procedures, and instruments are remarkably developed in the last 20 years, and the quality of surgery is now evaluated as almost the same level of the open surgery. M. Ohgami proposed the "Lesion lifting method" or wedge resection in 1987 (12). However "Laparoscopic gastric resection with systematic LN dissection" becomes popular. S. Kitano collected data of 260 wedge resections and 2,600 laparoscopic gastric resections performed up to 2004 and reported excellent results (13). Japanese Laparoscopic Surgery Study Group reported that the treatment results of 1,294 patients with distal, proximal, and total gastrectomy. The postoperative morbidity was 14.8%, the mortality was 0.0%, and the recurrence was found in only 6 cases (0.6%) (14). We are now introducing

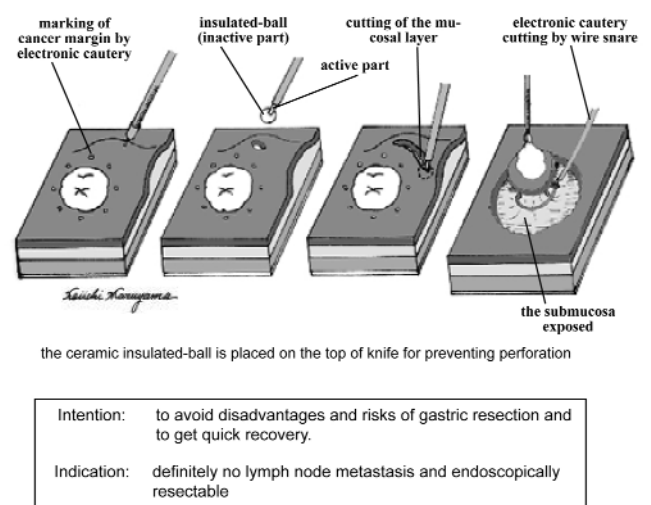


Figure 10. Endoscopic submucosal dissection (ESD) for mucosal cancer

actively "Robot machine" for gastric cancer surgery. Problems of this treatment are 1) few experts, 2) limitation in extended surgery, 3) expensive, and 4) time consuming.

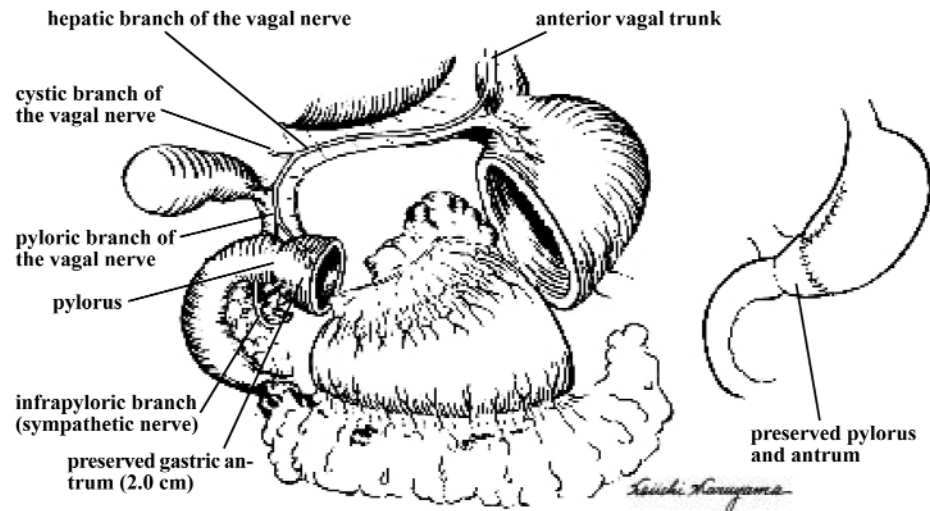
For T1 and N0 cancer, D2 lymphadenectomy is not necessary. The Japanese Guide Line proposed limited LN dissection excluding LNs around the celiac artery and common hepatic artery; "D1+alpha" and "D1+beta" (2).

Function preserving surgery

Considering postoperative QOL, several function preserving surgeries were proposed. "Pylorus and nerve preserving gastrectomy (PPG)" was firstly proposed for gastric ulcer treatment. The intention is to reduce dumping syndrome, post-gastrectomy gall stone, and digestive function disturbances (Fig. 11) (15). The indication is a small size cancer located at the middle third of the stomach with no possibility of metastasis at the supra-pyloric LN (No. 5 station), the infra-pyloric LN (No. 6 station), and the right cardiac LN (No. 1 station). This procedure is now widely accepted.

K. Maruyama proposed "Pancreas preserving total gastrectomy" in 1985 (Fig. 12) (16). This procedure preserves the pancreas parenchyma and the splenic vein and removes the spleen and the splenic artery, together with LN around the pancreas tail. It is well known that resection of the distal pancreas causes frequently pancreatic fistula, subphrenic abscess, and postoperative diabetes. Intention of this procedure is to reduce these complications. The indication is proximal cancer with no direct invasion to the pancreas and no obvious LN metastasis around it, particularly recommendable for diabetic patients. Hospital death was 3.1% for pancreas resection group (n=319) but 1.6% for pancreas preserving group (n=299). Surgical complications related to the pancreas were also lower in the pancreas preserving group than in the resection group; 19.6% and

Figure 11. Pylorus and nerve preserving gastrectomy (PPG)



Intention: to reduce dumping syndrome, post-operative gall stone, and digestive function disturbances.

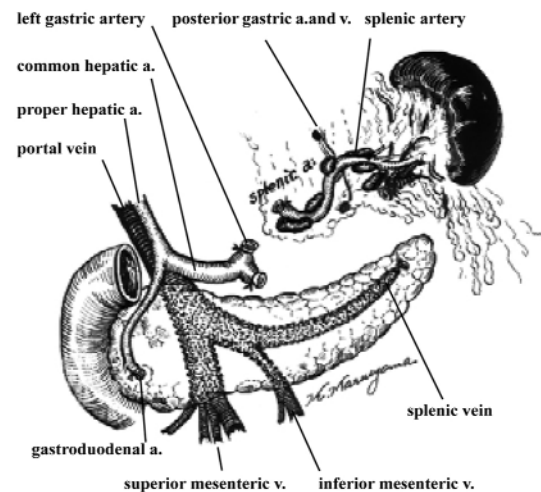
Indication: small cancer located in the middle stomach with no possibility of metastasis to the pyloric and right cardiac lymph nodes.

39.4% respectively. 5YSR for Stage II cancer was superior in the pancreas preserving group than the pancreas resection group; 70.0% and 54.6% respectively. This procedure is now internationally accepted.

Optimal extent of LN dissection

For the purpose to know the optimal extent of LN dissection, several information systems were proposed. "Computer estimation system" was completed in 1984 using data of 3,785 patients treated in the National Cancer Center in 1969-83 (17). This system was applied to 222 German patients and showed high sensitivity, specificity, and accuracy; e.g. 100%, 95%, and 96% respectively for N3 patients and 100%, 78%, and 89% respectively for N2 patients (18). E. Bollschweiler proposed a new computer system, "Artificial neuronal network" for prediction of LN metastasis (19). She reported high reliability in the estimation of LN metastasis.

The latest topic is "Sentinel node navigation surgery" in this field. The left side schema in Fig. 13 showed the sentinel node concept or principle. The idea is now accepted and clinically used for breast cancer, melanoma, head and neck tumor, etc. Y. Kitagawa made a detailed clinical study to introduce this procedure for gastric cancer surgery (Fig. 14) (20). He reported high detection rate, sensitivity, and accuracy; 97%, 94%, and 99% respectively in 210 cT1 and cT2 patients using a radioactive tracer; ^{99m}Tc tin colloid. He found 3.9 hot nodes in average in his series. He stressed that unnecessary LN dissection can be avoidable by the sentinel node navigation. However we have to consider the following important facts before introducing



Intention: to reduce postoperative complications caused by pancreas tail resection such as preventing pancreatic fistula, subphrenic abscess, and postoperative diabetes.

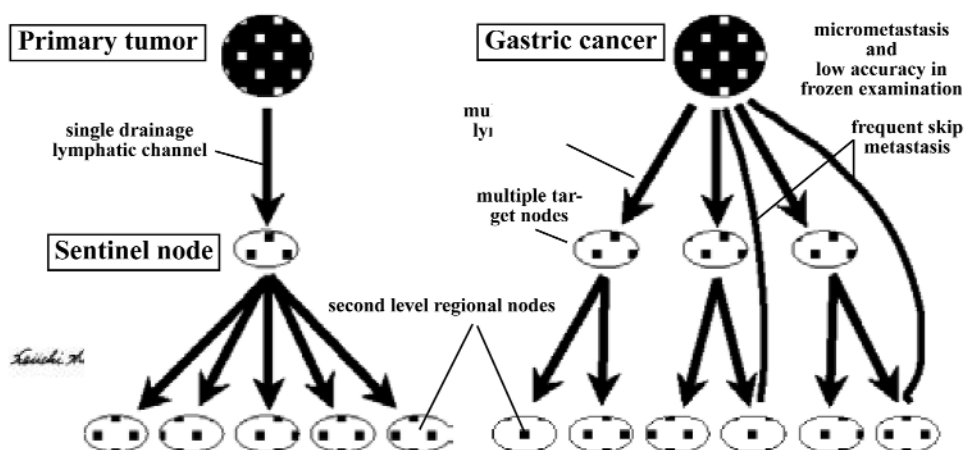
Indication: proximal cancer with no direct invasion to the pancreas and no obvious lymph node metastasis around it, particularly recommendable for diabetic patient.

Figure 12. Pancreas preserving total gastrectomy

left gastric artery posterior gastric a. and v. splenic artery proper hepatic a. common hepatic a. portal vein gastroduodenal a. splenic vein superior mesenteric v. inferior mesenteric v. **Intention:** to reduce postoperative complications caused by pancreas tail resection such as preventing pancreatic fistula, subphrenic abscess, and postoperative diabetes. **Indication:** proximal cancer with no direct invasion to the pancreas and no obvious lymph node metastasis around it, particularly recommendable for diabetic patient. To achieve accurate lymphadenectomy around the pancreas tail, the splenic artery and the spleen are removed together with fatty tissue including the lymph nodes. The pancreas parenchyma and the splenic vein are preserved

Figure 13. Sentinel node concept (left) and lymphatic streams of the stomach (right)

dye tracer: patent blue, lymphazurin, indocyanine-green, etc



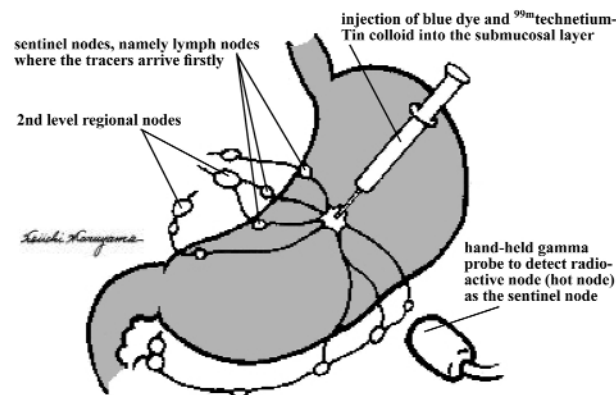
the procedure for gastric cancer; 1) so complicated and multiple lymphatic channels, 2) multiple target nodes, 3) frequent skip metastasis, 4) low accuracy in frozen examination, 5) frequent micrometastasis, 6) unclear advantages by limited LN dissection (Fig. 13) (21, 22). This procedure is now in trial mainly for early stage cancer by laparoscopic gastric resection.

Aggressive but safe surgery

The intention is to improve survival of advanced cancer by removing adjacent organs and N3/N4 nodes. The Nationwide Registry 1991 reported that 2,394 patients were treated by combined resection of neighboring organs

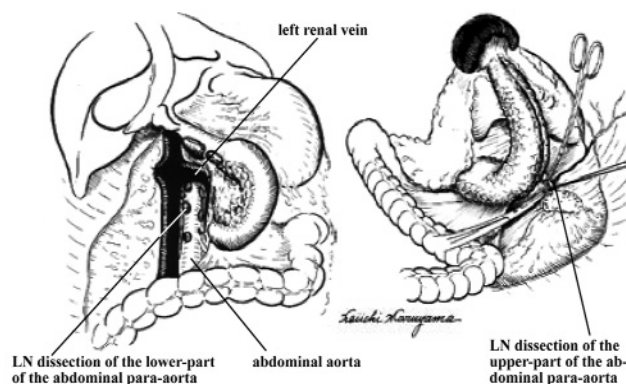
(30.2%) and the 5YSR was 49.3% (4).

Nationwide Registry 1991 reported that metastasis of “the para-aortic LN (N4)” was found in 4.5% of 7,935 resected cases, and 10.5% of the patients could survive more than 5 years by N4 dissection (4). The survival benefit of the “Para-aortic LN dissection” was not high. However, other leading institutions reported that 5YSR of the N4-positive patients was in between 11% and 23% after N4 dissection (23). We consider that important role of this procedure is removal of micrometastasis or undetectable metastasis at the N4 nodes. The surgical fields can be approached under extensive mobilization of the head of pancreas and the spleen/pancreas tail (Fig. 15). This procedure did not increase the mortality and morbidity by



Intention: to detect the first target lymph node(s) of metastasis from gastric cancer, namely “sentinel nodes”. In case no metastasis is confirmed, further LN dissection is not necessary.
Indication: early gastric cancer particularly for laparoscopic gastrectomy

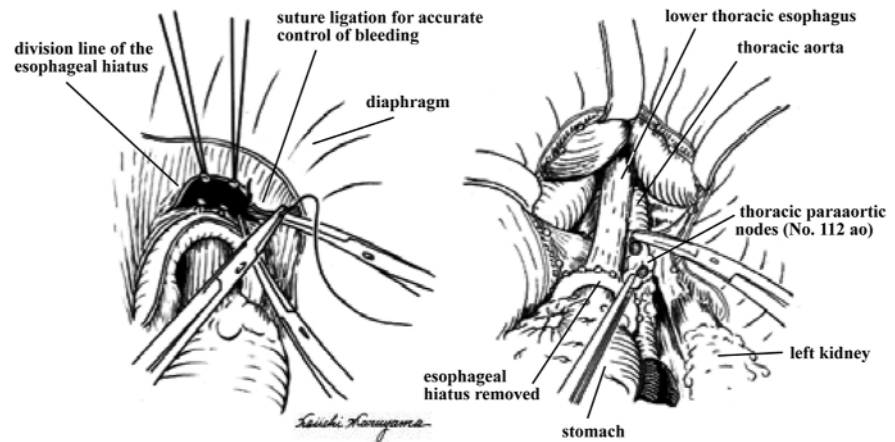
Figure 14. Sentinel node navigation for reasonable LN dissection
blue dye tracer: patent blue, lymphazurin, indocyanine-green, etc



Intention: to reduce the local recurrence by removing metastatic lymph nodes around the abdominal aorta.
Indication: M0 advanced cancer having possibility of para-aortic node metastasis, particularly for T3 and T4 cancer.

Figure 15. Para-aortic lymph node dissection (D4)

Figure 16. Mediastinal lymph node dissection by transdiaphragmatic approach



Intention:	to improve survival by removing metastatic lymph node around the lower esophagus through the diaphragm
Indication:	advanced gastric cancer in the esophago-gastric junction and subcardiac area.

specialized surgeons in specialized centers; 0.8% for hospital death, 1.1% for leakage, 3.6% for pancreatic fistula, and 1.5% for pneumonia in 523 patients (24). This procedure is indicated for M0 advanced cancer having possibility of N4 metastasis, particularly for T3 and T4 cancer with no macroscopic N4 metastasis.

Mediastinal LN metastasis was not rare for advanced proximal cancer with esophageal invasion. Most metastases were found in the lower para-esophageal LN (16.1%) and in the posterior mediastinal LN (3.2%) (25). These nodes can be removed by the “Trans-diaphragmatic mediastinal LN dissection” (Fig. 16). The 30 days mortality was 0%, and the morbidity was 18% in our series (25).

Conclusion

Figure 17 shows the decreasing trends of “incidence” of gastric cancer indicated by the upper lines in male and female in Japan (26). The figure showed also the decreasing trends of “death rate” shown by the lower lines. Interval between the incidence and death rate were expanding year by year, and it means increasing trend of cured population from gastric cancer. This trend was produced by development of the early detection and progress of the surgical treatment.

Surgery is the only one possible curative treatment for gastric cancer. Because of so many patients with this disease in our country, various new surgical procedures had been proposed and are in use clinically. Explanations of these procedures, intentions, indications, and treatment results were described in this paper. The authors would be happy if these information would be instructive for Romanian surgeons.

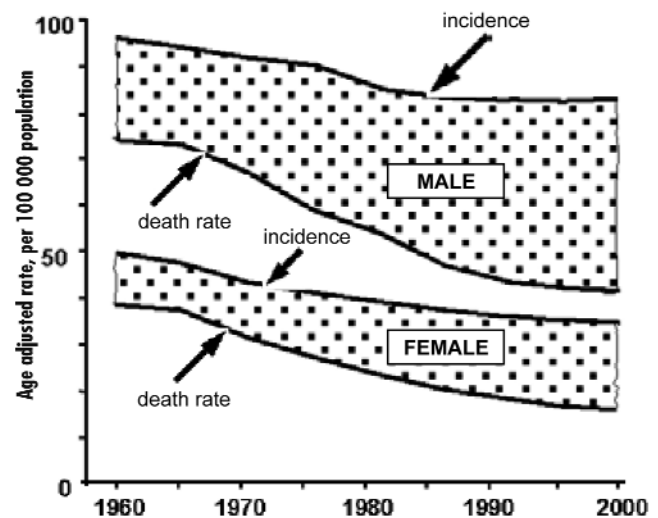


Figure 17. Trends of the incidence and death rate of gastric cancer.

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