厚生労働科学研究費補助金

がん臨床研究事業

高度進行胃がんの治療に関する研究

平成１６年度　総括研究報告書

主任研究者　　笹子　充

平成１７年（２００５）年４月

目　　次

厚生労働科学研究費補助金（がん臨床研究事業）
総括研究報告書

高度進行胃がんの治療に関する研究

主任研究者　笹子　充　国立がんセンター中央病院第一領域外来部長

研究要旨
予後不良の進行胃がんであるスキルス胃がん及び大型３型胃がんに対して、術前にTS-1＋シスプラチンによる化学療法を２コース実施後に、根治手術を行う治療法の開発に取り組んだ。昨年まで登録を行った第Ⅱ相試験の結果を集計・解析した。本治療法はGrade3以上の有害事象が15%以下と安全に行えること、治療完遂率が62%と期待通りの治療効果を認めること、ことに組織学的腫瘍効果で優れた成績を示すこと（Grade1b以上が48%）が判明した。第Ⅲ相試験のプロトコールを作成し、JCOG臨床試験審査委員会で第１回目の審査を受け、審査意見に基づいた最終バージョンを作成する段階である。

分担研究者
荒井　邦佳　東京都立駒込病院　部長
栗田　啓　独立行政法人国立病院機構四国がんセンター　部長
斎藤　和好　岩手医科大学第一外科　教授
塩崎　均　近畿大学医学部外科　教授
清水　武昭　新潟県厚生連長岡中央綜合病院　副院長
種村　廣巳　岐阜市民病院　副院長
梨本　篤　新潟県立がんセンター新潟病院　部長
二宮　基樹　広島市立広島市民病院　部長
福島　紀雅　山形県がん・生活習慣病センター　副部長、山形県立中央病院　医長
古河　洋　堺市立堺病院　院長
山村　義孝　愛知県がんセンター　部長

Ａ．研究目的

全体では70%近い治癒率を達成した胃がんにおいて、依然10%程度の５年生存率にとどまっているスキルス胃がんある いはそれに準ずる大きな３型胃がんの予後改善が本研究の目的である。スキルス胃がんは20代の若年者にも多く発生し、数多くの悲劇を生んできた。就労期の患者が多数を占める同疾患の予後改善の必要性は高く、その社会的な意義もきわめて大きい。

Ｂ．研究方法

治療法：術前にTS-1＋シスプラチン療法（TS-1は３週間投与、１週休薬、シスプラチンday8に投与）を２コース実施後に、D2郭清以上の郭清を伴う根治手術を行う。

治療法の評価方法：第Ⅱ相試験において安全性と治療の完遂率を評価し、基準以上の場合に、第Ⅲ相試験を行う。第Ⅱ相試験は既に登録を終了していたが、結果の集計と評価を行う。第Ⅱ相試験、第Ⅲ相試験ともJCOG胃がん外科グループの臨床試験として行う。したがって、JCOGのプロトコール審査委員会の評価を受け、最終的なプロトコールを決定する。また、データ管理もJCOGデータセンターに委託し、委託費を支払う。

（倫理面への配慮）

本研究として行われた第Ⅱ相試験、現在計画中の第Ⅲ相試験ともJCOG臨床試験審査委員会において科学性・倫理性の厳しい審査を受けて承認される。その後参加各施設の倫理審査委員会が試験の実施を承認するダブルチェックシステムをとっており、プロトコールは、ヘルシンキ宣言のみならず、被験者の個人情報保護等に関する条項も満たすべく作成されている。被験者は文書と口頭による十分な説明を受けたのち、自由意志に基づいて、文書にて同意する仕組みを取っている。

Ｃ．研究結果

昨年登録が終了した第Ⅱ相試験症例の治療が全例で総て終了し、データを集計解析した。本試験には50例が登録され

た。治療関連死は１例で、治療中の胃の原発巣からの出血死であった。血小板減少などの有害事象を伴う出血ではなく、治療開始間もなくのことでもあり、有害事象と治療の関連の可能性は低いものであった。Grade4の血液学的有害事象は低ナトリウム血症の１例のみで、Grade3は白血球減少6%、好中球減少14%、貧血10%と低率であった。非血液学的有害事象ではGrade4は無く、Grade3は食欲不振14%、悪心6%、その他は各１例ずつであった。有害事象のための治療中止は３例のみであった。50例中化学療法中の治療関連し（出血）１例と手術拒否の１例を除いた48例が手術を受けた。治癒切除は35例で行われ、非治癒切除が13例であった。組織学的所見を含めての根治手術達成（総合的治癒切除）は31例であったが、これ治療完遂率の期待値60%を上回っていた。術後の合併症は膵液瘻8%、腹腔内膿瘍6%、肺炎4%等、対象症例中の39例が胃全摘を受けたことを考えると、きわめて低頻度であった。プライマリーエンドポイントである治療完遂割合は62%で、期待値以上であり、前述の安全性とともに見込まれた効果を確認することができた。また、組織学的効果判定では胃がんに対する化学療法としては稀なCRを２例認めた。画像上のPRに匹敵すると思われる組織学的効果Grade1b以上の症例が24例有り、奏効率48%と解釈することができた。

また、第Ⅲ相試験のプロトコールはJCOGプロトコール審査委員会に平成17年２月に提出され、第１回目の審査が終了。いくつかの修正を要する点が指摘されたが、基本的には、高い評価を受けた。今後早急にプロトコール原案を修正し、第２回目の審査に提出する。

D．考察

以上より、本治療法（TS-1+CDDP＋根治手術）は第Ⅲ相試験の試験アームにふさわしいと考えられ、第Ⅲ相試験準備の最終段階にさしかかっている。この第Ⅲ相試験の対象は前記第Ⅱ相臨床試験と同じ大型３型・４型胃がんで、手術単独群を対照治療とする。第Ⅱ相試験では、主たる目的がfeasibilityの確認であったことから、適格性を臨床・画像検査のみで決めたが、本第Ⅲ相試験では診断的腹腔鏡検査を実施した上で、腹膜播種が無く、洗浄細胞診陰性の症例のみを対象として実施する予定である。播種陽性症例は別の臨床試験を計画中である。また、播種や肝転移がなく、肉眼的には治癒切除ができる場合は、洗浄細胞診陽性例では切除手術を行った上で補助化学療法を行うことが一般的で、同じ試験の対象とはならない。

本臨床試験が診断的腹腔鏡検査の標準的定着を促す可能性もある。すでにプロトコールはJCOGプロトコール審査委員会で第１回審査を終了し、現在審査委員の意見に従い修正中である。2005年夏までには試験を開始できると考えている。

また、本治療の有用性に関する情報は高度リンパ節転移を有し、遠隔転移のない胃がん症例に対する術前化学療法としても十分魅力的であり、現在既にJCOG胃がん外科グループでそれらの症例を対象とした第Ⅱ相試験を実施中である。

E．結論

TS-1+CDDP療法は安全性と治療効果に優れ、遠隔転移のない予後不良進行胃がん症例に対する新しい治療法となりうるポテンシャルを持つ。

F．健康危険情報

現在まで登録された症例では該当なし。

G．研究発表

１．論文発表

(1) Ushijima, T. and Sasako, M.: Focus on gastric cancer. Cancer Cell, 5: 121-125, 2004.

(2) Sasako, M.: Role of surgery in multidisciplinary treatment for solid cancers. Int J Clin Oncol, 9: 346-351, 2004.

２．学会発表

(1) 片井均、笹子三津留、佐野武、古河洋、藤谷恒明、福島紀雅、田中洋一、山村義孝、種村廣巳、辻仲利政（日本臨床腫瘍外科グループ(JCOG)胃がん外科グループ）：高度リンパ節転移を伴う進行胃がんに対する術前CPT11+CDDP療法+外科切除の第Ⅱ相臨床試験．第59回日本消化器外科学会定期学術総会、鹿児島、平成16年７月

(2) Tsuburaya, A., Sasako, M., Furukawa, H., Fukushima, N., Fujitani, T., Tanemura, H., Yamamoto, S., Gastric Cancer Surgical Study Group of JCOG: Preoperative adjuvant chemotherapy with irinotecan and cisplatin for gastric cancer with extensive lymph node metastasis: A multicenter phase IIstudy by Japan Clinical Oncology Group (JCOG0001). 2005 Gastrointestinal Cancers Symposium: Multidisciplinary Approaches to Gastrointestinal Malignancies and Premalignancies, Hollywood, Florida, U.S.A, 2005. 1.

(3) 嶋田善久、荒井邦佳、岩崎善毅、片

柳創、高橋慶一、山口達郎、松本寛、宮本英典：高度進行胃癌に対する術前化学療法としてのTS-1/CDDP併用療法の検討．第66回日本臨床外科学会総会、盛岡、平成16年10月
(4)平成人、栗田啓、野崎功雄、小森栄作、久保義郎、棚田稔、高嶋成光：切除可能高度進行胃癌に対する術前TS-1, CDDP併用療法に関する検討．第42回日本癌治療学会総会学術集会、京都、平成16年10月
(5)Taira, N., Kurita, A., Okita, A., Nozaki, I., Komori, E., Kubo, Y., Tanada, M., Takashima, S.: Evaluation of TS-1 combined with cisplatin for neoadjuvant chemotherapy in patients with advanced gastric cancer. 19th World Congress of International Society for Digestive Surgery, Yokohama, Japan, 2004. 12.
(6)種村廣巳、他：幽門側胃切除時のD3郭清．第42回日本癌治療学会総会、京都、平成16年９月
(7)梨本篤：進行胃癌に対する術前化学療法の意義と予後因子．第42回日本癌治療学会総会、京都、平成16年10月
(8)Nashimoto, A.: Evaluation of S-1 and Cisplatin combination chemotherapy as neoadjuvant chemotherapy for patients with advanced gastric cancer.19th World Congress of InternationalSociety for Digestive Surgery, Yokohama, Japan, 2004. 12.
(9)佐々木寛、二宮基樹、原野雅生、青木秀樹、小野田正、塩崎滋弘、大野聡、桧垣健二、高倉範尚：当院における高度進行胃癌に対する術前化学療法の経験．第42回日本癌治療学会総会、京都、平成16年10月
(10)見前隆洋、二宮基樹、佐々木寛、原野雅生、青木秀樹、小野田正、塩崎滋弘、大野聡、桧垣健二、高倉範尚：Docetaxel, 5-Fu併用化学療法により根治手術が可能となり組織学的にGrade3が得られた切除不能スキルス胃癌の１例．第42回日本癌治療学会総会、京都、平成16年10月
(11)佐々木寛、二宮基樹、原野雅生、青木秀樹、小野田正、塩崎滋弘、大野聡、桧垣健二、高倉範尚：5-FU＋タキソールによる術前化学療法により原発巣がCRとなった高度進行胃癌の１例．第66回日本臨床外科学会総会、盛岡、平成16年10月
(12)今村博司、古河洋、他：４型胃癌に対する左上腹内臓全摘術．第42回日本癌治療学会総会、京都、平成16年10月
(13)伊藤誠二、山村義孝、他：スキルス胃癌治療成績の変化-非切除の方針は妥当か一．第104回日本外科学会定期学術集会、大阪、平成16年４月

H．知的財産権の出願・登録状況
該当なし。

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ushijima, T., Sasako, M.	Focus on gastric cancer	Cancer Cell	5	121-125	2004
Sasako, M.	Role of surgery in multidisciplinary treatment for solid cancers	Int J Clin Oncol	9	346-351	2004

III. 研究成果の刊行物・別刷

「がん臨床研究事業」

主任研究者　　笹子　充

Focus on gastric cancer

Toshikazu Ushijima[1] and Mitsuru Sasako[2,*]

[1]Carcinogenesis Division, National Cancer Center Research Institute
[2]Department of Surgery
National Cancer Center Central Hospital, Tokyo, Japan 104-0045
*Correspondence: msasako@gan2.ncc.go.jp

Epidemiology and incidence statistics

Gastric cancer is the second most common cancer in the world (Ferlay et al., 2001). It is unique in that its time trend and geographical distribution are very informative in estimating its risk factors. In the US, the crude mortality rate in Caucasian males was 33/100,000 in the early 20th century, and this declined to 5/100,000 in the late 20th century. The declining trend is worldwide, and the decline began earlier in developed countries. However, even among them, mortality is still high in Korea (43/100,000), Russia (35/100,000), Japan (31/100,000), and Portugal (22/100,000). The age-adjusted incidence reaches as high as 70/100,000 in Korean and Japanese males. The male to female ratio is consistently two to one in many geographical regions.

The decline took place following the popularization of refrigerators, which resulted in a decreased intake of salt and an increased intake of fruit and vegetables (Palli, 2000; Potter et al., 1997). The preventive effects of fruit and vegetables are consistently confirmed by many epidemiological studies. Most epidemiological studies have shown the promoting effect of salt and the preventive effect of vitamin C. The effects of salt were also shown by animal experiments. Some epidemiological studies suggest that consumption of grilled meat/fish increases the risk, and that the consumption of carotenoids and green tea reduce the risk. Epidemiological data linking *N*-nitrosamines to gastric cancers have so far been inconclusive, although their carcinogenicity at high doses is proven.

Infection by *Helicobacter pylori* is prevalent in areas with high incidences of gastric cancers, and increases the risk of gastric cancer. However, in some Asian countries, such as India and Thailand, incidences of gastric cancers are not high in spite of the high *H. pylori* infection rates, a phenomenon known as the "Asian Enigma" (Miwa et al., 2002). Possible explanations for this include host genetic factors, different virulence among strains of *H. pylori*, and dietary factors. Polymorphisms of proinflammatory cytokine genes have been shown to associate with risk of *H. pylori*-related gastric cancers (El-Omar et al., 2000).

Animal models

A rat model for gastric cancers induced by a chemical carcinogen, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, has been widely used for a variety of purposes, such as evaluation of various promoting and preventing factors and clarification of genes involved in genetic susceptibility (Yamashita et al., 2002). A model in which *H. pylori* could infect an animal was established using Mongolian gerbils, which contributed to clarification of the strong promoting effect of *H. pylori* (Shimizu et al., 1999).

In addition, there have been more than 10 lines of genetically modified mice that show hyperplasia of the gastric epithelium and/or intestinal metaplasia (Gut et al., 2002). These mouse models were created by targeting genes involved in ion transport, signal transduction, transcriptional regulation, and cell adhesion. Development of gastric cancers was observed in mice lacking the pS2 trefoil protein, those lacking *Smad4/Dpc4*, those lacking the SHP2 binding site on the Il-6 family corepressor gp130, and those lacking *RUNX3* (Judd et al., 2004; Lefebvre et al., 1996; Xu et al., 2000; Li et al., 2002).

Disease mechanism and molecular targets

Histological classification and gastric/intestinal phenotypes

Histological classification of gastric cancers is different between Japan and Western countries. Generally, "differentiated" and "undifferentiated" types in Japanese classification correspond to "intestinal" and "diffuse" types, respectively, in the Western classification established by Lauren. It has been considered that intestinal-type gastric cancers are associated with intestinal metaplasia, whereas diffuse-type gastric cancers are originated from gastric mucosa proper. Recent analysis of gastric and intestinal phenotypes in early gastric cancers has shown that cancer cells with gastric phenotypes were present in both intestinal and diffuse types of gastric cancer. Furthermore, phenotypic expression in gastric cancer cells was shown to be independent of phenotypic changes in the surrounding gastric mucosa (Tatematsu et al., 2003).

Gastric cancer predisposition

Germline mutations of *E-cadherin* were first found in a large family from New Zealand in which diffuse-type gastric cancers took place at an early age (Guilford et al., 1998). Although *E-cadherin* germline mutations are very rare, the finding provided to be useful information for clinicians to manage high-risk patients. Gastric cancers, mainly of the intestinal type, can be associated with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, most cases of which are caused by germline mutations of mismatch repair genes *hMLH1* or *hMSH2*, and are more prominently manifested in older generations of HNPCC patients. Patients with familial adenomatous polyposis, which is caused by germline mutations of *APC*, and Peutz-Jeghers syndrome also have increased risk for gastric cancer (Oberhuber and Stolte, 2000).

Molecular alterations in gastric cancer

Many genes have been analyzed in attempts to understand the molecular bases for human gastric cancers, but only a few with frequent alterations have been identified (Table 1). Oncogenic activations of β-*catenin* (17%–27% in intestinal type) and K-*ras* (0%–18% in both histological types) have been found in human gastric cancers (Lee et al., 2002; Park et al., 1999). In addition, amplifications of the c-*erb*B2 and the c-*met* genes have each been found in approximately 10% of both histological types.

As for tumor-suppressor genes, *p53* mutations are repeatedly reported in gastric cancers of the diffuse type (0%–21%) and intestinal type (36%–43%) (Maesawa et al., 1995).

Table 1. Histology and genetic alterations of gastric cancers

	Diffuse type (%)	Intestinal type(%)
Oncogene activation		
β-*catenin*	0	17–27
K-*ras*	0–6	0–18
c-*erb*B2	12–13	12–13
Inactivation of tumor suppressor genes		
p53	0–21	36–43
APC	0–5	0
E-cadherin		
Mutation	33–50	0
Methylation	79	55
p16		
Mutation	0	0
Methylation	11*	50*
Microsatellite instability	5–32	23–41

*Incidences are overestimated due to analysis of CpG islands in exons.

Mutations of the *APC* tumor suppressor gene are found frequently in gastric adenomas, but only rarely in gastric cancers; this is clearly different from the similar frequencies of *APC* mutations in colorectal adenomas and carcinomas (Lee et al., 2002; Maesawa et al., 1995). Somatic mutations of *E-cadherin* are observed specifically in sporadic diffuse-type gastric cancers (33%–50%) (Becker et al., 1994). *RUNX3* was recently shown to be a tumor-suppressor gene of gastric cancers, although its mutations were rare (Li et al., 2002).

Microsatellite instability (MSI) is observed in 5%–10% of diffuse-type gastric cancers and in 15%–40% of intestinal-type gastric cancers. The major mechanism for the MSI in gastric cancer is inactivation of the mismatch repair gene *hMLH1* resulting from hypermethylation of its promoter (Fang et al., 2003). Similarly, mutation of the *p16* gene is infrequent, but hypermethylation of *p16* is common (25%–42% overall) in gastric cancer, with the intestinal type having higher incidence (Ding et al., 2003; Oue et al., 2002).

Factors that induce molecular alterations

Although *hMLH1* and *p16* can be inactivated in gastric cancers by mutations or by promoter hypermethylation, inactivation by methylation is much more frequent than mutation in sporadic gastric cancers. The second hit in *E-cadherin* germline mutation carriers is also generally due to methylation (Machado et al., 2001). A genome-wide scan for aberrant methylations revealed silencing of nine genes in gastric cancers (Kaneda et al., 2002). Even in noncancerous gastric mucosae (Waki et al., 2002), aberrant methylation can be present. These findings suggest that aberrant methylation is deeply involved in gastric carcinogenesis, and aberrant methylation seems to be useful as a new target for diagnostics and prevention of gastric cancers.

The presence of Epstein-Barr virus (EBV) is observed in 7%–20% of gastric cancers, being slightly more frequent in diffuse-type gastric cancers. EBV is clonal in cancer tissue, and is maintained as a plasmid. EBV has been shown to extend cell generations of gastric epithelial cells in in vitro cell culture, but it cannot immortalize them (Takada, 2000). Recently, EBV-associated gastric cancers were shown to be more frequently associated with promoter methylation of *p16* (Kang et al., 2002).

There has been discussion about whether intestinal metaplasia (IM) is a precancerous lesion for gastric cancers. Although gastric cancers are frequently accompanied by IM, no molecular alterations that cause both IM and gastric cancers have been identified. It is thus more likely that factors that induce molecular alterations for IM, such as *H. pylori* infection (Uemura et al., 2001), also induce molecular alterations for gastric cancers.

Diagnosis of gastric cancers

Most patients with gastric cancer are diagnosed when they undergo endoscopy and biopsy after exhibiting symptoms. In Japan, about 25% of patients are diagnosed by mass screening or a personal health check (Japanese National Gastric Cancer Registry). In high-risk areas of this disease, the most important issue is the education of general practitioners and the public to make them aware of the risk of this cancer. Early diagnosis used to be made by a barium meal study, especially in mass screening in Japan (*Oshima*, 1997). Endoscopy is being used more and more for secondary prevention in combination with a serum test of pepsinogen subtypes. However, there is a consensus that the efficacy of mass screening itself should be reevaluated (Tsubono and Hisamichi, 2000).

At an early phase of development, a well-differentiated carcinoma (WDC) replaces the mucosa of atrophic gastritis or IM without showing any invasion. As tumors progress, they start to invade the lamina propria mucosae or the muscularis mucosae, then the submucosal layer. As these invasive parts are often missed by biopsy, the lesions are often diagnosed as dysplasia. Thus, many lesions initially diagnosed as severe dysplasia turned out to be an invasive cancer, sometimes invading even the muscularis propria, after histological evaluation of resected materials (Fertitta et al., 1993).

Diagnostic criteria for early gastric cancers and endoscopic mucosal resection

Diagnostic criteria of WDC differs to some extent between the West and the East (Schlemper et al., 1997). In Western countries, the diagnosis of adenocarcinoma is made only when pathologists can recognize the evidence of invasion, while the term cancer is used in the East when cellular or structural atypia is evident, even without evidence of invasion. WHO classification now clearly states that the lesions called severe dysplasia/adenoma in the West are the same as noninvasive mucosal carcinoma in the East, and this is a result of pathologists' mutual communication and cooperation (Fenoglio-Preiser et al., 1997). The Western policy runs the risk of overlooking true cancers, but the Eastern policy may induce overtreatment. However, as the result of the development of the technique of endoscopic mucosal resection (EMR), the majority of such lesions are now treated endoscopically in Japan (Ono et al., 2001). Thus, paradoxically, "severe dysplasia" is often treated by surgery in the West, and "noninvasive mucosal carcinoma" is treated by EMR. This treatment can be applied exclusively to mucosal cancer, for which endoscopic ultrasound (EUS) is sometimes helpful. Because the histology of the entire specimen resected using EMR can be examined in detail, additional surgery can be applied without much delay if a patient's tumor is found to have submucosal invasion. Because of these potential advantages, distribution of the EMR technique to the West is urgently needed.

Metastases and their diagnosis

Gastric cancer remains a localized disease for a long time and metastasizes slowly. Table 2 shows the incidence of metastasis to lymph nodes, the liver, and the peritoneum according to tumor depth. Metastasis to sites other than these three sites is rare. Systemic metastasis seldom occurs until the late phase of

Table 2. Incidence of metastasis and five-year survival rates by tumor size and depth

Depth		Number of cases	Incidence (%)			Five-year survival rate (%)
			LN metastasis	Liver metastasis	Peritoneal metastasis	
pT1	M	1063	3.3	0.0	0.0	93.3
	SM	881	17.4	0.1	0.0	88.9
pT2	MP	436	46.4	1.1	0.5	81.3
	SS	325	63.7	3.4	2.2	65.8
pT3	SE	1232	78.9	6.3	17.8	35.5
pT4	SI	724	89.8	15.5	41.6	10.1
Overall		4683	47.8	4.5	11.5	60.3

Patients operated on between 1972–1991 at National Cancer Center Hospital, including exploratory laparotomy. pT1: pathologically confirmed tumor invasion of mucosa and/or muscularis mucosa (M) or submucosa (SM). pT2: pathologically confirmed tumor invasion of muscularis propria (MP) or subserosa (SS). pT3: pathologically confirmed tumor penetration of serosa (SE). pT4: pathologically confirmed tumor invasion of adjacent structures (SI).

local invasion (T3/4). By deeper invasion, nodal metastasis occurs more massively and to more distant areas. Nearly 20% of T2 tumors have metastasis at the second tier nodes. Systemic and local recurrences of T1/T2 lesions are rare when treated by proper lymph node dissection, while local recurrence is frequent after limited surgery (Sasako, 2003).

Conventional CT scanning is useful in detecting enlarged nodes, which are often irresectable. However, 25% of metastatic nodes are 5 mm or less and undetectable by any imaging diagnostic tool, including MRI, PET scan, or EUS (Noda et al., 1998).

Treatment of gastric cancers and its recent advances

Tumors without distant metastasis are potentially curable, and treatment comprises resection of the primary tumor and control of lymph node metastasis. For differentiated-type T1 mucosal cancers, EMR is often successful, as metastasis does not generally occur (Gotoda et al., 2000). The Japanese Gastric Cancer Treatment Guideline indicates the criteria for EMR as follows: mucosal cancer of intestinal type, no ulcer nor ulcer scar in the lesion, and size smaller than 21 mm (Nakajima, 2002). For more advanced lesions, gastrectomy of over 2/3 of the stomach with proper lymph node dissection is regarded as standard treatment even in the West (Sasako, 2003; Allum et al., 2002; NCCN Guideline [http://www.nccn.com/physician_gls/f_guidelines.html]), in spite of the negative results of two large randomized trials (Bonenkamp et al., 1999; Cuschieri et al., 1999).

Tumors with distant metastasis are mostly incurable at present, with the rare exceptions of those with solitary liver metastasis or peritoneal nodules. For these advanced or recurrent tumors, chemotherapy shows a modest effect, and cure by medical treatment is rare, even in combination with radiotherapy. Combination chemotherapy using 5-fluorouracil with other agents remains the most popular regimen.

Chemoradiotherapy and D2 surgery

Recently, chemoradiotherapy (CRT) after a potentially curative operation was shown to improve the results of surgery without lymph node dissection (MacDonald et al., 2001). As adjuvant chemotherapy has not proven its efficacy over surgery alone, these results strongly suggest the efficacy of radiotherapy to achieve good local control. However, the results achieved by limited surgery followed by CRT are still worse than those of extended surgery, so-called D2 nodal dissection. Currently, questions regarding whether CRT in combination with limited surgery can replace D2 surgery and whether CRT can improve the results of D2 surgery alone remain to be answered. The former should be evaluated in the Western specialized centers, where D2 surgery can be carried out safely with sufficient quality. If this proves the efficacy of CRT, both questions should be investigated in Japan. Meta-analysis evaluating the effect of adjuvant chemotherapy without irradiation after curative surgery for gastric cancer suggested strongly the effect of the treatment. As none of the large sized trials has proven the effect of adjuvant chemotherapy, it is urgent to establish standard adjuvant treatment. At the moment, a large randomized trial is going on using TS-1, which showed the highest response rate as a single agent in the past. In Western countries, neoadjuvant chemotherapy for advanced gastric cancer is now being tested in a few large phase III trials. Neoadjuvant CRT is just now under investigation as a phase II trial in some American institutions.

New chemotherapeutic agent

Some new chemotherapeutic agents, such as Irrinotecan, TS-1, and Docetaxel, show promise as being more effective than conventional drugs. A combination chemotherapy including TS-1 has shown a response rate of over 70% (Koizumi et al., 2003). Further studies may change the chemotherapy for gastric cancer.

Future challenges

Severe dysplasia/noninvasive mucosal carcinoma could contain different entities that have different abilities to invade the lamina propria mucosae. However, key molecular alterations that determine this progression are unknown. The presence of lymph node or distant metastasis is a very important factor in deciding a treatment strategy, but accurate diagnosis is still difficult. Clarification of molecular alterations that are closely linked with these characteristics will be beneficial to decide on a treatment strategy for individual cases. Popular use of EMR raises a new question, whether or not a secondary cancer will arise from the remnant stomach, and prediction of risk for developing gastric cancer is becoming more important. Recent genomic approaches demonstrate great potential for addressing these issues (Hasegawa et al., 2002). The more important and appropriate questions we ask, the more useful these new approaches will be.

References

Allum, W.H., Griffin, S.M., Watson, A., and Colin-Jones, D. (2002). Guidelines for the management of oesophageal and gastric cancer. Gut *50*, 1–23.

Becker, K.F., Atkinson, M.J., Reich, U., Becker, I., Nekarda, H., Siewert, J.R., and Hofler, H. (1994). E-cadherin gene mutations provide clues to diffuse

type gastric carcinomas. Cancer Res. *54*, 3845–3852.

Bonenkamp, J.J., Hermans, J., Sasako, M., and van de Velde, C.J.H., for the Dutch Gastric Cancer Group. (1999). Extended lymph-node dissection for gastric cancer. N. Engl. J. Med. *340*, 908–914.

Cuschieri, A., Weeden, S., Fielding, J., Bancewicz, J., Craven, J., Joypaul, V., Sydes, M., and Fayers, P. (1999). Br. J. Cancer *79*, 1522–1530.

Ding, Y., Le, X.P., Zhang, Q.X., and Du, P. (2003). Methylation and mutation analysis of p16 gene in gastric cancer. World J. Gastroenterol. *9*, 423–426.

El-Omar, E.M., Carrington, M., Chow, W.H., McColl, K.E., Bream, J.H., Young, H.A., Herrera, J., Lissowska, J., Yuan, C.C., Rothman, N., et al. (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature *404*, 398–402.

Fang, D.C., Wang, R.Q., Yang, S.M., Yang, J.M., Liu, H.F., Peng, G.Y., Xiao, T.L., and Luo, Y.H. (2003). Mutation and methylation of hMLH1 in gastric carcinomas with microsatellite instability. World J. Gastroenterol. *9*, 655–659.

Fenoglio-Preiser, C., Carneiro, F., Correa, P., Guilford, P., Lambert, R., Megraud, F., Munoz, N., Powell, S., Rugge, M., Sasako, M., et al. (1997). Gastric carcinoma. In Tumours of the digestive system, S. Hamilton and L. Aaltonen, eds. (Lyon, France: IARC Press), pp. 39–52.

Ferlay, J., Bray, F., Pisani, P., and Parkin, D.M. (2001). GLOBOCAN 2000: Cancer Incidence, Mortality, and Prevalence Worldwide, Version 1.0, Vol. *5* (Lyon: IARC Press).

Fertitta, A.M., Comin, U., Terruzzi, V., Minoli, G., Zambelli, A., Cannatelli, G., Bodini, P., Bertoli, G., Negri, R., Brunati, S., et al. (1993). Clinical significance of gastric dysplasia: a multicenter follow-up study. Gastrointestinal Endoscopic Pathology Study Group. Endoscopy *25*, 265–268.

Gotoda, T., Yanagisawa, A., Sasako, M., Ono, H., Nakanishi, Y., Shimoda, T., and Kato, Y. (2000). Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer *3*, 219–225.

Guilford, P., Hopkins, J., Harraway, J., McLeod, M., McLeod, N., Harawira, P., Taite, H., Scoular, R., Miller, A., and Reeve, A.E. (1998). E-cadherin germline mutations in familial gastric cancer. Nature *392*, 402–405.

Gut, M.O., Parkkila, S., Vernerova, Z., Rohde, E., Zavada, J., Hocker, M., Pastorek, J., Karttunen, T., Gibadulinova, A., Zavadova, Z., et al. (2002). Gastric hyperplasia in mice with targeted disruption of the carbonic anhydrase gene Car9. Gastroenterol. *123*, 1889–1903.

Hasegawa, S., Furukawa, Y., Li, M., Satoh, S., Kato, T., Watanabe, T., Katagiri, T., Tsunoda, T., Yamaoka, Y., and Nakamura, Y. (2002). Genome-wide analysis of gene expression in intestinal-type gastric cancers using a complementary DNA microarray representing 23,040 genes. Cancer Res. *62*, 7012–7017.

Judd, L.M., Alderman, B.M., Howlett, M., Shulkes, A., Dow, C., Moverley, J., Grail, D., Jenkins, B.J., Ernst, M., and Giraud, A.S. (2004). Gastric cancer development in mice lacking the SHP2 binding site on the IL-6 family co-receptor gp130. Gastroenterol. *126*, 196–207.

Kaneda, A., Kaminishi, M., Yanagihara, K., Sugimura, T., and Ushijima, T. (2002). Identification of silencing of nine genes in human gastric cancers. Cancer Res. *62*, 6645–6650.

Kang, G.H., Lee, S., Kim, W.H., Lee, H.W., Kim, J.C., Rhyu, M.G., and Ro, J.Y. (2002). Epstein-barr virus-positive gastric carcinoma demonstrates frequent aberrant methylation of multiple genes and constitutes CpG island methylator phenotype-positive gastric carcinoma. Am. J. Pathol. *160*, 787–794.

Koizumi, W., Tanabe, S., Saigennji, K., Ohtsu, A., Boku, N., Nagashima, F., Shirao, K., Matsumura, Y., and Gotoh, M. (2003). Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br. J. Cancer *89*, 2207–2212.

Lee, J.H., Abraham, S.C., Kim, H.S., Nam, J.H., Choi, C., Lee, M.C., Park, C.S., Juhng, S.W., Rashid, A., Hamilton, S.R., and Wu, T.T. (2002). Inverse relationship between APC gene mutation in gastric adenomas and development of adenocarcinoma. Am. J. Pathol. *161*, 611–618.

Lefebvre, O., Chenard, M.P., Masson, R., Linares, J., Dierich, A., LeMeur, M., Wendling, C., Tomasetto, C., Chambon, P., and Rio, M.C. (1996). Gastric mucosa abnormalities and tumorigenesis in mice lacking the pS2 trefoil protein. Science *274*, 259–262.

Li, Q.L., Ito, K., Sakakura, C., Fukamachi, H., Inoue, K., Chi, X.Z., Lee, K.Y., Nomura, S., Lee, C.W., Han, S.B., et al. (2002). Causal relationship between the loss of RUNX3 expression and gastric cancer. Cell *109*, 113–124.

MacDonald, J.S., Smalley, S.R., Benedetti, J., Hundahl, S.A., Estes, N.C., Stemmermann, G.N., Haller, D.G., Ajani, J.A., Gunderson, L.L., Jessup, J.M., and Martenson, J.A. (2001). Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N. Engl. J. Med. *345*, 725–730.

Machado, J.C., Oliveira, C., Carvalho, R., Soares, P., Berx, G., Caldas, C., Seruca, R., Carneiro, F., and Sobrinho-Simoes, M. (2001). E-cadherin gene (CDH1) promoter methylation as the second hit in sporadic diffuse gastric carcinoma. Oncogene *20*, 1525–1528.

Maesawa, C., Tamura, G., Suzuki, Y., Ogasawara, S., Sakata, K., Kashiwaba, M., and Satodate, R. (1995). The sequential accumulation of genetic alterations characteristic of the colorectal adenoma-carcinoma sequence does not occur between gastric adenoma and adenocarcinoma. J. Pathol. *176*, 249–258.

Miwa, H., Go, M.F., and Sato, N. (2002). H. pylori and gastric cancer: the Asian enigma. Am. J. Gastroenterol. *97*, 1106–1112.

Nakajima, T. (2002). Gastric cancer treatment guidelines in Japan. Gastric Cancer *5*, 1–5.

Noda, N., Sasako, M., Yamaguchi, N., and Nakanishi, Y. (1998). Ignoring small lymph nodes can be a major cause of staging error in gastric cancer. Br. J. Surg. *85*, 831–834.

Oberhuber, G., and Stolte, M. (2000). Gastric polyps: an update of their pathology and biological significance. Virchows Arch. *437*, 581–590.

Ono, H., Kondo, H., Gotoda, T., Shirao, K., Yamaguchi, H., Saito, D., Hosokawa, K., Shimoda, T., and Yoshida, S. (2001). Endoscopic mucosal resection for treatment of early gastric cancer. Gut *48*, 225–229.

Oshima, A. (1997). Secondary prevention: Screening methods in high-incidence area. In Gastric Cancer, T. Sugimura and M. Sasako, eds. (Oxford: Oxford University Press), pp. 199–212.

Oue, N., Motoshita, J., Yokozaki, H., Hayashi, K., Tahara, E., Taniyama, K., Matsusaki, K., and Yasui, W. (2002). Distinct promoter hypermethylation of p16INK4a, CDH1, and RAR-beta in intestinal, diffuse-adherent, and diffuse-scattered type gastric carcinomas. J. Pathol. *198*, 55–59.

Palli, D. (2000). Epidemiology of gastric cancer: an evaluation of available evidence. J. Gastroenterol. *35* (*Suppl 12*), 84–89.

Park, W.S., Oh, R.R., Park, J.Y., Lee, S.H., Shin, M.S., Kim, Y.S., Kim, S.Y., Lee, H.K., Kim, P.J., Oh, S.T., et al. (1999). Frequent somatic mutations of the beta-catenin gene in intestinal-type gastric cancer. Cancer Res. *59*, 4257–4260.

Potter, J.D., Chavez, A., Chen, J., Ferro-Luzzi, A., Hirohata, T., James, W.P.T., Kadlubar, F.F., Kavishe, F.P., Kolonel, L.N., Kono, S., et al., eds (1997). Stomach. In Food, Nutrition and the Prevention of Cancer: A global perspective (Washington, D.C.: World Cancer Research Fund/American Institute for Cancer Research), pp. 148–175.

Sasako, M. (2003). Principles of surgical treatment for curable gastric cancer. J. Clin. Oncol. *21*, 274s–275s.

Schlemper, R.J., Itabashi, M., Kato, Y., Lewin, K.J., Riddell, R.H., Shimoda, T., Sipponen, P., Stolte, M., Watanabe, H., Takahashi, H., and Fujita, R. (1997). Differences in diagnostic criteria for gastric carcinoma between Japanese and western pathologists. Lancet *349*, 1725–1729.

Shimizu, N., Inada, K.I., Tsukamoto, T., Nakanishi, H., Ikehara, Y., Yoshikawa, A., Kaminishi, M., Kuramoto, S., and Tatematsu, M. (1999). New animal model of glandular stomach carcinogenesis in Mongolian gerbils infected with Helicobacter pylori and treated with a chemical carcinogen. J. Gastroenterol. *34*, 61–66.

Takada, K. (2000). Epstein-Barr virus and gastric carcinoma. Mol. Pathol. *53*, 255–261.

Tatematsu, M., Tsukamoto, T., and Inada, K. (2003). Stem cells and gastric

cancer: role of gastric and intestinal mixed intestinal metaplasia. Cancer Sci. *94*, 135–141.

Tsubono, Y., and Hisamichi, S. (2000). Screening for gastric cancer in Japan. Gastric Cancer *3*, 9–18.

Uemura, N., Okamoto, S., Yamamoto, S., Matsumura, N., Yamaguchi, S., Yamakido, M., Taniyama, K., Sasaki, N., and Schlemper, R.J. (2001). Helicobacter pylori infection and the development of gastric cancer. N. Engl. J. Med. *345*, 784–789.

Waki, T., Tamura, G., Tsuchiya, T., Sato, K., Nishizuka, S., and Motoyama, T. (2002). Promoter methylation status of E-cadherin, hMLH1, and p16 genes in nonneoplastic gastric epithelia. Am. J. Pathol. *161*, 399–403.

Xu, X., Brodie, S.G., Yang, X., Im, Y.H., Parks, W.T., Chen, L., Zhou, Y.X., Weinstein, M., Kim, S.J., and Deng, C.X. (2000). Haploid loss of the tumor suppressor Smad4/Dpc4 initiates gastric polyposis and cancer in mice. Oncogene *19*, 1868–1874.

Yamashita, S., Wakazono, K., Sugimura, T., and Ushijima, T. (2002). Profiling and selection of genes differentially expressed in the pylorus of rat strains with different proliferative responses and stomach cancer susceptibility. Carcinogenesis *23*, 923–928.

Int J Clin Oncol (2004) 9:346–351
DOI 10.1007/s10147-004-0429-x

Mitsuru Sasako

Role of surgery in multidisciplinary treatment for solid cancers

Received: June 7, 2004

Abstract In the evolution of solid cancer, there are four steps: noninvasive tumor, local invasive cancer without metastasis, local invasive cancer with lymph node metastasis, and eventually systemic disease. For the first three phases, local treatment, including lymph node dissection, may cure the disease. The choice of local treatment depends on the tumor characteristics, but surgery remains important in many of these cancers. Gastric cancer is one of the typical tumors which remain locally invasive, with or without nodal metastasis, but without systemic metastasis for a rather long period. Metastasis to lymph nodes occurs, frequently even in T1 tumors, but seldom to other sites until the late stage. Thus, the target of local control is the regional lymph nodes. The Intergroup study IT-0116 proved the effect of chemoradiotherapy (CRT) for curable gastric cancer, and thus proved the insufficiency of limited surgery (D0/1). The conventional method of local control for gastric cancer is surgery, including regional lymph node dissection (D2). However, the superiority of D2 has not been proven by randomized controlled trials (RCTs). But all RCTs so far have a crucial problem in the quality of treatment given in the D2 arm. D2 is not a dangerous procedure if done by specialists in large-volume hospitals. D0/1 plus CRT is better than D0/1 alone, but it may be worse than D2 alone. The survival benefit of CRT after D2 is an open question. Establishing standard adjuvant chemotherapy after D2 is a more urgent clinical issue, and there is no reason to abandon D2 gastrectomy for curable gastric cancer in Japan.

Key words Role of surgery · Gastric cancer · Chemoradiotherapy · Local control

M. Sasako (✉)
National Cancer Center Hospital, Tokyo, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3543-9321
e-mail: msasako@gan2.ncc.go.jp

Presentation made at the ASCO-JSCO Joint Symposium in Sapporo, Japan, on October 22, 2003.

The role of surgery in multidisciplinary treatment for cancer

We believe that solid cancers evolve as follows: lesions without invasion, then locally invasive cancer, which will soon metastasize to regional lymph nodes and then to other organs as systemic disease. The initial lesion of cancer is sometimes noninvasive, and is therefore called dysplasia, in spite of cellular or structural atypia, in the West. There are many arguments about dysplasia and early noninvasive cancer between the West and Japan, including, recently, lung cancer. Due to the development of helical computed tomography (CT), very early cancers, i.e., possible noninvasive cancers, are now being diagnosed in many countries, including the United States and Japan. For a long time, in Japan, we have diagnosed these lesions (which are called dysplasia in the West) in the stomach or in the colon, as cancer. It is well known that many of these dysplastic lesions will invade in a rather short time, at which time they are locally invasive cancers (at this point, a diagnosis of cancer is made in the West). The lesions then start to show metastasis to the regional lymph nodes, and then finally, become systemic disease, with metastases in many distant organs. For noninvasive cancer or dysplasia, just observation or limited resection, such as endoscopic mucosal resection (EMR), is the best way to manage them. For locally invasive cancer, just a wide excision could be sufficient. However, as it is impossible to discriminate exactly between locally invasive lesions with and without regional lymph node metastasis, these lesions are often treated by a wide excision plus lymph node dissection. Recently, sentinel-node biopsy has been used to discriminate those lesions with or without nodal metastasis and to minimize the level of aggressive surgery for these tumors. If the tumor becomes systemic disease, local control plus systemic treatment is mandatory if we aim to cure the disease. As the weapon for local treatment, surgery is most frequently used, but radiation can also be used, depending on the tumor characteristics. Different cancers have different patterns of tumor development or evolution. For example, small-cell

lung cancer has a very short span of limited disease, and most of the lesions of this cancer are already local regional disease plus systemic metastasis when diagnosed. At the opposite extreme is gastric cancer. In Japan, more than half of newly diagnosed lesions are T1, early gastric cancers. Advanced lesions of gastric cancer still have only local invasion and regional lymph node metastasis, which can often be cured by surgery alone. Squamous cell cancer of the esophagus would be situated between these two extremes.

Focus on gastric cancer

Table 1 shows the pattern and incidence of metastasis from gastric cancer, according to the tumor depth.[1] Lymph nodes, liver, and peritoneum are the three frequently involved sites. Other sites in the body, such as lung, bone, brain or skin, may have metastasis from gastric cancer, but only at the end of the disease development, at the terminal stage in these patients.

Table 1. Biological behavior of gastric cancer: incidence of metastasis and 5-year survival

Depth	*n*	LN	Liver	Peritoneum	5-Year survival
pT1					
M	1063	3.3	0.0	0.0	93.3
SM	881	17.4	0.1	0.0	88.9
pT2					
MP	436	46.4	1.1	0.5	81.3
SS	325	63.7	3.4	2.2	65.8
pT3					
SE	1232	78.9	6.3	17.8	35.5
pT4					
SI	724	89.8	15.5	41.6	10.1
Overall	4683	47.8	4.5	11.5	60.3

Patients operated on between 1972 and 1991, at the National Cancer Center Hospital (NCCH), including those with exploratory laparotomy: there were 22 non-resected patients, in whom T was unknown

As shown in Table 1, metastasis occurs almost exclusively to lymph nodes until the primary tumor becomes T3. Liver metastasis occurs in just 6% of the patients with T3 tumor, and in 15.5% of those with T4 tumor. Peritoneal metastasis occurs only after the tumor has reached the serosa, becoming a T3 tumor; the incidence remains at less than 20% in T3 tumors. On the other hand, the incidence of lymph node metastasis is rather high, even in the early stage of disease evolution. Even T1 submucosal invasive tumors have nodal metastasis in nearly 20% of cases. If the tumor becomes T2, over 50% of patients have regional lymph node metastasis. If these nodal metastases were to be left behind after surgery, they would metastasize and eventually become systemic disease.

So, if the patients are treated by D2 or more extensive surgery, which is the standard treatment in Japan, local regional recurrence is not common, as shown in Table 2.[1] This means that D2 dissection can provide rather good local control. By far the commonest site of recurrence is the peritoneum, and systemic and hematogenous metastases are rare (just 7% of all treated patients). Therefore, in patients with gastric cancer, local control can lead to a fairly high success rate for cure. Only 28% of patients developed recurrence; thus, over 70% of patients survived without recurrence. If these tumors are treated by very limited surgery, local regional recurrence could be a big problem.

Dr. Gunderson[2] reported the pattern of failure after limited surgery with curative intent at his institute. Fifty-four percent of recurrences occurred only in the gastric bed, and recurrences reached nearly 90% if all those with local regional failure were included regardless of other type of recurrence. This shows the importance of local control for gastric cancer.

In gastric cancer, the lymph nodes are the most important metastatic site. Table 3 shows the topographical pN stage according to the tumor depth.[1] The deeper the tumor, the more frequently lymph nodes are metastatic and the more frequently distant regional nodes become metastatic. If the tumor becomes T3, three-fourths of patients have nodal metastasis. If the tumor remains as T1 or T2, we do not see distant regional lymph node metastasis very often.

Table 2. Primary site of recurrence after ≥D2

Depth	*n*	Recurrence	LN + RF	Peritoneum	Hematogenous (%)
pT1					
M	1063	2	0	0	2 (0.2)
SM	881	18	6	3	9 (1.0)
pT2					
MP	436	45	10	9	26 (5.9)
SS	325	74	15	28	31 (9.5)
pT3					
SE	1232	625	146	330	149 (12.1)
pT4					
SI	724	562	173	283	106 (14.6)
Overall	4683	1326 (28.3%)	330 (7.0%)	635 (13.6%)	323 (6.9%)

Patients operated on between 1972 and 1991, at the NCCH, including those with exploratory laparotomy

A large proportion of patients have N2 disease; even in T2 tumor, over 20% of patients have N2 disease, and in the T3 tumors, over 40% of patients have N2 disease. This means that main target of local control in gastric cancer is lymph node metastasis. There are several grounds for saying that good local control is essential to cure this cancer. First, Professor Siewert reported that R0 resection is by far the most important prognostic factor after curative operation.[3] Second, the results of the Intergroup study (IT-0116) showed that adding irradiation to adjuvant chemotherapy could improve the results of limited surgery alone, which could not be achieved by adjuvant chemotherapy alone.[4] Good local control by radiation, together with chemotherapy, could improve the results of treatment remarkably. The researchers of the Intergroup study also carefully analyzed the prognostic factors in the patients treated in that trial, and found that surgical under-treatment was an independent prognostic factor. This theory can be applied to some other solid cancers as well.

The preferred method of local control depends on the efficacy of treatment other than surgery. If we see a non-Hodgkin's lymphoma in the stomach, we do not operate on the patients now, and chemotherapy alone can often control both the primary site and the metastasis. Of course, chemoradiotherapy does work, too. Regarding squamous cell carcinoma of the esophagus, chemoradiotherapy can often control the primary tumor and the nodal metastasis, although the local recurrence rate is as high as 20%–30% after chemoradiotherapy. For gastric cancer, even chemoradiotherapy can seldom control an advanced primary tumor, but it may well control nodal disease. Based on the results of the IT-0116 study, if gastric cancer is treated by limited surgery plus chemoradiation (CRT), the primary lesion is controlled by the surgery, and micrometastases in lymph nodes are controlled by the chemoradiation. If gastric cancer is treated by D2 surgery, both the primary and these metastases are controlled by surgery.

Table 4 shows a comparison of two studies, the IT-0116 study, and the Japan Clinical Oncology Group (JCOG) 9501 study.[5] The JCOG 9501 study is a trial organized by the Gastric Surgery Division of JCOG to evaluate the role of paraaortic lymph node dissection, which is quite extensive surgery. There are remarkable differences between these two trials: in the IT-0116, surgery was rather limited (D0; very limited resection) in 54% of patients, and D1 surgery was done in 36%, while so-called Japanese-type surgery was done in only 10%. But in the JCOG 9501 study, half of the patients underwent D2 dissection, the standard surgery in Japan. The other half underwent much more extensive surgery (D3 dissection). Regarding adjuvant treatment, those allocated to the test arm in the IT-0116 study underwent 45-Gray radiotherapy together with chemotherapy (5-fluorouracil [5-FU] and leucovorin). In the JCOG 9501 trial, none of the patients underwent adjuvant treatment until they developed recurrence. There was no difference in tumor locations between these two trials, although researchers in the United States always say that they have more proximal tumors than antral tumors. Unlike the pattern of tumor location in the general population, a much larger proportion of patients in this American trial had antral tumors, while more tumors of the body were seen in the Japanese trial. Tumor depth is shown in Table 4: 14 T1, 74 T2, 175 T3, and 18 T4 in the IT-0116 study; and 23 T1, 257

Table 3. Lymph node metastasis according to the depth of tumor invasion

Depth	No.	pN+ (%)	pN0	pN1	pN2 (%)	pN3	pN4
T1							
M	619	14 (2)	605	9	5 (0.8)	0	0
SM	499	89 (18)	410	60	29 (5.8)	0	0
T2							
MP	276	126 (46)	150	74	47 (17)	5	0
SS	207	130 (63)	77	65	57 (28)	3	5
T3							
SE	646	484 (75)	162	171	266 (41)	28	19
T4							
SI	152	121 (80)	31	31	65 (43)	12	13
Total	2399	964 (40)	1435	410	469 (20)	48	37

In gastric cancer, the main target of local control is lymph node metastasis

Table 4. Comparison of the results of IT-0116 and JCOG 9501

	IT-0116	JCOG 9501
Surgery	D0/D1/D2-54%:36%:10%	D2/D3-50%:50%
Adjuvant	Radiation 45 Gy Chemotherapy 5-FU + LV	None
No of patients	281 (Test arm)	523
Tumor location	Antrum, 53%; corpus, 24%; cardia, 21%; multiple, 2%	Lower third, 41%; middle third 39%; upper third, 19%
pT stage (1:2:3:4)	14:74:175:18	23:257:230:13
Treatment-related deaths	3 (1.1%) + Postop.	4 (0.8%)
Survival	3-Year: 50% 5-Year: 42%	5-Year: 71.4 (66.5%–76.3%)

Table 5. Estimated 5-year survival of the IT-0116 patients if they would have undergone D2-3 surgery

IT-0116 patients	NCCH[a] 5-Year survival	Calculated survival proportion	CIH[b] 5-Year survival	Calculated survival proportion
T1, 14	92.2	12.9	96.6	13.5
T2, 74	77.5	57.4	80.6	59.6
T3, 175	47.1	82.4	40.2	70.4
T4, 18	29.9	5.4	17.4	3.1
42%		56.3%		52.2%

[a] Results of National Cancer Center Hospital[6]
[b] Results of Cancer Institute Hospital[7]

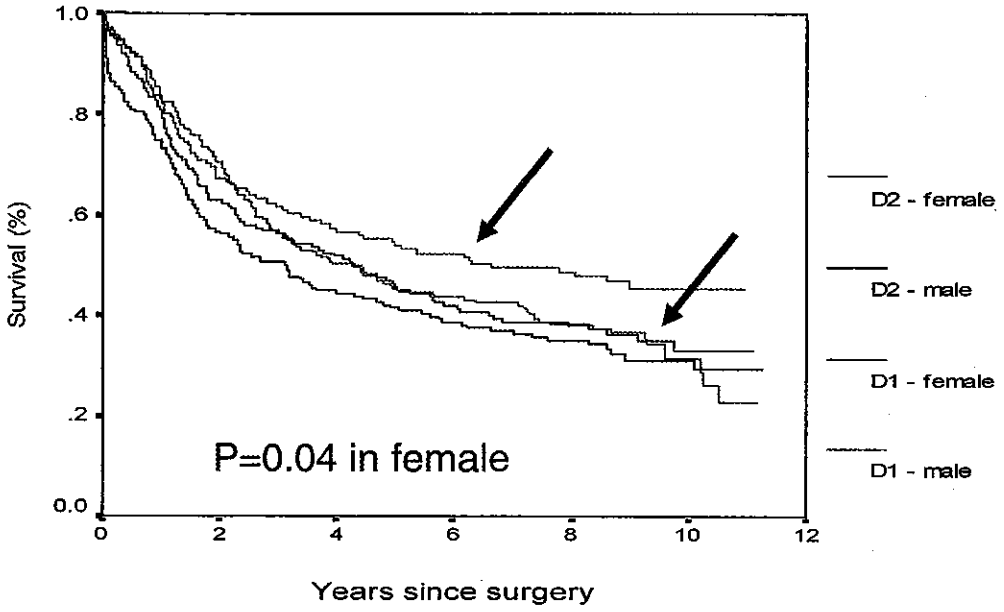

Fig. 1. D1 vs D2 for males and females. High postoperative mortality did not confound comparison in female patients

T2, 230 T3, and 13 T4 in the JCOG 9501. As to the treatment-related death rate (TRD), 1.1% was reported in IT-0116, and 0.8% in JCOG 9501. However, if the total population that could be candidates in this trial is considered, the TRD should be higher in IT-0116, because some postoperative deaths that occurred before enrolment in this trial were not counted. The survival results of IT-0116 are 50% at 3 years and 42% at 5 years, while the overall survival rate at 5 years is 71.4% in the JCOG 9501 study, although the observation time is not sufficient. As there is a non-inegligible difference of T-stage distribution between the two trials, this survival comparison is not fair. It is possible, however, to calculate the survival proportion by applying the survival rates of Japanese institutes by pT stage. The hypothetically estimated survival rates are then over 52%, which is about 10% better than the actual survival rate of the patients in the IT-0116 study (Table 5).

The results of the IT-0116 trial are interpreted as follows: (1) D0/1 surgery is proven to be inadequate treatment in terms of local control, (2) the results achieved are worse than the standard level of those treated by D2 surgery, (3) surgical under-treatment clearly undermined survival, (4) whether D0/1 + CRT can be as good as D2 alone should be tested by a RCT, (5) whether CRT after D2 can improve the results of this type of surgery alone is another question. At the same time, another question arose. Why was D2 not better than D1 in the western RCTs?

In fact, the Dutch and Medical Research Council (MRC) trials did not prove the effect of D2 dissection.[8,9] However, the quality of D2 dissection in these trials was questionable, with quite high postoperative mortality with extremely small hospital volume. The TRD rate of D2 was as high as 10% and the quality of postoperative care to avoid operative deaths was very poor, due to the small hospital volume. Not only in these trials but also in several other RCTs in surgery, a high TRD rate offsets the long-term effect of treatment. In the two trials on squamous cell carcinoma of the esophagus reported at the 39th annual meeting of the American Society of Clinical Oncology (ASCO), i.e., the German[10] and French[11] trials, a benefit of surgery after CRT was not seen in long-term survival, with a remarkable difference of the TRD rates between CRT alone versus CRT plus surgery. Based on the experience in these RCTs, we may say that proper D2 dissection is technically demanding surgery, requiring experience and specific postoperative care, and it should be carried out at specialist centers in the west.

In the Dutch trial, D2 started with a handicap of about 6%, within 3 months, but caught up with the curve of D1,

Table 6. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of D2 dissections per hospital/year	Mortality	Morbidity	Reference
Hong Kong[12]	RCT	30	7.5	3%	57%	Ann Surg
MRC[7]	RCT	200	1.5	13%	46%	Lancet
Dutch[6]	RCT	331	1.0	10%	43%	Lancet
Italian[13]	Phase II	191	8.0	3%	21%	JCO
Sue-Ling[14]	Retrospective	142	14.2	5%	17%	BMJ
Pacelli[15]	Retrospective	157	15.7	4%	22%	Br J Surg

Table 7. Mortality after major postoperative complications

Complications	Dutch trial (n = 711)		NCCH (1980s) (n = 1197)		P Value
Leakage	19/46	41.3%	12/84	14.3%	0.0005
Distal	9/22	40.1%	2/23	8.7%	0.012
Total	10/24	41.7%	10/60	16.7%	0.0047
Abscess/pancreatic fistula	19/91	20.9%	2/75	2.7%	0.0004

Experience is needed to manage major adverse effects to avoid treatment-related deaths TRD, which occur slightly more often in surgery than in chemotherapy. Hospital volume is a concern

although the difference never reached statistical significance. The hospital mortality for D2 and D1 showed a large difference, at nearly 10% for D2, and 4% for D1. But this difference was seen only in male patients, in whom hospital mortality was 4.2% for D1 versus 14% for D2. There was no difference in mortality between D1 and D2 in female patients. Accordingly, the hazard ratio between D1 and D2 by time for each sex is completely different. In female patients, the hazard ratio is almost constant. The survival curves by procedure by sex are shown in Fig. 1. As we would expect, the survival curves of the female patients do not cross, as typical model curves of survival showing a constant hazard, and the P value is 0.04. We can confirm that high immediate mortality easily offsets the long-term effect of any cancer treatment.

Table 6 shows the relation between the hospital volume and the TRD rates in many trials or consecutive series of D2 dissection for gastric cancer. The Dutch and MRC trials show extremely low numbers of patients treated per year, per hospital, and show extremely high hospital mortality, compared with other reports.

Table 7 shows the mortality after major complications, comparing the results of the Dutch trial and those of the National Cancer Center Hospital (NCCH) in the 1980s.[1] Even in a high-volume hospital, major complications, such as anastomotic leakage or intraabdominal abscess, were not rare. However, in the Dutch trial, over 40% of patients died when they developed anastomotic leak, while only 14% of such patients died in the NCCH. As to mortality after abdominal abscess, a difference of nearly ten times was observed. Experience is needed to manage major adverse effects to avoid TRD, which occurs slightly more often in surgery than in chemotherapy or CRT. In this regard, hospital volume is a concern.

The Japanese perspective of the role of D2 dissection in multidisciplinary treatment for advanced gastric carcinoma can be summarized as follows. The superiority of D2 has not been proven by RCTs. But all RCTs so far have a crucial problem in regard to the quality of treatment given in the D2 arm. D2 is not a dangerous procedure if it is done by specialists in large-volume hospitals. D0/1 plus CRT is better than D0/1 alone, but it may be worse than D2 alone. The survival benefit of CRT after D2 is an open question. Establishing standard adjuvant chemotherapy after D2 is a more urgent clinical issue. There is no reason to abandon D2 gastrectomy for curable gastric cancer in Japan.

References

1. Sasako M (2003) Principles of surgical treatment for curable gastric cancer. J Clin Oncol 23s(December 1 supplement):274–275
2. Gunderson LL, Sosin H (1982) Adenocarcinoma of the stomach: Area of failure in a re-operation series (second or symptomatic look) clinicopathologic correlation and implication for adjuvant therapy. Int J Radiat Oncol Biol Phys 8:1–11
3. Siewert JR, Boettcher K, Roder JD, et al. (1993) Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 80:1015–1018
4. Macdonald JS, Smalley SR, Benedetti J, et al. (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal jucntion. N Engl J Med 345:725–730
5. Sano T, Sasako M, Yamamoto S, et al. (2004) Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy – Japan Clinical Oncology Group Study 9501. J Clin Oncol 22:2767–2773
6. Sasako M, Sano T, Katai H, et al. (1997) Radical surgery in gastric cancer. In: Sugimura T, Sasako M (eds) Gastric Cancer. Oxford University Press, pp 223–248
7. Nakajima T, Yamaguchi T (1999) Appendix: Tubular analysis of Cancer Institute Hospital Data Base. In: Multimodality therapy for gastric cancer, pp 256
8. Bonenkamp JJ, Hermans J, Sasako M, et al. (1999) Extended lymph-node dissection for gastric cancer. N Engl J Med 340:908–914

9. Cuschieri A, Weeden S, Fielding J, et al. (1999) Patient survival after D1 and D2 resection for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 79:1522–1530
10. Stahl M, Wilke M, Walz MK, et al. (2003) Randomized phase III trial in locally advanced squamous cell carcinoma (SCC) of the esophagus: chemoradiation with and without surgery. J Clin Oncol 22 (Proceedings of ASCO meeting 2003): 250
11. Bonnetain F, Bedenne L, Michel P, et al. (2003) Definitive results of a comparative longitudinal qualiy of life study using the Spitzer index in the randomized multicentric phase III trial FFCD 9102 (surgery vs radiochemotherapy in patients with locally advanced esophageal cancer). J Clin Oncol 22 (Proceedings of ASCO meeting 2003): 250
12. Robertson CS, Chung SCS, Woods SDS, et al. (1994) A prospective randomized trial comparing R1 subtotal gastrectmy with R3 total gastrectomy for antral cancer. Ann Surg 220:175–182
13. Degiuli M, Sasako M, Ponti A, et al. (1998) Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. J Clin Oncol 16:1490–1493
14. Sue-Ling H, Johnston D, Martin IG, et al. (1993) Gastric cancer: a curable disease in Britain. BMJ 307:591–596
15. Pacelli F, Doglietto GB, Bellantone R, et al. (1993) Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. Br J Surg 80:1153–1156