はじめに

近年，再発危険因子の高い腫瘍に対しneoadjuvant chemotherapy（以下NAC）が微小転移の急激な増殖を未然に防ぐ可能性が報告されている[1,2]。現在，胃癌に対する術前化学療法（以下NAC）は胃癌治療ガイドラインでは，T3，T4を対象とした臨床研究として位置付けられている[3]。切除後予後不良とされる大型3型/4型/bulky N2進行胃癌に対し，TS-1およびCDDPを用いたNACを行ってきたのでその成績を報告する。

I．対象と方法

2003年6月～2004年9月，術前診断にて大型3型（腫瘍径が8 cm以上），4型胃癌，bulky N2の進行胃癌で術前画像上根治A，Bが可能と考えられる症例を対象とし，年齢が75歳以下，performance status（PS）0～1を条件とした。10例が登録され，これらの症例に対しTS-1 80～120 mg/bodyを21日間内服投与，TS-1開始8日目にCDDP 60 mg/m²を投与した。1週間の休薬を経て2コースのTS-1＋CDDPを行った。各コース終了後にUGI，GIF，CT検査を行い増悪がないことを確認し，2コース終了後21～34日に胃切除＋D2以上リンパ節郭清を行うこととした。増悪がみられればプロトコールを中止し，直ちに手術を行うか他の化学療法に変更することとした。有害事象の判定はNCI-CTC第2版[4]に準じた。手術にて根治度A/B症例には再発が確認されるまで術後補助療法は行わなかった。手術摘出標本の病理組織学的効果判定[5]がGrade 2以上をresponder，Grade 0～1 bをnon-responderとし，studyの完遂率，NAC後の組織学的効果判定について検討した。なお，本文中の用語はすべて胃癌取扱い規約第13版[5]に準じて表した。

II．結　果

1．症例の内訳（表1）

対象10症例の男女比は6：4，平均年齢60.7歳。肉眼病型では大型3型が6例で，うち1例はbulky N2を伴っていた。また4型が4例であった。

2．NACの副作用発現と手術成績（表1）

10例中2例は非完遂であった。1例（症例6）は1コース終了時の画像診断で増悪と判定されたため直ちに手術し，他の1例（症例5）は1コース目にgrade 3の食欲不振と下痢症状が出現し投与11日目で中断，2コース目はTS-1，CDDPを減量投与したが15日目でgrade 3の食欲不振が出現し中止，その後手術した。以上の結果，治療完遂率は8/10（80%）であった。NACの1，2コースを通じてgrade 3の副作用が3例（2例は食欲不振/下痢，1例は白血球減少）に出現した。RECISTガイドライン[6]による画像診断上効果判定は，PR 5例，SD 4例，PD 1例であった。手術術式は胃全摘＋D3が4例，胃全摘＋D2 5例，幽門側切除＋D3 1例であった。術後関連合併症は肝機能障害，リンパ漏，肺炎がそれぞれ1例ずつであった。在院死例はなかった。総合所見Stage ⅠA 2例，ⅠB 3例，Ⅱ1例，ⅢA 1例，Ⅳ3例であった。根治度A 5例，B 2例，C 3例であった。根治度Cの理由は，PM（＋），P1，CY 1各々1例ずつであった。根治度Cでは2例にpaclitaxelを中心にした化学療法が行われた。

NACの病理組織学的効果判定がGrade 2のresponderは5例で，いずれも画像診断でPRと判定された症例であった。またSDと判定された4例のうち2例はGrade 1a，Grade 0，1bが各々1例であった。PDの1例は組織学的にはGrade 1aであった。平均観察期間は298日（136～654日）で，現在までに4例（responderの1例，non-responderの3例）に再発を認め，その平均無再発期間は238日であった。

3．Down staging症例

症例1：65歳，女性。胃体中部の4型胃癌（図1a，b）。生検結果はsigであった。NAC 2コース終了後，画像上明らかな改善を認めた（図1c，d）。胃全摘＋脾動脈幹切除＋D2施行。摘出標本の肉眼所見では胃体中部に陥凹病変を認め（図2a），摘出標本の病理組織像はSS層まで多数の粘液結節が認められ（図2b，d），粘膜下層にわずかな癌細胞が認められるのみであった（図2c）。No 4dのリンパ節内にも粘液結節が認められ（図3a，b），No 8a，11pにも線維化がみられた（図3c，d）。病理組織学的効果判定はGrade 2であった。術後331日目にイレウスにて再手術し，大動脈周囲リンパ節転移および腹膜転移が確認されたが，PS不良のため化学療法は行えず，419日で癌死した。

症例3：61歳，男性。噴門部の大型3型胃癌で，食道への浸潤・圧排像がみられた。生検結果はpor 1であった。NAC 2コース施行後，著しい腫瘍の縮小と食道浸潤像の消失を認めた。CT像では胃上部の壁肥厚と脾門部付近のbulky N2を認めた（図4a，b）が，NAC後，著明な縮小がみられた（図4c，d）。胃全摘＋膵体尾脾切除＋D3を行った。切除胃の病理組織学的所見では，SS層に至るまで線維化がみられ（図5a，b），食道胃接合部付近の食道および胃の粘膜下層2か所に小癌蜂巣（por 1）を認めた（図5c，d）。リンパ節組織像では11dリンパ節（図6a），16a2latの2/12に線維化を認めた（図6b）。術後227日の現在，無再発生存中である。

表 1　TS-1＋CDDP を用いた術前化学療法症例

	症例	年齢	性	生検結果	肉眼型	副作用(NCI-CTC)	臨床効果(RECIST)	手術術式	総合所見 Stage	根治度	組織学的効果判定	術後療法	再発	無再発期間	生存期間	転帰
◎	1	65	F	sig	4型	grade 1 (食思不振)	PR	胃全摘＋脾動脈幹切除 ＋D 2	I A	A	Grade 2	なし	大動脈リンパ節 /腹膜	331	419	死亡
	2	47	F	tub 1 /tub 2	大型 3 型	grade 3 (白血球減少)	PR	幽門側切除＋D 3	IV	B	Grade 2	なし	なし	310	310	生存
◎	3	61	M	por 2	大型 3 型 /Bulky N 2	grade 1 (口内炎)	PR	胃全摘＋膵体尾脾切除 ＋D 3	I A	A	Garde 2	なし	なし	227	227	生存
	4	72	M	tub 2	大型 3 型	grade 1 (食思不振)	PR	胃全摘＋脾動脈幹切除 ＋D 2	I B	A	Grade 2	なし	なし	205	205	生存
△	5	68	M	tub 2	大型 3 型	grade 3 (食思不振 /下痢)	PR	胃全摘＋脾動脈幹切除 ＋D 3	I B	A	Grade 2	なし	なし	147	147	生存
△	6	75	F	sig	4型	grade 2 (白血球 /血小板減少)	PD	胃全摘＋脾温存＋D 2	I B	C (PM＋)	Grade 1 a	weekly paclitaxel	腹膜	211	654	生存
	7	50	F	por 2	4型	grade 3 (食思不振)	SD	胃全摘＋脾動脈幹切除 ＋D 2	IV	C (CY 1)	Grade 1 a	TS-1＋ paclitaxel	腹壁	289	385	死亡
	8	55	M	sig	4型	grade 1 (食思不振)	SD	胃全摘＋脾動脈幹切除 ＋横行結腸＋D 2	IV	C (P 1)	Grade 1 b	なし	大動脈リンパ節 /腹膜	122	336	死亡
	9	56	M	por 2	大型 3 型	grade 0	SD	胃全摘＋脾動脈幹切除 ＋D 3	II	A	Grade 0	なし	なし	157	157	生存
	10	58	M	tub 1 /tub 2	大型 3 型	grade 1 (食思不振)	SD	胃全摘＋脾動脈幹切除 ＋D 3	IIIA	B	Grade 1 a	なし	なし	136	136	生存

◎: down stage 確認症例　△: 非完遂例　: responders　: nonresponders

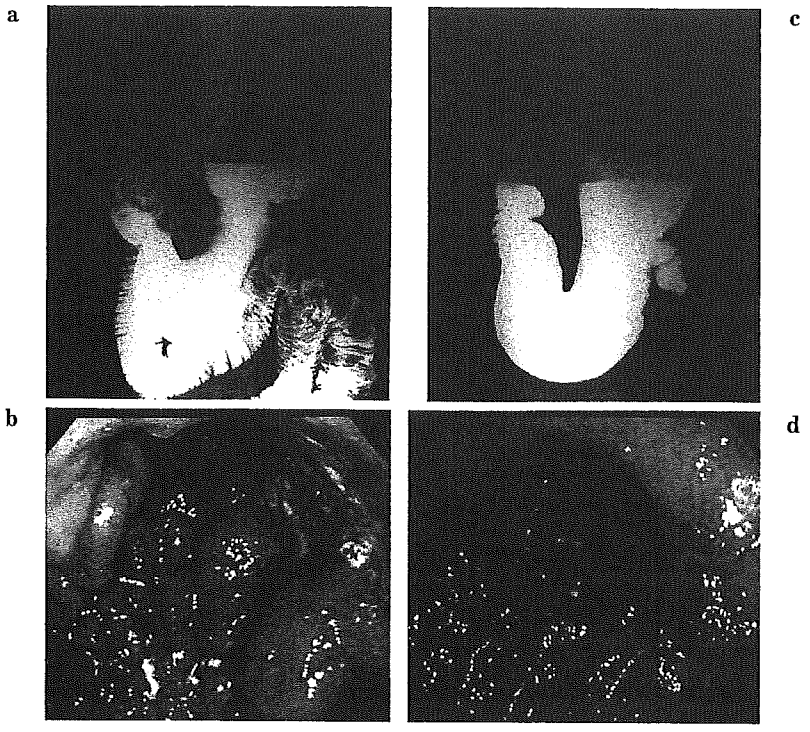

図 1　症例 1 の上部消化管造影，内視鏡像
a, b: 治療前
　胃体中部に 4 型病変を認める。
c, d: 治療後
　胃充盈像の胃壁の硬さは改善し，内視鏡像にて腫大皺襞の改善を認める。

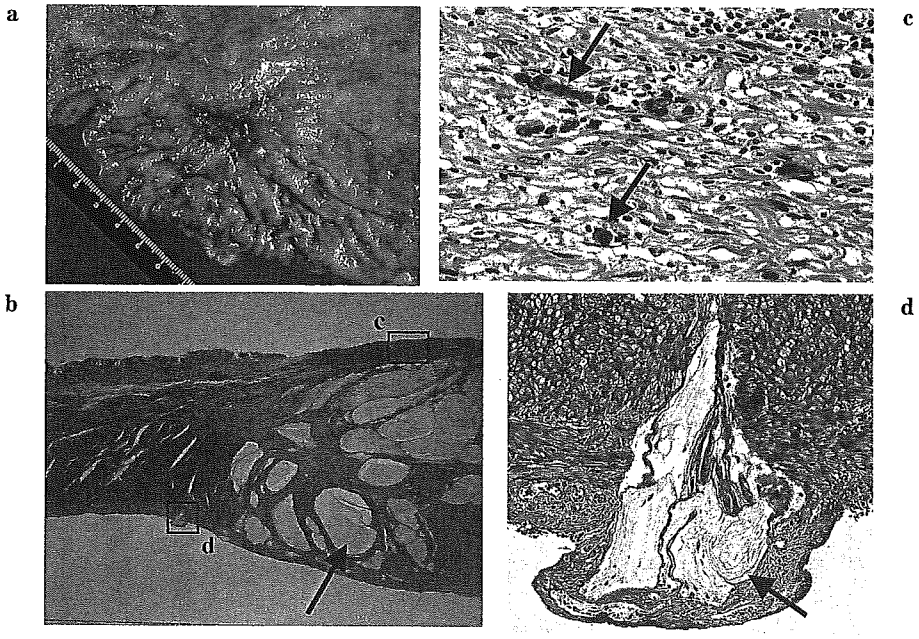

図 2　症例 1 の切除胃とその病理組織所見
a: 切除胃標本
　胃体中部に陥凹病変を認める。
b: 切除胃ルーペ像
　多数の粘液結節を認める（↑）が癌細胞の浮遊はみられない
c: 粘膜下層の病理組織像（×40）
　わずかな viable と思われる癌細胞を認める（↓）。
d: 漿膜下層の病理組織像（×10）
　漿膜下層にも粘液結節を認める（↑）。

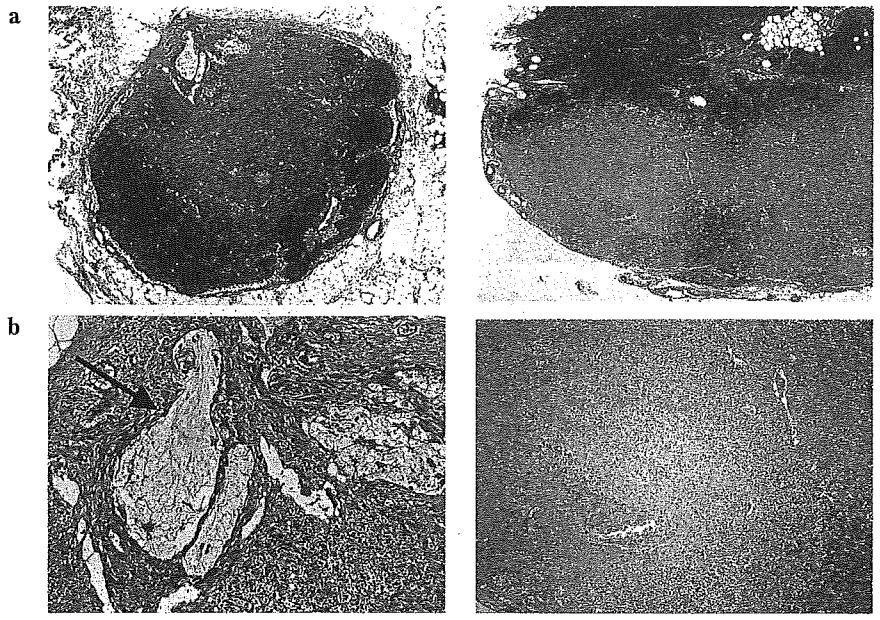

図 3　症例1のリンパ節病理組織所見
a: 4dリンパ節のルーペ像
b: 4dリンパ節の中拡大（×10）
　リンパ節内に粘液結節（→），線維化を認めるが癌細胞は認められない。
c: 8a，11pリンパ節のルーペ像
d: 8a，11pリンパ節の弱拡大（×4）
　リンパ節内に線維化を認めるが癌細胞は認められない。

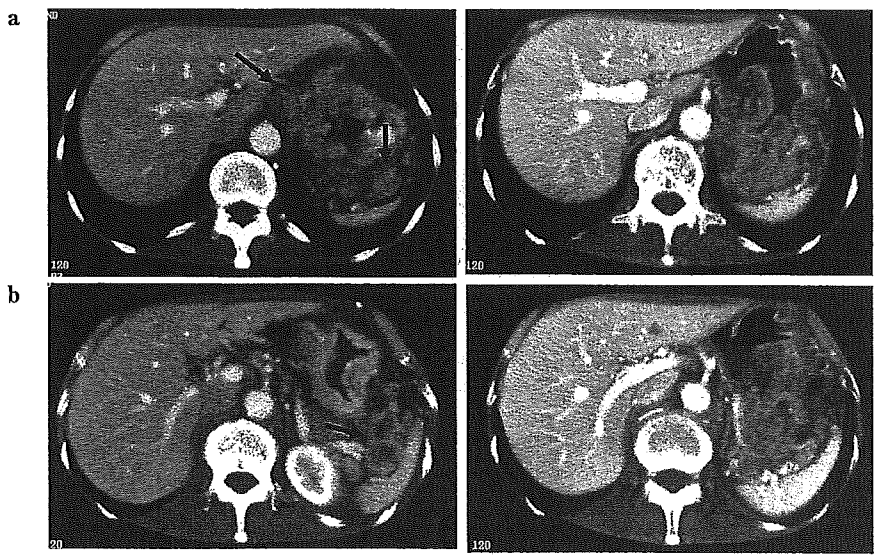

図 4　症例3のCT像
a, b: 治療前
a: 胃上部の壁肥厚と小弯側，大弯側に一塊となったリンパ節腫大を認める（↓）。
b: 脾門部付近にも一塊となったリンパ節腫大を認める（→）。
c, d: 治療後
　著明なリンパ節腫大の消失を認める。

III. 考　察

NACの目的には，根治不能症例にNACを行いdown stagingを図ってから根治手術しようという立場[7]と，切除可能症例に対しNACを行い微小転移巣の根絶を目指す[1,2]二つがある。近年，胃癌に対し高い奏効率を示す抗癌剤が出現してきたことと，術後補助化学療法の効果が明らかにされていないことにより術前化学療法が注目されている[8]。進行胃癌に対するTS-1+CDDP phase I/II studyでは76%という高い奏効率が報告されている[9]。このstudyは高い奏効率をもったこれら薬剤を用いたNACにより，切除予後不良な8cm以上の大型3

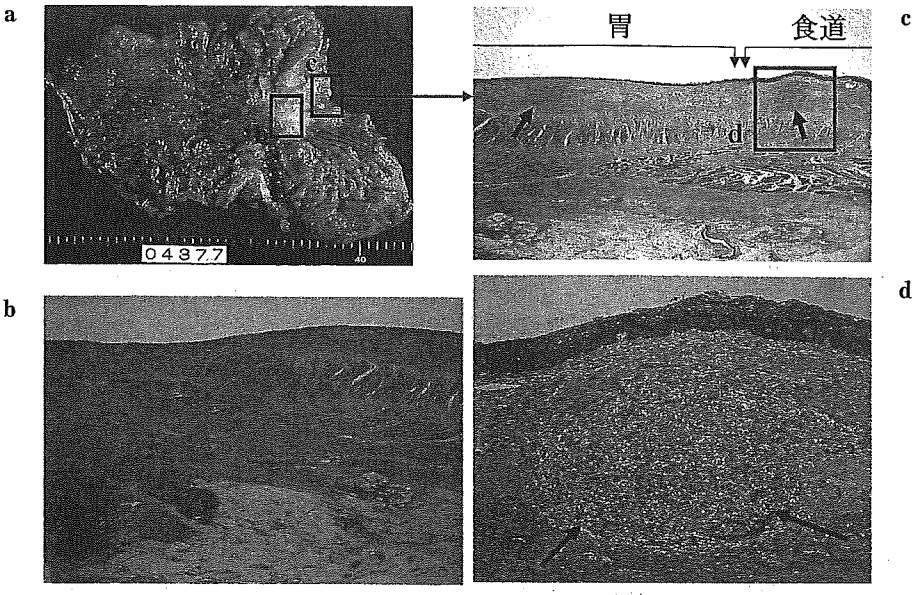

図 5 症例 3 の切除胃標本とその病理組織所見
a: 切除胃標本
b: 胃壁のルーペ像
病巣が存在したと思われる胃壁は SS 層に至るまで線維化がみられる。
c: 食道胃接合部付近に食道および胃粘膜下層の 2 か所に小癌蜂巣を認める（↑）。
d: 食道壁の病理組織像中拡大（×10）
por 1 病変の残存（↑）。

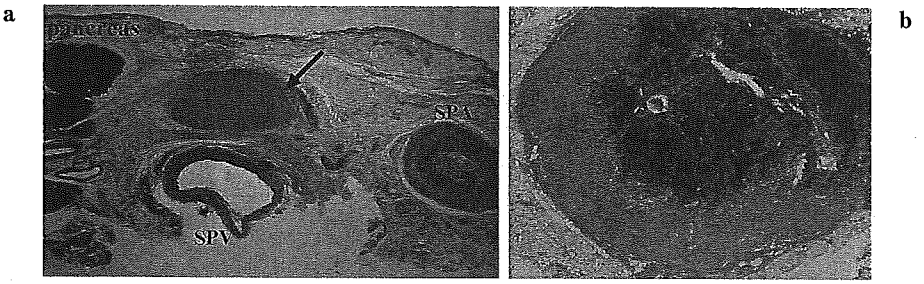

図 6 症例 3 のリンパ節病理組織所見
a: 膵尾部切片のルーペ像
11 d リンパ節が線維化し癌細胞が認められない（↓）。
（SPV: 脾静脈，SPA: 脾動脈）
b: 16 a 2 lat のルーペ像
2/12 に線維化を認める。

型[8]，4 型胃癌[8]および Bulky N 2 胃癌[10,11]の予後改善を期待して行われた。regimen は Japan Clinical Oncology Group（JCOG）の胃がん外科グループによる TS-1＋CDDP を用いた術前化学療法の study（JCOG-0210）に準じた。

TS-1＋CDDP 療法は高い有効性を示す反面，毒性も強いことが予想される。薬物毒性のため NAC 後の手術療法が行えなくなることを懸念し，NAC は 2 コースと設定した。また，NAC の有効性をより明確にしたいという目的で，根治度 A・B 症例には術後補助化学療法は再発が確認されるまで行わないこととした。

NAC の利点として薬剤効果が組織学的に評価できることがあげられている[12]。藪崎ら[13]は根治不能と診断された 37 例に TS-1＋CDDP の NAC を行い臨床診断にて 62.2%の高い奏効率を報告しているが，切除された 24 例のうち組織学的効果判定で Grade 2 が得られた症例は 6 例（25%）にすぎない。われわれの検討は，病理組織学的効果 Grade 2 を responder として評価した。その結果 5 例（10 例中）の responder が得られた。それらはいずれも RECIST[6]による画像効果判定でも PR という評価が得られた症例であった。

この study では切除可能症例を対象に NAC を行ってきたが，その問題点として化学療法無効例に手術時機を逸する可能性があげられる。症例 6 のように，NAC の効果は PD で，術後再発を来したものの術後 paclitaxel の weekly 投与に変更し，長期生存している症例もあるの

でNAC施行中，画像上増悪と診断される症例には早期にregimenを変更するか，術後薬剤を変更したadjuvant chemotherapyを考慮すべきと思われる。また，4例の再発例がいずれも4型の胃癌であることは，4型胃癌に対しては2コース以上のNACを行うか，術後補助化学療法の必要性を示唆している可能性がある。

組織学的見地からNACによるdown stagingが得られたと思われる症例がresponder 5例中2例に認められた。症例1は治療前T2（SS），N2　Stage ⅢAからpT1（SM），pN0，CY0，sP0，sH0 Stage ⅠAに，症例3は治療前T2(SS)，N3 Stage ⅣからpT1(SM)，pN0，CY0，sP0，sH0 Stage ⅠAにdown stagingされた症例と推察される。

NACが術後の生存期間に貢献できるかどうかについてはいくつかの報告があり[7,14,15]，responderの生存率は高い[7,15]という報告もみられるが，いまだNACが術後予後改善につながる明確なエビデンスは得られていない。今後，切除可能進行胃癌を対象として多施設共同研究によるNAC+surgeryとsurgery aloneとの第Ⅲ相試験による客観的評価の必要性がある。

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World J. Surg. 29, 1131–1134 (2005)
DOI: 10.1007/s00268-005-7703-6

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When Is Curative Gastrectomy Justified for Gastric Cancer with Positive Peritoneal Lavage Cytology but Negative Macroscopic Peritoneal Implant?

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Published Online: August 11, 2005

Abstract. For gastric cancer patients who have no peritoneal seeding at a macroscopic level but positive results in the peritoneal lavage cytology (PLC), the prognostic benefit expected by surgical resection is still controversial. During the period 1975–1994 as series of 417 consecutive patients without distant organ metastases underwent surgical resection for gastric cancer that had invaded the subserosal or deeper layers of the stomach wall. Immediately after laparotomy, the pouch of Douglas was washed with 100 ml of physiologic saline solution, and the fluid was collected for cytologic examination (four slide glasses) using Giemsa and Papanicolaou staining methods. According to the macroscopic (P) and cytologic (Cyt) results, the 417 patients were classified into three groups: P^+ (n = 97); P^-/Cyt^+ (n = 25); and P^-/Cyt^- (n = 295). Their 3-year survival rates after surgical resection were 4%, 24%, and 48%, respectively (p = 0.0001: P^-/Cyt^+ vs. P^-/Cyt^-; p = 0.0018: P^-/Cyt^+ vs. P^+. Among the 25 P^-/Cyt^+ patients, postoperative survival was not associated with the T stage, N stage, cellular atypism, or cluster formation but with the number of cancer cells per slide during PLC. The 3-year survival rate was 35% for the subgroup with fewer than 10 cancer cells per slide (17 patients) and 0% for the other subgroup with 10 or more cancer cells per slide (8 patients) (p = 0.017). For P^-/Cyt^+ patients, who represent a subgroup of gastric cancer patients with an intermediate survival rate between the P^-/Cyt^- and P^+ patients, the number of cancer cells observed during PLC offers a potent prognostic indicator for the gastrectomy.

Despite the recent spread of gastroscopic examinations, a large number of gastric cancers are diagnosed in advanced stages. Once the primary tumors invade directly into the subserosal or serosal layers of the gastric wall, cancer cells are more likely to spread into the abdominal cavity and consequently implant on the peritoneal surface (peritoneal dissemination) [1]. At present, when peritoneal implants at a macroscopic level (implant-positive, or P^+) are detected during laparotomy, it is generally accepted that gastrectomy does not provide a prognostic benefit for them. Even after a curative gastrectomy is performed for those who have no peritoneal seeding at a macroscopic level (implant-negative, or P^-), peritoneal dissemination is the most common cause of subsequent cancer death [2–4]. Thus, some authors have tried to detect occult peritoneal dissemination using peritoneal lavage cytology (PLC) for stricter indications of the curative gastrectomy [5, 10–10]. Although P^- patients with negative PLC (Cyt^-) resulted in far better long-term outcomes after resection than P^- patients with positive PLC (Cyt^+) [11, 12], it is still controversial whether curative gastrectomy should be abandoned for all P^-/Cyt^+ patients. It is of no doubt that the floating cancer cells in the peritoneal cavity do not always survive to form an implantation. Boku et al. reported that the 3-year survival rate after gastrectomy was 25% in P^-/Cyt^+ patients [11], but they did not mention any shared characteristics of this survival group.

Among Cyt^+ patients, there is wide variation in the number of cancer cells detected, the presence or absence of cluster formation, and the degree of cellular atypism. In reviewing the previous reports, only cluster formation was once taken into consideration by a small number of authors, but no definitive conclusions have yet been determined in association with patient survival [7, 13]. Thus, the present study was conducted to clarify whether curative gastrectomy should be abandoned for all P^-/Cyt^+ patients from the viewpoint of long-term outcome (by analyzing more detailed cytologic features).

Patients and Methods

During 1975–1994, a series of 417 consecutive patients underwent surgical resection with curative intent of gastric cancers that had invaded the subserosal or deeper layers of the stomach wall, at The Osaka Medical Center for Cancer and Cardiovascular Diseases. This group of patients included a number of cancer patients

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in whom macroscopic curative resection was considered possible, regardless of the presence of peritoneal implants. However, patients were excluded from the study when at the preoperative workup (laparoscopic staging) or at laparotomy numerous macroscopic peritoneal implants to distant peritoneum were found or when massive lymph node metastases beyond the surgical field or liver metastases were revealed. All patients whose resection was abandoned died within 2 years after laparotomy.

When such types of cancer extension were not proven, the peritoneal cavity was washed with 100 ml of physiologic saline solution (37°C), and the fluid was then collected from the pouch of Douglas. The collected fluid was immediately centrifuged at 2000 rpm for 3 minutes, and the sediment was smeared on four slide glasses. The slides were stained by Giemsa and Papanicolaou methods and diagnosed by cytologists who were blinded to the clinical information [14]. The PLC results were classified as positive when at least one cancer cell was detected; a suspicion of malignancy was classified as negative. The diagnosis of a cancer cell was based on nuclear size including the nuclear/cytoplasm (N/C) ratio, its anisokaryosis, membrane pattern, nucleoli pattern, and density of chromatin. Postoperatively, for the cytology-positive slides, the total numbers of cancer cells were counted, and the presence or absence of cluster formation of cancer cells was determined. The detected cancer cells were also examined as to whether they had severe nuclear atypism showing a high N/C ratio and dense chromatin (Fig. 1) [15–17]. In the gastrectomy cases, the distal two-thirds of the stomach or the entire stomach was removed, and a regional lymphadenectomy was done. Before closing the abdomen, the intraperitoneal space was washed with 2000 ml of physiologic saline.

After surgery, patients were followed at our outpatient clinic with an interval of 3 to 6 months, including physical checkups and laboratory examination of tumor markers such as the carcinoembryonic antigen (CEA). In addition, chest roentogenography, gastric endoscopy, and abdominal ultrasonography and computed tomography (CT) were performed to determine if tumor recurrence was present. If present, the site(s) were also determined.

Patient survival was calculated by means of the Kaplan-Meier method, and the statistical significance of the differences between curves was tested by the log-rank test. Significance was assumed if $p < 0.05$. The statistical analyses were performed using the StatView 5.0 program (SAS Institute, Cary, NC, USA).

Results

The 417 patients who had undergone surgical resection consisted of 256 men and 161 women with a mean age of 60 ± 12 years (range 27–87 years; median 61 years). According to both P and Cyt results, they were classified into the following three groups: P^+ ($n = 97$); P^-/Cyt^+ ($n = 25$); and P^-/Cyt^- ($n = 295$). Figure 2 shows the postoperative survival rates of these three groups. The 3-year survival rates after surgical resection were 4%, 24%, and 48%, respectively ($p = 0.0001$: P^-/Cyt^+ vs. P^-/Cyt^-; $p = 0.0018$: P^-/Cyt^+ vs. P^+). The median survival periods were 10.8, 18.4, and 30.0 months, respectively. The groups showed similar patterns in that most of deaths occurred within 30 postoperative months but were rare thereafter.

Among the 25 P^-/Cyt^+ patients, 17 patients died within 30 postoperative months (2.5 years) and 8 patients survived 30 months or more. Excluding one patient who is still alive at 5 years and another patient who died of other disease (noncancer), the other 23 patients died of cancer. The cause of cancer death was peritoneal dissemination in 19 patients (79%); liver metastases, lung metastases, and pleuritis carcinomatosa were seen in one patient each. Table 1 compares the background factors between the two subgroups, which were classified according to whether patients survived more than 30 postoperative months or not. As a result, age, gender, the depth of cancer invasion in the gastric wall, the status of nodal involvement (UICC classification), or the histologic type of cancer did not differ between the two subgroups.

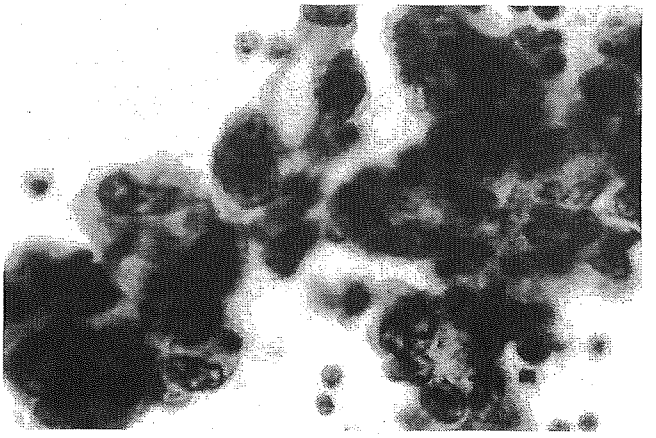

Fig. 1. Severe cellular atypism showing higher N/C ratio and dense chromatin. (Papanicolaou staining of intraperitoneal free cancer cells, ×40).

Importantly, the number of cancer cells per slide differed significantly ($p = 0.019$). Ten or more cancer cells were detected in 8 (47%) of 17 patients who died within 30 months but in none of the 30-month survivors. However, neither cluster formation nor severe nuclear atypism reached statistical significance. Figure 3 compares patient survival in association with the number of cancer cells. The 3-year survival was 35% in 17 patients with fewer than 10 cancer cells per slide, which was significantly better than 0% in the 8 patients with 10 or more cancer cells per slide ($p = 0.017$). The median survivals were 25.5 and 8.6 months, respectively. The latter subgroup had survival rates similar to those of the P^+ patients ($p = 0.96$) (Fig. 3).

Discussion

The fluid collected from the peritoneal washing contained not only exfoliated cancer cells but also mesothelial cells, histiocytes, and other nonmalignant cells. Floating cancer cells usually show a wide variety of degeneration. A strict definition was applied to the cancer cells that excluded suspicious or borderline malignant cells because we had previously considered it necessary not to overlook any candidates for longer-term survival during the gastrectomy. As a result, only 25 (8%) of 320 P^- patients showed positive cytology results despite direct invasion of their primary gastric cancers to the subserosal or deeper layers of the wall of the stomach. Likewise, among our 97 P^+ patients, the Cyt^+ rate was also low: 56% (54 patients). Similarly, Bonenkamp et al., with a

Table 1. Clinicopathologic characteristics of P^-/Cyt^+ patients (n = 25) with respect to survival after surgery.

Survival after surgery years	No. of patients, by years of survival after surgery		p
Parameter	≥ 30 months	< 30 months	
No. of Patients	8	17	
Age (years)	53.1 ± 12.3	62.3 ± 11.4	
Gender			0.48
Male	4	11	
Female	4	6	
Surgical resection			0.40
Distal gastrectomy	2	2	
Total gastrectomy	6	15	
Depth of tumor invasion			0.54
T2	4	6	
T3	4	9	
T4	0	2	
Lymph node involvement (UICC)			0.21
N1	4	3	
N2	1	6	
N3	3	8	
Histology			0.82
Differentiated	2	5	
Undifferentiated	6	12	
No. of cancer cells per slide			0.019
< 10	8	9	
≥10	0	8	
Cluster of cancer cells			0.94
Absent	2	4	
Present	6	13	
Large cancer cells with severe cellular atypism			0.054
Absent	8	11	
Present	0	6	
Major cause of death[a]			0.61
Peritoneal dissemination	6	13	
Other	1	4	

[a]Except for one patient who survived more than 5 years and is still alive.

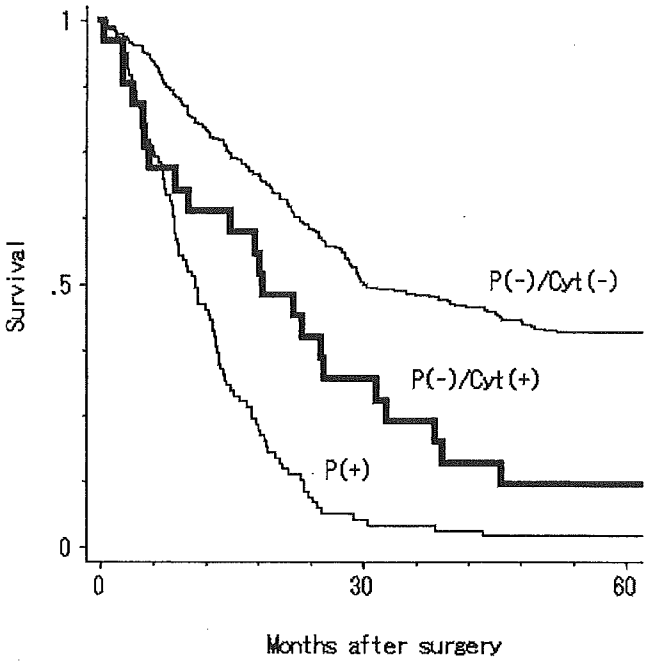

Fig. 2. Survival curves for patients with gastric cancer that invaded the subserosal or deeper layers with respect to peritoneal implants at a macroscopic level (P) and peritoneal lavage cytology (Cyt) results: P^+ (n = 97); P^-/Cyt^+ (n = 25); and P^-/Cyt^- (n = 295). (p = 0.0001 for P^-/Cyt^+ vs. P^-/Cyt^-. p = 0.0018 for P^-/Cyt^+ vs. P^+.

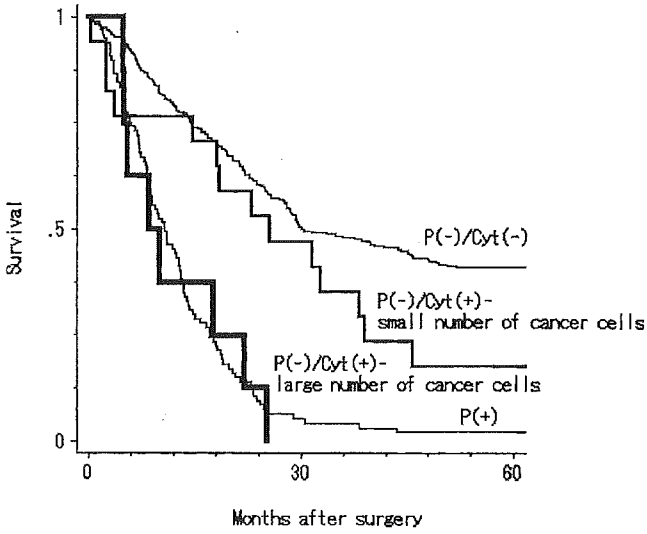

Fig. 3. Survival curves for P^-/Cyt^+ patients in association with the number of cancer cells. p = 0.017 for 8 patients with a large number of cancer cells by peritoneal lavage cytology (PLC) versus the 17 remaining patients. Survival curves did not differ significantly between the subgroup of patients with large numbers of cancer cells in the P^-/Cyt^+ group and the P^+ patients (p = 0.96).

strict definition like ours, showed that the sensitivity rate of PLC was as low as 28% to 60% [12]. Thus, we consider that no false-positive cases were included among our 25 Cyt^+/P^- patients.

In the present result, the P^-/Cyt^+ group showed an intermediate survival rate between the P^-/Cyt^- and P^+ groups (Fig. 2). Because similar results were reported by Boku et al. [11] and Bonenkamp et al. [12], it raises the question of whether a survival benefit would be gained by gastrectomy among P^-/Cyt^+ patients. Although both T and N stages are generally accepted as simple, potent indicators in cancer staging, all of our 25 P^-/Cyt^+ patients had both nodal involvement and T2 or more depth of cancer invasion. Thus, instead of N or T stages, some other prognostic indicators should be applied to such a limited group of P^-/Cyt^+ patients.

The present report seems to be the first to compare three cytologic features (number of cancer cells, cellular atypism, and cluster formation) in association with patient survival. It concluded that the number of cancer cells was the only significant prognostic factor (Table 1, Fig. 3). The survival curve in the subgroup with 10 or more cancer cells was similar to that of the P^+ group, and the survival curve in the subgroup with fewer than 10 cancer cells was similar with that of the P^-/Cyt^- group during the first 30 postoperative months (Fig. 3). Such a clear association with the number of cancer cells seems to be partly explained by the fact that the cancer cells were counted objectively, whereas the definition of cellular atypism is subjective, with a wide variation among cytologists.

Regarding cluster formation, an experimental study suggested that the up-regulation of adhesion molecules on cancer cells, which might be related to the clustering tendencies of cells, prevents apoptosis in vitro [18]. However, Majima et al. [13] suggested that cluster formation was of poorer prognosis, whereas Iitsuka et al. [7] reported that clusters were associated with a better prognosis. Considering that the presence or absence of cluster formation is easily judged by the microscopic observation itself, their opposite conclusions might have been partly due to artifacts (cell aggregation) that appeared during the cell treatment procedures.

Our classification based on the number of cancer cells is simple and requires no additional time-consuming procedure. In other words, it is practical for surgical decision-making, especially for laparoscopic staging, which is often applied to patients with gastric cancers that invaded the submucosal or deeper layers.

In this retrospective series, the P^-/Cyt^+ patients accounted for only 6% (25/417), and 23 of 25 patients underwent some postoperative chemotherapy. Whereas we recognize the possibility that these factors may have some impact on selection bias or outcome in the study and the importance of verification by further studies, newer therapies are needed for this subgroup. Our classification based on the number of cancer cells would be helpful for selecting the candidates more appropriately.

Although our subgroup with a small number (< 10) of cancer cells survived longer after gastrectomy than the other subgroup (≥ 10), 6 of 8 patients in the former subgroup finally died of peritoneal dissemination. When gastrectomy is applied to patients in the low cancer cell number subgroup, some adjuvant therapies, specifically focused on peritoneal dissemination, are needed. Some recent authors reported a few successful cases in which carcinoma of the peritoneum disappeared after chemotherapy [19]. Studies are also required to confirm which anticancer drug is most effective for controlling peritoneal dissemination.

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