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高度進行胃がんの治療に関する研究

平成１８年度　総括研究報告書

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目　　次

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主任研究者　笹子　三津留　国立がんセンター中央病院副院長

研究要旨
腹腔鏡検査で播種を含めた遠隔転移がないことが確認された大型3型・4型胃がんに対して、手術単独群を対照とし、試験アームはTS-1+CDDP療法を2コース行う術前化学療法を施行後に根治手術を行う無作為化第Ⅲ相試験を2005年10月より開始した。2006年に入り、倫理審査委員会による試験実施の承認が下りた施設の増加に伴い、登録ペースがよくなり、2006年5月、6月は月間4例の登録ペースとなり、7月初めには16例を登録していた。これからいよいよ本格的に登録が増える兆しがあったこの時期に、本研究にとって極めて重大な影響のある市販後臨床試験、ACTS-GC試験で第1回目の中間解析で有効中止となったという情報が入った。その結果、今後わが国では、ステージII以上の胃がんでは、TS-1の術後補助化学療法が標準治療となると考えられ、この時点で試験への登録を緊急に中止した。ACTS-GCの結果の詳細を確認後、本第Ⅲ相試験のプロトコール改訂作業に入った。研究参加者の討議の結果、対照群の治療を手術単独から術後TS-1による補助化学療法とし、試験治療群にも同じ補助化学療法を追加し、TS-1+CDDPによる術前化学療法の上乗せ効果を見る試験として、改訂した。2007年2月にJCOG効果・安全性評価委員会で改訂が承認され、登録の再開が決まった。

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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。がん対策基本法にうたわれた75才以下の生存率の改善にこの研究は極めて重要である。

Ｂ．研究方法

【研究形式】多施設共同の第Ⅲ相ランダム化比較試験（優越性試験）：プライマリーエンドポイントは全生存期間。
【研究対象】腹腔鏡検査を含めた臨床的検索で遠隔転移を伴わない、治癒切除可能な8cm以上の大型3型・4型胃がん症例。術前の画像診断で食道浸潤が3cm以下であり、登録時の年齢が20歳以上75歳以下、PS0,1、充分な経口摂取ができ、諸臓器の機能が良好で、患者本人の自由意志に基づく文書による同意を得ているこ

と。適格性を判断するために行う検査は総て日常臨床で通常行う検査であり、それらにより適格となった場合に、本試験に関する説明を行う。
【症例登録とランダム割付】JCOGデータセンターで中央登録し、施設、肉眼型、壁深達度、リンパ節転移程度を割付調整因子として最小化法にて割り付ける。対照群は手術単独であったが、前記臨床試験の結果を受けて、手術＋術後TS-1による補助化学療法と変更、試験治療はTS-1+CDDPによる術前化学療法2コース＋根治手術＋TS-1による術後補助化学療法である。
【治療内容】試験治療：術前TS-1(3週投与1週休薬）＋CDDP(day8)による化学療法を2コース行う。治癒切除可能症例ではD2以上の郭清を伴う根治手術を行い、術後6週以内よりTS-1単独による化学療法を手術後1年を目安に実施する。対照群：割付後早期に試験群と同様な内容の手術を行い、術後は試験治療と同じTS-1単剤による化学療法を1年を目安に実施する。
【解析方法】全生存期間を用いた中間解析は予定登録数の半数が登録された後の最初の定期モニタリング時および全症例が登録を完了して治療が終了する時期の2度予定する。中間解析は適切な方法で多重性を考慮して行う。最終解析は、全例登録後3年経過時点で行う。
【予定症例数】予定登録数は両群併せて300例とし、期待イベント数は276とする。算定根拠は標準治療群の3年生存率が15-20%、試験治療群が10%以上それを上回ることを検証するとし、片側$\alpha=0.05$でほぼ80%の検出力をもって検出できる。
【実施施設】JCOG胃がん外科グループに所属する消化器がんの基幹施設約30施設で実施する。
【年次計画】平成19年1-3月に改訂されたプロトコールの各施設のIRBの承認を得、登録を再開する。両群に補助療法が入ることになったため、以前の計画よりは登録同意率が上がると予想され、19年度より3-4年で全300例を登録予定とする。
（倫理面への配慮）
本研究は手術単独を対照群とした第Ⅲ相試験として開始したが、ACTS-GC試験の結果をふまえて標準治療が変わったことから、倫理的観点から、それが判明した時点で即刻登録を中止し、プロトコールの改訂に取り組んだ。改訂プロトコールは現在JCOG効果安全性評価委員会で審査中である。同委員会で承認され次第、各参加施設の倫理審査委員会で再度変更点に関する審査を受け、倫理性と同時に当該施設における参加の妥当性も検討される。本人に口答及び文章による説明を行い、文章による同意を得る。説明内容には、試験参加の自由、同意後の撤回の自由、質問の自由、個人情報の扱いなどが含まれ、試験の同意取得は、ヘルシンキ宣言、個人情報保護法、臨床研究に関する倫理指針の総ての要件を満たして行われる。

C．研究結果
本研究に先立ち、厚労科研「効果的医療技術の確立推進臨床研究事業」における『術前化学療法による高度進行胃がんの予後改善に関する研究』において、TS-1+CDDPの術前化学療法の安全性と有効性の評価を第Ⅱ相試験（JCOG0210)として実施した。同試験において、高い安全性と治療完遂割合が得られた。引き続き厚労科研がん臨床研究『高度進行胃がんの治療に関する研究』において、17年11月より手術単独を対照群として第Ⅲ相ランダム化試験（JCOG0501）を実施中であった。しかし、18年7月にTS-1の術後補助化学療法の有用性が証明されたことがわかった。この結果今後本邦では、ステージⅡ以上の胃がん治癒切除後はTS-1による補助化学療法を行うことが標準となる。同試験には、すでに16例登録されていたが、倫理的に手術単独を対照とすることはできないため、プロトコールの大改訂を目的に、7月25日にて登録を一時中止した。
改訂では、治療群では術前化学療法+根治手術+術後補助化学療法として、対照群は根治手術+術後補助化学療法と変更することになり、平成19年2月に改訂プロトコールは承認された。その後1例の登録があり、平成19年3月末では計17例が登録されたことになる。本改訂では、改訂前の症例数が少なかったこと、治療内容が手術単独とかなり異なることから新たに300例の集積を上乗せ、計316例の登録予定数とし、登録期間も6年半と延長した。

D．考察
以上より、本治療法（TS-1+CDDP＋根治手術）は第Ⅱ相試験での評価において、第Ⅲ相試験の試験アームにふさわしいと考えられた。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している。診断的腹腔鏡検査の使用は徐々に我が国で拡大しつつあるが、本臨床試験

が我が国における診断的腹腔鏡検査の標準的定着を促す可能性は充分に考えられる。
登録症例数が未だ少数であるが、ようやく参加施設が揃った時期であり、今後はあらゆる方法で参加施設を鼓舞しながら、積極的な試験への参加を呼びかけていく。年間60例を見込んでおり、月間5例であることから、当面は施設毎に対象症例数、その内の試験登録数と非登録例における非登録理由の把握を実施していく。
また、JCOG胃がん外科グループでは、同じレジメンを用いて高度リンパ節転移を有する局所進行胃がん症例に対する術前化学療法の第Ⅱ相試験も実施中であり、安全性情報等は共有していく。

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ち、第Ⅲ相試験を施行中である。

Ｆ．健康危険情報
現在まで登録された症例では該当なし。

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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
Yoshikawa, T., Sasako, M., et al.	Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial	British Journal of Surgery	93	1526-1529	2006
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土屋康紀、梨本篤、他	TS-1+CDDP療法１コースにてCRとなった進行胃癌の1例	癌と化学療法	33	807-809	2006
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伊藤誠二、小寺泰弘、望月能成、山村義孝	スキルス胃癌非切除の方針は妥当か？	外科治療	95	73-74	2006

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　三津留

Original article

Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial

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Background: Extended lymphadenectomy (D2) provides accurate nodal staging of gastric cancer. The aim of this study was to clarify the degree of stage migration seen with D2 combined with para-aortic lymph node dissection for gastric cancer invading the subserosa, the serosa and adjacent structures (T2ss–4) in patients considered not to have distant metastases (M0).

Methods: Between July 1995 and April 2001, 523 patients were recruited and randomized in a prospective phase III trial comparing D2 with D2 and para-aortic nodal dissection for T2ss–4 gastric cancer without macroscopic para-aortic nodal metastases. Stage migration was evaluated by Japanese Gastric Cancer Association staging in 260 patients who underwent D2 with para-aortic dissection by analysing pathological information from the dissected lymph nodes.

Results: Node (N)-stage migration was observed in 1 per cent (1 of 82) of patients with N1 disease, 20 per cent (12 of 59) with N2, 43 per cent (10 of 23) with N3 and 8·8 per cent (23 of 260) of all patients. Final stage migration occurred in 9 per cent (5 of 58) of patients with stage IIIa, 19 per cent (8 of 42) with stage IIIb, 56 per cent (9 of 16) with stage IVa and 8·5 per cent (22 of 260) of all patients. Metastasis to N4 nodes was found in 4 per cent (four of 95) of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. The overall incidence of N4 involvement was 8·8 per cent (23 of 260).

Conclusion: Extended para-aortic lymphadenectomy for gastric cancer provides accurate nodal staging and results in stage migration, which may improve stage-specific survival regardless of overall survival benefit.

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Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most common malignancy in Japan, South America and Eastern Europe[1]. Radical gastrectomy with regional lymphadenectomy is the mainstay of curative treatment for gastric cancer that has penetrated beyond the submucosa[2]. The procedure can be undertaken in the context of total or subtotal gastrectomy where (D2) lymphadenectomy indicates nodal dissection to the N2 level[3]. This has been the standard treatment for gastric cancer in Japan since the 1960s[4].

In the 1980s extended lymphadenectomy procedures were practised in many Japanese centres with the intention of improving the prognosis of patients with locally

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advanced gastric cancer. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected on the basis that 20–30 per cent of patients with non-early gastric cancer (more than T1) had microscopic metastasis present in para-aortic nodes[5–8]. The reported 5-year survival rate for patients with these nodal metastases was in the range of 14–30 per cent after extended para-aortic lymphadenectomy[5–9].

Based on these results, the Japanese Gastric Cancer Association defined para-aortic nodes as regional lymph nodes[10]. Conversely, the International Union Against Cancer (UICC)–tumour node metastasis (TNM) system classified metastases to para-aortic lymph nodes not as regional lymph node metastases (N) but as distant metastases (M)[11]. Keighley *et al.*[12] reported that median survival was less than 5 months in British patients with tumours involving para-aortic nodes, even after extended para-aortic nodal dissection.

From retrospective studies, it has been suggested that extended para-aortic lymphadenectomy improved prognosis compared with standard D2 dissection[9,13]. It may be, however, that extended surgery only provides more accurate staging information and that this stage migration may improve apparent stage- and N stage-specific survival[14]. The impact of stage migration has not yet been clarified.

A multi-institutional randomized clinical trial was therefore conducted by the Japan Clinical Oncology Group (JCOG) to evaluate the survival benefit of D2 gastrectomy with extended para-aortic dissection for T2ss–4 M0 gastric cancer (ss, subserosal) without macroscopic para-aortic nodal metastases. Morbidity and mortality results from this trial showed that D2 as well as extended surgery could be performed safely in specialized hospitals in Japan[15]. The present report evaluated the stage migration caused by D2 with para-aortic lymphadenectomy by analysing pathological information from dissected lymph nodes in this prospective trial. This is the first study to evaluate stage migration caused by para-aortic dissection.

Patients and methods

The randomized trial[15] was approved by the JCOG and the local ethics committees of each institution. Initially, the 12 institutions of the Gastric Cancer Surgery Study Group of the JCOG participated in the trial, followed by 12 additional institutions to increase recruitment. All data management and quality assurance were done by the JCOG data centre.

Between July 1995 and April 2001, 523 patients with T2ss–4 M0 tumours, without gross metastases in para-aortic nodes, were randomly assigned to D2 (263 patients) or D2 with para-aortic dissection with curative intent (260). Para-aortic lymph nodes of 1 cm in diameter or larger were diagnosed as metastases by computed tomography. After mobilization of the duodenum, nodal status was finally judged by palpation. The effects of stage migration were evaluated in the 260 patients who underwent D2 with para-aortic lymphadenectomy.

The 12th edition of the Japanese Gastric Cancer Association staging system was used[10]. Lymph nodes were divided to four groups: group 1 or N1 consisted of the perigastric nodes along the lesser curvature (stations 1, 3 and 5) and the greater curvature (stations 2, 4 and 6); group 2 or N2 consisted of the nodes along the left gastric artery (station 7), along the common hepatic artery (station 8), around the coeliac artery (station 9) and along the splenic artery (stations 10 and 11); group 3 or N3 consisted of nodes along the hepatoduodenal ligament (station 12), around the pancreas (stations 13, 15, 17 and 18) and along the superior mesenteric vein (station 14); and group 4 or N4 consisted of para-aortic lymph nodes (station 16). D2 dissection involved removal of all N1 and N2 nodes for tumours in the proximal and middle stomach, and additionally stations 12, 13 and 14 for tumours in the distal stomach. For D2 with para-aortic dissection, the para-aortic lymph nodes were removed in addition to the D2 dissection. Quality control concerning nodal dissection has been described; the median number of retrieved nodes was 54 (range 14–161) in D2 and 74 (range 30–235) in D2 with para-aortic dissection[15].

The lymph nodes of each station were retrieved individually from the specimen and numbered according to the Japanese Gastric Cancer Association staging system. The stomach and lymph nodes were stained with haematoxylin and eosin for histopathological examination.

Stage migration was calculated by assuming that patients had undergone hypothetical D2 dissection without para-aortic lymphadenectomy. Lymph nodes were staged according to the N1, N2 and N3 status, without N4 information (standard staging). Restaging was then undertaken after considering N4 status obtained by true extended para-aortic lymphadenectomy (extended staging). In this way, N-status migration could be determined when metastatic nodes were detected in the N4 levels. A final stage was determined in both the standard and extended staging by combining microscopic depth of invasion into the gastric wall (T status).

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Results

Lymph node metastases according to standard and extended staging are shown in *Table 1*. By applying extended staging, N-stage migration was observed in 1 per cent (1 of 82) of patients with N1 disease, 20 per cent (12 of 59) with N2, 43 per cent (10 of 23) with N3 and 8·8 per cent (23 of 260) of all patients. The final staging is shown in *Table 2*. Overall stage migration occurred in 9 per cent (five of 58) of patients with stage IIIa disease, 19 per cent (8 of 42) with stage IIIb, 56 per cent (9 of 16) with stage IVa and 8·5 per cent (22 of 260) of all patients.

Table 3 shows lymph node metastases classified according to depth of invasion. Metastases to N4 nodes were found in 4 per cent (four of 95) of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. The overall incidence of N4 involvement was 8·8 per cent (23 of 260).

Discussion

This study has clarified the incidence of microscopic metastases in patients with T2ss–4 M0 tumours and macroscopically negative para-aortic nodes.

Limited nodal dissection often provides inaccurate staging. Bunt *et al.*[14] analysed the migration effects in Japanese Gastric Cancer Association staging from the results of D1 and D2 surgery in a Dutch phase III trial and found that the rate of stage migration was 30 per cent when D2 surgery was applied instead of D1[14]. They also calculated the stage-specific survival rate based on reported survival rates and stage migration, and clarified that stage migration could improve stage-specific survival without a real survival benefit from D2 lymphadenectomy[14].

In this study, N-stage migration occurred in 8·8 per cent and overall stage migration was noted in 8·5 per cent of patients by applying extended staging instead of standard D2 staging. N- and stage-specific survival may therefore be improved owing to N stage and overall stage migration. Some Japanese surgeons have reported that extended nodal dissection can improve overall survival in patients with N2 tumours compared with standard D2 dissection[9,13]. These survival differences could be explained, in part, by the N-stage migration observed in this study. There seems no sense, therefore, in comparing D2 and more extended dissection by retrospective survival analyses based on the Japanese Gastric Cancer Association staging system.

Extended para-aortic lymphadenectomy influences Japanese Gastric Cancer Association staging and UICC–TNM staging. Metastases to para-aortic nodes are treated as distant metastases (M1) by TNM staging[11]. According to eligibility criteria in the present study, patients with metastases to distant organs such as liver and peritoneum were excluded. Para-aortic nodes were also negative macroscopically. The present results demonstrate that 8·8 per cent (23 of 260) of patients with T2ss–4 M0 gastric cancer and macroscopically negative para-aortic nodes have microscopic para-aortic nodal metastases. These patients then become classified as M1, so that extended lymphadenectomy causes M-stage migration, impacting on M-specific survival in the TNM classification.

In the present study, nodal metastases to N4 were observed in 8·8 per cent (23 of 260) of all patients and these positive nodes were found in 4 per cent (four of 95)

Table 1 Staging and migration of lymph node metastases

	Standard staging				Extended
	N0	N1	N2	N3	total
Extended staging					
N0	96				96
N1		81			81
N2			47		47
N3				13	13
N4		1	12	10	23
Standard total	96	82	59	23	260

Table 2 Disease stage and stage migration

	Standard staging							Extended
	Ia	Ib	II	IIIa	IIIb	IVa	IVb	total
Extended staging								
Ia	10							10
Ib		67						67
II			64					64
IIIa				53				53
IIIb					34			34
IVa						7		7
IVb				5	8	9	3	25
Standard total	10	67	64	58	42	16	3	260

Table 3 Depth of invasion and lymph node metastases

	Lymph node metastasis					
	N0	N1	N2	N3	N4	Total
Depth of invasion						
M	3					3
SM	7	4				11
MP	19	14	3	1		37
SS	44	28	14	5	4	95
SE	22	35	28	5	19	109
SEI	1		2	2		5
Total	96	81	47	13	23	260

M, mucosa; SM, submucosa; MP, muscular is propria; SS, subserosa; SE, serosa exposed; SEI, serosa exposed and invading adjacent organs.

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of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. Previous Japanese studies have reported that 20–30 per cent of patients with non-early gastric cancer had histological metastasis in the para-aortic nodes[5–8]. The present study confirmed N4 disease in localized advanced gastric cancer invading the subserosa or deeper. The slightly lower incidence of this finding in the present compared with previous studies may have been due to the inclusion of patients with macroscopically involved para-aortic nodes in the earlier studies.

Extended para-aortic lymphadenectomy for T2ss–4 M0 gastric cancer provides a revised nodal staging. This results in stage migration that may improve stage-specific survival regardless of a real survival benefit.

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An Icteric Type Hepatocellular Carcinoma with No Detectable Tumor in the Liver: Report of a Case

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Abstract
A 70-year-old man was admitted to our hospital with obstructive jaundice. Computed tomography revealed a tumor in the left intrahepatic bile duct extending to the common bile duct without any significant lesions in the liver. Cholangiography showed a filling defect due to an intraductal tumor. Cytology of the bile juice was negative and tumor markers were carcinoembryonic antigen 5.7 ng/ml, carbohydrate antigen 19-9 49 U/ml, α-fetoprotein 9 ng/dl, and PIVKA-II 19200 AU/ml. With a preoperative diagnosis of hilar bile duct carcinoma, a laparotomy was performed. The common bile duct was filled with a tumor and it extended into the bilateral intrahepatic bile ducts. The intraductal tumor was removed together with the extrahepatic bile ducts. An intraoperative histological examination of the tumor showed a well-differentiated hepatocellular carcinoma. No lesions were detected in the liver by ultrasonography, palpation during the operation, or a computed tomography scan after the operation. At 1 year postoperatively, no recurrence has been seen in this patient.

Key words Icteric type hepatocellular carcinoma · Intraductal growth · Obstructive jaundice

Introduction

Jaundice usually occurs in the later stage of hepatocellular carcinoma (HCC) due to underlying liver cirrhosis or extensive hepatic parenchymal invasion of the tumor. However, obstructive jaundice associated with HCC is a rare initial symptom caused by intraductal tumor growth, the migration of tumor necrosis, blood clots within the biliary tract, or compression of the biliary tract by the tumor.[1–6] These types have been classified as icteric type HCC by Lin et al.[2] Since Mallory et al.[1] first described a case of HCC accompanied with obstructive jaundice secondary to biliary hemorrhage from a tumor invading the cystic duct, a number of similar reports have been found in the literature.[3,7–10] In most of these cases, the main tumors were detected in the liver. We herein report a case of a successful resection of an icteric type HCC without a detectable original tumor in the liver.

Case Report

A 70-year-old man was admitted to our hospital because of obstructive jaundice with a diagnosis of unresectable hilar carcinoma. He had undergone bilateral percutaneous transhepatic cholangiodrainage (PTCD) for the relief of the jaundice at a previous hospital. Cholangiography through the PTCD tube showed a filling defect (about 8 cm in length) due to a intraductal thrombi through the left intrahepatic bile duct into the common bile duct at the level of the origin of cystic duct (Fig. 1A) and a variation of the bile duct was seen (Fig. 1B). Computed tomography (CT) revealed an enhanced mass extending through the left intrahepatic bile duct into the common bile duct with dilatation of the bilateral intrahepatic bile ducts, but without any tumor in the liver or lymph node swelling (Fig. 2). Angiography revealed neither an encasement of blood vessels nor tumor staining in the liver (data not shown). Cytology of the bile juice was negative. The serum tumor markers were as follows: carcinoembryonic antigen (CEA) 5.7 ng/ml, carbohydrate antigen (CA) 19-9 49 U/ml, α-fetoprotein (AFP) 9 ng/dl, and PIVKA-II 19200 AU/ml. Serologically, hepatitis B surface antigen was negative and hepatitis C virus antibody was positive. A final preoperative diagnosis was made

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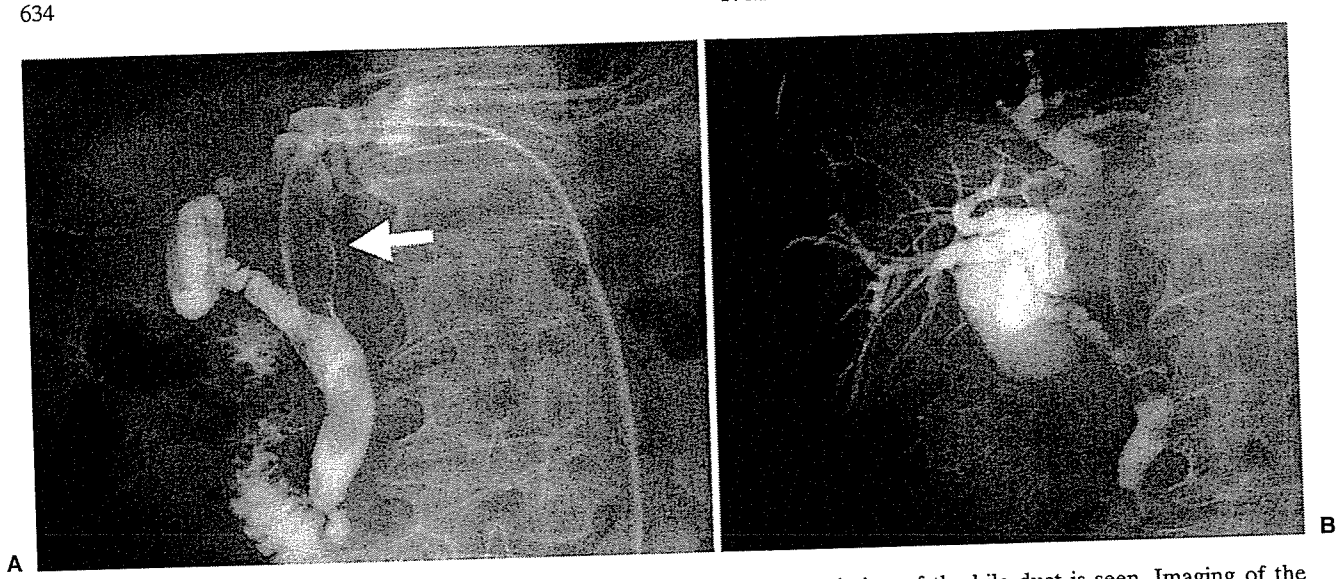

Fig. 1A,B. Cholangiography. **A** A filling defect (*arrow*) can be seen in the left intrahepatic bile duct into the common bile duct due to the intraductal tumor. Cholangiography through the left percutaneous transhepatic cholangiodrainage (PTCD) tube. **B** A variation of the bile duct is seen. Imaging of the cystic duct and gallbladder is enhanced by cholangiography through the right PTCD tube

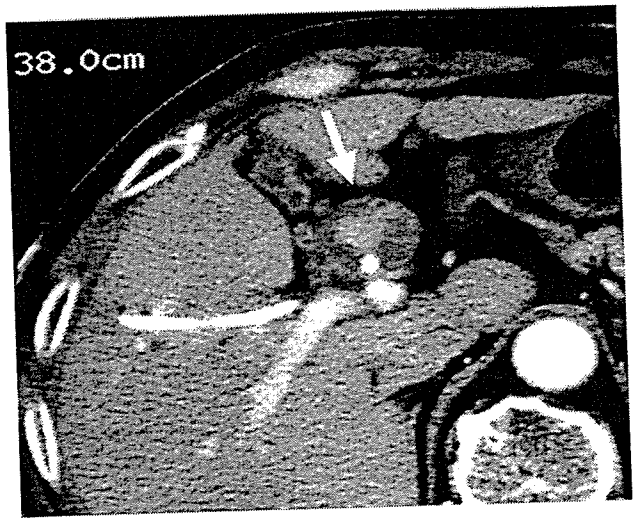

Fig. 2. Abdominal computed tomography. A mass (*arrow*) is seen in the left intrahepatic bile duct into the common bile duct

Fig. 3. Resected specimens of the bile ducts and the intraductal tumor. (*White arrow*, left intrahepatic bile duct; *black arrow*, B4; *white arrowhead*, right intrahepatic bile duct; *black arrowhead*, cystic duct

of bile duct carcinoma with papillary growth developing into the intrahepatic bile duct, and a laparotomy was carried out. The surface of the liver was rough and hard with cirrhotic changes. We first resected the common bile duct with the gallbladder and found the common bile duct to be filled with a tumor extending into the bilateral intrahepatic bile duct. An intraoperative frozen biopsy of the tumor revealed hepatocellular carcinoma indicating "tumor thrombi" in the bile duct. The intraductal tumor was removed together with the extrahepatic bile ducts (Fig. 3). The bilateral cut ends of the extrahepatic bile ducts were negative. Intraoperative ultrasonography and cholangioscopy showed no other lesion in the liver and the remnant bile duct through the secondary branch of the biliary tree. Reconstruction by a choledochojejunostomy was performed. A postoperative histological examination showed that the tumor itself was a well differentiated HCC (Fig. 4). The resected bile ducts were confirmed to be free from tumor involvement. The postoperative course was uneventful and at 1 year postoperatively the patient remains recurrence-free.

Discussion

Although HCCs frequently invades the portal and hepatic veins, an invasion of the bile duct causing

Fig. 4. Histopathological microscopy shows well-differentiated hepatocellular carcinoma (H&E, ×20)

obstructive jaundice is a rare phenomenon, namely, 0.2%–4.9% of such patients demonstrate HCC at the time of diagnosis.[6,11–14] Lin et al.[2] classified these tumors to be "icteric type hepatomas" and they classified them into the following three types by means of biliary obstruction:[6,11,15] tumor encasement of the biliary system at the hepatic duct (type 1), filling of free-tumor fragments or blood clots from the tumor (type 2), and extrinsic compression due to an enlarged tumor or malignant lymph node at the hepatic hilum (type 3). According to the classification of Lin et al., the present case was classified as type 2 icteric type HCC because we could not detect any tumor in the liver using either intraoperative ultrasonography, cholangioscopy, or postoperative CT.

In most cases of the icteric type of HCC, the main tumor is usually detected in the liver, thus it is a rare phenomenon that the original tumor is not detectable in the liver, as was seen in our case. We reviewed eight similar cases[16,17] (Table 1). In these cases, the origin of the tumor thrombi in the bile duct was believed to be (1) from the lesion of HCC in the liver, or (2) from ectopic liver tissue in the bile duct. We could not find any tumor in the liver in the present case, and it is thus difficult to clearly define the origin of the tumor thrombi.

The diagnosis of the icteric type of HCC without a detectable main tumor in the liver is difficult. In the reviewed cases with the available data, all of the preoperative diagnoses were bile duct carcinoma (BDC) or bile duct tumor (BDT). Although none of these cases was diagnosed to have HCC preoperatively, the serum AFP levels[11] and imaging examination including CT,[18] endoscopic retrograde cholangiography (ERC),[14,15] percutaneous transhepatic cholangiography,[14,15] and

Table 1. Collected cases from the literature of icteric type hepatocellular carcinoma without a detectable tumor in the liver

Case	Age (years)	Sex	HBs Ag	HCV Ab	AFP	PIVKA-II	Location of the tumor thrombi	Preoperative diagnosis	Therapy	Histology	Patterns of recurrence	Outcome (after operation)
1	62	F	—	—	5	—	CBD	BDC	—	—	—	Died (3 months)
2	59	M	No	—	17.5	—	rt IHBD–CBD	BDT	Thrombectomy	Mod.	—	Died (1 year)
3	65	M	No	Yes	12.7	2.6	B5 branch–rt EHBD	BDC or mixed HCC	Liver resection	Mod. + poor		Alive (5 months)
4	53	M	Yes	No	21	—	B3 branch–CBD	BDC	Thrombectomy	—	IH	Died (8 months)
5	55	F	No	—	<5	N.D.	Anterior branch	BDC	Thrombectomy, liver resection	Poor	IH	Died (5 months)
6	35	M	Yes	No	6	9	lt HBD	BDC	Thrombectomy, liver resection	Poor	IH	Died (3 years)
7	57	F	—	—	—	—	CBD	—	Thrombectomy	—	IH	Died (41 months)
8	48	M	—	—	—	—	rt IHBD–CBD	—	Thrombectomy	—	IH	Died (10 months)
9 (present case)	70	M	Yes	No	9	19200	lt IHBD–CBD	BDC	Thrombectomy	Well		Alive (12 months)

HBs Ag, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; AFP, alpha-fetoprotein; N.D, not done; CBD, common bile duct; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct; BDC, bile duct carcinoma; BDT, bile duct tumor; IH, intrahepatic metastasis; —, no data available; lt, left; rt, right; HCC, hepatocellular carcinoma; Mod., moderate

magnetic resonance cholangiography[19] could be helpful for the differential diagnosis between BDC (BDT) and HCC. Among them, the cholangiograms could be the most helpful in the case of negative tumor markers. Intraluminal filling defects and irregular cutting surface, which were found to be blood clots or necrotic tumor debris, are different from the conventional cholangiographic appearance of BDC.[15] A retrospective analysis in the present case did not show a typical intraluminal filling defect as is the case with BDC. The elevation of PIVKA-II and the positive HCV markers, which we overlooked in the present case, would thus be helpful for accurately diagnosing this type of HCC although the PIVKA-II level may not be reliable in the presence of obstructive jaundice. Based on previous reports, the icteric type of HCC shows invasive growth and no tumor capsule formation such as seen in hilar cholangiocarcinoma,[13,18,19] while the tumor did not show any invasive growth in the present case. An accurate diagnosis, however, cannot be reached until either tumor biopsies or a resection is performed.[20]

Although the ideal treatment of the icteric type of HCC would be a complete extirpation of the tumor, the same as for other malignant tumors, the total resection rate of these tumors is very low.[6,11,13–15,19,21,22] One of the reasons for this may be due to the hepatic parenchymal insufficiency exaggerated by persistent obstructive jaundice and the low hepatic reserve function associated with cirrhosis. Immediate biliary drainage is recommended for icteric type HCC and an operation should be performed after the relief of jaundice and a subsequent evaluation of the hepatic reserve function.[12,21] According to the operative methods in our reviewed cases, 5 out of the 8 cases, including our case, received a thrombectomy through a choledochotomy while 3 cases received a hepatic resection with a thrombectomy. Regarding the surgical procedures in the three patients who underwent a hepatic resection, a hepatic lobectomy was performed in two patients and a segmentectomy in one to resect the intrahepatic bile duct and the tumor thrombus in it. In two of these three cases, based on the available information, no main tumors were detected in the resected specimens. In the present case, however, the liver function was estimated preoperatively to marginally allow the performance of a left hepatic lobectomy, and the low functional level was confirmed as being due to obvious cirrhosis. To avoid liver dysfunction after the operation we considered that a resection of the extrahepatic bile ducts should be sufficient to complete the tumor removal because of the lack of any detectable tumors in the secondary branch of the biliary tree as assessed by intraoperative cholangioscopy and intraoperative ultrasonography. Although a hepatic resection for regional tumors of the intrahepatic bile duct is usually necessary when performing a curative resection for this type of HCC, a complete thrombectomy with a choledochotomy may therefore be adequate if the negative cut ends of the bile ducts and the absence of regional intrahepatic tumors can be confirmed, as in the present case.

The prognosis of icteric type HCC has been reported to be poor[11–13,15] although Lau et al.[6] reported, in a study of 49 icteric type HCC patients, that the overall survival of these patients was similar to that of HCC patients with no jaundice and he concluded that a good palliation and occasional cure were possible with proper treatment. However, the icteric type of HCC with no detectable hepatic tumor has a poor prognosis as in our reviewed cases, although it is necessary to collect more similar cases with a longer-term follow-up for a better evaluation of the prognosis. Regarding the patterns of recurrence in the icteric type of HCC with no detectable main tumor, intrahepatic metastases, one of which might be the origin of the intraductal tumor, developed in all five patients based on the available information. Moreover, these recurrent cases included two patients who had undergone a thrombectomy with a liver resection. Considering this, the difficulty in accurately determining to optimal degree of a liver resection might thus influence the poor prognosis of ictric type HCC with no detectable hepatic tumors, if the tumor thrombi in the bile duct originate from a lesion in the liver. A postoperative examination of the liver thus seems to be important for the early detection of recurrence, and at the very least, a curative surgical resection and postoperative intensive monitoring of potential hepatic lesions are necessary to improve the prognosis.

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症 例

TS-1+CDDP療法1コースにてCRとなった進行胃癌の1例

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Advanced Gastric Cancer Responding to Pathological CR after Neoadjuvant TS-1 Combined with CDDP Therapy —Report of a Case: Yasunori Tsuchiya*1, Atsushi Nashimoto*1, Satoru Nakagawa*1, Hiroshi Yabusaki*1, Yasumasa Takii*1, Yoshiaki Tsuchiya*1, Otsuo Tanaka*1 and Tamaki Ohta*2 (*1*Dept. of Surgery, Niigata Cancer Center Hospital, *2Dept. of Pathology, Niigata Cancer Center Hospital*)

Summary

A 54-year-old woman with advanced gastric cancer was referred to our hospital. Because it was the yearend, we selected neoadjuvant TS-1 combined with CDDP therapy. TS-1 (60 mg bid) was administered orally for 21 consecutive days, and CDDP (60 mg/m²) was infused intravenously on day 8. One course was completed without serious toxicities. The primary tumor revealed partial response (PR) with no lymph node metastasis judged from barium meal study and upper GI endoscopic findings. After 3 weeks, a simple total gastrectomy with lymph node dissection was performed. The pathological diagnosis proved that there were no cancer cells in the primary lesion or regional lymph nodes, suggesting a complete response (CR) to chemotherapy. The postoperative course was uneventful, and she has been fine as an outpatient. Key words: TS-1+CDDP therapy, Advanced gastric cancer, Neoadjuvant chemotherapy (NAC), Complete response (CR) (*Received Jul. 15, 2005/Accepted Dec. 13, 2005*)

要旨 症例は54歳，女性。空腹時胃部不快感にて近医を受診し，胃体中部の3型胃癌（por 2）を指摘され当科紹介となる。年末のため，TS-1/CDDP療法による術前化学療法（NAC）を1コース施行後，手術を行う方針とした。化学療法後，胃X線および上部消化管内視鏡検査にて原発巣の縮小を認め，PRと判定した。約3週間の休薬期間後，胃全摘術が施行された。切除標本の肉眼的所見は3型胃癌でsSE，sN 1，sH 0，sP 0，sM 0，CY 0，Stage IIIAであった。しかし，病理組織学的所見では高度線維化を認めるのみで胃癌組織は消失しており，リンパ節転移もなく組織学的効果判定はGrade 3であった。術後経過は順調で外来での補助化学療法はせずに経過観察中である。

はじめに

進行胃癌に対するTS-1+CDDP療法は，その奏効率の高さから注目されており[1]，われわれも高度進行胃癌あるいは根治切除不能と診断された胃癌症例に対し，2000年10月よりTS-1+CDDP療法を2コース施行してきた[2]。今回われわれは，根治術が可能と考えられた進行胃癌症例に対して，手術待機中に術前化学療法（NAC）としてTS-1+CDDP療法を施行したところ，病理組織学的CRが得られた症例を経験したので報告する。

I. 症 例

症例: 54歳，女性。

主訴: 空腹時上腹部不快感。

既往歴・家族歴: 特記すべき事項なし。

現病歴: 2004年夏ごろより空腹時上腹部不快感にて発症。12月に近医を受診し，上部消化管内視鏡検査にて胃体中部・小弯に3型胃癌を指摘され，生検でも低分化腺癌（por）と診断された。12月中旬，当科紹介受診した。年末のため，外来にて術前化学療法を施行する方針とし，

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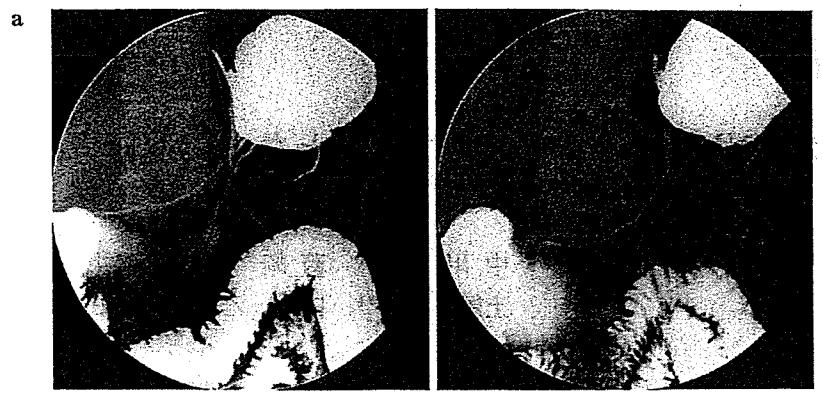

図 1 上部消化管造影
a: 化学療法前
胃体中部・小弯から後壁にかけて不整形のやや深い陥凹と陥凹辺縁で途絶する fold の集中を認めた。
b: 化学療法後
陥凹面の縮小化，集中する fold の平坦化を認めた。

図 2 上部消化管内視鏡検査および化学療法前の生検組織
a: 胃体上部から胃体下部・小弯から後壁にかけて 3 型胃癌を認めた。
b: 深く陥凹した潰瘍面を biopsy したところ中分化型管状腺癌（tub 2）～充実型低分化型腺癌（por 1）と診断された。
c: 化学療法終了後，病変の縮小化，平坦化が認められた。

TS-1＋CDDP 療法（TS-1 120 mg/day，21 日間連続経口投与，CDDP day 8 に 60 mg/m²を点滴静注）を開始した。治療中，軽度の悪心，食欲低下が出現したが重篤な有害事象は認められなかった。1 コース終了後，約 3 週間の休薬期間をおき，手術目的にて当科入院となった。

入院時現症: 身長 153 cm，体重 68 kg。眼球結膜に黄疸なし。眼瞼結膜に貧血なし。胸腹部に異常所見なし。Virchow リンパ節は触知せず。Schnitzler 転移は認めなかった。

検査成績: GOT 71 IU/*l*，GPT 68 IU/*l*，γ-GTP 107 IU/*l* と軽度の肝機能異常を認めたが，その他の血液・生化学検査には異常を認めず，腫瘍マーカーはすべて正常範囲内であった。

胃 X 線検査: 胃体中部・小弯を中心に不整形の陥凹と陥凹辺縁で途絶する fold の集中を認めた（図 1 a）。化学療法終了後，陥凹の縮小化，集中する fold の軽減化が認められた（図 1 b）。画像上の縮小率は 2 方向測定で 58%であり，partial response（PR）と判定した。

上部消化管内視鏡検査: 胃体上部から胃体下部・小弯から後壁にかけて 3 型胃癌を認め（図 2 a），深い陥凹面から生検したところ中分化型管状腺癌（tub 2）～充実型低分化型腺癌（por 1）と診断された（図 2 b）。化学療法後，病変の縮小化，平坦化を認め（図 2 c），内視鏡上も PR と判定した。

腹部 CT 検査: 主病巣は描出されず，転移を示唆する所見は認められなかった。

入院後経過: 胃体中部・小弯から後壁にかけての進行胃癌との診断にてリンパ節郭清を伴う胃全摘術を施行し，Roux-en Y 吻合にて再建した。術後経過は良好で第 14 病日に退院した。

切除標本肉眼所見: 病変は MU 領域小弯に存在し，腫瘍径 60×60 mm の 3 型胃癌と思われた（図 3 a）。肉眼的には T 3(SE)，N 1，H 0，P 0，CY 0，Stage IIIA と診断した。

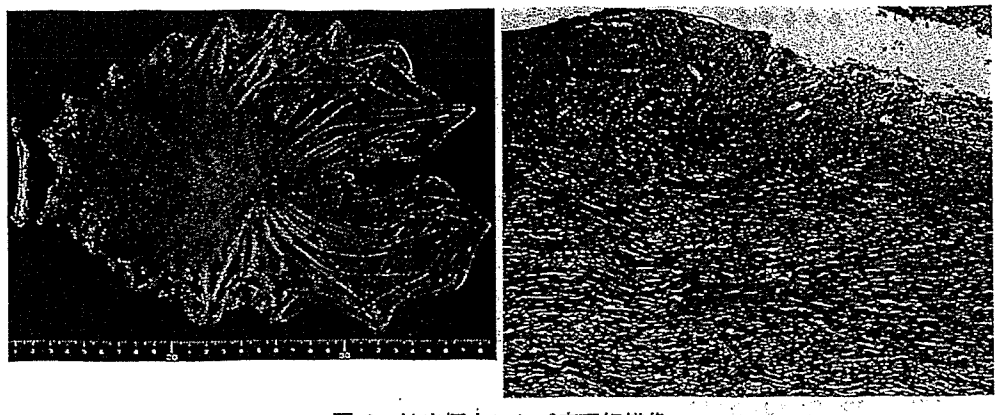

図 3 摘出標本および病理組織像
a: 病変は MU 領域小弯中心に存在し，腫瘍径 60×60 mm の IIc 類似進行胃癌と思われた。
b: 階段状切片にて病変全体を検索したが，高度線維化を認めるのみで癌細胞の遺残はなかった。

病理組織学的所見: 段階状半連続切片にて検索したが，高度線維化を認めるのみで癌細胞の遺残は認められなかった（図 3 b）。所属リンパ節には転移を認めず，胃癌取扱い規約第 13 版[3]の薬物の組織学的効果判定基準に準じて Grade 3 と診断した。術後補助療法は施行していない。術後 6 か月を経過したが，現在のところ再発兆候なく元気に外来通院中である。

II. 考　察

TS-1＋CDDP 療法[1]は TS-1＋CPT-11 療法や CPT-11＋CDDP 療法[4]などとともに第 I/II 相試験において高い奏効率を示した。また，安全性，コンプライアンスのよさより，近年好んで用いられており，われわれも NAC として TS-1＋CDDP 療法を行っている。以前に原発巣の癌組織は消失し，周囲のリンパ管内微小癌組織が存在した症例を報告したが[5]，病理学的に CR が得られる症例は非常にまれである。本症例は根治術が可能な進行胃癌であったが，年末にかかるという時期的・社会的な特殊性により，JACCRO GC-01 のプロトコールにのっとり TS-1＋CDDP 療法を NAC として 1 コースのみ施行後，手術することとなった。術後，摘出標本を肉眼的に検索した時点では著明な病変の縮小はあったが，原発巣の遺残，No. 3 リンパ節転移陽性と判断した。しかし，病理組織学的検索にて原発巣・所属リンパ節ともに癌細胞をまったく認めず，高度な成熟した線維化の所見を呈するのみであり，病理組織学的 CR と判定された。高度線維化は主病巣の漿膜下層（SS）まで及んでおり，さらに No. 3 リンパ節にも同様の所見が認められた。この所見は，かなり早い段階で化学療法が奏効していたことを示唆しており，薬剤感受性が非常に良好な癌腫であったと同時に癌細胞量が比較的少なかった可能性もある。また，化学療法施行前はリンパ節転移を有する，深達度 SS の進行胃癌と考えられ，手術により切除しきれない微小転移巣を有していた可能性も否定できない。実験的レベルではあるが，原発巣切除に伴う tumor dormancy の解除，また手術操作による surgical stress で癌転移が増強する[6]ことは実証されている。本症例の場合は，NAC 後における微小転移の残存は考えにくい。遺残した癌細胞の再発・転移の危険性を著しく軽減したと思われる本化学療法の果たした役割は大きい。このような観点においても，現在 JCOG で術前治療なしでは根治切除が困難か，根治切除が行えても予後が極めて不良な高度リンパ節転移を有する胃癌に対する術前補助化学療法として，TS-1＋CDDP 療法の有効性と安全性の評価が行われているが，結果がたいへん興味深い。今後は根治術が可能と思われる進行胃癌症例に対し，術後補助化学療法から術前補助化学療法にパラダイムシフトする方向性を考慮すべき時期にきているのかもしれない。

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