Chemotherapeutic regimens, including S-1, have recently produced clinical responses and survival benefits in patients with gastric cancer in Japan; even in non-resectable, advanced gastric adenocarcinoma and head and neck squamous cell carcinoma (10, 11). The efficacy of S-1 has also been demonstrated in the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) (12). S-1 has many advantages. These include a high efficacy, excellent tolerability, a good side effect profile, and suitability for administration in an outpatient setting. Furthermore, the combination of S-1 and CDDP has been shown to be efficacious for stage IV gastric adenocarcinoma and head and neck squamous cell carcinoma (13, 14), as well as in neoadjuvant chemotherapy for unresectable advanced gastric cancer (15, 16).

The patient was emotionally upset at the time of diagnosis of early-stage esophageal and advanced gastric cancer, which occurred during his follow-up examination. We hypothesized that administration of neoadjuvant chemotherapy for concurrent advanced gastric cancer provided the unique opportunity for a complete response to take place in his early-stage esophageal cancer.

Either chemotherapy or surgical resection, with or without esophageal preservation is usually selected as the initial treatment for advanced esophageal cancer. However, in terms of dysphagia, the functional outcome of esophagectomy is worse than that of chemotherapy (17). Furthermore, esophagectomy is associated with high mortality and morbidity rates. Surgical mortality rates have been reported as high as 5%, even at high-volume centres (18). This suggests that chemotherapy may offer functional and prognostic merits over esophagectomy in patients with early-stage esophageal cancer.

In conclusion, this case confirms the potential for complete response to S-1 plus CDDP chemotherapy in early-stage esophageal cancer. The accumulation of further such cases may enhance our understanding of this phenomenon and lead to the development of new treatment strategies for early-stage esophageal cancer.

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Complete Response to Chemoradiotherapy in a Patient with Synchronous Double Gastric and Esophageal Cancer

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Abstract. *A 77-year-old man with early synchronous double primary gastric and esophageal cancer showed complete response (CR) to chemoradiotherapy (CRT) with fluorouracil (5-FU) and cis-diamminedichloroplatinum (CDDP) and 60 Gy total dose of radiation. Gastrointestinal endoscopy had revealed type IIc squamous cell carcinoma in the lower oesophagus and type IIc adenocarcinoma in the mid-stomach region. Synchronous double primary early-stage esophageal and gastric cancer was diagnosed. The patient's age and chronic obstructive pulmonary disease (COPD) contraindicated radical esophageal surgery. Therefore, we decided to first administer CRT with 5-FU and CDDP for the esophageal cancer, and subsequently perform partial gastrectomy for the gastric cancer. After the CRT, neither of the tumors recurred. CR to CRT for the esophageal cancer and CR to chemotherapy for the gastric cancer were achieved. Conclusion: CRT with 5-FU and CDDP can produce CR in cases of early esophageal and gastric cancer.*

The standard treatment for early stage esophageal and gastric cancers is esophagectomy and gastrectomy without endoscopic mucosal resection, respectively. Although the prognosis of early-stage gastric cancer has improved owing to the advances in endoscopic therapy, the prognosis of early-stage esophageal cancer remains relatively poor (1, 2). The prognosis of double primary cancer in patients with esophageal cancer is worse than that of a single malignancy (3). Furthermore, synchronous double primary gastric cancer has a worse prognosis than metachronous cancer (4-6). Cases of complete response (CR) to chemoradiotherapy (CRT) administered for synchronous double primary early-stage esophageal and gastric cancer are rare. Here, we report one such case.

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Key Words: Double gastric and esophageal cancer, chemoradiotherapy, complete response.

Case Report

A 77-year-old man who had undergone surgery for prostrate carcinoma was consulting his family doctor for postoperative follow-up and chronic obstructive pulmonary disease (COPD). In July 2007, he was referred to the Department of Digestive Surgery, Nihon University School of Medicine, Itabashi Hospital, because of esophageal and gastric tumors that were identified during a follow-up examination. Upper gastrointestinal endoscopy revealed two 2.5×2.5 cm, type IIc tumors: one in the lower esophagus (Figure 1A) and the other in the lower stomach (Figure 2A). Analysis of the biopsy specimens revealed that that the esophageal tumor was a moderately differentiated squamous cell carcinoma, while the gastric tumor was a moderately differentiated adenocarcinoma. The patient's condition was diagnosed as early stage synchronous double primary cancer of the esophagus and stomach. Computed tomography did not show any evidence of metastasis.

The patient's age and COPD contraindicated radical esophageal surgery. Therefore, we decided to first administer CRT with fluorouracil (5-FU) and *cis*-diamminedichloroplatinum (CDDP) for the esophageal cancer, and subsequently perform partial gastrectomy for the gastric cancer. CRT was carried out according to the Japan Clinical Oncology Group (JCOG) 9516 regimen (7). CDDP was administered at a dose of 100 mg/m^2 on days 1 and 29, and 5-FU was administered at a dose of 900 mg/m^2 daily from days 1 to 4 and 29 to 32. Fractionated radiotherapy was administered from days 1 to 21 and 29 to 49; a total dose of 60 Gy was administered 5 times a week at the rate of 2 Gy fraction. The radiation fields encompassed the primary esophageal lesion and regional lymph nodes. After the completion of the CRT, the response of the tumor to the CRT was clinically and pathologically evaluated by performing upper gastrointestinal endoscopy: the esophageal and

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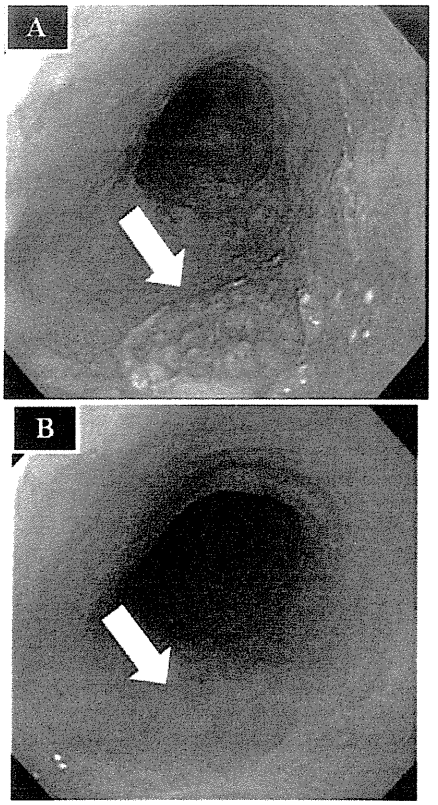

Figure 1. *A: In July 2007, upper gastrointestinal endoscopy revealed a 2.5×2.5 cm, type IIc, mid-esophageal tumor. B: In September 2009, after the chemoradiotherapy, upper gastrointestinal endoscopy revealed complete disappearance of the mid-esophageal tumor and absence of new lesions.*

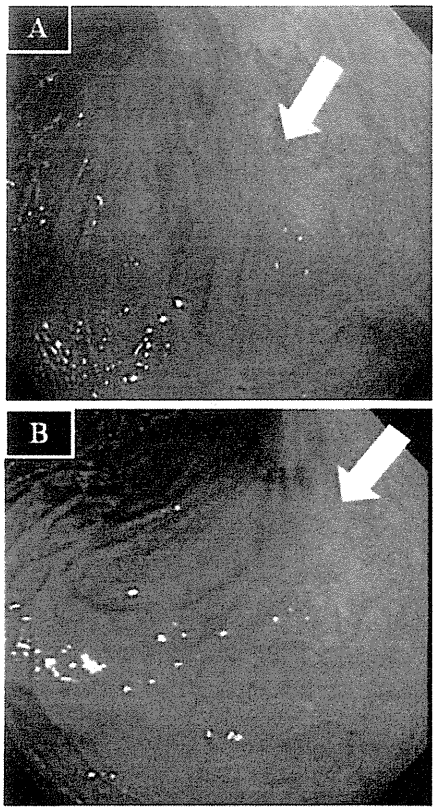

Figure 2. *A: In July 2007, upper gastrointestinal endoscopy revealed a 2.5×2.5 cm, type IIc, tumor of the lower stomach. B: In September 2009, after the chemoradiotherapy, upper gastrointestinal endoscopy revealed complete disappearance of the tumor of the lower stomach and absence of new lesions.*

gastric tumors were found to have regressed to scar lesions (Figure 1B) and (Figure 2B). The biopsy specimens obtained from both the scar lesions were negative for cancer. We concluded that the patient showed CR to CRT for the early esophageal cancer and CR to chemotherapy for the gastric cancer. Over the next 4 months, periodic upper gastrointestinal endoscopic examinations were conducted to detect any further esophageal or gastric lesions. After CRT, the patient did not receive adjuvant chemotherapy or any other anticancer treatment. By August 2010, upper gastrointestinal endoscopy had been performed thrice, and no further lesions had been identified. At 33 months after the complete disappearance of the tumors, the patient is still alive without any signs of tumor recurrence.

Discussion

Cases of CR to CRT administered for synchronous double primary early-stage esophageal and gastric cancer are rare. Several retrospective studies have reported a CR rate of 17-36% to CRT for advanced esophageal cancer (8-10). However, the efficacy of CRT in the treatment of early esophageal cancer is still unknown. In contrast, the rate of the CR to chemotherapy for advanced gastric cancer is as low as 0-0.7% (11, 12). CR to chemotherapy for early gastric cancer is very rarely reported because most cases are treated with surgical resection or endoscopic mucosal resection as these procedures give good clinical results. Moreover, dysphagia after gastrectomy is not as severe as that after esophagectomy, and gastrectomy is not highly associated with high mortality and morbidity.

CRT may be effective in early oesophageal cancer (13), and chemotherapy in early gastric cancer. Although advances in endoscopic therapy have improved the prognosis of early esophageal cancer (14, 15), the outcome is still not acceptable (1, 2). Cases of CR to CRT administered for synchronous double primary early stage esophageal and gastric cancer are rare. In general, either radiotherapy or surgery with or without esophageal preservation is selected

as the initial treatment. Only a few studies have reported the efficacy of CRT for early-stage esophageal cancer, and the optimal treatment approach is still undefined. The dysphagia experienced after esophagectomy is worse than that experienced after CRT (16). Furthermore, esophagectomy is associated with high mortality and morbidity, being associated with a 5% surgical mortality rate even at high-volume centers (12). Some studies have compared the outcomes of esophagectomy with those of CRT in a population-based sample of elderly patients with early-stage esophageal cancer; the survival rate of patients with squamous cell carcinoma did not significantly differ between CRT and esophagectomy groups. Patients with radio- and chemosensitive early esophageal cancer seem to have prognostic and functional merit (17).

In our patient, we hypothesize that CRT administration for the concurrent early stage esophageal cancer stimulated the response of the gastric cancer to chemotherapy. Chemosensitivity to 5-FU and CDDP is not very suitable for advanced gastric cancer (18). In Japan, S-1 (Taiho Pharmaceutical, Tokyo, Japan) is a key chemotherapeutic agent used against gastric cancer (19). Its efficacy has been proven in trials of S-1 for gastric cancer and the combination of S-1 and CDDP for stage IV gastric cancer patients (12). S-1 has many advantages, including its high efficacy, excellent tolerability, low side-effect profile, and the ease of administration in an outpatient setting. In the light of our case, we believe that patients with early gastric cancer could be cured by using highly efficacious S-1 chemotherapy. Further research is needed to improve esophageal and gastric preservation in patients with early cancer.

In conclusion, this case confirms the possibility of CR to radiotherapy and chemotherapy for early esophageal and gastric tumors. Further study of such cases will promote further understanding of CR, and it may also lead to the development of a new treatment strategy for early esophageal and gastric cancer.

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症 例

S-1単独療法が著効し組織学的CRが得られた高度進行残胃癌の1例

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〔*Jpn J Cancer Chemother* 38(7): 1191-1195, *July*, 2011〕

A Patient with Advanced Remnant Gastric Cancer Responding Completely to S-1 Monotherapy: Asuo Okaniwa[*1], Isao Murayama[*1], Yoshihiro Watanabe[*1], Ichiro Hayashi[*1], Tetsuo Hasegawa[*1], Yuichi Kasakura[*2], Noriko Kinukawa[*3], Norimichi Nemoto[*3] and Masashi Fujii[*4] (*[1]*Dept. of Surgery, Sonoda Dai-ichi Hospital, *[2]*Dept. of Surgery, Sonoda Dai-san Hospital, *[3]*Dept. of Pathology, Surugadai Nihon University Hospital, and *[4]*Dept. of Digestive Surgery, Nihon University School of Medicine*)

Summary

A 74-year-old man with anemia visited our hospital. When he was 42 years old, he was diagnosed with duodenal ulcer and underwent gastrectomy with Billroth Ⅱ construction. A gastrointestinal endoscopic examination revealed an ulcerative lesion at the remnant stomach, and the pathological examination of the biopsy specimen showed moderate to poorly differentiated adenocarcinoma. Abdominal CT scan revealed liver and para-aortic lymphnode metastases. He received daily oral administration of S-1 at a dose of 100 mg/body, bid, 4 weeks on and 2 weeks off. After 4 courses of S-1, CT scan showed a complete response of the liver and also para-aortic lymphnode metastasis. He underwent total remnant gastrectomy with D2 dissection. Histological examination revealed no residual cancer cells in the surgically removed stomach and lymphnodes, and he was diagnosed a complete pathological response (Grade 3). He refused adjuvant S-1, but is in good health without recurrence 2 years after the operation. **Key words**: S-1, Pathological CR, Remnant gastric cancer (*Received Apr. 15, 2011/Accepted May 11, 2011*)

要旨 われわれは初診時切除不能残胃癌に化学療法が奏効し，根治切除施行，病理学的CRが得られた症例を経験したので報告する。症例は74歳，男性。42歳時，十二指腸潰瘍にて幽門側胃切除 Billroth Ⅱ法再建が施行されている。貧血を指摘され，当科を受診した。精査の結果，残胃癌，肝転移，大動脈周囲リンパ節転移にて根治切除不能と診断し，S-1単剤で4週投与2週休薬にて治療を開始した。3コース終了後CT上肝転移，大動脈周囲リンパ節が消失，さらに1コース投与後CRと判定した。患者の承諾を得て審査開腹し，根治切除可能と判断し残胃切除術を施行した。切除標本にて病理組織学的CRと診断された。補助化学療法は患者拒否により施行していないが，術後2年現在再発なく生存中である。

はじめに

最近の化学療法の進歩により根治切除不能胃癌に化学療法が奏効し，根治切除可能となる症例を頻繁に経験するようになった。また，それらの症例のなかには病理学的complete response（CR）がみられたとする報告もある[1-6]。残胃癌は診断が困難であり，初診時に根治切除不能症例も多い。われわれは残胃癌，肝転移，大動脈周囲リンパ節転移にて根治切除不能と診断し，S-1単剤にて治療を開始，CT上肝転移，大動脈周囲リンパ節が消失したため審査開腹し，根治切除可能と診断して手術を施行，切除標本にて病理組織学的CRと診断された症例を経験したので報告する。

Ⅰ．症 例

患者: 74歳，男性。

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岡庭明日生

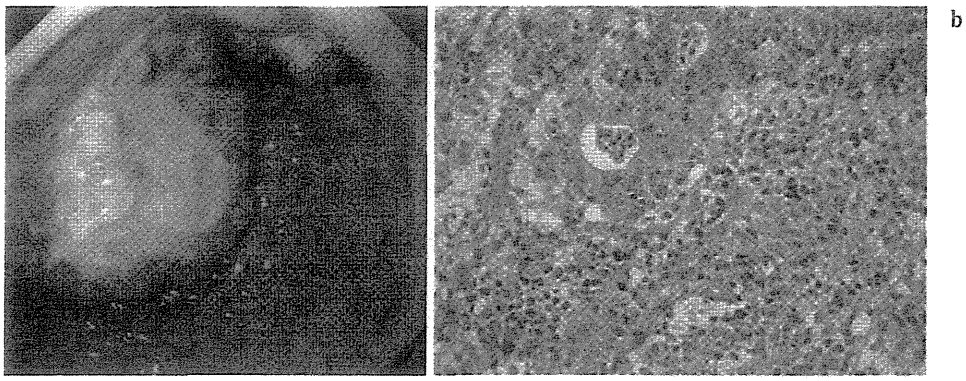

図 1 化学療法前内視鏡，病理所見
a: 噴門より 5 cm の前弯～小弯にかけて半周性の 2 型腫瘍を認めた。
b: 生検による病理組織診断は中分化～低分化型腺癌であった。

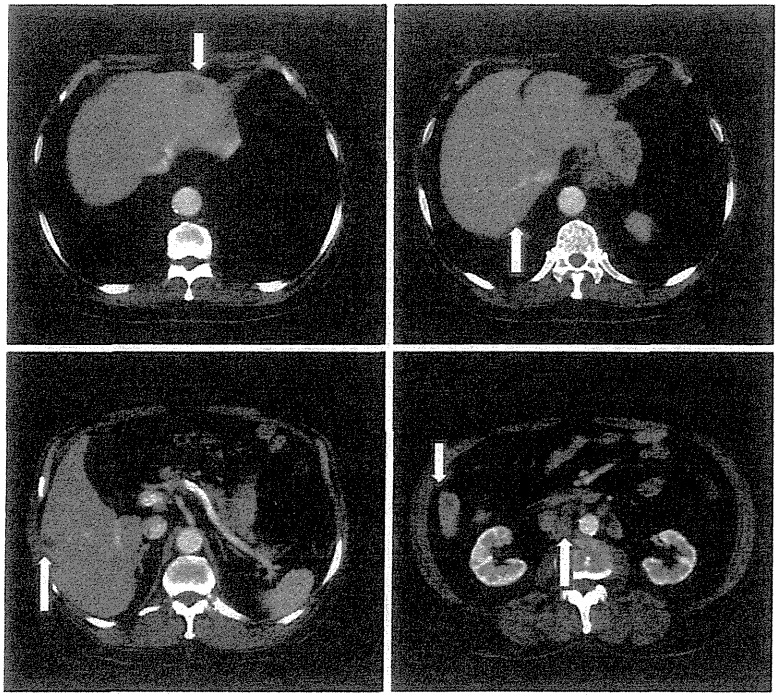

図 2 化学療法前腹部 CT
残胃全体の壁肥厚あり。肝 S3，S5，S6 に多発の肝転移を認め，残胃小弯ならびに大動脈周囲（No. 16）に多数のリンパ節の腫大を認めた。

主訴: 貧血。

既往歴: 42 歳時 十二指腸潰瘍。他院にて幽門側胃切除 Billroth Ⅱ法再建，66 歳時 視床出血。

家族歴: 特記すべきことなし。

現病歴: 視床出血治療後，当院脳神経外科外来通院中であった。定期検査にて貧血を指摘され，精査目的で当科を受診した。

初診時現症: 身長 167 cm，体重 79 kg。体温 36.0℃。眼瞼結膜にやや貧血を認め，眼球結膜に横染なし。腹部は平坦・軟で，腫瘤・表在リンパ節は触知しない。腹部正中に手術瘢痕を認めた。

初診時検査所見: Hb 8.2 g/dL と貧血を認める以外特記する異常値はみられなかった。CEA 2.1 ng/mL，CA19-9 1.2 U/mL，AFP 3.8 ng/mL で，腫瘍マーカーはそれぞれ正常値範囲内であった。上部消化管造影では残胃吻合部の狭窄が認められ，上部消化管内視鏡検査にて噴門より 5 cm から前弯～小弯にかけて半周性の 2 型腫瘍を認めた（図 1a）。生検による病理組織診断は中分化～低分化型腺癌であった（図 1b）。腹部 CT 検査にて残胃全体の壁肥厚あり。肝 S3，S5，S6 に多発の肝転移を認め，残胃小弯ならびに大動脈周囲（No. 16）に多数のリンパ節の腫大を認めた（図 2）。

治療経過: CT による評価から胃癌取扱い規約（旧 13 版）に基づき cTX，cN3，cM0，cH1，cP0: c-Stage Ⅳと診断し，患者の同意を得て S-1 による化学療法を開始した。S-1 100 mg/day を初回は 2 週間投与 1 週間休薬と

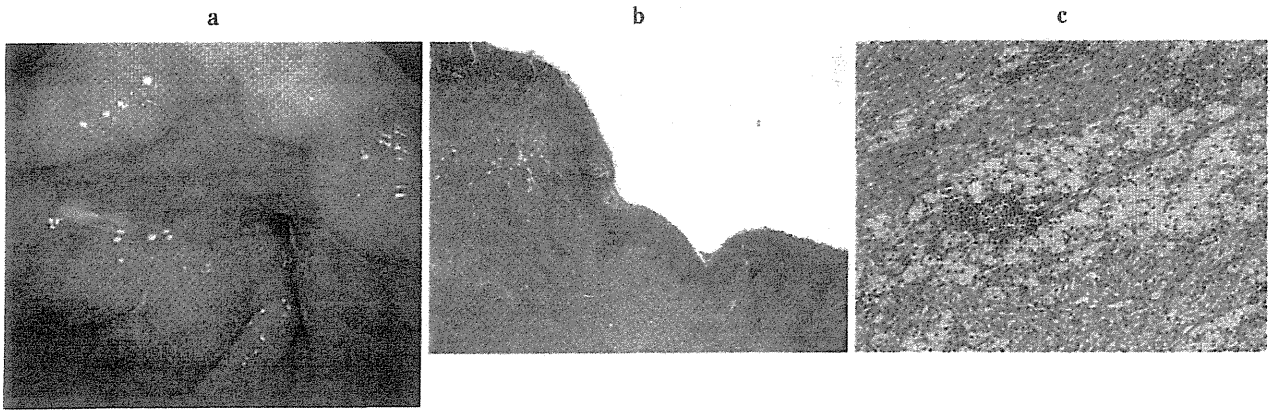

図 3　術後内視鏡，病理所見
a: 化学療法後の上部消化管内視鏡では，腫瘍はⅡc様に変化し生検ではGroup Ⅱの所見であった。
b: 組織標本は壊死組織を伴う潰瘍であり，固有筋層～漿膜下に及ぶ線維化がみられた。
c: マクロファージとリンパ球の集簇が筋層内に認められるがviableな腫瘍組織は認められない。

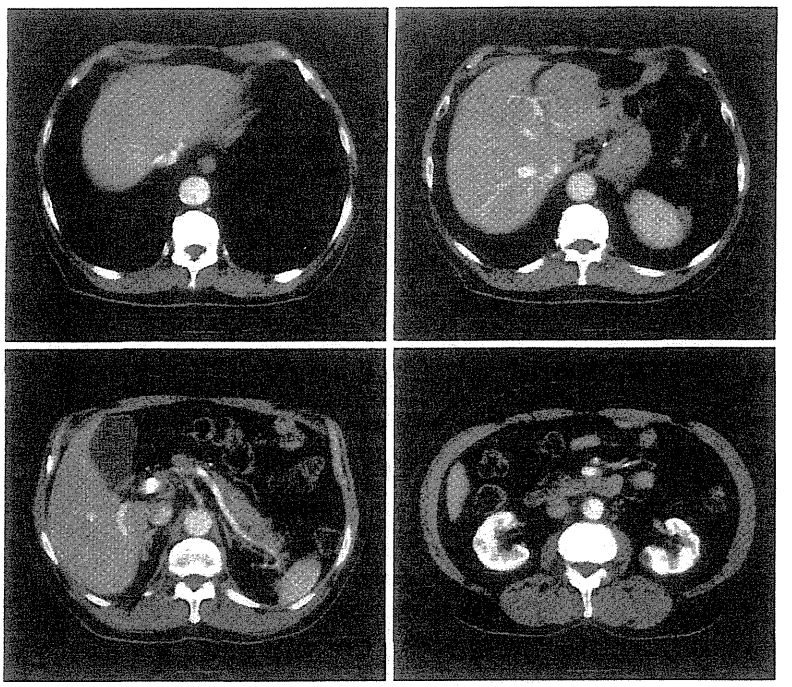

図 4　化学療法後腹部CT
残胃の壁肥厚はほぼ消失。多発の肝転移もほぼ消失，さらに大動脈周囲を含めたリンパ節腫脹も消失した。

し，有害事象のないことを確認後，以後4週投与2週休薬とした。3コース施行後の内視鏡検査にて，腫瘍はⅡc様に変化し（図3a），生検にてGroup Ⅱ，CT検査で胃の壁肥厚はほぼ消失。多発肝転移もほぼ消失，さらにリンパ節腫脹も消失した。そのため原発巣・転移病巣ともにCRと判断した（図4）。

その後も4週投与2週休薬を1コース続けた後のCT診断により，引き続きCR継続のため患者の同意を得て，化学療法開始から6か月後に試験開腹術を施行した。

試験開腹による術中所見では，少量の腹水を認め，細胞診に提出した。残胃は結腸前Billroth Ⅱ法再建がなされているがBraun吻合はない。肉眼的肝転移消失，大動脈周囲リンパ節腫脹なし，腹膜播種なく根治切除可能と判断，あらかじめ患者の承諾を得ており，残胃全摘術（D2リンパ節郭清）にコンバートし，Roux-en Y吻合再建を行った。

切除標本肉眼所見: 残胃（U領域）吻合部近傍に瘢痕化を伴う陥凹性病変が認められた。

病理組織学的所見: 腹水細胞診陰性。摘出残胃病変は潰瘍底壊死組織を伴う潰瘍であり，固有筋層～漿膜下に及ぶ線維化がみられた。マクロファージとリンパ球の集簇は認められたがviableな腫瘍組織は認められず，リンパ節転移（0/7）病理学的CRと診断された（図3b，c）。患者は，術後合併症なく第21病日に軽快退院した。術後

補助化学療法は患者の同意を得られず施行していない。現在，術後2年経過し再発兆候はみられず社会生活を営んでいる。

Ⅱ．考　察

残胃癌は初回胃切除から10年以上経過してから発症しやすいといわれ，胃外科術後障害研究会の全国アンケート調査[7]の887例では再建別法でBillroth Ⅰ法が368例，Billroth Ⅱ法が519例集計された。このうち初回良性は65.2%（578/887）である。残胃癌手術までの介在時間はBillroth Ⅰ法が21.1年，Billroth Ⅱ法が31.5年と報告されている。組織型は分化型，未分化型はほぼ同数である。残胃占拠部位はBillroth Ⅰ法では非断端部，Billroth Ⅱ法では吻合部に多いと報告されている。本症例はBillroth Ⅱ法再建術後32年であり，病変の主体は吻合部近傍，組織型は中～低分化腺癌であった。

切除不能残胃癌の治療は通常の切除不能胃癌と同様化学療法が第一選択となる。しかしながら，初回手術による血管構築破壊による薬剤到達性や，経口剤の吸収や薬理動態などの報告はほとんどない。また，残胃癌が化学療法に奏効しconversion treatmentに移行できた症例の報告も少なく，組織学的CR例も極めてまれである[8]。

進行再発胃癌の標準的化学療法は，JCOG9912の結果，S-1単剤の5-fluorouracil注射剤との非劣性が報告され[9]，続くSPIRITS試験でS-1単剤に比べS-1/cisplatinの優越性が報告された[10]。その結果，S-1/cisplatinが現在標準化学療法として確立されている。しかしながらcisplatinは腎毒性が強く，毒性軽減のために大量の補液を必要とするため入院治療が余儀なくされる。外来通院での実施可能性を求めて，TOP-002試験ではS-1単剤とS-1/CPT-11との比較試験[11]，JACCRO GC-03試験（START trial）ではS-1単剤とS-1/docetaxelとの比較試験[12]が行われている。しかしながら，両試験とも統計学的な優越性が得られず，現在もS-1/cisplatinのみが標準化学療法としてガイドライン治療として推奨されている。

本症例でも標準化学療法であるS-1/cisplatin併用療法の説明を行ったが，患者の希望により入院治療を要しないS-1単独療法を選択した。また，残胃症例のため消化器系有害事象の発現を考え推奨用量である120 mg/body（80 mg/m^2）から100 mg/bodyに減量して治療を開始し，有害事象を観察後に推奨用量への漸増を考えていた。しかしながら，100 mg/bodyにても効果発現がみられたため，以後も100 mg/bodyで治療を継続した。

S-1単剤の臨床効果におけるCR例については，第Ⅱ相試験で1例（1/101）みられている[13]。その後，SPIRITS試験ではS-1単剤群で1例（1/106），S-1/cisplatin併用群で1例（1/87）のCR例がみられ，TOP-002試験ではS-1単剤群（0/93），S-1/CPT-11群（0/94）両群ともCR例はみられず，JACCRO GC-03試験において，S-1単剤群で4例（4/244），S-1/docetaxel併用群で1例（1/228）のCR例が報告されている。上記3試験におけるS-1単剤におけるCR率は1.13%（5/443），併用群におけるCR率は0.49%（2/409）であり，CR例はむしろ単剤群に多くみられている。

SPIRITS試験ならびにJACCRO GC-03試験における層別解析では，腹膜播種などの標的病変のない症例ではS-1/CDDP，S-1/docetaxelなどの併用群で有意に生存期間の中央値の延長が証明されたが，肝転移やリンパ節転移などの標的病変のある症例では，S-1単剤と併用群の生存期間の中央値に差がないとの報告がある。本症例のような残胃原発巣，肝転移，リンパ節転移を有するような標的病変のある症例には，患者の状態，希望によりS-1単剤での治療開始も念頭に入れてもよいと考えられる。

本症例は化学療法が奏効し，根治切除可能になったために結果的に術前に化学療法が行われたことになる。しかしながら，術前化学療法には二通りのコンセプトがある。一つは真の意味での術前化学療法であり，術前臨床診断にて拡大リンパ節郭清や合併切除により根治切除可能ではあるが，非根治切除も予想される症例を対象として，ダウンステージングを期待して行うneoadjuvant chemotherapy（NAC）である。もう一つは術前診断根治切除不能例を対象として行った化学療法が奏効し，結果的に臨床上根治切除可能となった本症例のような場合で，pseudo NACあるいはconversion treatmentと称される。本症例は典型的なconversion treatmentである。

術前化学療法はヒトによる制癌剤感受性試験と考えられる。本症例でS-1単独療法が効果を発揮した要因としては，腫瘍のS-1に対する高感受性が考えられる。われわれは，切除可能大腸癌において術前2週間の短期UFT投与後に切除標本の組織学的効果を検討した。その成績でもGrade 3の効果がみられた症例が126例中3例，Grade 2以上の効果は25%にみられている[14]。本症例は，S-1単剤にて期待できる約1%の臨床的CR症例がconversion treatmentにより組織学的に証明された残胃癌では極めてまれな症例と考えている。患者は術後補助化学療法を希望せず経過観察中であるが，再発時には高感受性を示したS-1をベースにした化学療法での再治療を考えている。

おわりに

S-1単独療法で組織学的CRが得られた肝転移を有する切除不能残胃癌の1例を報告した。S-1/cisplatin療法が進行再発胃癌の標準化学療法であるが，計測可能病変である肝転移，リンパ節転移症例においてはS-1単剤治療にても奏効し，conversion treatmentへの移行や生命延長効果が期待される。

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Long-Term Outcome of Combined Interferon-α and 5-Fluorouracil Treatment for Advanced Hepatocellular Carcinoma with Major Portal Vein Thrombosis

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Key Words

Hepatocellular carcinoma · Interferon · Portal vein tumor thrombosis · Arterial infusion chemotherapy

Abstract

Background/Aim: We previously reported the beneficial effects of a combination therapy of interferon (IFN)-α/5-fluorouracil (FU) for advanced hepatocellular carcinoma (HCC) with tumor thrombi in the major portal branches. This report describes the results of longer follow-up and includes more than twice the number of patients relative to the previous report; it also evaluates the clinical predictor on the response to the combination therapy and long-term survival. ***Methods:*** The study subjects were 102 patients with advanced HCC and tumor thrombi in the major branches of the portal vein (Vp3 or 4). They were treated with at least 2 courses of IFN-α/5-FU. ***Results:*** No major treatment-related complications were noted. In the 102 patients, 40 (39.2%) showed objective response [11 (10.8%) showed complete response, 29 (28.4%) partial response], 8 (7.9%) showed no response and 54 (52.9%) showed progressive disease. ***Conclusion:*** IFN-α/5-FU combination therapy is a promising modality for advanced HCC with tumor thrombi in the major portal branches.

Introduction

The prognosis of patients with advanced hepatocellular carcinoma (HCC) remains poor, particularly in patients with tumor thrombi in the major trunk of the portal vein (Vp4) [1–3]. The mortality rate is very high in patients with unresectable tumors and the quality of life is poor due to intractable ascites or esophageal bleeding. Even in patients with resectable HCC, the prognosis is extremely poor despite aggressive surgery [4, 5]. In such a situation, conventional therapies generally have no clinical effect on HCC associated with portal tumor thrombi due to poor efficacy and possible complications [6, 7]. Arterial infusion chemotherapy has also been attempted, but its effectiveness is still unsatisfactory for portal venous tumor thrombus (PVTT) [8, 9]. Therefore, a new strategy is required for patients with intractable HCC and tumor thrombi in the major branch of the portal vein.

Several recent studies have indicated the beneficial effects of interferon (IFN)-α-based combination chemotherapies for HCC [10–15], in spite of the lack of satisfactory results from IFN-α monotherapy [16]. We also reported the clinical efficiency of IFN-α and 5-fluorouracil (5-FU) combination therapy for advanced HCC with PVTT and intrahepatic metastasis [17–22].

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Table 1. Patient characteristics

	Patients (n = 102)
Age, years	59.6 ± 9.4
Gender, male/female	94/12
Hepatitis virus	
HBV (+), HCV (–)	27
HBV (–), HCV (+)	54
HBV (+), HCV (+)	14
HBV (–), HCV (–)	9
Unknown	2
Granulocytes, /ml	4,420 ± 1,648
Platelets, $\times 10^4$/ml	13.3 ± 6.7
Serum albumin, g/dl	3.24 ± 0.44
Serum bilirubin, mg/dl	0.98 ± 0.36
Prothrombin time, s	17.9 ± 2.0
Child–Pugh classification	
A	38
B	63
C	4
Unknown	1
AFP, ng/ml	
<5	4
≥5	101
Unknown	1
PIVKA-II, mAU/ml	
<40	3
≥40	102
Unknown	1

The present study is the long-term outcome of the clinical effects of the combination therapy of subcutaneous IFN-α and arterial infusion of 5-FU in 102 patients with HCC associated with Vp4 and multiple intrahepatic metastases (IM3) [1], as an extension to our previous work [18, 19].

Patients and Methods

Patients and Selection Criteria

This was a single-arm open-label study, based on our pervious reports [18, 19]. Between December 1997 and December 2008, 102 patients with advanced HCC were enrolled. All patients were confirmed radiologically to have tumor thrombi in the main trunk of the portal vein (Vp4) and IM3. The diagnosis was based on liver function tests, serum α-fetoprotein (AFP), serum protein induced by vitamin K absence or antagonist-II (PIVKA-II) and imaging techniques including computed tomography (CT) scan, magnetic resonance imaging (MRI), hepatic angiography and arterial portography.

The following were the eligibility criteria for selection for intra-arterial combination therapy: (1) age of more than 20 years and less than 75 years; (2) tumor thrombi invading at least one of the main branches of the portal vein; (3) presence of multiple intrahepatic metastases in more than three segments (IM3); (4) absence of extrahepatic metastases; (5) a granulocyte count of more than 2,500/μl and less than 12,000/μl; (6) a red blood cell count of more than 8.0 g/dl; (7) a platelet count exceeding 8×10^4/μl; (8) GOT and GPT of less than 100 IU/l; (9) total bilirubin less than 1.4 g/dl; (10) serum BUN less than 30 mg/dl; (11) serum creatinine less than 1.5 mg/dl; (12) successful implantation of intra-arterial catheter and drug delivery system; (13) a performance status of level 0–2 (Eastern Cooperative Oncology Group, ECOG) [23]. These eligibility criteria were based on our previous report [18, 19]. All patients signed informed consent documents approved by the institutional review board attesting to the fact that they were aware of the investigational nature of the study and were willing to try the combination therapy.

The baseline characteristics of the enrolled 102 patients who received IFN/5-FU combined treatment are shown in table 1 (age, gender, hepatitis virus, granulocytes, platelet, albumin, bilirubin, prothrombin time, Child-Pugh classification, AFP and PIVKA-II).

Treatment Protocol of IFN/5-FU Combination Therapy

In each of the 102 patients, an intra-arterial catheter was inserted through the subclavian or femoral artery, with a subcutaneously implanted drug delivery system [24]. Each patient was treated with subcutaneous IFN-α (OIF; Otsuka Pharmaceutical Co., Tokushima, Japan) and intra-arterial infusion of 5-FU (Kyowa Hakko Co., Tokyo, Japan). One cycle of the treatment consisted of 4 weeks. IFN-α (5×10^6 U, 5 MU) was administered subcutaneously on days 1, 3 and 5 of each week, resulting in a total dose of 60 MU in a cycle. Continuous infusion chemotherapy (5-FU, 300 mg/m^2/day) through the proper hepatic artery was performed on the 1st and 2nd weeks via a catheter connected to a subcutaneously implanted drug delivery system. Two- or three-week rest period (cessation of drug therapy) separated the treatment cycles. All anticancer therapies were discontinued when adverse effects reached level 2 of the ECOG classification [23] (with the exception of platelet and leukocyte counts of less than 40,000 and 2,000/mm^3, respectively, since these parameters were often low prior to treatment due to the associated liver cirrhosis) [18, 19].

Evaluation of Response to IFN/5-FU Combination Therapy

A pretreatment evaluation was conducted at the commencement of IFN-α/5-FU protocol and posttreatment evaluation after completion of the 2-cycle treatment, almost 3 months later. The evaluation was performed using CT or MRI, and changes in serum tumor markers, such as AFP and PIVKA-II. All cases were compared at these two time points for the evaluation of antitumor effect. The objective response was classified according to the ECOG criteria [23]. Complete response (CR) was defined as normalization of tumor markers and disappearance of all tumors and portal vein thrombosis on CT and/or MRI. Partial response (PR) represented a decrease in tumor markers and 50–99% regression on the two-dimensional measurement. No change (NC) represented less than 50% regression or less than 25% progression. Progressive disease (PD) represented more than 25% progression. In addition, we also evaluated progression-free and overall survival rates. The follow-up period was 12–120 months.

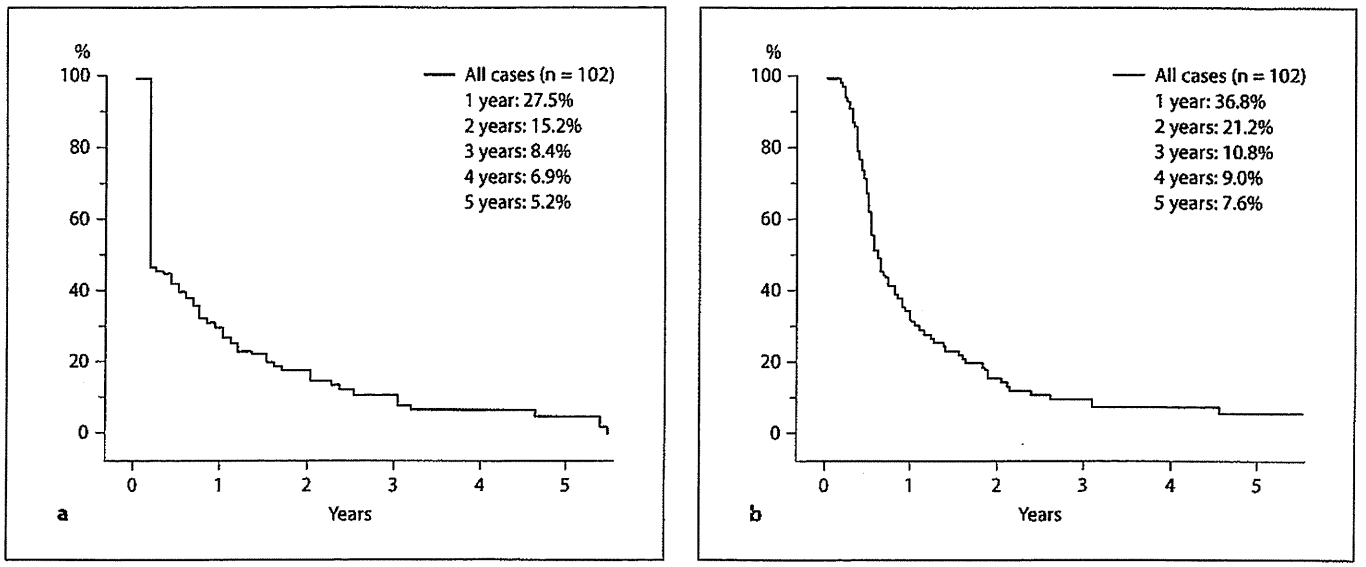


Fig. 1. Kaplan-Meyer analysis for efficiency of IFN/5-FU combination therapy. **a** Progression-free survival curve in all cases. The median progression-free survival period was 2.0 months, and the 1-, 3- and 5-year progression-free survival rates were 27.5, 8.4 and 5.2%, respectively. **b** Overall survival curve in all cases. The median overall survival period was 9 months, and the 1-, 3- and 5-year survival rates were 36.8, 10.8 and 7.6%, respectively.

Statistical Analysis

The Breslow-Gehan-Wilcoxon univariate test was used to examine the possible relationship between the effect of therapy (CR, PR vs. NC, PD), Child-Pugh score, serum AFP, serum PIVKA-II, Okuda score and CLIP score [3]. Survival curves were constructed using the Kaplan-Meier method. Differences in distribution between groups were compared by the χ^2 test and differences in mean values by Student's t test. All data were expressed as means ± SD. A p value less than 0.05 denoted the presence of a statistically significant difference.

Results

Clinical Response to Combination Therapy

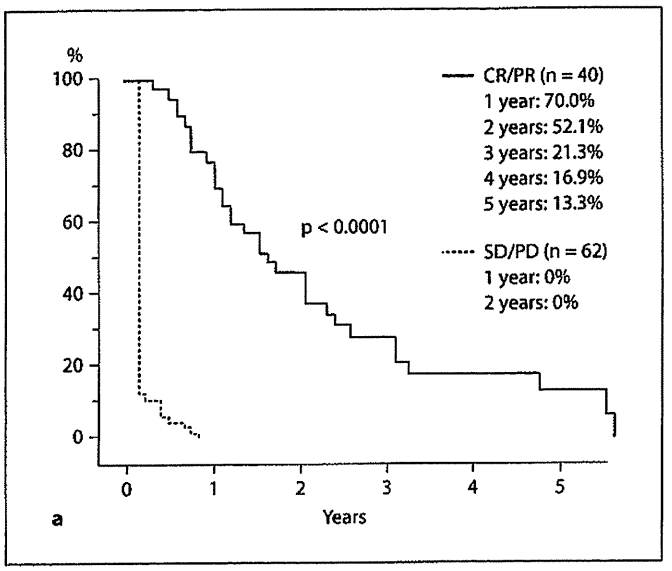
All patients completed at least two cycles of the IFN/5-FU combination therapy. For patients who showed clinical response, we continued this combination therapy, while in those who showed no effect, we stopped the treatment after the completion of the second cycle, because of the extensive progression of HCC.

With regard to the clinical effect, 40 (39.2%) showed objective response, 11 (10.8%) showed CR, 29 (28.4%) showed PR, 8 (7.9%) showed NC and 54 (52.9%) showed PD. With respect to time to progression, the median progression-free survival period was 2.0 months, and the 1-, 3- and 5-year progression-free survival rates were 27.5, 8.4 and 5.2%, respectively. Furthermore, the median overall survival period was 9 months, and the 1-, 3- and 5-year survival rates were 36.8, 10.8 and 7.6%, respectively. The median progression-free survival period of CR/PR cases (n = 40) was 18.5 months and that of NC/PD cases (n = 62) was 2.0 months. The 1-, 3- and 5-year progression-free survival rates of CR/PR cases were 70.0, 21.3 and 13.3%, respectively, and those of NC/PD cases were 0, 0 and 0%, respectively.

The median survival time of CR/PR cases (n = 40) was 25 months and that of NC/PD cases (n = 62) was 6 months. The median follow-up time of survived patients was 30 months. The 1-, 3- and 5-year survival rates of CR/PR cases were 82.7, 28.6 and 18.9%, respectively, and those of NC/PD cases were 4.8, 0 and 0%, respectively. The progression-free survival and overall survival curves are shown in figures 1 and 2, respectively. There were significant differences in the progression-free survival and the overall survival between responders (CR/PR) and nonresponders (NC/PD) ($p < 0.0001$).

Adverse Effects

None of the patients developed side effects related to catheter insertion or subcutaneous implantation of the drug delivery system. However, 8.8% of patients developed grade 3 leukopenia, thrombocytopenia or anae-



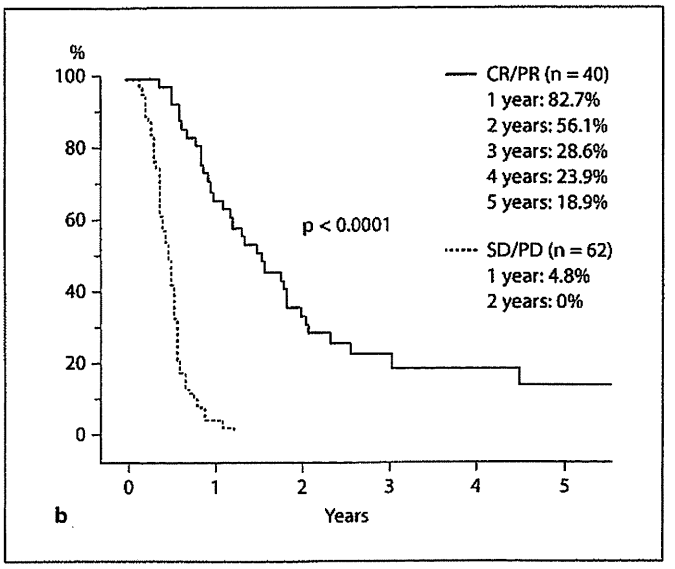


Fig. 2. Kaplan-Meyer analysis for efficiency of IFN/5-FU combination therapy. **a** Progression-free survival curves in CR/PR and NC/PD cases. The 1-, 3- and 5-year progression-free survival rates of CR/PR cases were 70.0, 21.3 and 13.3%, respectively, and those of NC/PD cases were 0, 0 and 0%, respectively. **b** Overall survival curves in CR/PR and NC/PD cases. The 1-, 3- and 5-year survival rates of CR/PR cases were 82.7, 28.6 and 18.9%, respectively, and those of NC/PD cases were 4.8, 0 and 0%, respectively. There were significant differences in the progression-free survival and the overall survival between responders (CR/PR) and nonresponders (NC/PD) ($p < 0.0001$).

mia, but drip transfusion of granulocyte colony-stimulating factors was not used during this study. Nonhematological toxicities included grade 1 or 2 fever (100% of patients), chilling sense (92.3%), nausea (6.9%), diarrhea (3.6%), gastric ulcer (2.9%), flu-like syndrome (100%), skin reaction (4.9%), general fatigue (31.3%) and depression (2.9%). The side effects are summarized in table 2.

Clinical Correlations

Finally, we compared the responders (CR/PR) (n = 10) with nonresponders (NC/PD) (n = 20) in terms of serum AFP (within normal range; <5), serum PIVKA-II (normal range; <45), Child-Pugh score, OKUDA score and CLIP score by univariate analysis. Serum AFP, PIVKA-II, Child-Pugh score, OKUDA score and CLIP score did not correlate with the response to combination therapy, similar to our previous report [19] (data not shown).

Table 2. Adverse effects

	Patients (n = 102)			
	grade 1	grade 2	grade 3	grade 4
Hematological				
Leukopenia	14	23	6	0
Anemia	0	1	3	0
Thrombocytopenia	16	20	9	0
Nonhematological				
Fever	97	5	0	0
Chilling sense	94	0	0	0
Nausea	7	0	0	0
Diarrhea	4	0	0	0
Gastric ulcer	0	3	0	0
Flu-like syndrome	102	0	0	0
Skin reaction	5	0	0	0
General fatigue	32	0	0	0
Depression	3	0	0	0

Discussion

In this study, we showed the beneficial effects of IFN-α/5-FU combination therapy in patients with multiple lesions and tumor thrombi in the major branches of the portal vein (Vp3 or 4), as our third report on this combined treatment. The efficacy of such treatment was 39.2% in our patients with highly advanced HCC, which was almost similar to the others and our previous reports of patients with the same stage HCC [15, 19, 25]. The

prognosis of such patients is extremely poor and survival is generally limited to a few months after diagnosis, despite multimodal therapies even in cases suitable for surgical resection [26]. The combination treatment IFN-α and 5-FU markedly decreased tumor size and levels of tumor markers with an encouraging response rate and prolonged survival time in the responders. Furthermore, the clinical response completely reflected the survival benefits, as shown in figures 1 and 2. There are several other reports about the possibilities as a treatment for advanced HCC with PVTT, such as intra-arterial infusion chemotherapy with 5-FU and CDDP [27–29] or transarterial chemoembolization [30]. A certain level of antitumor effect has been shown in 5-FU and CDDP intra-arterial chemotherapy for the lower stage of HCC patients, but not just for PVTT; antitumor effect for the HCC partially including PVTT patients were not significant compared to IFN-α/5-FU combined treatment in terms of median survival time, response rate and overall survival. Transarterial chemoembolization was reported as an effective treatment for advanced HCC with PVTT in RCT, but the clinical outcome was not better than IFN and 5-FU combined treatment. From these findings, the clinical result of IFN and 5-FU combined treatment was promising for the disastrous advanced HCC with PVTT patients.

On the other hand, no response to the combination therapy was seen in 60.8% (62/102) of the patients in this study. To advance the effect of IFN-α/5-FU combination therapy and to increase the response rate, it is necessary to investigate the mechanism of IFN-α/5-FU combination therapy. Among the nonresponders, there were only a few NC (8/102) in this study, in spite of the mostly chemo-resistant disease. We reasoned this finding to the following; the HCC in this series was far advanced and HCC progression was extremely rapid and aggressive. Under such conditions, almost all nonresponders died within 12 months (59/62); 40 of 62 cases (64.5%) within 6 months. For nonresponders to this treatment, however, the survival period was too short to allow receiving another treatment modality. Therefore, accurate prediction of chemosensitivity is desirable not only for loss of a limited chance for another possible treatment but also to avoid potentially serious side effects. However, there are no suitable markers that could distinguish patients who are likely to respond to this combination chemotherapy from those who are not. In this point, Obi et al. [15] recommended to start the combination therapy with close monitoring of response, preferably that of tumor biomarkers, and treatment should be continued if there is a response after the first cycle of chemotherapy.

Several mechanisms for the anticancer effects of IFN-α, with or without 5-FU, have been proposed [31–34]. We showed previously that IFN-α and 5-FU synergistically inhibit tumor cell proliferation with cell cycle arrest [35] and induced apoptosis by regulating the apoptosis-related molecules [36] as well as an antiangiogenic effect [37]. We also reported that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), its receptor pathway [38] and Fas and Fas-L pathway [39] partially contributed to the antitumor effects of IFN-α and 5-FU combination therapy. About apoptosis induction, the close involvement of P53 has been reported [40, 41]. Moreover, IFN-α suppresses the proliferation of all type I interferon receptor 2 (IFNAR2)-positive HCC cell lines in vitro through mechanisms related to apoptosis or inhibition of cell cycle [42]. The importance of IFNAR2 expression for the anticancer effect of IFN/5-FU was highlighted in a similar situation in our previous report [35, 36, 43]. In addition, we reported the significance of Ep-CAM [44] and IGFR-7 [45] as a noble biomarker to assess the antitumor effect of IFN/5-FU combined treatment. CD133 may be related to antitumor effect of IFN and 5-FU as a predictor in perspective of cancer stem cell [46].

The combination of IFN/5-FU is not effective against extrahepatic metastases. This is understandable because 5-FU, administered into the hepatic artery, will not reach extrahepatic tissues in high concentration. However, systemic administration of 5-FU or related agents may be effective against extrahepatic lesions in combination with IFN-α [47]. This possibility is highly interesting since the implantation of dwelling catheter is one of the demerits of the present combination therapy [15]. Recently, several molecularly targeting agents have been developed and applied for HCC treatment [48–51]. Especially sorafenib is the first agent leading to improved overall survival with advanced HCC, revealed in a phase III clinical trial [51]. These molecularly targeting agents are a very effective therapeutic modality, which has the different mechanism of antitumor effect from IFN/5-FU combination as an cytotoxic medicine. We reported actually that PTK/ZK, a kind of molecularly targeting medicine, enhanced the antitumor effect of IFN/5-FU in vitro [52]. After this, mutual interaction and sharing roles might be very important for the progression of the treatment for intractable advanced HCC.

In conclusion, we demonstrated the long-term outcome about the efficacy of IFN/5-FU combination therapy for advanced HCC patients with tumor thrombi in major branches of the portal vein.

Acknowledgment

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Prognostic Value of Endoscopic Biopsy Findings After Induction Chemoradiotherapy With and Without Surgery for Esophageal Cancer

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Objective: To investigate the value of endoscopic biopsy in predicting the clinicopathological response and survival in patients with esophageal cancers who received chemoradiotherapy (CRT) alone or CRT followed by surgery.

Background: Endoscopic biopsy examination after CRT for esophageal cancer has been used to confirm the presence of residual tumor before surgery, but there is little or no information on the clinical significance of the results of endoscopic biopsy in neoadjuvant or definitive CRT.

Methods: We studied 189 patients who underwent endoscopic biopsy after induction CRT (40 Gy) for esophageal cancer, consisting of 123 patients who received neoadjuvant CRT (40 Gy) followed by surgery and 66 patients who underwent definitive CRT (mostly more than 60 Gy). The correlations between the results of endoscopic biopsy and clinicopathological factors, including response to CRT and survival, were examined.

Results: For neoadjuvant CRT, endoscopic biopsy findings correlated significantly with pathological tumor regression and lymph node involvement, although the majority of cases with negative biopsy (64%) displayed residual tumor cells in the surgical specimen. The 5-year survival rate was significantly higher in patients with negative biopsy (48.3%) than in those with positive biopsy (21.8%, $P = 0.006$). For definitive CRT, patients with negative biopsy at the time of 40 Gy showed clinical complete response to CRT ($P = 0.002$) and had significantly better 3-year survival (57.0%) than those with positive biopsy (22.5%, $P = 0.0008$).

Conclusions: The results of endoscopic biopsy examination after induction CRT can predict the response to CRT and prognosis of patients who receive CRT with and without surgery.

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Esophagectomy is traditionally used as the standard treatment of locoregional esophageal cancer. However, the majority of patients who undergo curative resection subsequently develop locoregional or systemic recurrence, leading to unfavorable prognosis.[1–4] To improve prognosis, multimodal therapy, including chemotherapy and radiotherapy, in addition to surgery, has been used.[5–7] In fact, preoperative chemoradiotherapy (CRT) is widely used for treatment of patients with locally advanced esophageal cancers. Although controversy exists as to whether preoperative CRT offers survival benefits, previous studies reported that neoadjuvant CRT before surgery increased complete resection rates and improved prognosis in patients with good response to CRT,[5–14] with pathological complete response (pCR) being achieved in 15% to 32% of patients who received preoperative CRT.[15–20]

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Chemoradiotherapy alone without surgical resection is used as another treatment option for locally advanced esophageal cancer. Previous studies that compared neoadjuvant CRT followed by surgery with CRT alone suggested that the prognosis of patients treated with CRT alone is comparable with that of patients who underwent neoadjuvant CRT followed by surgery, especially in those who show good response to preoperative CRT.[21,22] This raises the question of whether or not the patients who achieve complete response (CR) after preoperative CRT actually need subsequent surgical resection. Thus, early assessment of the response to induction therapy may make it possible to individualize therapy on the basis of the response to CRT.

Various imaging studies, including computed tomography (CT), endoscopy, and endoscopic ultrasound, have been used to evaluate the clinical response to preoperative (induction) CRT.[23–27] Furthermore, several recent studies have demonstrated that 18-fluorodeoxyglucose positron emission tomography (PET) imaging after induction therapy can predict outcome.[28–31] Several studies carried out previously examined whether endoscopic biopsy can accurately predict the presence of residual tumor after neoadjuvant CRT for esophageal cancers, but the value of post-CRT endoscopic biopsy in predicting the response to treatment and survival in patients who underwent CRT with or without surgery is not clear.[32–35]

In the present study, we determined whether endoscopic biopsy after induction CRT (40 Gy) can predict the histopathological response and prognosis of patients who were subsequently treated with surgery or continued the course of definitive CRT only. Moreover, we also analyzed whether endoscopic biopsy after induction CRT provides useful information for selection of further therapy.

MATERIALS AND METHODS

Patients and Treatment Protocols

Between January 1994 and December 2007, 584 patients with thoracic esophageal cancers underwent surgery at the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan. Among them, 128 patients underwent esophagectomy after neoadjuvant CRT for thoracic esophageal cancer. During the same period, 141 patients with thoracic esophageal cancers received definitive CRT alone without surgical resection. Of these 269 patients who received CRT as initial treatment of thoracic esophageal cancer, 123 patients who underwent endoscopic biopsy after neoadjuvant CRT and 66 patients who underwent endoscopic biopsy at the time of 40 Gy irradiation in the definitive CRT group were included in the present study. Basically, neoadjuvant CRT followed by surgery was selected for patients who had invasive thoracic esophageal cancers (T3-T4) without distant organ metastasis or those whose tumor was located in the upper third of the thoracic esophagus with infiltration of the cervical esophagus. On the contrary, definitive CRT was basically provided for patients who elected to be treated with CRT as curative treatment. During the time of this study, all patients who had started receiving CRT as neoadjuvant intent underwent esophagectomy even if clinical CR was achieved after neoadjuvant

CRT. All 189 patients were diagnosed with squamous cell carcinoma of the thoracic esophagus by pretreatment biopsy samples.

To evaluate the response to CRT, endoscopy was routinely performed after neoadjuvant CRT and at the time of 40 Gy irradiation during the course of definitive CRT. Basically, 3 or more biopsies were taken at endoscopic evaluation. Patients who did not undergo endoscopic examination because of CRT-related toxicity, those who did not have a biopsy by endoscopic examination, and those who did not have sufficient amounts of tissue biopsy samples for histopathological examination were excluded from the study. Endoscopic evaluation was necessary after 40 Gy in the neoadjuvant CRT group and after 60 Gy in the definitive CRT group. However, endoscopic evaluation after 40 Gy in the definitive CRT group was optional for this study. There were no significant clinical differences between patients with endoscopic biopsy and those without endoscopic biopsy for patients who underwent definitive CRT (Table 1).

The CRT treatment regimen included administration of a single daily fraction of 2 Gy concurrently with cisplatin and 5-fluorouracil. 5-fluorouracil was administered by continuous intravenous administration at a dose of 400 mg/m^2 in combination with cisplatin at 10 mg/m^2 administered by drip for 5 days per week. Patients who underwent neoadjuvant CRT followed by surgery received a total dose of 40 Gy radiation, in combination with chemotherapy. On the contrary, those on definitive CRT received a total dose of more than 54 Gy (range, 54–68 Gy). In the neoadjuvant CRT, patients underwent endoscopic biopsy within 1 week of the completion of neoadjuvant CRT and underwent surgical resection 4 to 6 weeks after the completion of neoadjuvant CRT. Among the 123 patients who underwent surgical resection, 34 patients underwent transthoracic esophagectomy with 2-field lymphadenectomy, 63 underwent transthoracic esophagectomy with 3-field lymphadenectomy, and 26 patients underwent esophagectomy using the trans-hiatal approach. In the definitive CRT, patients underwent endoscopic biopsy at the time of 40 Gy irradiation (within 1 week), and after an interval of 1 to 2 weeks, radiation was delivered up to 54 to 68Gy. Four to 6 weeks after the completion of definitive CRT, endoscopic biopsy was obtained again to evaluate the clinical response of CRT. Complete follow-up information until death or July 2009 was available for all patients.

In this study, all patients were staged before and after surgery according to the criteria of the International Union Against Cancer (UICC). Pretreatment clinical staging was based on oesophagogeography, endoscopy, and CT of the neck, chest, and upper abdomen by using continuous 5-mm-thick slices. Bronchoscopy was performed when tracheobronchial involvement was suspected. From March 2000, PET was also used in our facility for clinical staging where possible. Lymph nodes were diagnosed as metastasis-positive on CT scan if they were greater than 1.0 cm in maximum transverse diameter. Lymph nodes visible but smaller than 1.0 cm on the long axis on CT scan were regarded as metastasis-positive only if focal prominent 18-fluorodeoxyglucose uptake, relative to normal mediastinal activity, was also detected on the PET scan.

The protocol of this retrospective study was approved by the Human Ethics Review Committee of Osaka University Graduate School of Medicine and a signed consent form was obtained from each subject.

TABLE 1. Patients' Characteristics

	Neoadjuvant CRT	Definitive CRT		
		Biopsy (+)	Biopsy (−)	*P* value
n	123	66	75	
Mean age	61.0	66.1	65.6	0.623
Gender (male/female)	107/16	58/8	68/7	0.592
Tumor location				
Upper	61 (50)	19 (29)	18 (24)	0.189
Middle	44 (36)	33 (50)	48 (64)	
Lower	18 (14)	14 (21)	9 (12)	
Tumor depth				
cT1	0 (0)	20 (30)	22 (29)	0.417
cT2	19 (15)	8 (12)	6 (8)	
cT3	39 (32)	20 (30)	20 (27)	
cT4	65 (53)	18 (28)	27 (36)	
Nodal status				
cN0	36 (29)	32 (48)	38 (51)	0.796
cN1	87 (71)	34 (52)	37 (49)	
Mean radiation dose (Gy)	40.0	61.6	60.6	0.173
Clinical response				
CR	12 (10)	37 (56)	32 (43)	0.125
PR	86 (70)	16 (24)	23 (31)	
NC/PD	25 (20)	13 (20)	20 (26)	

CR indicates complete response; NC/PD, no change or progressive disease; PR, partial response.

Evaluation of Clinical Response

After completion of neoadjuvant or definitive CRT, all patients were restaged by CT scan, endoscopy, and, in recent cases, PET to evaluate the clinical response to CRT. The response was categorized on the basis of the World Health Organization response criteria for measurable disease and the criteria of the Japanese Society for Esophageal Diseases.[36] A CR was defined as complete regression of disease for at least 4 weeks on the basis of CT scan and/or PET scan and endoscopy. The patient was not considered as to have achieved CR when persistent ulceration and/or presence of cancer cells in biopsy samples were confirmed on endoscopy.[37] Partial response was defined by more than 50% reduction in the size of the primary tumor and lymph node metastasis, as confirmed by CT and endoscopy. *Progressive disease* was defined by an increase of more than 25% in the size of the primary tumor or the appearance of new lesions. Cases that did not meet the criteria of partial response or progressive disease were defined as no change.[36,37]

Histopathological Examination

The histopathological findings were classified according to the UICC TNM classification. The degree of histopathological tumor regression in the surgical specimens was classified into 5 categories.[36,38] The extent of viable residual carcinoma at the primary site was assessed semiquantitatively, on the basis of the estimated percentage of viable residual carcinoma in relation to the macroscopically identifiable tumor bed that was evaluated histopathologically. Therapy-induced changes included reactive changes such as necrosis, fibrosis, foamy histiocytes, mucosal edema, vascular changes in the tumor periphery, and giant cell reactions. Such characteristics were considered signs of neoplastic regression after neoadjuvant CRT. The percentage of viable residual tumor cells within the entire cancerous tissue was assessed as follows: grade 3, no viable residual tumor cells (pCR); grade 2, less than one-third of residual tumor cells; grade 1b, one-third to two-thirds of residual tumor cells; grade 1a, more than two-thirds of residual tumor cells; grade 0, no significant response to CRT.[36,38]