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ORIGINAL ARTICLE

Surgical treatment for gastrointestinal metastasis of non-small-cell lung cancer after pulmonary resection

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Abstract
Purpose. Gastrointestinal metastasis is not common in recurrent non-small-cell lung cancer (NSCLC) patients. There is thus limited information on clinical outcome for these patients. This report presents the clinical characteristics and outcomes of patients with gastrointestinal metastasis after pulmonary resection.
Methods. The study retrospectively analyzed nine NSCLC patients with gastrointestinal metastases.
Results. Gastrointestinal metastases were observed in the small intestine ($n = 4$), colon or rectum ($n = 4$), and stomach ($n = 1$). All of the patients were symptomatic. The median survival after gastrointestinal recurrence was 10.8 months. Gastrointestinal surgery was performed in five patients, whereas no cancer treatment was indicated in the remaining four patients. Three patients who underwent surgery for a solitary metastasis survived for more than 2 years after surgery with no other recurrence.
Conclusion. Surgical resection of gastrointestinal metastasis is indicated not only for symptom relief but also for providing a potentially long-term survival if the patients are properly selected.

Key words Gastrointestinal metastasis · Non-small-cell lung cancer · Surgery

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Introduction

Surgical resection is the most effective treatment for early-stage non-small cell lung cancer (NSCLC), and it can provide the maximum opportunity for cure and improved survival. Despite complete surgical resection, however, 50%–60% of patients with stage I–IIIA NSCLC relapse and die from their lung cancer.[1] Once the disease has recurred, it is seldom curable.[2] The most common sites of recurrence are the regional lymph nodes, lung, liver, bone, brain, and adrenal glands.[3]

The gastrointestinal tract is one of the target organs of metastatic disease in NSCLC patients. Gastrointestinal metastasis often produces serious symptoms that impair the patients' quality of life, such as intestinal obstruction, gastrointestinal discomfort, hemorrhage, and abdominal pain.[4] It also may cause life-threatening events.

The principal strategy for metastatic disease in distant organs is chemotherapy because the disease is recognized as a systemic one. The physicians often hesitate to perform chemotherapy in patients with gastrointestinal metastasis because the treatment itself may increase the risk of perforation or bleeding. Meanwhile, surgical resection can be considered to prevent such a life-threatening event. According to previous reports, locoregional therapy such as surgery and radiotherapy yield excellent outcomes as well as symptom controls in a subset of patients with brain or adrenal gland metastases.[5,6] Surgical treatment for gastrointestinal metastasis has not been well described.

This report presents the clinical characteristics and outcomes of the patients with gastrointestinal metastasis after pulmonary resection.

Patients and methods

Patients

A total of 1552 patients underwent surgical treatment for NSCLC at the Osaka Medical Center for Cancer and Cardiovascular Diseases between January 1988 and December 2007. The institutional database included clinicopathological information and the postoperative clinical course, which includes the recurrence sites. The database was examined retrospectively, and the patients who had recurrence of the disease in gastrointestinal organs were identified to select the optimal patients for this study. Patients who underwent palliative or incomplete lung surgery for intrathoracic diseases were excluded. Patients were also excluded if they had any other metastatic disease before the gastrointestinal metastasis. However, patients with other metastatic foci were included if they were found at the same time as the gastrointestinal metastases or had been well controlled before the pulmonary resection, such as solitary brain metastasis. The performance status (PS) was evaluated according to Eastern Cooperative Oncology Group (ECOG) guidelines. The primary variables were patient age, sex, symptoms, stage at the time of pulmonary resection, histology, metastatic sites, and the interval between pulmonary resection and diagnosis of gastrointestinal metastasis.

Diagnosis of gastrointestinal metastasis

Patients were typically scheduled for clinic visits at 3-month intervals for the first 2 years after surgery. Patients suspected to have gastrointestinal recurrence during the follow-up period were instructed to undergo chest/abdominal computed tomography (CT), an endoscopic examination, and a histological examination with endoscopic guidance. In addition, the patients were examined before determining the treatment strategy if they had a metastatic lesion other than in the gastrointestinal tract; they were subjected to magnetic resonance imaging (MRI) of the brain and bone scintigraphy or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). The interval from the date of pulmonary resection to the date of the diagnosis of gastrointestinal recurrence was recorded. The survival time was measured from the date of the diagnosis of the gastrointestinal metastasis to the date of the most recent follow-up examination or the date of death.

Statistical analysis

The statistical analysis was performed using the StatView version 5.0 software package (Abacus Concepts, Berkeley, CA, USA). The overall survival curves were estimated using the Kaplan-Meier technique.

Results

Patient characteristics

Gastrointestinal metastasis was recorded in nine patients (0.58%). The clinical information for each patient is summarized in Table 1. Two patients with solitary brain metastasis (cases 6, 8), that were well controlled after either stereotactic radiosurgery or surgical removal, were included. One patient (case 3) received adjuvant chemotherapy after pulmonary resection.

Symptoms and diagnosis of gastrointestinal metastasis

All of the patients had gastrointestinal symptoms (Table 1). Gastrointestinal metastases were observed in the small intestine (n = 4), colon or rectum (n = 4), and stomach (n = 1). More than two metastatic tumors in gastrointestinal organs were observed simultaneously in two patients (cases 4, 7). A histological diagnosis of recurrent NSCLC was obtained by endoscopic biopsy in three patients (cases 1, 6, 7), by surgical specimens in four patients (cases 2–5), or by autopsy (cases 7, 8). In most of the patients, the histological type was large-cell carcinoma or pleomorphic carcinoma. The diagnosis was not difficult because these histological types are rare as a primary gastrointestinal malignancy. One patient (case 9) was diagnosed in a different hospital by radiological examinations and underwent treatment there. Although histological examination was not obtained for this patient, the gastrointestinal metastasis from lung cancer may be a valid diagnosis according to the report from the hospital.

Multiple metastatic diseases were detected in six patients by systematic examination, but no intrathoracic recurrences (e.g., lymph node or pulmonary metastases) were observed in any of the patients.

Treatment

Gastrointestinal surgery was performed in five patients (cases 1–5). The interval from the pulmonary resection to the gastrointestinal metastasis was 1.2–19.6 months (median 6.9 months). Surgical procedure included resection of the intestinal metastasis with immediate anastomosis in all patients. The recurrent disease was completely removed in three patients (cases 1–3) who had a solitary metastasis. No cancer treatment was indicated owing to poor performance status in three (cases 6–8) of the four

Table 1 Clinicopathological findings in nine patients with gastrointestinal metastases

No.	Age[a] sex	His.	stage	GI metastatic site	Metastasis other than GI organs	Symptoms	PS	Treatment	Interval[b] (months)	Survival[c] (months)	Outcome
1	66/F	Pleo	IIIB	Colon	None	Melena	0	Surgery	6.7	40	AWD
2	68/M	Large	IIIB	Small intestine	None	Anemia	0	Surgery	9.5	93.6	AWD
3	70/F	Por Ad	IA	Rectum	None	Melena	1	Surgery	19.5	46.9	DOC
4	48/M	Large	IIB	Small intestine	Adrenal	Melena, vomiting	2	Surgery	9.4	14.9	DOD
5	83/M	Pleo	IIB	Colon	Liver	Abdominal mass	0	Surgery	6.9	3.7	DOD
6	51/M	Large	IV	Stomach	Skin (multiple)	Anemia	3	Supportive cares	2.2	0.4	DOD
7	57/M	Pleo	IIIB	Small intestine, Stomach	Liver, Kidney	Anemia, Ileus	2	Supportive cares	1.2	1.1	DOD
8	69/M	Por Ad	IV	Colon	Adrenal, brain	Unknown	2	Supportive cares	14.3	0.2	DOD
9	70/M	Large	IB	Small intestine	Adrenal, Pancreas	Melena	0	Supportive cares	4	10.8	DOD

GI, gastrointestinal; His, histology; por, poorly differentiated; Ad, adenocarcinoma; Large, large cell carcinoma; Pleo, pleomorphic carcinoma; AWD, alive without disease; DOD, dead of disease; DOC, dead of other causes
[a]Age when GI metastasis was diagnosed
[b]Interval from pulomonary resection to GI metastasis
[c]Survival after gastrointestinal metastases

patients who did not undergo surgery, and the fourth (case 9) had multiple metastases diagnosed within a short interval after pulmonary resection.

Symptom control and survival after gastrointestinal metastasis

The median survival of all nine patients after gastrointestinal recurrence was 10.8 months. The overall survival rates at 1 and 3 years after recurrence were 44.4% and 33.3%, respectively (Fig. 1). Three patients (cases 1–3) who underwent surgery for a solitary metastasis had not developed any other metastasis after surgery for more than 2 years. Two patients (cases 4, 5) who had undergone surgery to control the symptoms associated with gastrointestinal metastasis died of the disease within a year after surgery; however, the symptoms subsided after surgery, and the patients were able to enjoy oral food intake for several months. Interestingly, no additional gastrointestinal recurrence was observed in the patients who underwent surgery for the first recurrence. In contrast, four patients who did not undergo gastrointestinal surgery died less than a year after their gastrointestinal metastases were diagnosed.

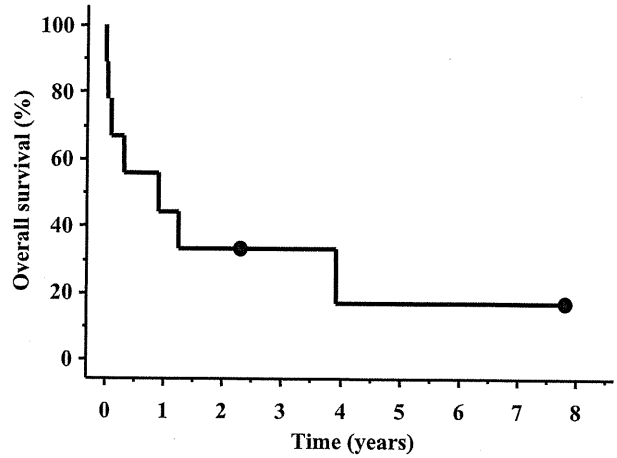

Fig. 1 Kaplan-Meier curve for the overall survival of patients with gastrointestinal metastasis from non-small-cell lung cancer

Discussion

In one study, the most common site of first recurrence was the intrathoracic lesion in 44% of recurrent NSCLC patients, the extrathoracic lesion in 44%, and combined intrathoracic and extrathoracic lesions in 12%.[7] The common extrathoracic metastatic sites are brain (32%), bone (23%), liver (9%), and adrenal gland (6%). The occurrence rate of gastrointestinal metastasis was 0.19% of all lung cancer patients[8] and 0.5% of patients who were treated surgically[9] in previous studies. Gastrointestinal metastasis is seen in only a small proportion of the population of NSCLC patients with recurrence, but it is important in clinical practice. Gastrointestinal recur-

rence may cause abdominal symptoms such as pain or distention, gastrointestinal obstruction, and bleeding, which are symptoms not usually associated with thoracic disease. Gastrointestinal metastasis from lung cancer may occur at the late or terminal stage over the course of the disease.[10] Therefore, most patients with gastrointestinal metastasis receive only palliative or supportive care.

The current study selected patients who were considered potential candidates for treatment of their gastrointestinal metastases. The occurrence rate was 0.58%. All patients were symptomatic, and the clinical symptoms due to gastrointestinal recurrence appeared within 20 months of pulmonary resection. The median interval from pulmonary resection to gastrointestinal metastasis was 6.9 months, and the median survival was 10.8 months in this study. The disease-free interval from complete resection to any kind of recurrence was reported to be 11.5 months in one study[7] and 12.2 months in another.[11] Gastrointestinal metastasis may therefore tend to develop earlier than metastases at other sites.

Gastrointestinal metastases may occur with any kind of NSCLC histology. Large-cell carcinoma and squamous cell carcinoma are relatively common.[12,13] There were three cases of pleomorphic carcinoma histology in the current series. This should be noted because pleomorphic carcinoma is a rare type of histology, being found in approximately 1.3% of all surgical patients with primary NSCLC in the database. The clinical behavior of pleomorphic carcinoma is known to be aggressive, with frequent distant metastases. Gastrointestinal organs should be taken into consideration as possible metastatic site in patients with pleomorphic carcinoma.

The most important treatment option for recurrent NSCLC is chemotherapy. Nevertheless, chemotherapy was not indicated for the gastrointestinal recurrence in any patients in this study. Chemotherapy was thought to increase the risk of gastrointestinal perforation and bleeding. In fact, a case of intestinal perforation that may have resulted from necrosis of the tumor caused by chemotherapy was described in a series of small bowel metastases from primary lung carcinoma.[14]

We considered surgery an option to manage gastrointestinal metastasis. There are two principal objectives of such surgery. One is to treat the disease, and the other is to relieve the symptoms associated with the metastasis. The clinical impact of surgical resection of a gastrointestinal metastasis has not been thoroughly discussed. Five patients underwent gastrointestinal surgery in this study. It should be emphasized that three patients are experiencing long survivals after resection without another recurrence. In addition, the gastrointestinal symptoms in the remaining two patients were well controlled after surgery. In contrast, four patients who did not undergo surgery had a shorter survival after the diagnosis of gastrointestinal metastasis. Notably, three died within only 2 months. Therefore, resection of gastrointestinal metastasis may provide benefits in terms of both symptom control and survival if the patients are properly selected.

The long-term survivors in this study had a metachronous solitary metastasis after a relatively long interval (≥6 months) between pulmonary resection and discovery of the gastrointestinal metastasis. There are two small clinical series that included patients who underwent resection of a gastrointestinal metastasis (Table 2). Three long-term survivors after resection were described in those reports. In contrast to the survivors in the current study, one of those patients had synchronous gastrointestinal metastases and two had multiple metastatic lesions outside the gastrointestinal tract. These conflicting data indicated that a disease-free interval or the number of metastatic foci was not always a predictor for long survival after resection. More clinical information is therefore necessary to identify indicators to select optimal patients for resection of gastrointestinal metastasis.

Conclusion

Although an initial recurrence of NSCLC after complete resection rarely develops in gastrointestinal organs, it

Table 2 Summary of previous and present reports in gastrointestinal metastases

Study	No. of cases	Surgery for GI metastasis (yes/no)	Interval between diagnosis of lung cancer and discovery of GI metastasis (mean)	Median Survival (median)	Survival duration after surgery	Long-survivors after GI surgery
Berger (1997)	7	6/1	11.2 months	120.0 days	7.5 months	Alive at 22 months ($M = 1$)
Kim (2009)	10	6/4	147.0 days	96.5 days	17.5 months	Alive at 33 and 63 months ($M = 2$)
Present report	9	5/4	6.9 months	10.8 months	27.7 months	Shown in Table 1

may nevertheless cause life-threatening symptoms and lead to shortened survival. Surgical resection of gastrointestinal metastasis is indicated not only for symptom relief but for providing the potential of a long-term survival if the patients are properly selected.

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「がん診療と地域連携」
地域におけるがん診療連携（大阪府の地域連携パス実例報告）

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1. がん診療における地域連携の整備が求められている背景

我が国のがん対策は、現在、平成18年4月に施行されている「がん対策基本法」および同年6月策定の「がん対策推進基本計画」により総合的に推進され、さらに平成20年3月策定された「がん診療連携拠点病院の整備に関する指針」により具体的な機能強化が図られている。これらがん対策の根本的目標は、全国どこでも質の高い医療（地域に関わらず等しく、がんの状態に応じた適切な医療）が提供できるような医療体制つくり（いわゆる、がん診療の均てん化）である。これは、地域医療は患者さんの視点に立ち、安心・信頼の出来る医療サービスが提供できるよう、医療機関の機能分担と連携による地域完結型診療体制を目指すべきとする第5次医療法改正（平成19.4施行、地域医療の見直し）の目標とも合致する。

実際には、先ず地域単位として各都道府県にいくつかの2次医療圏を設け、各医療圏に専門的ながん医療が提供できる中核的医療機関を整備することから始まった。地域がん診療連携拠点病院の指定であり（国指定拠点病院）、さらに地域がん診療連携拠点病院を各都道府県単位で纏めていく基幹的役割を担う都道府県がん診療連携拠点病院の指定である。これらがん診療連携拠点病院は該当地域（2次医療圏）で指定要件に示されている質の高いがん診療体制、研修体制、情報提供体制を保持し、医療圏内の各施設と連携協力体制を構築しなくてはならない。

この医療圏における医療施設との連携協力体制（病病・病診連携）の強化の中に、連携ツールとして地域連携クリテイカルパスの整備が平成24年4月までに実現するよう求められている。

1. 大阪府がん診療連携協議会と地域連携パス部会の発足

平成14年頃大阪府は全国一のがん死亡率が高い都道府県で、汚名返上のため早急にがん医療の改善対策が要求され、大阪府は行政指導型のがん診療機能強化事業を立ち上げた。大阪府立成人病センターを中心に大阪府下大学病院やがん診療に実績ある病院施設が集まり大阪府がん拠点病院連絡協議会を設け、がん登録、医師研修、がん診療連携ネットワーク体制などの整備事業に取り組み始めていた。そこに前述の国指定がん診療連携拠点病院の整備が掲げられたため、平成19年、大阪府がん診療連携協議会の発展的設置となった。

大阪府がん診療連携協議会の発足に先立ち、がん医療連携に関する現状アンケート調査が行われた。平成19年頃のがん診療連携・がん地域連携パスに関する調査では、大阪府下5大学とがん診療連携拠点病院（N=11）中、1施設のみしか地域連携パスを導入していたに過ぎず（数施設で試行あるいは試案されていた）、疾患も乳がんなどごく一部のがんに限られていた[1]。当時、地域連携パスは非がん疾患には普及し始めていたが、多くの施設ががん地域連携パスに関して未知の状態であった。

一方、平成20年4月に大阪府がん診療連携協議会にて、地域連携パス部会（以下、パス部会）発足が了解された。地域連携パスの整備のために先ず取りかかったことは、パス対象疾患（5大がんと前立腺がん）とパス適応に関し、基本的なコンセプトの検討であった。そのコンセプトとは、1）パスを用いて行われる診療はガイドラインなどに記された標準的診療であること、2）診療が拠点病院と連携医間で機能分担が明記され連携されていること、3）大阪府下のどの拠点病院でも診療内容が共通である統一型パスにすること、4）パス適応となる患者病態は明記され、先ずは比較的病態の安定している早期例（検診や根治治療後）を対象とすることなどを決め、引き続いて各ワーキンググループを結成しパス作成に取りかかった[1]。

2. 作成された地域連携パス

各ワーキンググループは、がん診療連携拠点病院医師、すでに病病・病診にて連携実績のある連携医、薬剤師、看護師、MSWなどのメンバーを構成し、平成20年8月から班会議を行い（肝がんは平成21年2月より作成開始）、診療計画表、患者用診療計画表、患者用ハンドブックの作成を行った（図1）。平成21年3月頃にほぼ完成し（肝がんは平成21年7月）、平成21年度の7月に行われたパス部会とがん診療連携協議会で概ね承認されるに至った。

大阪府成人病セ・呼吸器外科 より
利益相反の開示については、本文の最後に掲載しています
転載依頼連絡先：大阪府・成人病セ・呼吸器外科　東山 聖彦（大阪府大阪市東成区中道1-3-3）

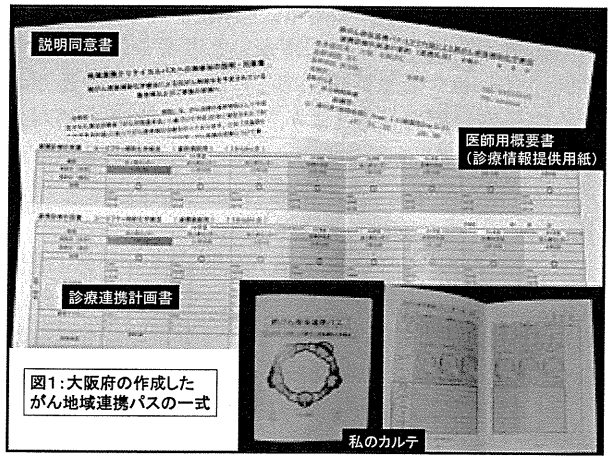

図1:大阪府の作成したがん地域連携パスの一式

作成された地域連携パス(初版)は、胃がん・大腸がん・肺がん・乳がん根治手術後に抗がん剤の内服投与される術後補助化学療法(あるいは内分泌療法)パス、胃がん・大腸がん・乳がん・肝がん根治手術後(あるいは治療後)の経過観察パス、そして血清PSA値高値の前立腺がん疑い患者に対する検査パスである。平成22年1月には、肺がんにも術後経過観察パスが追加作成されている(表1)[2]。

表1　大阪府統一型がん地域連携パス　H21.7作成 H22.4改訂

術後補助化学療法パス

	対象	抗がん剤(内服)	期間・コース
肺がん	非小細胞肺癌 外科治癒切除 病期 IA期(2cm以上)またはIB期	UFT	2年
胃がん	外科治癒切除 病期II, III期	TS-1	1年間
大腸がん	外科治癒切除 病期II(mp癌)、II, III期	UFT-ロイコボリン ゼローダ	8コース
			8コース
乳がん	治癒切除、RT終了後、点滴抗がん剤投与後	ノルバデックス アリミデックス ゾラデックス	

術後経過観察パス

肺がん	非小細胞肺癌 外科治癒切除 病期 IA期(2cm以上)またはIB期で、UFT非投与症例		
胃がん	外科治癒切除 病期II, III期		
大腸がん	外科治癒切除 病期II(mp癌)、II, III期		
肝がん	TAE後、外科治癒切除		

検査パス

前立腺がん	血清PSA高値例		

5大がんではいずれも比較的早期のがんで、治療後非担がん状態(外科根治手術治療後)と考えられる患者さんを対象としている。日常的な診療は連携医で行い、一定の期間間隔で拠点病院主治医を受診する循環式連携パスである。CT画像診断など大きな検査は基本的には拠点病院で行い、抗がん剤の処方や一般採血検査などは拠点病院と連携医の両者で行なう。これら診療内容の全貌は診療計画表にて明記されている。なお患者は病状と診療状況、服薬状況が記載されたハンドブック(わたしのカルテ)を常に携帯し、拠点病院医師や連携医がその診療情報を共有できるようにした。特に抗がん剤やホルモン療法のパスでは、薬剤師(調剤薬局)や看護師にも診療情報(特に病状や投薬内容、薬剤の副作用状況)が分かるように作成されている[2]。

3. 連携ネットワーク作りと地域連携パスの試験運用

平成21年7月にほぼ作成された大阪府の地域連携パスの試験運用のために、各拠点病院と連携医との連携登録が行われた。ただちに連携医の先生への地域連携パス説明会、意見交換会・勉強会さらにパスセミナーなどの開催が企画され、大阪府がん診療連携協議会は、大阪府下全体のパス説明会を平成21年1月に、意見交換会を3月に行った。さらに各拠点病院でも説明会や勉強会が逐次行われ、連携登録の協力が依頼された。例えば大阪府立成人病センターでは、近隣の主な医師会施設に加え、当センターへしばしばご紹介いただいている診療所や一般病院の先生を中心に参加を募り、手上げ方式で連携登録を行った[1]。

一方、府下の薬剤師や保健所にも地域連携パスの協力要請を行い、大阪府薬剤師会や府下保健所に説明会を開催した。さらに大阪府のがん地域連携パスについて、WEBにて公開したり(大阪がん情報提供コーナー[2], clinical path.jp[3]など)、医学界新聞(平成22年7月)[4]、出版社による書物(平成22年5月)[1]や薬剤メーカー小冊子[5,6]にも詳しく掲載し、多くの医療関係者に理解していただけるよう広報活動を行った。

平成21年12月にはがん診療連携拠点病院15施設中7施設(47%)[1]、平成22年3月末には、10施設(67%)において一部のパスが運用できるまでに至った。

4. 平成22年4月を迎えて

平成22年4月に、大阪府がん診療連携協議会パス部会では2つの大きな変化を迎えた。一つは大阪府がん診療拠点病院(府指定拠点病院、平成22年4月の時点では36病院、平成23年4月では43施設)が連携協議会参加となり、他の一つは地域連携パスに対する診療報酬算定の導入である。

現在(平成23年4月)、府指定拠点病院43施設は国指定がん診療連携拠点病院(14施設)が整備する地域連携パスに協力することが求められている。2次医療圏を単位とした国指定の拠点病院の中に、府指定がん拠点病院が具体的にどの様に診療ネットワークを構築するのか、大きな課題である。大阪府は府指定拠点病院が、将来、国指定拠点病院へとステップアップを望むものであれば積極的にネットワーク整備が必要と説明している。大阪府の場合、地域連携パスは統一型であるため、2次医療圏内のがん診療連携拠点病院と府指定拠点病院とが医療圏内連携連絡協議会などを設け、連携医を共有しながらネットワークを構築し協力してこうとする地区がある。また、地区医師会やいくつかの医療施設が纏まり地域連携パス説明会を合同で開催している地区もある。今後も大阪府は国指定と府指定拠点病院は協議会やパス部会を纏まって運営して方針なので、「統一パスの共有」と「連携医の共有」による拠点病院間同士の協力体制は必要であると考えている[1]。

一方、がん地域連携パスに対する診療報酬加算の導

入はがん地域連携診療のインセンチブとして画期的であったが、その算定方法や手続きが複雑で混乱も生じている。拠点病院のがん治療連携策定料（B005-6-1）と連携医のがん治療連携指導料（B005-6-2）の詳細は省くが、実際に上手く算定できているか平成22年末に調査を行ったところ、策定料も指導料とも満足できる返事は得られていない（図2：策定料）。地域連携パスの運用上、拠点病院と連携医がどの様な診療報酬が請求できるのか、診療情報提供料との使い分けは？など、曖昧な点が多い。がん地域連携パスは大腿骨頭骨折や脳卒中などの連携パスとは異なり多くが循環型パスのため、その報酬システムも複雑にならざるをえず、今後さらに検討や改善が必要である。

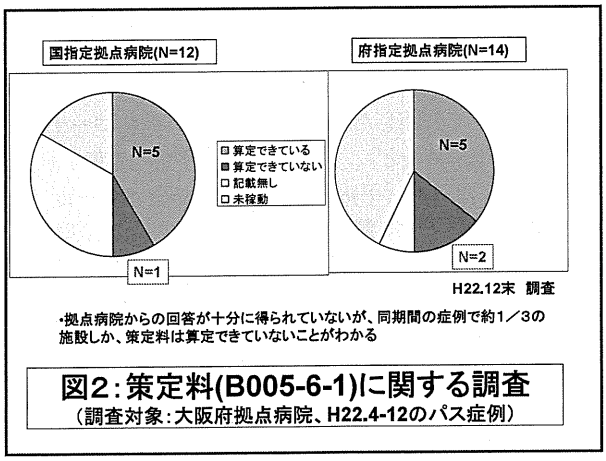

図2：策定料(B005-6-1)に関する調査
（調査対象：大阪府拠点病院、H22.4-12のパス症例）

5. 地域連携パス部会で特に議論してきたこと（大阪府の場合）

大阪府は地域連携パス部会を年2回開催している[1)]。平成20年頃はパス作成に専念し、平成21年には作成されたパスの運用やネットワーク構築について討議してきた。実際に試験運用されると不明確な点や不都合な点が多く発見され、その都度改善できるところは討議している。いくつか話題となった点を示す。

1）地域連携パス運用のための院内システムの構築と院内周知[1)]

地域連携パスを立ち上げる上で、拠点病院の院内システムを整備し医療関係者の周知を図ることは、きわめて重要である。パス部会ではすでに実績ある拠点病院のシステムを紹介し、院内システムの整備の勉強会などを行っている。

地域連携パスが開始される際、適応を決め最初に患者へ説明を行うのは拠点病院主治医であるが、さらに詳細な説明は説明担当者が行う（多くは医療連携担当者、コーデイネーター、看護師など）。なお連携医への連携依頼の連絡などは、当施設では主治医が行っている。

一方、拠点病院内の医師は地域連携パスに対し温度差が様々であるが、院内周知は徹底しておくことは必要である。パスに関係ない診療科医療関係者にも本診療システムの理解が必要である。時間外や祝日曜日の当直者に地域連携パスの情報がないと患者や連携医からの問い合わせや緊急要請に応じられない。院内周知のための院内説明会はもとより、当直室に地域連携パスの対応マニュアルを設けたり、電子カルテからも患者リストや対応が分かるように整備する必要がある。

2）連携医（連携施設）と連携様式

大阪府で作成された統一型がん地域連携パス（術後補助化学療法か術後経過観察パス）では、連携登録をどのような先生にお願いしたらよいのか、いつも議論となっている。国・行政による指針によれば、連携医は一般総合医であるかかりつけ医（多くは拠点病院へご紹介頂いた先生）が好ましいとしている。しかし実際のがん診療では緊急対応性・安全性を常に考慮しなくてはならず、連携医は一般総合病院（いわゆる後方支援病院）やがん専門医の診療所（クリニックなど）が相応しい、あるいは限定すべきであるという意見も多い。抗がん剤を用いるパス診療では、薬剤副作用に関する専門的知識が必要である。しかし一方では、高齢者や循環器・消化器併存症が多いがん患者にとって、日常的にはかかりつけ医の先生に連携診療をお願いする方が便利で好ましい場合も多い。大阪府のパス連携は循環式を基本とするため（拠点病院主治医と連携医のいわゆる2人主治医制）、その安全性をできるだけ確保できるように工夫をしている。パスに組み込まれている診療計画書や「わたしのカルテ」にがんの再発や薬剤投与に関する注意事項を記載して連携診療の安全性が確保できるように工夫したり、連携医には最新のがん情報に関しては各拠点病院で行われるパスセミナー・勉強会などを開催し専門的情報を提供したり、薬剤メーカーによる連携医訪問指導システムを新たに導入した[1)]。また拠点病院には連携医からの緊急対応の手順をきっちり作成するように指導している（前述）。大阪府では連携医はかかりつけ医を原則としているが、一部の拠点病院では連携医をがん専門医に限定したリレー式連携パス（拠点病院治療後、以降は連携医が診療を全て行う様式）も運用している。

連携様式はご紹介頂いた先生（元紹介医、かかりつけ医の場合が多い）との連携を基本とし（U型連携）、既に拠点病院との登録済みの場合はそのまま連携を開始し、未登録の場合には新たに連携登録の手続きを直ちにお願いして地域連携パスを開始する。ただし元紹介医が連携に否定的な場合では、該当地域の既に登録済みの別の施設へ紹介することもある（J型連携）。また検診施設や拠点病院内からの患者さんでは、拠点病院治療後に登録済みの施設に連携をお願いしている（I型連携）。

3）大阪府統一型地域連携パスの種類について

平成20年以降、パスの種類と適応については各がんの特定の病期病態に絞ってきた。しかしがん患者さんの発病から終末期の全経過からみればきわめて限定

的な時期のみの連携パスであり、「切れ目のない連携診療」を掲げる国や、現場の医療関係者、患者からはもっと適応を広くしたパスを作成してほしいという意見が見られる。そこで以下のような疾患や病態にも適応を広げ、現在、パス部会で新しいパスを作成中である。

早期胃がんに対する内視鏡的手術後経過観察パス
泌尿器科癌術後（早期膀胱がん、前立腺がんなど）経過観察パス
乳がん術後に対する分子標的薬（ハーゼプチン）治療パス
緩和ケアパス　などである。

特に緩和ケアパスは担がん患者を対象とする地域連携パスで始めての試みである。現在、がん診療連携協議会緩和ケア部会のグループとで原案を協議している。緩和診療を拠点病院と地域の連携医とで情報を共有しながら連携できるような診療情報書（診療情報計画書というより、診療情報をお互いに共有できる情報書）を作成中である。乳がんハーゼプチンを用いた補助化学療法パスは、連携医を乳がん専門医に限定した地域連携パスである。

6. 大阪府の統一型がん地域連携パスの進捗状況と今後の展望

1）拠点病院の進捗状況

平成22年末に行われたアンケート調査では、がん診療連携拠点病院14施設では12施設（86%）が、一部のパスを運用している。しかもその内3施設では5大がん全てが運用されている。一方、府指定拠点病院でも既に8施設以上で一部のパス運用が始まっている。

2）がん種別パス件数の検討

図3に、今までに大阪府下のがん地域連携パスの運用された件数を示す。本格運用となった平成22年4月から12月までの期間に運用開始されたパス455件では、乳がんが圧倒的に多く約70%（314件）を占めている。続いて胃がん、前立腺がん（検査パス）、大腸がん、肝がん、肺がんの順であった。

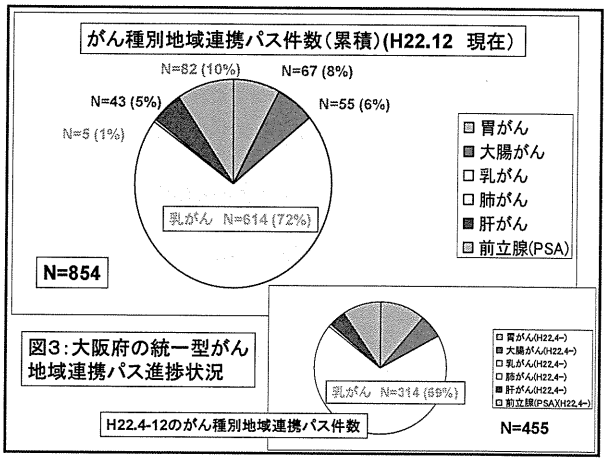

図3：大阪府の統一型がん地域連携パス進捗状況

3）地域連携パスのバリアンス分析

平成22年4月以降、実際的運用が始まり様々なパスの問題点が発生している。その中で、最も興味深いはパスのコンプライアンスがどの程度なのかである。個々の細かいバリアンス（逸脱エベント）発生頻度やパス脱落（パス診療から全く外れてしまう）状況を、現在、アンケート調査している。都道府県がん診療拠点病院である大阪府立成人病センターでは、本格運用以降63件（内、49件が乳がんパス）のパス中3件（4.7%）が脱落している。その理由は、がん再発が2件、患者さんのパス途中からの拒否が1件であった。

拠点病院におけるパス脱落頻度やコンプラアンスの分析は、診療報酬算定実態の検討とともに今後の改訂版作成作業を行う上で重要である。

4）今後の展望

大阪府の統一型地域連携パスを本格的運用し約1年が過ぎ、多くのがん診療連携拠点病院は、運用件数の増加、連携ネットワーク構築と登録医の増加など実績を少しずつ残し、体制を築き上げてきた。しかし一方では、年2回行われるパス部会でもなかなか上手く解決できない事項も多々発生している。パス運用面では、拠点病院内のシステム周知の不備やコーデイネーター不足の問題があり、連携構築面では、患者や連携登録の広報不足やネットワークのＩＴ化問題、さらに診療報酬算定の周知不足（前述）などがあげられる。今年度には先ずはパス改訂版作成に向け、そのバリアンス分析調査を行っている。

利益相反

著　者	報　酬	保有株	特許使用料	講演料	原稿料	研究費	その他の報酬（研究とは直接無関係な、旅行、贈答品など）
東山　聖彦	なし	なし	なし	なし	なし	なし	なし

がん臨床研究の利益相反に関する指針(http://jsco.umin.ac.jp/ijco/index.html)

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A multi-institutional phase II trial of consolidation S-1 after concurrent chemoradiotherapy with cisplatin and vinorelbine for locally advanced non-small cell lung cancer

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ABSTRACT

Aim: To evaluate the efficacy and feasibility of the consolidation therapy of the oral fluoropyrimidine agent S-1 after concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).

Methods: Eligible patients had unresectable stage III NSCLC with performance status of 0 or 1. Chemoradiotherapy at a total dose of 60 Gy consisted of cisplatin (80 mg/m^2) on days 1 and 29, vinorelbine (20 mg/m^2) on days 1, 8, 29 and 36. Sequential consolidation S-1 therapy was commenced at a dose of 80–120 mg twice daily on day 57 with two cycles of 4 weeks administration and 2 weeks withdrawal.

Results: Of the 66 patients, 65 were evaluated. Chemoradiotherapy was completed in 57 (87.7%) patients, and S-1 consolidation therapy was administered in 45 (69.2%) and completed in 31 (47.6%). Grade 3 pneumonitis developed in three patients with one dying of it. The response rate was 61.5% (95% confidence interval [CI], 48.6–73.3%). The median progression-free survival was 10.2 (95% CI, 8.6–13.7) months and median survival time 21.8 (95% CI, 15.6–27.6) months. The 1- and 3-year survival rates were 73.9% and 34.0%, respectively.

Conclusions: Chemoradiotherapy with cisplatin and vinorelbine followed by S-1 consolidation demonstrated a reasonable overall survival in patients with stage III NSCLC. However, less than half of the patients completed this regimen, and the additional effect of S-1 was marginal compared with historical control.

Conclusions: We concluded that chemoradiotherapy alone is still the recommended standard treatment for patients.

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1. Introduction

Lung cancer remains the leading cause of cancer related deaths worldwide.[1] Non-small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and approximately 30% of patients have locally advanced lung cancer.[2] The standard treatment for locally advanced NSCLC patients involves concurrent thoracic radiotherapy (TRT) and chemotherapy.[3]

A treatment regimen has been developed in Japan using cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy to patients with locally advanced NSCLC.[4,5] To improve survival, docetaxel consolidation therapy is conducted following the same regimens administered to NSCLC patients.[6] This is based on the concept of clinical trial SWOG 9504[7] that suggested that consolidation chemotherapy was a promising strategy for the treatment to NSCLC patients. However, a drawback is the fact that a majority of the patients in the Japanese study were not able to continue with the consolidation of docetaxel due to treatment related pneumonitis.[6]

S-1 is an oral fluoropyrimidine agent designed to enhance anticancer activity and reduce toxicity through the combined use of an oral fluoropyrimidine agent (tegafur), a dihydropyrimidine dehydrogenase inhibitor (5-chloro-2,4-dihydroxypyridine) and an orotate phosphoribosyl transferase inhibitor.[8] S-1 was shown to produce active response as a single agent for metastatic NSCLC with minimal toxicity.[9] S-1 has been launched for use as an adjuvant therapy for early stage lung cancer,[10] chemoradiotherapy for stage III,[11] frontline chemotherapy[12] and 2nd or 3rd[13] line chemotherapy in advanced stages of the disease.

Based on a promising efficacy with S-1, we hypothesised that chemoradiotherapy followed by S-1 consolidation would be feasible and clinically active. Hence, the Japan National Hospital Organization Study Group for Lung Cancer (JNHOSGLC) conducted a multicentre, phase II study for patients with unresectable stage III NSCLC, where chemoradiotherapy was administered to patients followed by S-1 consolidation therapy (UMIN000002381). The primary objective was to determine the response rate, while secondary objectives were to determine the safety of this new regimen and to estimate progression-free and overall survival.

2. Patients and methods

2.1. Eligibility criteria

Patients with histologically or cytologically confirmed NSCLC at unresectable stage III disease were eligible for this study. Stage III was decided based on the 6th AJCC Cancer Staging Manual.[14] Eligible stage IIIA disease was defined by the presence of multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT). Eligible stage IIIB disease was assigned either by N3 (contralateral mediastinal) or by T4 from invasion of mediastinal structures, heart, great vessels, trachea, carina, oesophagus or vertebral body. Confirmation of T4 or N3 status was established according to T4 involvement found at the time of thoracotomy or thoracoscopy; involvement of the trachea or carina by bronchoscopy; unequivocal invasion of the heart, oesophagus, aorta or vertebral body by CT scan, or magnetic resonance imaging; or biopsy of contralateral mediastinal N3 nodes. Eligible patients also needed to meet the following criteria: measurable disease of 20 mm or more in size; no prior history of chemotherapy or TRT; Eastern Cooperative Oncology Group performance status of 0 or 1; aged between 20 and 74 years; have leucocytes $\geqslant$ 4000/mL, platelets $\geqslant$ 100,000/mL, and haemoglobin $\geqslant$ 9.5 g/dL, serum creatinine < institutional upper limit of normal, and partial pressure of arterial oxygen $\geqslant$ 70 mmHg. Patients were excluded if they had infections; apparent interstitial pneumonitis or fibrosis on chest CT; irradiation field larger than half of an ipsilateral lung; severe complications; another active cancer. The ethics committee of each participating institution approved the protocol, and all patients provided written informed consent before the start of the study. For staging, all patients underwent CT of the thorax and abdomen, and either a brain CT scan or magnetic resonance imaging (MRI). A radio isotopic bone scan was also performed for all patients. Positron emission tomography was not necessary for enrolment.

2.2. Therapy

Treatment consisted of a chemoradiotherapy phase with two cycles of cisplatin and vinorelbine followed by a consolidation phase with two cycles of S-1. Chemoradiotherapy consisted of cisplatin at 80 mg/m^2 on days 1 and 29; vinorelbine at 20 mg/m^2 on days 1, 8, 29 and 36; and concurrent TRT at a total dose of 60 Gy. Sequential S-1 consolidation therapy at doses of 80-120 mg/body twice per day was started on day 57 with two cycles of 4 weeks administration and 2 weeks withdrawal. The dose of S-1 was determined based on body surface area (BSA): 80 mg was delivered when BSA was less than 1.25/m^2, 100 mg when 1.25/m^2 < BSA < 1.50/m^2 and 120 mg when BSA $\geqslant$ 1.50 m^2.

Concurrent TRT began on day 2 of chemotherapy by using a linear accelerator (6–10 megavolt), in 2-Gy, single and daily fractions for five consecutive days per week to provide a total dose of 60 Gy. A curative radiation field was constructed by using a plain chest radiograph and a contrast-enhanced computed tomography (CT) scan. The initial dose (approximately 40 Gy) was administered to the primary tumour, the ipsilateral hilum with a 2-cm margin, and involved mediastinal lymph nodes with a 1-cm margin. Prophylactic radiation fields were not planned except for subcarinal lymph nodes. Subsequently, a 20-Gy dose was given as a booster in accordance with tumour shrinkage. An initial TRT dose of 40 Gy was administered to the antero-posterior parallel–opposed pair of portals. Oblique anterior and posterior fields were required to avoid over dosage of the spinal cord.

The criteria for starting consolidation chemotherapy included completion of two cycles of cisplatin and vinorelbine, a full dose of thoracic radiotherapy, and the absence of a progressive disease, as well as being in good general condition.

2.3. Evaluation

All eligible patients who received treatment were considered assessable for response and toxicity measures. Chest X-rays,

blood counts and blood chemistry studies were repeated once a week during the treatment period. Follow-up studies including CT scan were performed once a month during the treatment period and every 3 months after treatment. The response was evaluated in accordance with Response Evaluation Criteria in Solid Tumours (RECIST). For evaluation of the antitumour effects, an extramural review was conducted. Acute toxicity was graded according to the NCI Common Toxicity ver. 3.0.

2.4. *Statistical methods*

We calculated the sample size based on Fleming's single-stage design for phase II study. We set a response rate of 60% as a baseline survival rate and 75% as the high level of interest with a power of 0.8 at a one-sided significance level of .05, requiring an accrual of at least 62 eligible patients. Assuming the loss of follow-up cases, a minimum of 65 patients was required for this study. Progression-free and overall survival was estimated using the Kaplan–Meier method, with corresponding two-sided 95% confidence interval (CI) for median times. For progression-free survival, follow-up measures were conducted during the study enrolment to document evidence of disease progression or death, or last documented progression-free status. Overall survival was measured from the study enrolment to the date of death or last contact. Statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC).

3. Results

3.1. *Patient characteristics*

Sixty-six patients were enrolled between January 2006 and July 2009. One patient that did not receive any protocol treatment was not assessable and therefore not included in the analysis. Baseline patient characteristics and demographics are listed in Table 1. The median age was 63 years (range, 45–73 years), and 55 patients were male and 10 patients were female. Thirty patients (46%) were at stage IIIA and 35 patients (54%) were at stage IIIB. Histological studies showed squamous cell carcinoma in 33 patients, adenocarcinoma in 23 patients and other cancers in nine patients.

3.2. *Treatment delivery*

Of the 65 patients, 57 patients (87.7%) completed the concurrent portion of the regimen. Failure to complete the concurrent therapy was due to toxicities such as grade 3 pneumonitis ($n = 1$) and ileus ($n = 1$), delay in chemotherapy for more than 2 weeks ($n = 3$), pneumonia ($n = 1$), deteriorating condition ($n = 1$) and surgery ($n = 1$). Forty-five patients (69.2%) proceeded to consolidation therapy. Reasons for failing to proceed to consolidation therapy included chemoradiotherapy toxicities such as persistent neutropenia ($n = 2$) and renal failure ($n = 2$), pneumonia ($n = 1$) declining performance status ($n = 1$), cardiac ischaemia unrelated to the treatment ($n = 1$), progressive disease documented on restaging after completion of the concurrent therapy ($n = 1$), vertigo ($n = 1$), refusal to undergo consolidation therapy ($n = 1$) and surgery ($n = 1$). A total of 31 patients (47.6%) completed the two cycles of consolidation therapy. Early discontinuation of the consolidation therapy included toxicity of more than grade 2 pneumonitis ($n = 9$), declining performance status ($n = 1$), disease progression ($n = 2$), cerebral infarction unrelated to the treatment ($n = 1$) and refusal of the therapy ($n = 1$).

3.3. *Response and survival*

The overall response rate during the study was 61.5% (95% CI, 48.6–73.3%) with one complete response and 39 partial responses. Stable disease and progressive disease occurred in 19 patients (29.2%) and six patients (9.2%), respectively. One patient had an inadequate reassessment. The estimated median progression-free survival was 10.2 months (95% CI, 8.6–13.7 Fig. 1). Kaplan–Meier estimates of progression-free survival were 44.6% (95% CI, 32.1–57.1%) at one year and 17.9% (95% CI, 6.3–29.5%) at three years. The estimated median duration of survival in all patients was 21.8 months (95% CI, 15.6–27.6; Fig. 2). Twenty-three patients remained alive after a median follow-up of 37.7 months (range, 12.5–54.3 months). Kaplan–Meier estimates of overall survival were 73.9% (95% CI, 63.2–84.5%) at one year and 34.0% (95% CI, 21.2–46.9%) at three years.

3.4. *Toxicity*

Grade 3 or 4 toxicities for the concurrent treatment phase are summarised in Table 2. Among the 65 assessable patients, one patient had a grade 3 pneumonitis (1.5%) while there were no grade 3 or 4 treatment-associated oesophagitis. The most common grade 3 or 4 haematological toxicities were leukopaenia (56.8%) and neutropenia (53.7%).

Table 3 summarises the grade 3 or 4 toxicities for the 44 patients who received consolidation therapy. It is apparent that minimal toxicity was observed in patients who received consolidation therapy. The most common grade 3 or 4 toxicity was anaemia (8.9%). Leukopaenia or neutropenia was observed in just three patients (6.7%) and severe oesophagitis was not observed. Seven patients developed grade 2 pneumonitis and two grade 3 pneumonitis during consolidation therapy. One patient died three months after chemoradiotherapy as the result of pneumonitis.

4. Discussion

This is the first phase II study to investigate the use of the oral fluoropyrimidine agent S-1 as a consolidation drug after chemoradiotherapy in stage III NSCLC. Our data indicated a reasonable survival with a median survival time (MST) of 21.8 months and a three-year survival rate of 34.0%. In addition, tumour response was demonstrated to be 61.5% and clinically active. However, less than half of the patients completed this regimen (47.6%) and it is unlikely that this treatment is feasible.

This study was originally designed to extend and enhance the concept of consolidation as reported in SWOG 9504,[7] a phase II study, where docetaxel was administered after cisplatin, etoposide (PE) and TRT to patients with stage III

NSCLC. Although a significant MST of 26 months was observed in that study, this finding could not be replicated in a phase III study. Dr. Hanna and colleagues reported that consolidation with docetaxel after PE and TRT could not improve survival compared with chemoradiotherapy alone with the same MST range of 23 months in each arm.[15]

Previous studies in Japan showed that chemoradiotherapy using cisplatin and vinorelbine elicits high response and survival rates in patients with stage III NSCLC. A phase I study showed an MST of 30.4 months with a three-year survival rate of 50% in 18 patients.[4] A retrospective study using the recommended dose demonstrated an MST of 21 months and a three year survival rate of 33% in 73 patients, where the chemotherapy cycle was originally planned with a maximum of three cycles but with a median of two (mean 2.4, ranges 1–3).[5] Our treatment regimen was also designed based on the aforementioned phase I trial and is almost identical to that of the retrospective study with the exception of using consolidation S-1, and the results indicated an MST of 21.8 months and a three-year survival rate of 35%. Considering the retrospective study as a historical control, the comparable survival data between the two studies suggest that the effect of S-1 consolidation is marginal and unclear. Although a phase III trial is needed to conclude the benefit of consolidation of S-1, different administrative methods for the drug may be more appropriate to patients with stage III NSCLC, as chemoradiotherapy including cisplatin and S-1 was reported to be active and promising.[11]

Table 1 – Patient Characteristics (N = 65).

	No. of patients	%
Gender		
Male	55	84.6
Female	10	15.4
Age, years		
Median	63	
Range	45–73	
Performance status		
0	27	41.5
1	38	58.5
Stage		
IIIA	30	46.2
IIIB	35	53.8
Histology		
Squamous cell	33	50.7
Adenocarcinoma	23	35.4
Large cell	2	3.1
Other	7	10.8

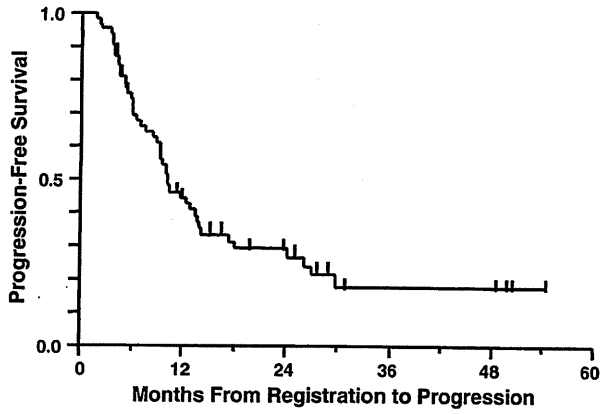

Fig. 1 – Progression-free survival of patients treated with cisplatin + vinorelbine + concurrent thoracic radiotherapy followed by S-1.

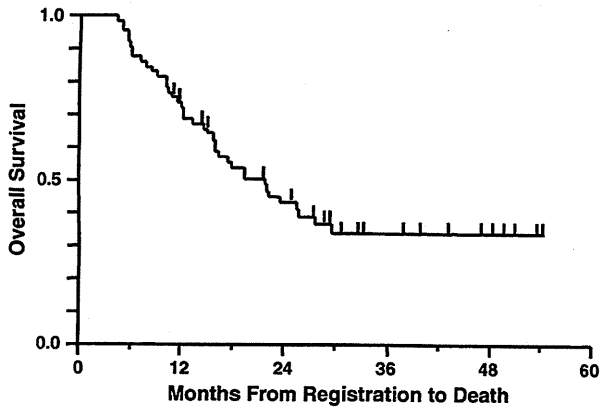

Fig. 2 – Overall survival of patients treated with cisplatin + vinorelbine + concurrent thoracic radiotherapy followed by S-1.

Cisplatin, vindesine, and mytomicin (MVP) were used for chemoradiotherapy in patients with stage III NSCLC in other studies, which is a preceding regimen of cisplatin and vinorelbine. In a phase III study of WJTOG 0105,[16] the standard treatment arm of MVP and concurrent TRT yielded an MST of 20.5 months with four cycles of chemotherapy. In another phase III trial in Japan,[17] the same regimens produced an MST of 23.7 months with two cycles of chemotherapy. Although the difference in MST may come from a split form of radiotherapy delivery in the WJTOG study, no survival benefits were observed from the addition of two cycles of chemotherapy. Again, these results are consistent with our finding that the effect of consolidation is marginal.

Feasibility is another problem in this study. Although 57 patients (87.7%) completed the concurrent portion of the regimen, only 31 patients (47.6%) finished the consolidation phase. Nine developed grade 2 or 3 pneumonitis in the 45 patients during the S-1 consolidation. In previous study, docetaxel consolidation following cisplatin, vinorelbine and TRT was reported as not feasible in Japanese patients. Almost the same 86% completed chemoradiotherapy, however, 34 patients (37%) finished consolidation therapy, whereas 14 of the 25 patients that participated in the consolidation phase developed pneumonitis.[6] On the other hand, in the aforementioned SWOG 9504, 74 patients (88%) completed chemoradiotherapy and 49 patients (59%) finished consolidation. An ethnic difference has been suggested in toxicity in NSCLC patients[18] and it is possible that pneumonitis is more common in Japanese compared to Caucasian, and further research will be required. In haematological toxicities in our study, the incidence of grade 3 or 4 neutropenia and leukopaenia were 53.7% and 56.8%, respectively, which is similar to previous reports.[5] Considering other side effects, a lower incidence of oesophagitis was

Table 2 – Major toxicities, chemoradiotherapy ($N = 65$).

	Grade 3		Grade 4	
	No.	%	No.	%
Haematologic				
Leukopaenia	27	41.5	10	15.3
Neutropenia	25	38.4	10	15.3
Anaemia	3	4.6	2	3.0
Thrombocytopenia	0	0.0	0	0.0
Neutropenic fever	4	6.1	0	0.0
Nonhaematologic				
Nausea	2	3.0	0	0.0
Vomiting	0	0.0	0	0.0
Anorexia	2	3.0	0	0.0
Oesophagitis	0	0.0	0	0.0
Pneumonitis	1	1.5	0	0.0

Table 3 – Major toxicities, consolidationl S-1 ($N = 45$).

	Grade 3		Grade 4	
	No.	%	No.	%
Haematologic				
Leukopaenia	2	4.4	0	0.0
Neutropenia	1	2.2	0	0.0
Anaemia	3	6.7	1	2.2
Thrombocytopenia	0	0.0	0	0.0
Neutropenic fever	0	0.0	1	2.2
Nonhaematologic				
Nausea	0	0.0	0	0.0
Vomiting	0	0.0	0	0.0
Anorexia	0	0.0	0	0.0
Oesophagitis	0	0.0	0	0.0
Pneumonitis	2	4.4	0	0.0

observed in our study. Severe radiation-related oesophagitis usually occurred in concurrent chemoradiotherapy and the incidences were reported to be in the range of 17–28%.[15,19] However, there have been several reports that minimal side-effects of oesophagitis were seen in the regimes using vinca alkaloids[5,16,17] and including ours, and further study is needed to confirm this association.

In conclusion, chemoradiotherapy with cisplatin and vinorelbine followed by S-1 consolidation demonstrated a reasonable overall survival in patients with stage III NSCLC. However, considering the questionable feasibility and marginal additional effect of S-1, it is recommended that chemoradiotherapy alone is still the standard patient treatment.

Conflict of interest statement

None declared.

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IMAGING, DIAGNOSIS, PROGNOSIS

Low Wilms' Tumor Gene Expression in Tumor Tissues Predicts Poor Prognosis in Patients with Non-Small-Cell Lung Cancer

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We elucidated the relationship between prognosis of non-small-cell lung cancer (NSCLC) and Wilms' tumor gene (*WT1*) mRNA expression in tumor tissue. The WT1 mRNA expression levels of the fatal cases were lower as compared with those of the survival cases. Overall survival (OS) and disease-free survival (DFS) of the high WT1 expression group were longer than of the low expression group. As for squamous cell lung cancer (SQLC), low WT1 expression was significantly associated with lymph node metastasis. Cox analysis revealed that the gene level was a significant prognostic factor in OS and DFS. Low WT1 expression predicted poor prognosis in patients with NSCLC.

Keywords Lung cancer; Oncogenes; Tumor suppressors; Tumor immunology

INTRODUCTION

The Wilms' tumor gene (*WT1* gene), which was cloned from pediatric renal tumor (Wilms' tumor), is located at 11p13 (1, 2). The gene encodes zinc finger transcription factor (1) and is associated with normal development of the renal system as well as with Wilms tumor (2). Originally, the *WT1* gene was reported to be a tumor-suppressive gene (3). In sporadic unilateral Wilms' tumor, one allele of this gene contains a 25-bp deletion, while such deletion is not observed in the germline of affected individuals. These observations are consistent with somatic inactivation of a tumor-suppressive gene. The gene product suppressed transcription of some growth factors *in vitro*, such as insulin-like growth factor (IGF)-II, IGF-I receptor, platelet-derived growth factor-A, transforming growth factor-beta (4–8), and proto-oncogenes *bcl-2* and *c-myc* (9). Moreover, it has also been demonstrated that the *WT1* gene inhibits ras-mediated transformation (10). These data suggest that the *WT1* gene acts as a tumor suppressor.

On the contrary, several investigations have reported that the *WT1* gene acts as a proto-oncogene. Aberrant overexpression of the *WT1* gene was detected in leukemia cells (11–13), and the gene was associated with leukemogenesis (14). As described above, the biological function of the *WT1* gene is diverse, and according to types or situation of tumors, the gene may act either as a proto-oncogene or as a tumor-suppressive gene.

In non-small-cell lung cancer (NSCLC) cells, we have reported on the overexpression of the *WT1* gene by reverse transcriptase-polymerase chain reaction (RT-PCR) (15). However, the relation between gene expression level and prognosis of lung cancer patients has not been fully investigated. Most studies hitherto have focused on hematological tumors (16, 17) and sarcomas (18–20), and for carcinomas, very few reports exists (21). In this study, we planned to clarify the relationship between WT1 mRNA expression and survival rate of patients who underwent surgical resection of NSCLC.

MATERIALS AND METHODS

Patients

From May 2002 to November 2004, a total of 356 patients with lung tumor received surgical resection at the Kinki-Chuo Chest Medical Center, Osaka, Japan. Of the 319 patients who were diagnosed as having primary NSCLC in surgical specimens, a total of 98 patients met our eligibility criteria. Patient characteristics are shown in Table 1. NSCLC stages were classified according to the UICC TNM classification (22). The follow-up algorithm after surgery was as follows: The patients of stages I and II had physical examination, chest X-ray examination, and tumor marker tests every 3 or 4 months for the first 2 years postoperatively, and thereafter every 6 months. For the patients of stages III and IV,

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Table 1. Clinical Background of the Patients

Characteristics		
Age, year	Range	38–81
	Median	68
Sex, no. (%)	Male	55 (56.1)
	Female	43 (43.9)
Histology, no. (%)	Adenocarcinoma	63 (64.3)
	Squamous cell carcinoma	28 (28.6)
	Large-cell carcinoma	7 (7.1)
Tumor size, no. (%)	11~20 mm	15 (15.3)
	21~30 mm	38 (38.8)
	31~40 mm	23 (23.5)
	41~50 mm	11 (11.2)
	~51 mm	11 (11.2)
pathological stage, no. (%)	IA	30 (30.6)
	IB	34 (34.8)
	IIA	6 (6.1)
	IIB	6 (6.1)
	IIIA	15 (15.3)
	IIIB	6 (6.1)
	IV	1 (1.0)
Adjuvant therapy, no. (%)	None	60 (61.2)
	UFT	30 (30.6)
	Others	8 (8.2)

interval and modality of examinations were chosen according to clinical condition of the patients. Five-year postoperative mortality was observed. This study was approved by the Institutional Review Board of the National Hospital Organization Kinki-Chuo Chest Medical Center. All patients gave their written, informed consent before enrollment.

RNA purification and RT-PCR

Cancer tissues were obtained just after the surgical resection of lung, snap frozen in Isogen (Nippon Gene, Toyama, Japan) and stored at −20°C until use. The tissues were soaked in RNAlater (Qiagen, Valencia, CA) at 4°C overnight and then were stored at −80°C until use. Total RNA was isolated from frozen lung tissues using Isogen according to the manufacturer's instruction. RNA was dissolved in diethylpyricarbonate (DEPC)-treated water and quantified by a spectrophotometer. Total RNA was isolated from the sample tissues using Trizol (Invitrogen, Leek, the Netherlands) according to the manufacturer's instruction, dissolved in DEPC-treated water and quantified by a spectrophotometer according to the absorbance at 260 nm. RNA was converted into cDNA, as described previously, with a minor modification (17). In brief, 3 μg of total RNA in DEPC-treated water was incubated at 65°C for 5 min and then mixed with 25 μl of RT buffer (50 mM Tris-HCl, pH 8.3; 75 mM KCl; 3 mM $MgCl_2$; and 10 mM dithiothreitol) containing 600 U of Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI), 500 μM of each dNTP, 200 ng of oligo dT primers, and 80 U of RNase inhibitor (Promega). The reaction mixture was then incubated at 37°C for 2 h, boiled for 5 min, and stored at −20°C until use. To determine relative WT1 expression levels, cDNA (3.0 μl for WT1 and 2.0 μl for β-actin) was added to the PCR buffer (100 mM Tris-HCl, pH8.3; 500 mM KCl; and 3 mM $MgCl_2$) containing 200 μM of each dNTP, 1.25 U of AmpliTaq Gold (PE Applied Biosystems, Foster city, CA), 0.5 μM forward and reverse primers, and 200 nM TaqMan probe in a total volume of 50 μl. The sequences of primers and probes used are as follows: WT1: forward primer (F1), 5′GATAACCACACAACGCCCATC3′; reverse primer (R1), 5′CACACGTCGCACATCCTGAAT3′; probe, 5′FAM-ACACCGTGC GTGTGTATTCTGTATTGG-TAMRA3′. β-actin: forward primer, 5′CCCAGCACAATGAAGATCAA GATCAT3′; reverse primer, 5′ATCTGCTGGAAGGTGGA CAGCGA3′; probe, 5′FAM-TGAGCGCAAGTACTCC GTGTGGATCGGCG-TAMRA3′. After activation of AmpliTaq Gold polymerase at 95°C for 10 min, PCR was performed for 40 cycles (95°C for 30 sec/63°C for 60 sec). Sequences of WT1 reverse and β-actin forward primers spanned two consecutive exons, from exon 6 to 7 and from exon 4 to 5, of respective gene in order to avoid amplification of the corresponding genome sequences. Standard curves for the quantification of WT1 and β-actin were constructed from the results of simultaneous amplification of serial dilutions of the cDNA from WT1-expressing K562 leukemic cells, whose WT1 expression level was defined as 1.0, as described previously (11). Real-time PCR and subsequent calculations were performed on an ABI Prism 7700 Sequence Detector System (PE Applied Biosystems). To normalize the difference in RNA degradation and in RNA loading for RT-PCR in individual samples, the values of levels of WT1 gene expression divided by those of β-actin gene expression were defined as relative WT1 expression levels in the samples. All experiments were performed in duplicate.

Statistical analysis

Survivals were calculated by the Kaplan–Meier method, and the log-rank test was used to evaluate the difference in survival.

Chi square test was used for comparison of the background of each subgroup. The Kendall's tau or Spearman's rho rank correlation coefficient was used to measure correlation of parameters. The Mann–Whitney test was used for comparison of the WT1 mRNA expression level of each subgroup. For multivariate analysis, the Cox proportional hazard regression analysis with a step-up procedure was employed, utilizing likelihood ratio as the criterion for adding significant variables. The SPSS version 15.0J software was used for statistical calculation. Statistical significance was assumed for $p < .05$.

RESULTS

Of the 319 patients who were diagnosed with primary NSCLC in surgical specimens, we excluded 36 patients whose tumor size was 10 mm or less with a longer axis from this study because we gave priority to clinical necessity of formalin fixation for pathological staging. Out of the 283 patients, 103 patients who was able to understand the purpose of this investigation and gave written informed consent to this study became candidates for this investigation, and RNAs were extracted from their tumor tissues. Among them, five

patients were excluded because their RNAs had degraded. Consequently, a total of 98 patients met our eligibility criteria.

No patients received chemo- or radiotherapy before surgery. For the patients with stage IA tumor, no adjuvant therapy was carried out. For the patients with stage IB and IIIA tumor, options of adjuvant therapy were presented. For the seven patients with stage IIIB and IV tumor, therapy was selected according to clinical condition of the patients. As a result, 30 patients received postoperative tegafur-uracil (UFT) therapy. Eight patients received postoperative therapy other than UFT: five patients radiotherapy, one chemo-radiotherapy, and two combination chemotherapy.

During the postoperative follow-up of the 98 patients for 5 years, 20 patients died: 15 patients died of lung cancer, two of respiratory failure due to interstitial pneumonia, two of cerebrovascular disease, and one of respiratory failure of unknown cause. The WT1 mRNA expression did not show normal distribution, and median of the fatal cases and the survival cases was 0.0043 (range 0.0018–0.5220, interquartile range 0.0008–0.0250) and 0.0141 (range 0.0020–0.6100, interquartile range 0.0025–0.0677), respectively. Thus, for the fatal cases, the WT1 mRNA expression level was over a lower range as compared with that of the survival cases.

A cutoff value of WT1 mRNA expression to predict survival was estimated from the receiver operating characteristic (ROC) curve analysis (Figure 1). The patients were divided into two groups based on the optimal cutoff value of WT1 mRNA expression level 0.0057 (sensitivity was 0.679, and 1 – specificity was 0.350): the high WT1 expression group (60 patients) and the low WT1 expression group (38 patients). Overall survival (OS) of the high WT1 expression group was significantly longer ($p < .01$) than that of the low expression

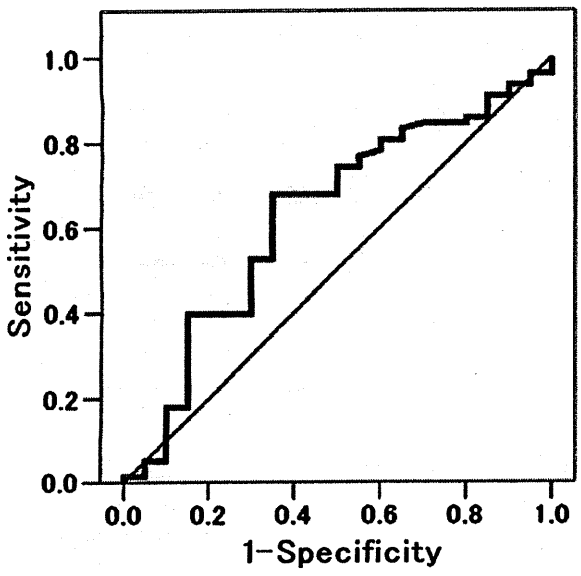

Figure 1. Receiver operating characteristic (ROC) curve analysis using WT1 mRNA expression rate and overall survival rate. The optimal cutoff value of WT1 mRNA expression was 0.00565 (sensitivity was 0.679, and 1 – specificity was 0.350).

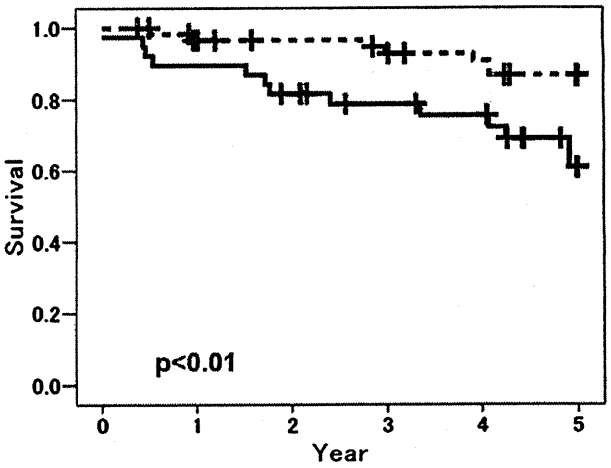

Figure 2. Overall survival (OS) rates of the high (broken line) and low (solid line) WT1 expression groups. OS rate of the low WT1 expression group was significantly lower than the high WT1 expression group ($p < .01$).

group (Figure 2). With regard to disease-free survival (DFS) for all the 98 patients, the low WT1 expression group showed a trend toward lower DFS compared with the high WT1 expression group ($p = 0.07$) but no significant differences were observed between the two groups (Figure 3A). In subset analysis for patients at stages I and II, no significant difference in DFS was observed between the high and the low WT1 expression group (Figure 3B). For patients at stages III and IV, the DFS of the low WT1 expression group was significantly lower than that of the high WT1 expression group ($p < .03$) (Figure 3C).

Then, we evaluated the relationship between WT1 mRNA expression and status of lymph node metastasis (Table 2). In subset analysis for histology, weak but significant negative correlation was observed in the 27 SQLC patients between WT1 mRNA expression level and lymph node metastasis (p-n factor) by the Kendall's tau ($p < .03$) and Spearman's rho ($p < .02$) rank correlation coefficient tests. The number of SQLC patients without lymph node metastasis was significantly larger (chi square test, $p < .01$) in the low WT1 expression group than in the high expression group. On the other hand, for the 63 ADLC patients, no significant correlation was observed between WT1 mRNA level and lymph node metastasis.

Table 2. Correlation of WT1 mRNA Expression Level and Lymph Node Metastasis

	All cases ($n = 96$)		Squamous cell carcinoma ($n = 27$)		Adenocarcinoma ($n = 63$)	
	r^a	p	r	p	r	p
Kendall's tau	−0.018	.82	−0.355	.03	0.056	.60
Spearman's rho	−0.022	.83	−0.438	.02	0.068	.60

[a]correlation coefficient.