with in vitro sensitive drugs yielded better prognosis. This study was not controlled randomized study. Not all of the patients without in vitro sensitive agents were given empirical chemotherapy. Under these conditions, it is impossible to certify the prognostic benefit of drug sensitivity test for NSCLC. However, MST of the patients treated with in vitro sensitive regimen was longer than MSTs for the patients treated with empirical standard chemotherapy and the response rate of in vitro optimal regimen was 72.7%. These data suggest that this assay identifies a subset of patients who do well when treated by assay directed therapy. On the other hand, the patients treated with standard empirical chemotherapy which were judged ineffective by CD-DST had no responders, and shorter MST of 4.5 months. These data suggest that this assay identifies a subset of patients who do particularly poorly when treated with chemotherapy in general. In this study number of patients is too small to conclude the usefulness of CD-DST. Further examinations including not only randomized controlled study with unresectable lung cancer but prospective study for adjuvant chemotherapy with resected lung cancer needs to be done.

References

1. Bunn PA, Kelly K (1998) New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. Clin Cancer Res 5:1087–1100
2. Kobayashi H, Tanisaka K, Doi O, Kodama K, Higashiyama M, Nakagawa H, Miyake M, Taki T, Hara S, Yasutomi M, Hanatani Y, Kotake K, Kubota T (1997) An in vitro chemosensitivity test for solid human tumors using collagen gel droplet embedded cultures. Int J Oncol 11:449–455
3. Koezuka M, Kondo N, Kobayshi H, Hara S, Yasutomi M, Nishida S, Hashimoto S, Asano H (1993) Drug sensitivity test for primary culture of human cancer cells using collagen gel embedded culture and image analysis. Int J Oncol 2:953–959
4. Kobayashi H (2003) Development of a new in vitro chemosensitivity test using collagen gel droplet embedded culture and image analysis for clinical usefulness. Recent Results Cancer Res 161:48–61
5. Cartazar P, Johnson BE (1999) Review of the efficacy of individualized chemotherapy selected by in vitro drug sensitivity testing for patients with cancer. J Clin Oncol 17:1625–1631
6. Sobin LH, Wittekind CH (eds) (1997) Lung and pleural tumours. In: UICC: TNM classification of malignant tumours, 5th edn. Wiley, New York, pp. 91–100
7. Tanigawa N, Kitaoka A, Yamakawa M, Tanisaka K, Kobayashi H (1996) In vitro chemosensitivity testing of human tumours by collagen gel droplet culture and image analysis. Anticancer Res 16:1925–1930
8. Shaw GL, Gazdar AF, Phelps R, Linnoila I, Ihde DC, Johnson BE, Oie HK, Pass HI, Steinberg SM, Ghosh BC, Walsh TE, Nesbitt JC, Cotelingam JD, Minna JD, Mulshine JL (1993) Individualized chemotherapy for patients with non-small cell lung cancer determined by prospective identification of neuroendocrine markers and in vitro drug sensitivity testing. Cancer Res 53:5181–5187
9. Gazdar AF, Steinberg SM, Russell EK, et al (1990) Correlation of in vitro drug-sensitivity testing with response to chemotherapy and survival in extensive-stage small cell lung cancer: a prospective clinical trial. J Natl Cancer Inst 82:117–124
10. Cortazar P, Gazdar AF, Woods E, et al (1997) Survival of patients with limited-stage small cell lung cancer treated with individualized chemotherapy selected by in vitro drug sensitivity testing. Clin Cancer Res 3:741–747
11. Simon GR, Ruckdeschel JC, Williams C, Cantor A, Chiappori A, Lima CMR, Antonia S, Haura E, Wagner H, Robinson L, Sommers E, Alberts M, Bepler G (2003) Gefitinib (ZD1839) in previously treated advanced non-small cell lung cancer: experience from a single institute. Cancer Control 10:388–395
12. Ikeda S, Hata E, Ohta M, Tsubota N, Hamajima N, Saito Y, Wada H, Suemasu K, Ohta M (2003) A randomized phase III trial of adjuvant chemotherapy with UFT for completely resected pathological stage I (T1N0M0, T2N0M0) adenocarcinoma of the lung. Prog Proc Euro Cancer Conf 39:S322 abstract
13. Yamaue H, Tanimura H, Noguchi K, et al (1992) Chemosensitivity testing of fresh human gastric cancer with highly purified tumour cells using the MTT assay. Br J Cancer 66:794–799

Early Pulmonary Resection for *Mycobacterium Avium* Complex Lung Disease Treated With Macrolides and Quinolones

Masazumi Watanabe, MD, PhD, Naoki Hasegawa, MD, PhD, Akitoshi Ishizaka, MD, PhD, Keisuke Asakura, MD, Yotarao Izumi, MD, PhD, Keisuke Eguchi, MD, PhD, Masafumi Kawamura, MD, PhD, Hirohisa Horinouchi, MD, PhD, and Koichi Kobayashi, MD, PhD

Departments of Surgery and Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

Background. The purpose of this study was to examine the postoperative outcomes of patients with *Mycobacterium avium* complex (MAC) lung lesions persisting despite treatment with multiple antibiotics.

Methods. Patients with localized pulmonary lesions persisting despite extensive state-of-the art antimicrobial chemotherapy became candidates for surgical resection. Twenty-two patients who were expected to retain sufficient postoperative pulmonary function were included in this study. These patients received chemotherapy for 2 to 37 months (mean, 17). Surgical procedures were lobectomy (n = 15), segmentectomy (n = 4), and partial lung resection (n = 6). Three patients underwent bilateral resections.

Results. *Mycobacterium avium* complex causing bronchiectasis or cavitary lesions was detected preoperatively in all 22 patients. There was no major operative morbidity or mortality. Postoperative chemotherapy was continued for 6 to 35 months. All patients were alive and well at follow-ups ranging from 6 to 164 months (median, 46). Both vital capacity and forced expiratory volume in 1 second after surgery were maintained at 89% and 84% of the preoperative values, respectively. *Mycobacterium avium* complex disappeared from sputum after surgery in all patients. In 1 patient, 4 months after resection of a cavitary lesion, MAC-positive sputum presumed to be from the contralateral lung lesion became negative during continuation of chemotherapy.

Conclusions. The long-term outcomes of patients operated on for MAC resistant to antimicrobial chemotherapy were excellent. For such patients, we recommend surgery before the disease becomes exceedingly advanced and nonresectable. Additionally, in extensive disease, the excision of large cavitary bacterial foci may assist the medical management of contralateral lesions.

(Ann Thorac Surg 2006;81:2026–30)

The detection of nontuberculous mycobacterial lung diseases has improved as a result of advances in diagnostic methods [1, 2]. *Mycobacterium avium* and *Mycobacterium intracellurare*, generally referred to as the *Mycobacterium avium* complex (MAC), are the most common in Japan. Although MAC has been treated with multiple drugs, including clarithromycin or levofloxacin, cure with medications alone remains difficult to achieve, especially in patients with cavitary or bronchiectatic lesions. Therefore, surgical resection continues to play an important role in the management of this disorder. The aim of this study was to retrospectively examine the outcomes of patients who underwent pulmonary resections for MAC disease.

Patients and Methods

This study was carried out in accordance with the guidelines set by the Japanese Ministry of Health, Labor, and Welfare. The Institutional Review Board approved this study, and informed consent was waived. Surgical and medical records of all patients who underwent pulmonary resection for MAC pulmonary disease between January 1, 1990, and July 31, 2005, at Keio University Hospital were reviewed. Smears, cultures, and polymerase chain reaction examinations of sputum or bronchial washings were performed before surgery. Samples submitted to the microbiology laboratory were concentrated and decontaminated by standard methods. Smears were screened by both the fluorochrome method and Ziel-Nielsen staining. At the same time, samples were tested by an Amplicor Mycobacterium DNA detection kit (Roche Diagnostics, Tokyo, Japan), and cultured in a liquid medium (BBL MGIT; Becton Dickinson, Franklin Lakes, New Jersey). Microdilution antimycobacterial susceptibility test, BrothMIC, (Kyokuto

Accepted for publication Jan 5, 2006.

Address correspondence to Dr Watanabe, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan; e-mail: masazumi@sc.itc.keio.ac.jp.

Published by Elsevier Inc

0003-4975/06/$32.00
doi:10.1016/j.athoracsur.2006.01.031

Table 1. Clinical Characteristics of Patients

Patient	Age (years)/ Sex	Diagnostic Manifestation	Pretreatment (Duration, Months)	Main Lesion	Surgical Procedure	Posttreatment (Duration, Months)	Outcomes (Months)
1	34/M	Hemoptysis	INH+RFP+EB 20	Ectasis	R Low Lobectomy	INH+RFP+EB 6	164A
2	51/W	CXR	INH+RFP+CAM+OFLX 30	Ectasis[a]	R Mid Lobectomy+Up Wedge / L lingula segmentectomy+Up Wedge	INH+RFP+CAM 6	101A
3	59/W	Hemoptysis	CAM 12	Ectasis[a]	R Mid lobectomy+Up Wedge	RFP+CAM 12	78A
4	34/W	CXR	INH+RFP+CAM+LVFX 6	Cavity	R Up Wedge/L Up Wedge	INH+RFP+CAM+ LVFX 7	73A
5	61/W	Cough, sputum	RFP+INH+CAM 20	Ectasis[a]	R Mid Lobectomy+S6 Wedge	INH+RFP+CAM 7	69A
6	49/W	CXR, hemoptysis	INH+RFP+EB 24	Cavity	R S2 segmentectomy	CAM+EB 7	61A
7	57/M	Sputum	RFP+EB+CAM 6	Ectasis	R Low Lobectomy	RFP+EB 3	59A
8	61/W	CXR	LVFX+CAM 15	Ectasis[a]	R Mid Lobectomy	CAM+LVFX 6	59A
9	55/W	Sputum	INH+RFP+CAM 7	Ectasis	RS6 segmentectomy+Up Wedge	LVFX 6	59A
10	52/W	CXR	CAM+LVFX 7	Ectasis[a]	L Up Wedge/R Mid Lobectomy+Up Wedge	CAM+LVFX 5	51A
11	59/W	Sputum	RFP+EB+CAM+SPFX 37	Cavity	R Up Lobectomy+Low Wedge	RFP+EB+CAM+ SPFX_35	46A
12	41/M	CXR	INH+RFP+EB 24	Cavity	R Up Lobectomy	INH+RFP+EB_6	46A
13	63/M	CXR	EB+RFP+CAM 12	Cavity	R Up Wedge	EB+RFP+CAM 6	46A
14	77/M	Cough, sputum	INH+RFP+EB 2	Ectasis	R Up Wedge	INH+RFP+EB 6	36A
15	72/W	CXR	CAM 8	Ectasis[a]	R Mid Wedge	CAM 6	23A
16	58/M	CXR	EB+RFP+CAM 20	Cavity	R S1,2 segmentectomy	CAM 6	22A
17	53/W	Hemoptysis	CAM 33	Ectasis[a]	R Mid Lobectomy	CAM 9	20A
18	37/M	CXR	EB+RFP+CAM+LVFX 14	Cavity	R Up Lobectomy	EB+RFP+CAM+ LVFX 6	19A
19	54/W	Hemoptysis	INH+RFP+EB+SM+ PZA24_CAM32	Cavity	R Mid Lobectomy+Low Wedge	CAM 6	16A
20	60/W	Sputum	EB+RFP+CAM+LVFX+ KM24	Ectasis[a]	R Up+Mid Lobectomy	EB+RFP+CAM6	15A
21	71/W	CXR	CAM+LVFX 20	Ectasis[a]	R Mid Lobectomy+S6 segmentectomy	CAM 6	14A
22	30/W	CXR	EB+RFP+CAM+LVFX+ SM 14	Ectasis	R Up Lobectomy	CAM 6	6A

[a] Middle lobe or lingular type.

A = alive; CAM = clarithromycin; CXR = chest roentogenogram; EB = ethambutol; INH = isoniazid; KM = kanamycin; L = left; Low = lower lobe; LVFX = levofloxacin; M = man; Mid = middle lobe; OFLX = ofloxacilin; PZA = pirazinamid; R = right; RFP = rifampicin; SM = streptomycin; SPFX = suparfloxacin; Up = upper lobe; W = woman; Wedge = wedge resection.

Pharmaceutical Industrial, Tokyo, Japan) was performed to examine drug sensitivity in 9 recent cases. Minimum inhibitory concentrations of 10 drugs were measured.

The surgical indications in this series of patients were (1) MAC disease refractory to multiple drug therapy, including clarithromycin, rifampicin, ethambutol, or levofloxacin; (2) localized pulmonary lesions; and (3) sufficient predictive postoperative pulmonary function.

Results

Patient Population

Between January 1, 1990, and July 31, 2005, pulmonary resections for MAC were performed in 15 women and 7 men ranging in age between 30 and 77 years (mean, 54). The main characteristics of the patient population are shown in Table 1. No patients suffered from immunodeficient disorders, such as human immunodeficiency virus. One patient, however, had primary lung cancer combined with MAC pulmonary disease. All patients underwent lung resection to treat MAC disease and not for diagnostic purposes.

Preoperative Condition and Chemotherapy

Ten asymptomatic patients with abnormal findings on chest roentgenograms at health maintenance examinations were diagnosed with MAC disease. The other 12 patients had symptoms, including productive cough in 6

Table 2. Results of Pulmonary Function Test Before and After Surgery

	Total Cases (n = 18)			Lobectomy[a] (n = 11)		
	Before Surgery	After Surgery	*p* Value	Before Surgery	After Surgery	*p* Value
Vital capacity (L)	3.08 ± 0.77	2.74 ± 0.84	0.0001	2.98 ± 0.68	2.73 ± 0.82	0.007
Percent vital capacity (%)	99.4 ± 11.1	92.3 ± 14.2	0.02	95.6 ± 10.3	91.3 ± 14.4	0.21
FEV1.0 (L)	2.34 ± 0.67	1.97 ± 0.65	0.0001	2.33 ± 0.78	1.98 ± 0.70	0.0003
FEV1.0% (%)	72.4 ± 20.7	73.6 ± 10.8	0.82	70.2 ± 25.9	74.0 ± 12.6	0.67

[a] Lobectomy includes both lobectomy and wider resection.

FEV = forced expiratory volume.

and hemoptysis in 6. All patients had either a cavitary or a bronchiectatic lesion on chest computed tomography (CT). The lesions were predominantly cavities in 8 and predominantly bronchiectasis in 14 patients. In 9 women, the lesions were in the middle lobe or the lingular segment, that is, the so-called middle lobe or lingular type.

The MAC infections were confirmed in all patients from cultures or MAC-polymerase chain reaction methods performed in sputum or bronchoalveolar lavage fluid before surgery, according to the criteria of the American Thoracic Society [3]. All patients had received preoperative medications for 2 to 37 months (mean, 17). Clarithromycin was administered in 18 patients, combined with a new quinolone agent such as levofloxacin, ofloxacin or sparfloxacin in 9, and with rifampicin and ethambutol in 6 patient. Single-drug therapy was performed in 3 patients because they refused combined drug therapy because of adverse effects. In 9 recent cases, drugs were selected according to the results of microdilution antimycobacterial susceptibility test.

The performance status at the time of surgery was 0 in 19 patients and 1 in 3 patients.

Medical Therapy in Our Hospital

The outline of MAC medical therapy at the outpatient clinic of internal medicine in the recent 5-year period is as follows. Patients who were found at health screenings without symptoms were followed up for 3 to 6 months at the outpatient clinic. If the findings on chest roentgenogram worsened during this period, chemotherapy was started even in asymptomatic patients. Twenty-five patients with primary MAC disease were treated in our hospital during this 5-year period. Two patients had cavitary lesions, and other patients had bronchiectatic lesions or granular shadows. Each patient was treated by rifampicin, ethambutol, clarithromycin, and levofloxacin basically. The findings of sputum culture converted from positive to negative in 20 patients within 6 months. In the other 5 patients, the sputum culture remained positive, and consequently, these 5 patients underwent pulmonary resection. (Note: 5 of these 22 patients who underwent surgery are included in this study. The other patients in this study were referred to us from other facilities after receiving initial medical therapy.)

Surgical Procedures and Pathology

Bilateral lung resections were performed in 3 patients, including sequential bilateral resections within 1 day in 1 patient (no. 4). Resections of multiple lung regions were performed in 10 patients. The primary surgical procedures consisted of lobectomy in 14, bilobectomies in 1, segmentectomy in 4, and wedge resection of the lung in 6 patients. All wedge resections were performed using stapling devices. In 1 patient with lung cancer, the tumor was excised by left lower lobectomy, and partial resection of the upper lobe was performed for MAC. Wedge resection was performed by thoracoscopy using three ports in 3 patients. Lobectomy was performed assisted by thoracoscopy in 1 patient. We limited the thoracoscopic procedures to cases with small lesions because direct palpation is important to secure enough surgical margin in MAC patients. Thoracoplasty was performed in 1 patient (no. 11), with right upper lobectomy, because of insufficient expansion of remaining middle and lower lobes and existence of large postresectional pleural space.

Microscopic findings showed granulomatous inflammation with necrosis in all cases. In all surgical specimens, MAC was confirmed by microbiological methods including polymerase chain reaction.

Postoperative Follow-Up

Patients after surgery received follow-up every 3 or 4 months. Chest roentgenographic finding was checked in every patient. Smears, cultures, and polymerase chain reaction examinations of sputum were performed in patients with sputum. There was no postoperative mortality or major complication. One patient needed home oxygen therapy soon after discharge, but it was discontinued 2 months after surgery. All patients were alive 6 to 164 months after surgery. The median survival was 46 months. The results of postoperative pulmonary function testing, which was performed at more than 6 months after surgery (range, 6 to 156 months; median, 52), were available in 18 patients and are shown together with the preoperative data in Table 2. Both vital capacity and forced expiratory volume in 1 second were reduced significantly after resection. Both values, however, were maintained at 89% and 84% of preoperative values, respectively. The results were not significantly different

between patients who received lobectomy or wider resection (n = 11). The performance status after surgery was unchanged in all patients. The nutritional status of these patients was good and was not different before and after surgery.

Postoperative chemotherapy was administered to all patients. Positive sputum finding was observed in 2 patients after resection but became negative after postoperative chemotherapy. In 1 patient (no. 11), MAC-positive sputum detected after surgery became negative 4 months later while on chemotherapy. In another patient (no. 20), contralateral MAC lesions regressed after the resection of a large cavitary lesion.

Comment

The management of MAC pulmonary infection has made progress since the introduction of oral macrolides, and quinolones antibiotics. However, recent reports indicate that the medical treatment of MAC remains challenging. The conversion rates of sputum cultures from positive to negative with clarithromycin-containing regimens has been reported to be between 54% and 87% [4–8]. Moreover, reported recurrence rates after conversion range between 20% and 44% [4, 5, 7, 8]. Therefore we performed this retrospective study to evaluate the role of surgical resection after chemotherapy containing macrolides and quinolones.

Our main surgical indication is the persistence of localized lesions despite administration of multiple drugs listed earlier. Despite the administration of clarithromycin for 6 to 37 months in 18 patients who had cavitary or bronchiectatic lesions, the MAC lesions had persisted; and these organized MAC-infected lesions were uncontrollable by drug therapy alone, including clarithromycin. As recommended by several others [9, 10], we proceeded with surgical treatment early, when medical treatment appeared ineffective, before the lesions had become inoperable. In all our patients, the findings of MAC in the sputum became negative after surgery. Compared with reported postoperative conversion rates between 87% and 100% [9–13], our favorable results may attributable to the early performance of surgery.

Reports of long-term results of medical treatment for MAC pulmonary disease are very few. In the study of Kobashi and colleagues [14], the response rate of 115 patients treated according to proposed guidelines (rifampicin plus ethambutol plus streptomycin plus clarithromycin) was significantly better than that before the guidelines were established in primary MAC disease. However, poor outcomes, namely, "worsening" and "death," were still high in secondary MAC disease, at 23.1% and 10.3%. Although our follow-up is shorter, complete resection appeared to improve prognosis.

The MAC diseases were found at health maintenance examination in 10 asymptomatic patients of 22 (45%) in this series. The other 12 patients had mild symptoms. Because we performed surgery at an early stage of the disease, the rates of wedge or segmental resections were higher than reported by others. None of our patients required a pneumonectomy, and none suffered a major postoperative complication. Reported rates of major complications, such as bronchopleural fistulae and respiratory failure, associated with more invasive surgery, have been 0% to 42% [9–13]. Therefore, it appears important to avoid invasive surgery, such as pneumonectomy, if possible. Both vital capacity and forced expiratory volume in 1 second after resection were reduced slightly in this series. The performance status after surgery, however, was maintained even in lobectomy cases.

Our surgical procedures did not routinely include thoracoplasty, even after upper lobectomy, which was performed in 4 of our patients. We performed thoracoplasty in a single patient, who presented with a huge residual pleural space. Several authors [10, 13] have recommended muscle flaps to buttress the bronchial stump, and obliterate the empty space after pneumonectomy.

We performed three thoracoscopic wedge resections in this series of patients. Although it is a less invasive and technically easier procedure, resections of bronchiectatic lesions with secure surgical margins are difficult. Wedge resection was performed mainly for small cavitary lesion keeping enough margin along the bronchial wall with palpation in this series. Therefore, we limited our thoracoscopic wedge resections to one side and performed minithoracotomies on the other side in 1 patient (no. 4).

We observed 2 noteworthy patients, in whom contralateral lesions improved without organizing pulmonary changes, after resection of large cavitary lesions. We hypothesize that the resection of major bacterial foci may facilitate the chemotherapeutic management of lesions not associated with cavities or bronchiectasis.

In conclusion, we recommend that surgical treatment of MAC pulmonary lesions be performed before the disease becomes too advanced, and difficult to resect. Patients treated with a clarithromycin-containing regimen for more than 6 months for MAC pulmonary disease with cavitary or bronchiectatic lesions, even when asymptomatic, should be viewed as candidates for surgery, as it is associated with low morbidity and mortality. In extensive disease, after the resection of major cavitary bacterial foci, the contralateral lesions can be further managed postoperatively by chemotherapy.

References

1. Kennedy TP, Weber DJ. Nontuberculous mycobacteria. An underappreciated cause of geriatric lung disease. Am J Respir Crit Care Med 1994;149:1654–8.
2. Kennedy MP, O'Connor TM, Ryan C, et al. Nontuberculous mycobacteria: incidence in Southwest Ireland from 1987 to 2000. Respir Med 2003;97:257–63.
3. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 1997;156(Suppl):S1–25.
4. Wallace RJ Jr, Brown BA, Griffith DE, et al. Clarithromycin regimens for pulmonary Mycobacterium avium complex. The first 50 patients. Am J Respir Crit Care Med 1996;153:1766–72.

5. Tanaka E, Kimoto T, Tsuyuguchi K, et al. Effect of clarithromycin regimen for Mycobacterium avium complex pulmonary disease. Am J Respir Crit Care Med 1999;160:866–72.
6. Field SK, Cowie RL. Treatment of Mycobacterium avium-intracellulare complex lung disease with a macrolide, ethambutol, and clofazimine. Chest 2003;124:1482–6.
7. Kobashi Y, Matsushima T. The effect of combined therapy according to the guidelines for the treatment of Mycobacterium avium complex pulmonary disease. Intern Med 2003; 42:670–5.
8. Griffith DE, Brown BA, Cegielski P, et al. Early results (at 6 months) with intermittent clarithromycin-including regimens for lung disease due to Mycobacterium avium complex. Clin Infect Dis 2000;30:288–92.
9. Ono N, Satoh K, Yokomise H, et al. Surgical management of Mycobacterium avium complex disease. Thorac Cardiovasc Surg 1997;45:311–3.
10. Shiraishi Y, Nakajima Y, Takasuna K, et al. Surgery for Mycobacterium avium complex lung disease in the clarithromycin era. Eur J Cardiothorac Surg 2002;21:314–8.
11. Pomerantz M, Madsen L, Goble M, et al. Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections. Ann Thorac Surg 1991;52: 1108–11.
12. Tsunezuka Y, Sato H, Hiranuma C. Surgical outcome of mycobacterium other than mycobacterium tuberculosis pulmonary disease. Thorac Cardiovasc Surg 2000;48:290–3.
13. Nelson KG, Griffith DE, Brown BA, et al. Results of operation in Mycobacterium avium-intracellulare lung disease. Ann Thorac Surg 1998;66:325–30.
14. Kobashi K, Matsusima T. Comparison of clinical features in patients with pulmonary Mycobacterium-avium complex (MAC) disease treated before and after proposal for guidelines. J Infect Chemother 2004;10:25–30.

Requirements for Recertification/Maintenance of Certification in 2006

Diplomates of the American Board of Thoracic Surgery who plan to participate in the Recertification/ Maintenance of Certification process in 2006 must hold an active medical license and must hold clinical privileges in thoracic surgery. In addition, a valid certificate is an absolute requirement for entrance into the recertification/maintenance of certification process. if your certificate has expired, the only pathway for renewal of a certificate is to take and pass the Part I (written) and the Part II (oral) certifying examinations.

The American Board of Thoracic Surgery will no longer publish the names of individuals who have not recertified in the American Board of Medical Specialties directories. The Diplomate's name will be published upon successful completion of the recertification/maintenance of certification process.

The CME requirements are 70 Category I credits in either cardiothoracic surgery or general surgery earned during the 2 years prior to application. SESATS and SESAPS are the only self-instructional materials allowed for credit. Category II credits are not allowed. The Physicians Recognition Award for recertifying in general surgery is not allowed in fulfillment of the CME requirements. Interested individuals should refer to the *Booklet of Information* for a complete description of acceptable CME credits.

Diplomates should maintain a documented list of their major cases performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. If more than 100 cases occur in 1 year, only 100 should be listed.

Candidates for recertification/maintenance of certification will be required to complete all sections of the SESATS self-assessment examination. It is not necessary for candidates to purchase SESATS individually because it will be sent to candidates after their application has been approved.

Diplomates may recertify the year their certificate expires, or if they wish to do so, they may recertify up to two years before it expires. However, the new certificate will be dated 10 years from the date of expiration of their original certificate or most recent recertification certificate. In other words, recertifying early does not alter the 10-year validation.

Recertification/maintenance of certification is also open to Diplomates with an unlimited certificate and will in no way affect the validity of their original certificate.

The deadline for submission of applications for the recertification/maintenance of certification process is May 10 each year. A brochure outlining the rules and requirements for recertification/maintenance of certification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, 633 N St. Clair St, Suite 2320, Chicago, IL 60611; telephone: (312) 202-5900; fax: (312) 202-5960; e-mail: info@abts.org. This booklet is also published on the website: www.abts.org.

Percutaneous cryoablation of small pulmonary malignant tumors under computed tomographic guidance with local anesthesia for nonsurgical candidates

Masafumi Kawamura, MD,[a] Yotaro Izumi, MD,[a] Norimasa Tsukada, MD,[a] Keisuke Asakura, MD,[a] Hiroaki Sugiura, MD,[b] Hideki Yashiro, MD,[b] Keiko Nakano, MD,[b] Seishi Nakatsuka, MD,[b] Sachio Kuribayashi, MD,[b] and Koichi Kobayashi, MD[a]

S. Kuribayashi, K. Kobayashi (*in front*), S. Nakatsuka, H. Yashiro, Y. Izumi, K. Asakura, N. Tsukada, M. Kawamura (*in back*), (*left to right*).

Objective: Cryoablation of pulmonary metastases might be a useful therapy for nonsurgical candidates.

Methods: The procedure was performed after achievement of local anesthesia for 35 tumors in 20 patients (12 male and 8 female patients; mean age, 57 years). The primary end point was the safety and feasibility of cryoablation, and the secondary end point was tumor control assessed by follow-up dynamic computed tomographic scanning performed every 3 months.

Results: Of the 22 sessions of cryoablation, pneumothorax occurred in 11, hemoptysis occurred in 8, and there was 1 case of phrenic nerve palsy. The mean hospital stay was 2.6 days. There was local recurrence of 7 (20%) tumors in 7 (35%) patients during a 9- to 28-month (median, 21 months) follow-up period. One-year survival according to the Kaplan-Meier method was 89.4%.

Conclusion: Percutaneous cryoablation therapy for metastatic lung tumors is feasible and minimally invasive, with satisfactory local control.

GTS

Cryoablation is used to treat hepatocellular carcinoma[1] or prostate carcinoma,[2] but although Wang and associates[3] have reported their experience of more than 200 cases of percutaneous pulmonary cryoablation during local anesthesia without major complications, the feasibility and efficacy of this technique for lung tumors have not been established.

Experiments in pigs have shown that a 2- or 3-mm-diameter cryoablation probe can freeze an area (known as an "ice ball") 2 to 3 cm in diameter and 4 cm in length after 2 cycles of freezing and thawing.[4] Furthermore, a technique of puncturing the center of small intrapulmonary nodules under computed tomographic (CT) fluoroscopic guidance has been developed from the experience of CT-guided lung biopsy.

The surgical approach for small pulmonary metastases is usually a wedge (or incomplete) resection, which is considered sufficient for local curability. Good results after complete resection of isolated pulmonary metastases from extrathoracic malignancies have been reported,[5] although others report that the extent of resection does not affect the prognosis.[6] However, because patients with metastatic pulmonary tumors are likely to develop new lesions after treatment, the loss of pulmonary function associated with therapy should be minimal.

Therefore we considered that percutaneous cryoablation under CT guidance with local anesthesia as a locally curative treatment for small lung tumors (<3 cm in diameter) should be possible and feasible. Our prospective study was approved by the institute's ethical review board.

From the Divisions of General Thoracic Surgery[a] and Diagnostic Radiology,[b] School of Medicine, Keio University, Tokyo, Japan.

Received for publication Oct 8, 2005; revisions received Dec 8, 2005; accepted for publication Dec 22, 2005.

Address for reprints: Masafumi Kawamura, MD, Division of General Thoracic Surgery, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan (E-mail: kawamura@sc.itc.keio.ac.jp).

J Thorac Cardiovasc Surg 2006;131:1007-13

0022-5223/$32.00

doi:10.1016/j.jtcvs.2005.12.051

Abbreviations and Acronyms

CT = computed tomography
PD = progressive disease
PR = partial response
RECIST = Response Evaluation Criteria in Solid Tumors
RFA = radiofrequency ablation
SD = stable disease

GTS

Methods

Patient Selection

The study group comprised 20 consecutive patients with metastatic pulmonary tumors at Keio University Hospital from November 2002 through February 2004 selected according to the following criteria: (1) maximum tumor size less than 3 cm in diameter; (2) less than 5 metastatic tumors; (3) projected life expectancy of greater than 1 year; (4) absence of active extrapulmonary metastasis; (5) performance status of 0 to 1 on the Eastern Cooperative Oncology Group scale; (6) definite pathologic diagnosis of a metastatic tumor or obvious clinical features of pulmonary metastasis; (7) provision of written informed consent; and (8) normal coagulability.

The characteristics of the patients and the main reasons for the choice of cryoablation as an alternative to surgical resection are shown in Table 1.

TABLE 1. Characteristics of patients treated with cryoablation

Age, y (mean [range])		57 (36-75)
Sex (n)		
Male		12 (60%)
Female		8 (40%)
Previous treatment for pulmonary metastases		
Chemotherapy		8 (40%)
Radiotherapy		2 (10%)
Immunotherapy		1 (5%)
Pulmonary resection		4 (20%)
Main reason for no resection		
Refusal of surgical intervention		6 (30%)
Inadequate predicted postoperative pulmonary reserve		5 (25%)
Extrapulmonary metastases		8 (40%)
Asthma		1 (5%)
Primary cancer	Cases	Tumors
Colorectal cancer	6 (30%)	10 (29%)
Lung cancer	5 (25%)	9 (26%)
Hepatic cancer	2 (10%)	5 (14%)
Soft tissue sarcomas	2 (10%)	4 (11%)
Head and neck cancer	2 (10%)	3 (9%)
Uterus cancer	2 (10%)	3 (9%)
Renal cancer	1 (5%)	1 (3%)
No. of metastatic tumors		
Solitary		11 (55%)
2		5 (20%)
3		2 (10%)
4		2 (10%)
Distribution of metastatic tumors		
Unilateral		17 (85%)
Bilateral		3 (15%)
Tumor size		
≤10		13 (37%)
11~20		17 (49%)
21~30		5 (14%)

Cryoablation Technique

Cryoablation was performed after achievement of local anesthesia by one thoracic surgeon and one radiologist. Before leaving the ward, each patient received an intramuscular injection of atropine sulfate (0.5 mg) and pentazocine (15 mg). In the CT room a 21-gauge guide needle was inserted into the center of the targeted tumors under fluoroscopic guidance, and when it was in the optimal position, a stainless-steel sheath for the cryoprobe, consisting of an inner guiding sheath and an external sheath, was inserted over the needle. The external sheath for a 2-mm-diameter cryoprobe (CRYOcare Cryosurgical Unit; Endo-care, Irvine, Calif) has inner and outer diameters of 2 and 3 mm, respectively, and for a 3-mm cryoprobe, these are 3 mm and 4 mm, respectively. After the inner sheath was removed, either a 2- or 3-mm cryoprobe was inserted through the external sheath, which is 180 mm long, equivalent to the length of the cryoprobe, and therefore the cryoprobe tip was located at the end of the sheath (Figure 1). The cryoprobe uses high-pressure argon and helium gas for freezing and thawing, respectively, on the basis of the Joule-Thompson principle. Cryoablation consisted of 2 cycles of 5 minutes of freezing followed by thawing until the temperature of the cryoprobe increased to 20°C and then a third cycle of 10 minutes of freezing followed by thawing (Figure 2). The air in the lung can interfere with the creation of the ice ball. When the cryoprobe is inserted into normal pulmonary parenchyma, initial freezing can make an ice ball of 1 cm in diameter only because the air prevents conduction of low temperatures and there is not enough water in the parenchyma. However, after thawing, the massive intra-alveolar hemorrhage[4] excludes the air and results in a larger ice ball that forms in the following freezing. Therefore we performed 3 freeze-thaw cycles to make an ice ball of 2.5 to 3.0 cm in diameter. The 2- or 3-mm diameter cryoprobe can freeze an area of 2 cm and 3 cm in diameter, respectively, and 4 cm long after 3 cycles of freezing and thawing. Therefore for tumors smaller than 2 cm, only 1 cryoprobe is usually inserted, and for 2- to 3-cm tumors, 2 cryoprobes are used to secure a freezing margin.

After the cryoprobe is removed, fibrin glue is infused into the outer sheath, and when it coagulates, the outer sheath is removed while the inner sheath is used to push the coagulated fibrin into the track of the cryoprobe. This is done to reduce the risk of bleeding and pneumothorax.

It takes 20 to 30 minutes to place a guide needle into the optimal position in the targeted tumor, and cryoablation is not performed until all gauge needles are inserted.

Figure 1. Two cryoprobes are inserted under computed tomographic (CT) guidance. CT scans can be taken as needed during the cryoablation procedure.

Evaluation and Statistical Analysis

The primary end point of this study was the early outcome and feasibility of using cryoablation for pulmonary metastatic tumors smaller than 3 cm. The secondary end point was the effect of cryoablation on radiographically determined tumor control. We also evaluated the type and frequency of complications, radiographic evidence of tumor response after cryoablation treatment, and overall survival.

Patients underwent a preoperative chest CT scan and a repeat scan on the day after the cryoablation procedure. Follow-up dynamic CT chest scans of patients without iodine allergy were carried out at 1-month and then 3-month intervals. Increase of the treated lesion size on follow-up CT scan was diagnosed as local recurrence. In some cases CT-guided needle biopsy was added to obtain a definite diagnosis. Changes in tumor mass after cryoablation were measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) protocol,[7] which is based on objective measurements of lesion size before and after treatment. Complete response means lesion disappearance (scar) or less than 25% of original size. Partial response (PR) means a greater than 30% decrease in the sum of the largest diameter of all targeted lesions. Stable disease (SD) means a less than 30% decrease in the sum of the largest diameter of all targeted lesions. Progressive disease (PD) means an increase of greater than 20% in the sum of the largest diameter of all targeted lesions. Change in each tumor size is also important for evaluating the efficacy of cryoablation because patients with metastatic lung tumors usually have multiple metastatic lesions. Therefore change in each tumor was evaluated with the same protocol as RECIST. Because cryoablation can cause scar formation during the healing process, the lesion size after treatment alone does not necessarily reflect treatment efficacy. Therefore in addition to RECIST, clinical outcome according to the follow-up CT scan after more than 1 year can be noted.

The Kaplan-Meier method was used to analyze cumulative survival after the initial cryoablation.

Results

A total 35 pulmonary tumors in 20 patients (12 male and 8 female patients; mean age, 57 years; age range, 36-75 years) were treated with cryoablation. Eastern Cooperative Oncology Group performance status was 0 in 19 patients and 1 in 1 patient. In all cases cryoablation was performed percutaneously under CT guidance with local anesthesia without any major complications. None of the patients had major complications associated with the procedure. The pulmonary metastases were from colorectal cancer (n = 6), previously resected non–small cell lung cancer (n = 5), head and neck cancer (n = 2), soft tissue sarcoma (n = 2), hepatic cancer (n = 2), uterine cancer (n = 2), and renal cancer (n = 1). The number of metastases was 1 in 11 patients, 2 in 5 patients, 3 in 2 patients, and 4 in 2 patients; 3 patients had bilateral metastases, and of them, 2 underwent cryoablation twice with an interval of 1 to 2 months, and the other patient underwent simultaneous cryoablation for the metastases. Therefore a total of 22 sessions of cryoablation were performed. The size of the treated lesions was 6 to 10 mm in 13 tumors, 11 to 20 mm in 17 tumors, and 21 to 30 mm in 5 tumors (mean tumor size, 13.3 mm).

The main reasons why those patients underwent cryoablation instead of surgical intervention were refusal of surgical intervention in 6 patients, inadequate predicted postoperative pulmonary reserve in 5 patients, extrapulmonary metastases in 8 patients, and asthma in 1 patient (Table 1).

Pneumothorax occurred in 11 of the 22 sessions, primarily after the completion of the ablation procedure. A chest tube was inserted in 1 case, transient needle aspiration was performed in 3 cases, and in 7 cases no additional treatment was given. In 7 cases a small amount of pleural effusion was detected on a chest CT scan carried out on postoperative day 1, but no additional treatment was required. Pleural dissemination was detected during the follow-up period in 1 patient whose postoperative CT scans did not show any pleural effusion. Because there had been multiple pulmonary metastases on the lung surface, it is unclear whether the cryoablation induced pleural dissemination. Hemoptysis occurred during 8 sessions and subsided in a few days in all patients. There was no apparent correlation between tumor location and the incidence of hemoptysis. Phrenic nerve palsy occurred during 1 session for a tumor located near the left phrenic nerve and had not improved when the patient died of brain metastases 9 months later (Table 2).

Mean hospital stay after treatment was 2.6 days (range, 2-9 days), although for the initial 5 sessions, it was 5.4 days. There were no treatment-related deaths or conversion to surgical intervention.

The response to cryoablation according to RECIST was complete response in 2 patients, PR in 8 patients, SD in 8 patients, and PD in 2 patients, giving a response rate of 50%. In 3 of 8 patients with PR and 2 of 8 patients with SD,

GTS

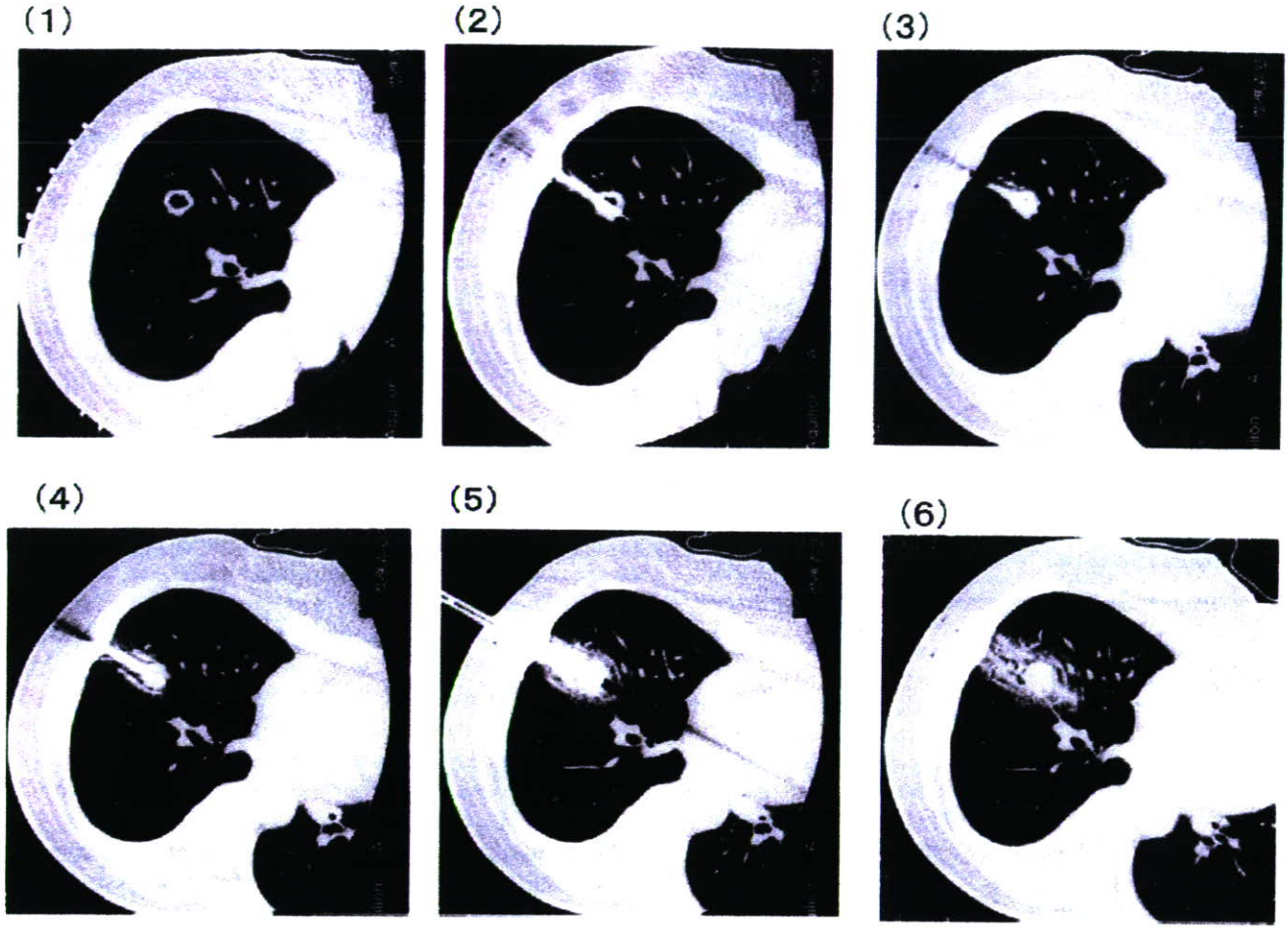

Figure 2. Sequential changes of the pulmonary parenchyma on computed tomographic scanning after freezing and thawing. *1*, The metastatic tumor is located in right S4. *2*, The cryoprobe penetrates the tumor. *3*, Five minutes after the beginning of first freezing, the change of surrounding lung is quite small. *4*, After first thawing, consolidation along the cryoprobe can be seen. *5*, Five minutes after the beginning of second freezing, extension of the consolidated area can be seen. *6*, After third thawing.

there was tumor recurrence. The response of each tumor was complete in 8 patients, partial in 11 patients, SD in 14 patients, and PD in 2 patients, giving a response rate of 54.3%.

One patient died of brain metastases 9 months after cryoablation, and another patient died of bone and kidney metastases 10 months later, but neither had pulmonary local recurrence. The remaining 18 patients survived more than 1 year. The follow-up period was 9 to 28 months (median, 21 months), and in the 9 to 12 months after cryoablation, there was local recurrence of 7 (20%) tumors (median time to progression of 9 months) in 7 (35%) patients: 5 patients underwent repeat cryoablation without complications, 1 patients initially refused surgical intervention and underwent surgical resection, and 1 patients was given chemotherapy for both the recurrent and new lesions. There was 1 case of suspected subcutaneous recurrence along the insertion track, which was surgically resected. To date, there have been no cases of local recurrence after repeat cryoablation (Table 3).

TABLE 2. Complications after cryoablation

Complication	No.	%
Pneumothorax	11	50
Chest tube	1	4.5
Manual aspiration	3	13.5
Course observation	7	32
Pleural effusion	6	27
Hemosputum	9	41
Phrenic nerve palsy	1	4.5
Chest wall implantation	1	4.5

TABLE 3. Radiographic response and clinical result

Patient no.	Primary tumor	Nodules treated with cryoablation	RECIST	Each tumor's response	Clinical outcome (prognosis after initial cryoablation)
1	Synovial sarcoma	1	CR	CR	New pulmonary lesions (18 POM dead)
2	NSCLC	2	PR	PR, SD	Disease free (27 POM alive)
3	NSCLC	1	PR→PD	PR→PD	Recryoablation for local recurrence (26 POM alive with new pulmonary lesions)
4	Colon cancer	1	SD	SD	New pulmonary lesions (25 POM alive)
5	Head and neck cancer	1	SD	SD	New pulmonary lesions (24 POM alive)
6	Colon cancer	1	PD	PD	Recryoablation for local recurrence (18 POM alive with new pulmonary lesions)
7	Colon cancer	4	SD→PD	PR, SD, SD, SD→PD	Surgical resection for local recurrence (21 POM disease free)
8	Lung cancer	1	PR→PD	PR→PD	Recryoablation for local recurrence (21 POM disease free)
9	Colon cancer	1	SD	SD	Surgical resection for subcutaneous implantation (21 POM alive with new pulmonary lesions)
10	Hepatic cancer	4	PR	PR, SD, SD, CR	New metastatic lesions (19 POM alive)
11	NSCLC	2	PR	PR, PR	Brain metastasis (9 POM dead)
12	Head and neck	2	SD→PD	CR, SD→PD	Recryoablation for local recurrence (18 POM disease free)
13	NSCLC	3	PR→PD	CR, PR, SD→PD	Chemotherapy for local recurrence and new lesions (18 POM alive)
14	Neurofibrosarcoma	3	CR	CR, CR, CR	New metastatic lesions (18 POM alive)
15	Hepatic cancer	1	SD	SD	Disease free (16 POM alive)
16	Colon cancer	2	PR	CR, PR	Bone and kidney metastases (10 POM dead)
17	Renal cancer	1	PR	PR	Disease free (14 POM alive)
18	Uterus cancer	1	PD	PD	Recryoablation for local recurrence (14 POM disease free)
19	Colon cancer	1	SD	SD	New metastatic lesions (14 POM alive)
20	Uterine cancer	2	SD	PR, SD	Disease free (12 POM alive)

RECIST, Response Evaluation Criteria in Solid Tumors; *CR*, complete response; *POM*, post operative months; *NSCLC*, non-small cell lung cancer; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease.

The 1-year survival rate after the initial cryoablation therapy for metastatic pulmonary tumors was 89.4%, as determined by using the Kaplan-Meier method (Figure 3).

Discussion

Surgical intervention is the usual option for local cure of metastatic pulmonary cancer, and wedge resection, which preserves residual pulmonary function better than radical lobectomy with mediastinal lymph node dissection, results in local curability to some extent. According to the International Registry of Lung Metastases,[5] the 5-year survival rate after incomplete resection for a metastatic lung tumor is 13% and 36% after complete resection, which suggests that surgical treatment might contribute to survival. However, some patients with advanced cancer might not tolerate surgical resection. Hence if equally effective, a less invasive therapy is preferable. This is why we evaluated the local curability, as well as the feasibility, of cryoablation. Although cryoablation has been performed for hepatic[1] or prostate[2] cancer and achieved acceptable results, in most cases it has been performed after achievement of general or epidural anesthesia. In our clinical study all the procedures

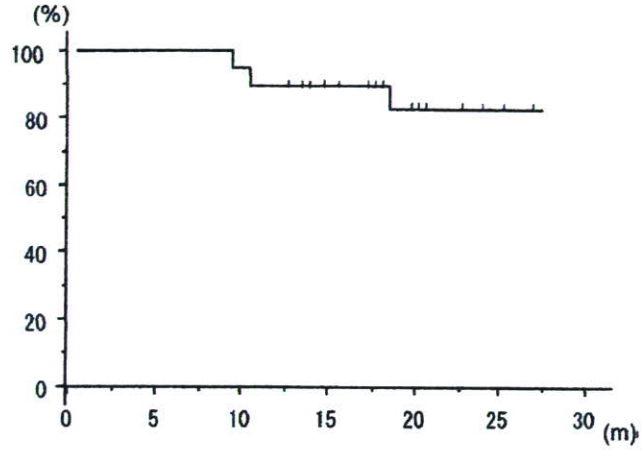

Figure 3. Accumulated survival curve by means of the Kaplan-Meier method.

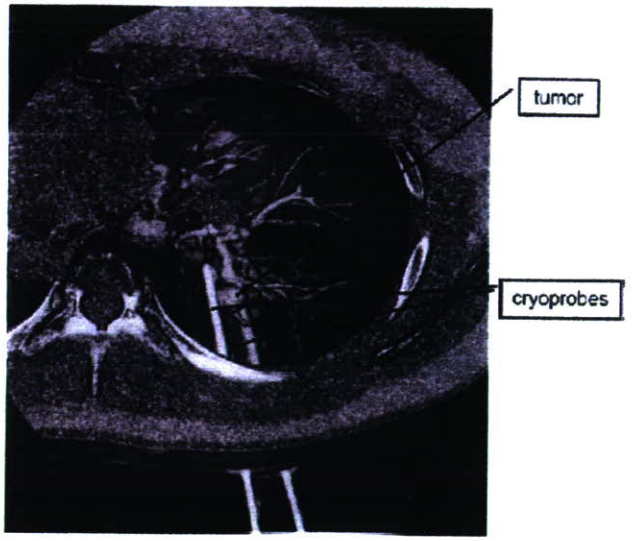

Figure 4. Cryoprobe can approach to the hilar lesions. A case with 6 peripheral and 1 central metastases: 6 peripheral metastases had been resected surgically. A centrally located tumor is shown in a 3-dimensional computed tomographic image. Two cryoprobes are inserted into the lung. Because the tumor was located close to a large vessel, 2 probes are inserted almost parallel, like chopsticks, so as to encase the tumor. This avoids vessel and airway damage, and preserves pulmonary function.

were performed after administration of local anesthesia only, which is similar to the conditions in the study by Wang and colleagues.[3] Moorjani and associates[8] reported the effect of cryoanalgesia on the intercostal nerves, and from the viewpoint of treatment-associated pain, cryoablation seems an ideal technique. However, some patients complained of dull pain in the anterior chest after treatment, which we suspect was related to freezing of the intercostal nerves, and it usually disappeared within a few months.

One patient required a chest tube for pneumothorax, but for the other 10 cases of a small amount of air leakage, transient manual aspiration was sufficient to control it. Hemothorax requiring chest tube drainage did not occur. Izumi and coworkers[9] observed from animal experiments that the coagulated blood surrounding the outer sheath apparently prevents massive air leakage and bleeding in the damaged pulmonary tract. The patient with the chest tube remained in the hospital for 9 days after treatment, but the average hospital stay was 2.6 days, which is shorter than the 4.5 days after video-assisted wedge resection at the same hospital.

As for other complications, hemoptysis occurred in 50% of sessions. In animal experiments rupture of the capillary wall and hemorrhage in the alveolar space were observed microscopically in the frozen area after thawing.[4] We suppose this phenomenon is a kind of hemorrhagic pulmonary edema caused by the death of endothelial cells. Therefore hemoptysis seems inevitable after pulmonary cryoablation and is not a serious condition because it is caused by the rupture of capillaries rather than large vessels. Actually, hemoptysis was not usually associated with shortness of breath.

There are some reports on the use of radiofrequency ablation (RFA) for pulmonary malignancies.[10-13] The RFA devices are more compact and cheaper than those for cryoablation. It was reported that in RFA 1 retreated patient with metastatic disease died of massive hemoptysis 21 days after open RFA of a central nodule.[10] Because the patient had also undergone brachytherapy 4 days prior, the cause of the fistula between the bronchus and the large pulmonary vessel was unclear; however, the authors state that they have ceased using RFA for central nodules since that complication.

We used cryoablation for centrally located tumors in 3 cases without any major complications (Figure 4), although the number of patients in this study is small. We know that the bronchial wall can resist temperatures of $-120°C$ to $-130°C$ because tracheas obtained from cadavers for transplantation can be deep-frozen.[14,15] Some reports suggest that the collagenous architecture of the central bronchi and vasculature is preserved by endobronchial cryotherapy.[16-18] On the other hand, the wall of large blood vessels heated by circulating blood during cryoablation seems to preserve the vessel wall structure.

Because metastatic lung tumors are expected to potentially associate with the other latent metastatic lesions in the lung, pulmonary reserve after treatment seems important. When cryoablation can be applied to centrally located tumors, greater pulmonary reserve is expected after cryoablation than after a surgical procedure such as lobectomy, which is usually required for the resection of those tumors (Figure 4).

For tumors larger than 2.0 cm in diameter, 2 or more cryoprobes are usually inserted around the tumor, but in those cases, the ice ball is irregular in shape, and it is difficult to accurately assess the positional relationship of the tumor and ice ball on CT images, although 3-dimensional CT should help. However, more basic research is required, and we do not use cryoablation for tumors larger than 3.0 cm in diameter. Nevertheless, there was local recurrence of approximately 20% of the ablated tumors and further improvements in the technique, and the CT images are necessary to decrease this rate. Of course, another cause of local recurrence after cryoablation is that the metastatic tumor might have satellite lesions or there is microinvasion into the lymph ducts, and local treatment, such as cryoablation or wedge resection, has the limitation to curative local control of metastatic lung tumors.

The response of the tumors was evaluated according to RECIST, and even though the marked scar formation around the tumor after cryoablation would seem to make accurate evaluation of tumor size on CT images impossible, of the 11 of 14 tumors diagnosed as SD by RECIST, local recurrence has not occurred during follow-up of more than 14 months. Long-term follow-up with CT scanning periodically is thought to be the most appropriate way to evaluate local control of tumors after cryoablation. Positron emission tomography might also be very useful to evaluate local control, although we have not done this in the present study. Because all cases of recurrence occurred 6 to 12 months (median, 9 months) after cryoablation, particular attention must be given to this period, especially for the common metastatic lung tumors, although longer observation of low-grade malignant tumor is necessary. A larger multi-institutional study would be ideal to further evaluate feasibility, but we need to collect more data before such studies can be designed. We also need to train individuals to gain better recognition of this technique. At our institution, we start by training the techniques necessary for CT-guided biopsy.

Conclusion

Percutaneous cryoablation therapy for metastatic lung tumors was feasible and minimally invasive, with satisfactory local control. This technique could also be used without any serious complications for tumors located near the hilar pulmonary vessels. However, the number of patients enrolled in this study was small, and thus the efficacy of cryoablation for the treatment of metastatic lung cancer is still unclear. A larger phase II study comparing cryoablation with wedge resection, stereotactic radiotherapy, or RFA therapy is necessary to determine its efficacy and role in the local control of metastatic lung tumors. Overall, we consider that with further studies and more accurate estimation of the ablated volume, eventually in selected cases cryoablation might not be inferior to wedge resection for the local control of metastatic lung tumors.

References

1. Seifert JK, Junginger T. Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature. *Technol Cancer Res Treat.* 2004;3:151-63.
2. Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chemick M. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology.* 2002;60(suppl):3-11.
3. Wang H, Littrup PJ, Duan Y, Zhang Y, Feng H, Nie Z. Thoracic mass treated with percutaneous cryotherapy: initial experience with more than 200 procedures. *Radiology.* 2005;235:289-98.
4. Izumi Y, Oyama T, Ikeda E, Kawamura M, Kobayashi K. The acute effects of transthoracic cryoablation on normal lung evaluated in a porcine model. *Ann Thorac Surg.* 2005;79:318-22.
5. Dastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, et al. Long term results of lung metastasectomy: prognostic analyses based on 5206 cases: the International Registry of Lung Metastases. *J Thorac Cardiovasc Surg.* 1997;113:37-49.
6. Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. *Chest.* 2001;119:1069-72.
7. Tsuchida Y, Therasse P. Response evaluation criteria in solid tumors (RECIST): new guidelines. *Med Pediatr Oncol.* 2001;37:1-3.
8. Moorjani N, Zhoo F, Tian Y, Liang C, Kaluba J, Maiwand MO. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostals nerves: a human prospective randomized trial and histological study. *Eur J Cardiothorac Surg.* 2001;20:502-7.
9. Izumi Y, Oyama T, Kawamura M, Kobayashi K. Lung biopsy with a 12 gauge cutting needle is possible using an insertion sheath in animal model. *Acad Radiol.* 2004;11:1278-81.
10. Herrera LJ, Fermando HC, Perry Y, Gooding WE, Buenaventure PO, Christie NA, et al. Radiofrequency ablation of pulmonary malignant tumors in nonsurgical candidates. *J Thorac Cardiovasc Surg.* 2003; 125:929-37.
11. Yasui K, Kanazawa S, Sano Y, Fujiwara T, Kagawa S, Miura H, et al. Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. *Radiology.* 2004;231:850-7.
12. Dupuy DE, Zagoria RJ, Akerley W, Mayo-Smith WW, Kavanaugh PV, Safran H. Percutaneous radiofrequency ablation of malignancies in the lung. *Am J Roentgenol.* 2000;174:57-9.
13. Sewell PE, Jackson MD, Vance RB, Wang YD. Assessing radiofrequency ablation of non-small cell lung cancer with positron emission tomography (PET) [abstract]. *Radiology.* 2000;217:551.
14. Yokomise H, Inui K, Wada H, Hasegawa S, Ohno N, Hitomi S. Reliable cryopreservation of trachea for one month in a new trehalose solution. *J Thorac Cardiovasc Surg.* 1995;110:382-5.
15. Yokomise H, Inui K, Wada H, Ueda M, Hitomi S. Reliable long-term cryopreservation of trachea for tissue banks. *Transplant Proc.* 1996; 28:1119-20.
16. Maiwand MO. The role of cryosurgery in palliation of tracheo-bronchial carcinoma. *Eur J Cardiothorac Surg.* 1999;15:764-8.
17. Deygas N, Froudarakis M, Ozenne G, Verguon JM. Cryotherapy in early superficial bronchogenic carcinoma. *Chest.* 2001;120:26-31.
18. Iomasson JP. Bronchoscopic cryotherapy. *J Bronchol.* 1995;2:145-53.

Surg Today (2006) 36:270–273
DOI 10.1007/s00595-005-3147-8

SURGERY TODAY

Long-Term Survival After Incomplete Resection of Immunohistochemically Diagnosed T0N1 Lung Cancer: Report of a Case

YOTARO IZUMI[1], MAKIO MUKAI[2], KOJI KIKUCHI[3], and KOICHI KOBAYASHI[1]

[1]Division of Thoracic Surgery, Department of Surgery, and [2]Division of Diagnostic Pathology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[3]Department of Thoracic Surgery, Saitama Medical Center, Saitama Medical School, Saitama, Japan

Abstract
A 63-year-old man who had undergone resection of colon cancer 15 years previously was found to have a right hilar mass on chest X-ray, and an elevated serum carcinoembryonic antigen level. The hilar lymph nodes were resected with the right upper lobe, and the initial diagnosis was colon cancer metastasis to the right hilar lymph nodes. Although the resection was incomplete, and no additional treatment was given, the patient remained free of recurrence for 10 years. This prompted us to reconsider our diagnosis using immunohistochemistry. The resected lymph nodes were found to be positive for thyroid transcription factor 1 (TTF-1) and cytokeratin 7, and negative for surfactant apoprotein (SAP), cytokeratin 20, and napsin A. The neuroendocrine markers and thyroglobulin were also negative. These findings led us to diagnose T0N1 lung cancer. There are reports of patients with clinical T0N1,2 lung cancer having exceptionally good prognoses despite noncurative treatment; however, to our knowledge, this is the first case of a patient with T0N1 lung cancer diagnosed by immunohistochemistry, with a good prognosis despite incomplete resection. In this case, TTF-1 and cytokeratin staining was particularly helpful in the differential diagnosis.

Key words T0N1 lung cancer · Adenocarcinoma · Metastasis · Hilar lymph node

Introduction

Unknown primary cancer metastasis to the hilar or mediastinal lymph nodes is well documented, but relatively uncommon.[1–6] We report a case of metastasis of adenocarcinoma to the right lung hilar lymph nodes, which was initially thought to be colon cancer metastasis based on the patient's past history and histology, but was subsequently diagnosed as T0N1 lung cancer by immunohistochemistry.

Case Report

A 63-year-old man, who had undergone right hemicolectomy for ascending colon cancer, diagnosed as moderately differentiated adenocarcinoma, T3N1M0, Dukes' C, stage III, 15 years earlier, was referred to our hospital for treatment of a cyst in the upper maxillary sinus. During the course of treatment his serum carcinoembryonic antigen (CEA) level was found to be elevated to 1620 ng/ml, and systemic evaluation was done. Chest X-ray showed a nodular shadow in the right lung hilum (Fig. 1), and chest computed tomography (CT) showed enlargement of the right superior interlobar lymph node (#11s)[7] (Fig. 2). No lesions were found in the lung, but gallium scintigraphy showed strong uptake in the right hilum. There was no evidence of gastrointestinal tract recurrence or other metastases. Bronchoscopy revealed no abnormalities except for a closed posterior upper lobe bronchus; a result of posterior segmentectomy of the right upper lobe to treat pulmonary tuberculosis 39 years earlier.

Since malignant right hilar lymph node enlargement was highly suspected, we performed an explorative thoracotomy. There was extensive intrathoracic adhesion from the previous surgery, with notable enlargement of lymph nodes #11s and the upper lobar lymph nodes (#12u).[7] No other intrathoracic lesions were macroscopically evident. Intraoperative biopsy from #11s revealed adenocarcinoma, suspicious of metastasis from colon cancer, on frozen section. Upper sleeve completion lobectomy was necessary to achieve curative resection, but the firm adhesion between the pulmonary

Reprint requests to: Y. Izumi
Received: November 8, 2004 / Accepted: September 13, 2005

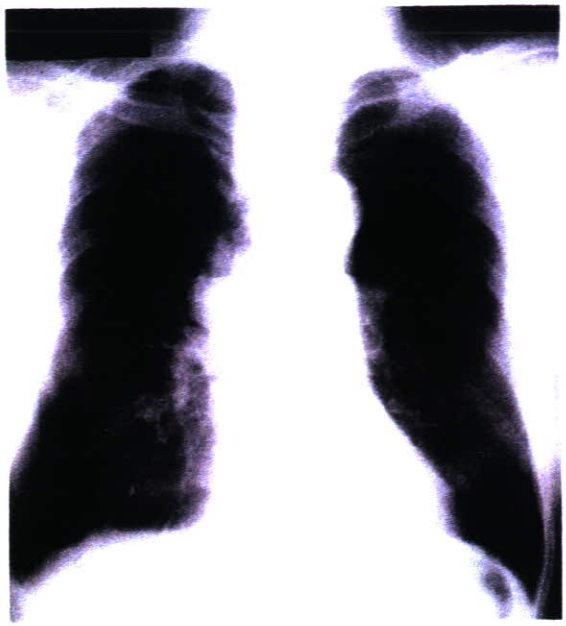

Fig. 1. Chest X-ray film showing a mass shadow in the right hilum

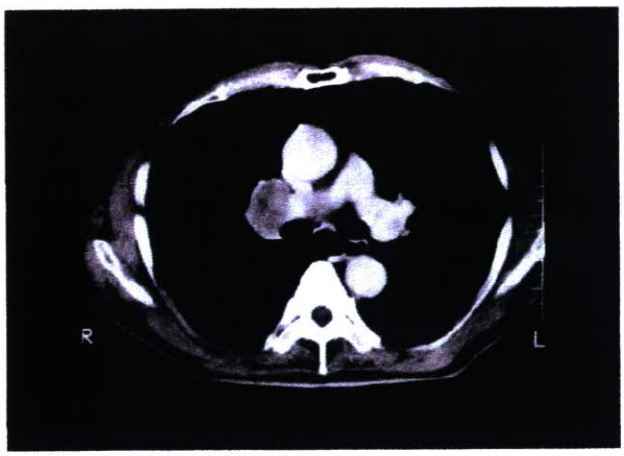

Fig. 2. Computed tomography scan showing enlargement of the right hilar lymph nodes

artery and the intermediate bronchus made this impossible. The #11s lymph node was dissected from the intermediate bronchus, and the enlarged hilar lymph nodes were resected by completion lobectomy. Remnant cancer tissue probably remained around the intermediate bronchus.

In the fixed specimen, the enlarged #12u lymph node was seen adjacent to the anterior upper lobe bronchus (Fig. 3, arrow). No lesions were found in the resected upper lobe. Histologic examination revealed that lymph nodes #11s and #12u were extensively infiltrated by metastatic adenocarcinoma (Fig. 4a,b), being similar in

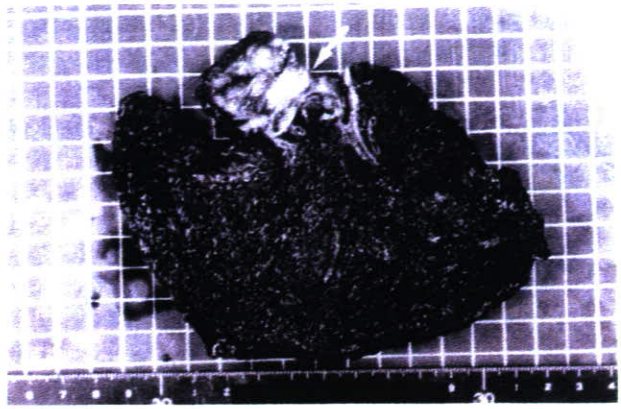

Fig. 3. Fixed specimen showing the resected lung and enlarged upper lobar lymph node. *Arrow* indicates the anterior upper lobe bronchus

appearance on hematoxylin — eosin to the previously resected colon carcinoma (Fig. 4c,d). The serum CEA level had normalized to 3.4 ng/ml by 3 months after the resection.

Our initial diagnosis was metastasis of colon cancer to the hilar lymph nodes, based on the patient's past history of colon cancer, and the morphology of hematoxylin — eosin staining. The patient was followed up closely because we thought that the appearance of thoracic as well as abdominal metastasis was inevitable, but the patient remained disease-free for 10 years despite no additional treatment. This prompted us to reconsider our diagnosis, using markers that were unavailable at the time of the initial diagnosis. Immunohistochemistry was carried out and comparisons were made between the primary colon lesion and the metastatic lymph nodes. The results indicated that the lymph node metastasis was most likely from lung adenocarcinoma, and hence we made a final diagnosis of T0N1 lung cancer (Table 1).

Discussion

Hematoxylin — eosin staining revealed that the cancer epithelium in the resected lymph nodes from this patient was morphologically of the colonic type rather than the lung type, even when reviewed retrospectively (Fig. 4b). Direct comparisons between lung cancer and colon cancer lung metastases using molecular analyses are still unusual. This is partly because it is considered that the distinction can usually be made morphologically. To our knowledge, thyroid transcription factor 1 (TTF-1) and surfactant apoprotein (SAP) have never been used to directly compare lung cancer and colon cancer. In the present study, SAP and napsin A were

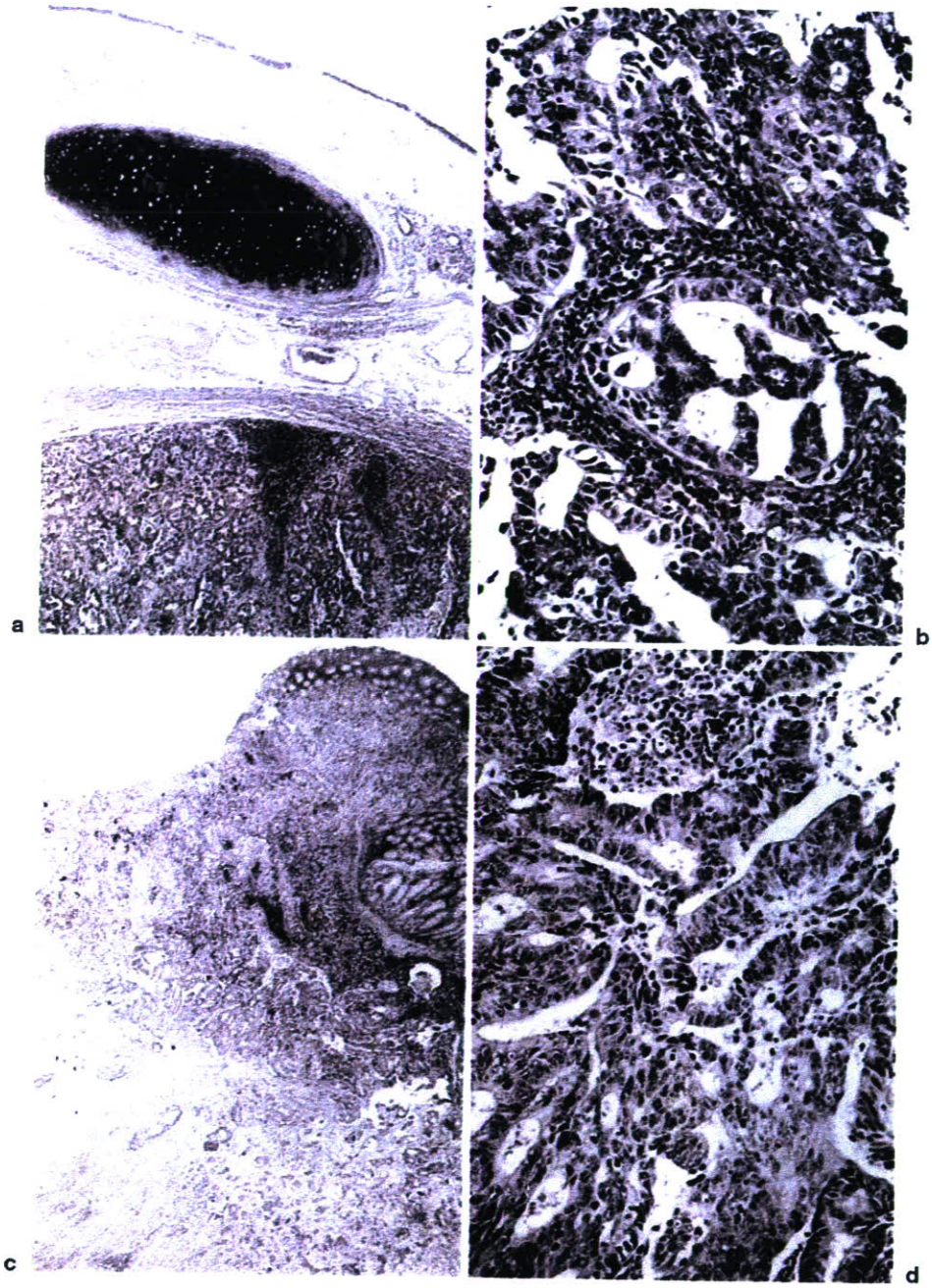

Fig. 4. a Lymph node adjacent to the bronchus extensively infiltrated by cancer (H&E, ×4). **b** Lymph node at higher magnification showing metastasis of moderately differentiated adenocarcinoma (H&E, ×20). **c** Primary colon carcinoma showing extensive infiltration through the muscularis propria (H&E, ×4). **d** Higher magnification of colon carcinoma showing moderately differentiated adenocarcinoma (H&E, ×20). **b,d** The metastatic adenocarcinoma in the lymph nodes was very similar to the previously resected colon carcinoma

both negative in the lung lymph node lesion. Napsin A is a relatively new marker with high specificity for lung adenocarcinoma.[8] Although napsin A was negative in the present case, the profiles of TTF-1, and cytokeratin 7 and 20, together with the absence of neuroendocrine markers and thyroglobulin, suggested that the lymph node adenocarcinoma was of lung origin.[9–11] Furthermore, no thyroid lesion was detected on follow-up CT scans. The diagnosis of lung cancer partly explained the long disease-free interval, and is consistent with the fact that there are only two known reports of mediastinal or hilar lymph node metastasis from colon cancer without other evident intra-abdominal or pulmonary metastases.[12,13] However, it is difficult to perceive that curative resection was achieved in this patient, and it is a mystery why he has remained disease-free for 10 years.

The prognosis associated with unknown primary cancer is generally poor, with reported 5-year survival rates of 2.8% to 6%, and median survival of 4–8 months.[1–6] However, Masaki et al. suggested that patients with

Table 1. Immunohistochemical comparison of the colon lesion and the hilar lymph nodes

	Colon	Hilar lymph node
SAP	Negative	Negative
TTF-1	Negative	Positive
CEA	Positive	Positive
Cytokeratin 7	Negative	Positive
Cytokeratin 20	Positive	Negative
Mucin-2	Positive	Negative
Napsin A	Not done	Negative
Chromogranin A	Not done	Negative
NCAM	Not done	Negative
Synaptophysin	Not done	Negative
NSE	Not done	Negative
Thyroglobulin	Not done	Negative

SAP, surfactant apoprotein; TTF-1, thyroid transcription factor 1; CEA, carcinoembryonic antigen; NCAM, neural cell adhesion molecule; NSE, neuron-specific enolase

hilar or mediastinal lymph node cancer of unknown origin, many of which are clinically considered to be T0N1,2 lung cancer, have better prognoses than those with lung cancer of an equivalent stage.[14] The longest survival in their series was 9 years, after lymph node resection alone without lung resection, and they also discussed the possibility of cancer originating from the lymph node per se.[14] Three cases of T0N1,2 lung cancer diagnosed by immunohistochemistry were recently reported.[15,16] The prognoses of these patients were good, ranging from 24 to 64 months, but all of them had undergone curative resection, and one had also received adjuvant chemotherapy. To our knowledge, our case represents the first T0N1 lung cancer supported by immunohistochemistry, with a good prognosis despite incomplete resection. Although we think that T0N1 lung cancer is the most accurate diagnosis for this patient, questions remain about his prognosis. Further studies are needed to clarify the origin and biology of these cancers for more appropriate diagnosis and treatment.

References

1. Holmes FF, Fouts TL. Metastatic cancer of unknown primary site. Cancer 1970;26:816–20.
2. Didolkar MS, Fanous N, Elias EG, Moore RH. Metastatic carcinomas from occult primary tumors. A study of 254 patients. Ann Surg 1977;186:625–30.
3. Stewart JF, Tattersall MH, Woods RL, Fox RM. Unknown primary adenocarcinoma: incidence of overinvestigation and natural history. Br Med J 1979;1:1530–3.
4. Greager JA, Wood D, Gupta TKD. Metastatic cancer from an undetermined primary site. J Surg Oncol 1983;23:73–6.
5. Altman E, Cadman E. An analysis of 1539 patients with cancer of unknown primary site. Cancer 1986;57:120–4.
6. Hamilton CS, Langlands AO. ACUPS (adenocarcinoma of unknown primary site): a clinical and cost benefit analysis. Int J Radiat Oncol Biol Phys 1987;13:1497–503.
7. Kawate N, Kobayashi K, Kono M. Regional lymph nodes. In: The Japan Lung Cancer Society, editors. Classification of lung cancer (in Japanese). Tokyo: Kanehara; 2000:p. 6–9.
8. Hirano T, Gong Y, Yoshida K, Kato Y, Yashima K, Maeda M, et al. Usefulness of TA02 (napsin A) to distinguish primary lung adenocarcinoma from metastatic lung adenocarcinoma. Lung Cancer 2003;41:155–62.
9. Loy TS, Calaluce RD. Utility of cytokeratin immunostaining in separating pulmonary adenocarcinomas from colonic adenocarcinomas. Am J Clin Pathol 1994;102:764–7.
10. Zamecnik J, Kodet R. Value of thyroid transcription factor-1 and surfactant apoprotein A in the differential diagnosis of pulmonary carcinomas: a study of 109 cases. Virchows Arch 2002;440:353–61.
11. Nishizuka S, Chen ST, Gwadry FG, Alexander J, Major SM, Scherf U, et al. Diagnostic markers that distinguish colon and ovarian adenocarcinomas: identification by genomic, proteomic, and tissue array profiling. Cancer Res 2003;63:5243–50.
12. Satur CM, Gebitekin C, Da Costa PE, Saunders NR. Recurrence of rectal carcinoma in the mediastinum. South Med J 1993;86:697–8.
13. Nakajima J, Kotsuka Y, Yagyuu K, Kohno T, Ohtsuka T, Tanbara K, et al. Solitary rectal carcinoma metastasis to the left hilar lymphnodes: a case report (in Japanese with English abstract). Nihon Kyobu Shikkan Gakkai Zasshi 1995;33:197–201.
14. Masaki Y, Gomibuchi M, Tanaka S, Sasai T. Mediastinal lymph-node carcinoma with no apparent primary lesion (in Japanese with English abstract). Kyobu Geka 1997;50:743–7.
15. Kawano R, Hata E, Sakaguchi H, Ikeda S, Yokota T. Two cases of T0 lung cancer with hilar and mediastinal lymph node metastasis (in Japanese with English abstract). Nihon Kokyuuki Geka Gakkai Zasshi 2003;17:117–22.
16. Suzuki Y, Ogawa N, Ishiwa N, Ito T. Resection of a primary lung lesion after resection of a malignant hilar lymph node of unknown origin (in Japanese with English abstract). Haigan 2002;42:283–7.

Total Cavopulmonary Connection: Open Anastomosis of an Extracardiac Conduit With Vacuum-Assisted Venous Drainage

Ryo Aeba, MD, Ryohei Yozu, MD, Masanori Morita, CP, and Toru Matayoshi, CP

Division of Cardiovascular Surgery, Keio University, Tokyo, Japan

Insertion of a tube conduit for total cavopulmonary connection is sometimes technically demanding due to the crumpled stump of the inferior vena cava caused by a tourniquet of the inferior vena cava near the division line. Herein we describe an alternative in which the anastomosis is completed during removal of the tourniquet with the application of vacuum-assisted venous drainage. This new technique may alleviate, if not completely eliminate, a concern associated with total cavopulmonary connection with extracardiac conduit in small patients.

(Ann Thorac Surg 2006;81:1146–7)

Total cavopulmonary connection using an extracardiac conduit technique has become one of the most commonly used modifications of Fontan-type operations [1, 2]. However, the insertion of a tube conduit is sometimes technically demanding due to the crumpled stump of the inferior vena cava (IVC) caused by a tourniquet of the IVC near the division line. We present a new technique using an open anastomosis of the IVC and a tube conduit with the application of vacuum-assisted venous drainage.

Technique

After general anesthesia is administered and the patient is prepared and draped, a midline sternotomy is performed. For patients with a previous bi-directional cavopulmonary shunt the pericardial adhesions are dissected only around the IVC and the neighboring right branch pulmonary artery. Cardiopulmonary bypass is established after cannulation of the ascending aorta, superior vena cava, and IVC. Straight and pliable venous cannula (Thin-Flex Single Stage Venous Drainage Cannula [Edwards Lifesciences LLC, Irvine, CA]) are used. The tip of the IVC venous cannula is positioned as usual, 2 cm below the diaphragm level. A tourniquet is applied to the IVC at the diaphragm level. The IVC is divided at the cavo-atrial junction, and the atrial stump is primarily closed by sutures. A slightly oversized polytetrafluoroethylene tube graft is selected and trimmed. Venous drainage is augmented with a vacuum-assisted negative pressure of between 40 and 60 mm Hg. An air bubble sensor is interposed in the venous drainage tube to recognize excessive air drawing, which could potentially lead to air blockage of the tube. The tourniquet for the IVC is released in order to achieve an open anastomosis of the graft with the IVC. Essentially no venous blood is spilled from the IVC stump. The cardiotomy sucker tip is placed in the IVC lumen to further facilitate the bloodless anastomosis technique that is needed (Fig 1). The other end of the conduit is anastomosed to a transverse incision in the inferior aspect of the right branch pulmonary arterial wall. Again, vacuum-assisted venous drainage is potent enough to eliminate the need for vascular clamping of the pulmonary artery. Finally, cardiopulmonary bypass is terminated.

Comment

Extracardiac conduit total cavopulmonary connection has been increasingly accepted as the procedure of choice for modified Fontan operations, because the hemodynamic properties in the reconstructed systemic venous route are excellent, and the suture load on the atrial wall is minimal. These characteristics promise better long-term morbidity and mortality. As an increasing number of patients undergo total cavopulmonary connection at a younger age, a small-sized tube graft is inevitably implanted, although an over-sized tube graft is desirable for such growing patients. The conventional technique with a tourniquet of the IVC near the division line may result in a heavily crumpled IVC stump. This makes the end-to-end anastomosis technique of the IVC stump and the tube graft highly demanding, especially in cases with a significant size mismatch between the two. The open technique allows a full expansion of the IVC wall and the placement of the sucker in the IVC lumen, thus assuring the surgeon more precise suture performance in such a difficult situation.

The open technique with vacuum-assisted venous drainage has been used in adult patients undergoing cardiac transplantation with bi-caval anastomosis [3], in

Accepted for publication Dec 17, 2004.

Address correspondence to Dr Aeba, Division of Cardiovascular Surgery, Keio University, 35 Shinanomachi, Shinjuku, Tokyo, 160-8582 Japan e-mail: aeba@sc.itc.keio.ac.jp.

Published by Elsevier Inc

0003-4975/06/$32.00
doi:10.1016/j.athoracsur.2004.12.011

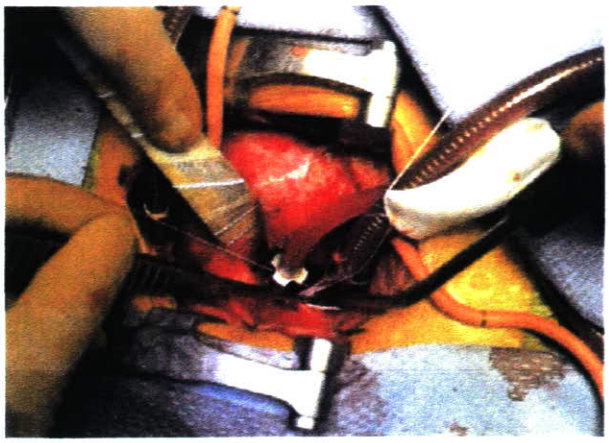

Fig 1. Surgeon's view of an open anastomosis with a tube graft and the inferior vena cava stump. Note a full expansion of the inferior vena cava wall and the placement of the sucker in the inferior vena cava lumen, thus assuring the surgeon's more precise suture performance.

which the IVC drainage was through the femoral vein. In our case, a direct IVC cannulation rather than peripheral venous drainage was used because of the small sizes that were involved. Our experience shows that direct IVC cannulation does not necessarily exclude an open IVC technique. Potential drawbacks of this technique include air blockage of the circuit tube and failure to suck some of the hepatic venous blood. Each surgical team applying this technique should individualize the position and type of the IVC cannula to achieve optimal venous drainage.

In summary, open IVC anastomosis with vacuum-assisted venous drainage through direct access is a feasible, safe, and useful procedure even in pediatric patients. This new technique may alleviate, if not completely eliminate, a concern associated with extracardiac conduit total cavopulmonary connection in small patients.

References

1. Azakie A, McCrindle BW, Van Arsdell G, et al. Extracardiac conduit versus lateral tunnel cavopulmonary connections at a single institution: impact on outcomes. J Thorac Cardiovasc Surg 2001;122:1219–28.
2. Nakano T, Kado H, Ishikawa S, et al. Midterm surgical results of total cavopulmonary connection: clinical advantages of the extracardiac conduit method. J Thorac Cardiovasc Surg 2004; 127:730–7.
3. Aklog L, Sepic J, Filsoufi F, Byrne JG, Adams DH. Open inferior vena caval anastomosis during bicaval heart transplantation. Ann Thorac Surg 2002;73:671–2.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Use of Hemoglobin Vesicles During Cardiopulmonary Bypass Priming Prevents Neurocognitive Decline in Rats

Masataka Yamazaki, Ryo Aeba, Ryohei Yozu and Koichi Kobayashi

Circulation 2006;114;220-225
DOI: 10.1161/CIRCULATIONAHA.105.000562
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539